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Original Research
130 Antibiotic utilization improvement with the Nanosphere Veigene Gram-Positive Blood Culture assay by S. G. Beal et al
144 The SUCCESS model for laboratory performance and execution of rapid molecular diagnostics in patients with sepsis by M. Dekmezian et al
151 Impact of the DASH diet on endothelial function, exercise capacity, and quality of life in patients with heart failure by L. Rifai et al
157 A survey-based analysis of symptoms in patients with postural orthostatic tachycardia syndrome by A. Lee et al
160 An interactive web-based project to stimulate internal medicine resident reading using board-type questions by M. Tuncer-Kara et al

Review Article
163 The acute respiratory distress syndrome by A. M. Modrykamien and P. Gupta

Historical Study
172 History of neurologic examination books by C. J. Boes

Case Studies
180 Cecal adenocarcinoma presenting as colonic intussusception in adulthood by J. Gonzales-Hernandez et al
183 Large-volume barium aspiration by G. I. Hundemer et al
185 Effect of resection of an orbital arteriovenous malformation on central venous pressure by V. Srisung et al
188 Acute nonthrombotic streptococcal myocarditis resembling ST-elevation acute myocardial infarction in a young patient by J. L. Aguirre et al
191 Invited commentary: What is the definition of SPAM? Even if you cannot define it, you must recognize it! by W. A. Schiavone
192 Cardiac arrhythmias during myocardial infarction by D. L. Glancy et al
194 Takotsubo cardiomyopathy associated with hyperthyroidism treated with thyroidecetomy by S. Omar et al
196 Ventricular tachycardia storm with a chronic total coronary artery occlusion treated with percutaneous coronary intervention by T. A. Mixon
200 Myocardial ischemic hyperacute T-wave oversensing leading to a defibrillator shock storm by L. Chhabra et al
204 Usefulness of percutaneous closure of patent foramen ovale for hypoxia by A. S. Munkres et al
207 Mitral stenosis and acute ST elevation myocardial infarction by J. Carrillo et al
210 Effectiveness of exclusion of a persistent sciatric artery aneurysm with an Amplatzer™ plug by A. Lee et al
213 Immune thrombocytopenia associated with consumption of tonic water by F. D. Winter Jr.
217 Pancreatic cystic cell ataxia and the pancreatogenic syndromes by S. Atar et al
221 Carcinoma of the lungs causing enlarged kidneys by W. Srisung et al
224 Mixed epithelial and stromal tumors of the kidney discovered incidentally at autopsy by V. Podduturi and J. M. Guileyardo
227 Superior sagittal sinus thrombosis as the initial presentation of renal cell carcinoma by M. P. Reddy et al
229 Hepatocellular carcinoma with extension to the heart via the inferior vena cava by M. Oncale and B. Lewis
231 Leprosy in a Texan by G. L. Vick et al

Interview, Editorials, and Book Review
237 Alan Marshall Miller, MD, PhD: a conversation with the editor by A. M. Miller and W. C. Roberts
247 Probability and uncertainty in clinical and forensic medicine by J. M. Guileyardo
250 Experience as a physician to the Major League Baseball All-Stars series against Japan by J. D. Cantwell
254 Directions to a lost place: a parable for modern times by M. Davis
256 Book review: Users’ Guides to the Medical Literature by B. Warren

From the Editor
258 Facts and ideas from anywhere by W. C. Roberts

Miscellaneous
233 Baylor news
255 Reader comments: Lupus erythematosus flare-up and myopericarditis as triggers and comorbidities of takotsubo syndrome (J. E. Madras)
266 2014 publications of the Baylor medical and scientific staff
286 Selected published abstracts of Baylor researchers

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Currently, Baylor Research Institute is conducting more than 800 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. Clinical research studies conducted through Baylor Research Institute that are enrolling patients

<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>
</table>
| Asthma and pulmonary disease                | Chronic obstructive pulmonary disease, asthma (adult)                                      | Rose Boehm, (CRC, RRT, RCP) 214-818-9405 RoseBoehm@BaylorHealth.edu  
Jana Holloway, RRT, CRC 214-820-9688 janaholloway@baylorhealth.edu  
Cara Kraft 214-865-1169 Cara.Kraft@baylorhealth.edu |
| Cancer                                       | Breast, ovarian, endometrial, prostate, brain, lung, bladder, colorectal, pancreatic, and head and neck cancer; hematological malignancies, leukemia, multiple myeloma, non-Hodgkin’s lymphoma; melanoma vaccine; bone marrow transplant | Grace Townsend 214-818-8472 cancer.trials@BaylorHealth.edu |
| Treatment-naïve colorectal cancer            |                                                                                           | Allisson Cox 214-820-6679 marya.correll@baylorhealth.edu |
| Diabetes (Dallas)                           | Type 1 and type 2 diabetes, cardiovascular events                                         | Kris Chionh 214-820-3416 kristen.chionh@BaylorHealth.edu |
| Pancreatic islet cell transplantation for type 1 diabetics, who either have or have not had a kidney transplant | Keni Purcell, RN 817-922-4640 keni.purcell@baylorhealth.edu |
| Diabetes (Fort Worth)                       | Type 2; cardiac events                                                                      | Trista Bachand, RN 817-922-2587 trista.bachand@baylorhealth.edu |
| Pancreatic islet cell transplantation for type 1 diabetics, who either have or have not had a kidney transplant | Keni Purcell, RN 817-922-4640 keni.purcell@baylorhealth.edu |
| Gastroenterology                            | Healthy subjects needing colonoscopies                                                      | Allisson Cox 214-820-6679 marya.correll@baylorhealth.edu |
| Inflammatory bowel disease                   |                                                                                           | Dr. Themistocles Dassopoulos 469-800-7180 T.Dassopoulos@baylorhealth.edu |
| Heart and vascular disease (Dallas)         | Aortic aneurysms, coronary artery disease, hypertension, poor leg circulation, heart attack, heart disease, congestive heart failure, angina, carotid artery disease, familial hypercholesterolemia, renal denervation for hypertension, diabetes in heart disease, cholesterol disorders, heart valves, thoracotomy pain, stem cells, critical limb ischemia, cardiac surgery associated with kidney injury, pulmonary hypertension | Merielle Boatman 214-820-2273 Merielle@BaylorHealth.edu |
| Heart and vascular disease (Fort Worth)     | Atrial fibrillation, atrial fibrillation post PCI                                          | Meagan King 817-922-2583 Meagan.king@baylorhealth.edu |
| Heart and vascular disease (Legacy Heart)   | At risk for heart attack/stroke; previous heart attack/stroke/PAD; cholesterol disorders; atrial fibrillation; overweight/obese; other heart-related conditions | Angela Germany 469-800-6409 lhcresearch@baylorhealth.edu |
| Heart and vascular disease (Plano)          | Aortic aneurysm; coronary artery disease; renal stent for uncontrolled hypertension; poor leg circulation; heart attack; heart disease; heart valve repair and replacement; critical limb ischemia; repair of aortic dissections with endografts; surgical leak repair; atrial fibrillation; heart rhythm disorders; carotid artery disease; congestive heart failure; gene profiling | Tina Worley 469-814-4712 c19459@BaylorHealth.edu |
| Hepatology                                  | Liver disease                                                                             | Jonnie Edwards 214-820-6243 jonnie.edwards@baylorhealth.edu |
| Infectious disease                          | HIV/AIDS                                                                                  | Bryan King, LVN 214-823-2533 bryan.king@ntdc.org |
|                                               | Hepatitis C, hepatitis B                                                                   | Jonnie Edwards 214-820-6243 jonnie.edwards@baylorhealth.edu |
| Nephrology                                  | Homocystine and kidney disease, dialysis fistulas, urine/protein disorders in cancer patients | Dallas Clinical Trials Office 214-818-9668 Fabienne.english@baylorhealth.edu  
Dr. Harold Zerlip 214-358-2300 Harold.Zerlip@baylorhealth.edu |
| Neurology                                    | Stroke                                                                                    | Darlene Bunpian, MPH 214-818-2523 darlene.bunpian@baylorhealth.edu |
| Migraine                                     |                                                                                           | Ognih Lan Doan 214-818-2522 ognih.doen@baylorhealth.edu |
| Multiple sclerosis                           |                                                                                           | Portland Pleasant, RN 214-820-7003 portland.pleasant@baylorhealth.edu |
| Neurosurgery                                 | Cerebral aneurysms                                                                         | Kenneth Layton, MD 214-827-1600 KennethL@baylorhealth.edu |
| Rheumatology (9900 NL Central Expressway)   | Rheumatoid arthritis, psoriatic arthritis, lupus, gout, ankylosing spondylitis             | Giselle Huet 214-987-1253 ruth.huet@baylorhealth.edu  
Krystine Cethoute 214-987-1249 krystine.cethoute@baylorhealth.edu |
| Transplantation                              | Bone marrow, blood stem cells                                                              | Grace Townsend 214-818-8472 Grace.Townsend@BaylorHealth.edu  
Gabrielle Ethington 214-818-8326 gabrielle@baylorhealth.edu |
| Solid organs                                 |                                                                                           | Jonnie Edwards 214-820-6243 jonnie.edwards@baylorhealth.edu |
| Weight management                           | Obesity                                                                                    | Kris Chionh 214-820-3416 kristen.chionh@BaylorHealth.edu |
| Women’s health (Fort Worth)                 | Endometriosis and endometrial ablation                                                    | Theresa Cheyne, RN 817-922-2579 theresa.cheyne@baylorhealth.edu |

Baylor Research Institute is dedicated to providing the support and tools needed for successful clinical research. To learn more about Baylor Research Institute, please contact Kristine Hughes at 214-820-7556 or Kristine.Hughes@BaylorHealth.edu.
Antibiotic utilization improvement with the Nanosphere Verigene Gram-Positive Blood Culture assay

Stacy G. Beal, MD, Cody Thomas, MD, Neelam Dhiman, PhD, Daniel Nguyen, PharmD, Huanying Qin, MS, Jennifer M. Hawkins, MS, Mhair Dekmezian, MD, Raul Benavides, MD, and Jessica Njoku, PharmD

New technologies offer rapid identification of organisms and antimicrobial resistance markers in blood cultures several hours faster than conventional methods. We sought to determine whether implementation of the Verigene® Gram-Positive Blood Culture (BC-GP) assay paired with a well-defined results reporting algorithm would lead to earlier deescalation of empiric therapy for inpatients with methicillin-sensitive Staphylococcus aureus (MSSA) and vancomycin-resistant Enterococcus (VRE) bacteremia. The algorithm design focused on lessening the demand for pharmacist time by using electronic communications where possible. Our study compared inpatients with MSSA and VRE bacteremia from the time period before (pre-BC-GP) and after (post-BC-GP) implementation of the assay on June 25, 2013. The time from blood draw to identification and susceptibility results was decreased by 36.4 hours ($P < 0.001$) in the post-BC-GP group. The mean time from collection to the first dose of optimal antibiotics was reduced in the post-BC-GP group by 18.9 hours ($P = 0.004$) overall, with a 20.6-hour reduction ($P = 0.009$) for patients with MSSA and a 20.7-hour reduction ($P = 0.077$) for patients with VRE. Additionally, the percent of patients on empiric therapy who were placed on optimal antibiotics at any time after the Gram stain result was available increased from 64% (45/70) pre-BC-GP to 80% (43/54) post-BC-GP. The BC-GP led to an increased rate of deescalation of empiric antibiotics and a reduction in the time to optimal antibiotics for patients with MSSA and VRE bacteremia.

A variety of tests can identify organisms directly from positive blood culture bottles. These include matrix-assisted laser desorption/ionization time of flight (1), DNA hybridization (2), and polymerase chain reaction (3, 4). The Verigene Gram-Positive Blood Culture (BC-GP) assay (Nanosphere, Inc., Northbrook, IL) is a multiplex, DNA hybridization assay that detects 3 genera, 9 species, and 3 resistance markers directly from blood cultures positive for gram-positive organisms. It takes 2.5 hours to produce results. This study focused on the impact of implementing the rapid detection of methicillin-sensitive Staphylococcus aureus (MSSA) and vancomycin-resistant Enterococcus (VRE) using the Verigene BC-GP test on patients with these two organisms. The primary objective was to measure the reduction in time from blood culture collection to the first dose of optimal antibiotics. We also assessed the length of hospital stay for patients before and after implementation of the BC-GP for survivors.

METHODS

This was a single-center, retrospective, nonrandomized comparison before and after an intervention for patients admitted with MSSA and VRE bacteremia to Baylor University Medical Center at Dallas (BUMC), a 1079-bed tertiary referral center. Blood cultures were performed at the affiliated reference laboratory, med fusion, in Lewisville, Texas, which is approximately 20 miles from BUMC. All patients with MSSA bacteremia from December 15, 2012, to December 13, 2013, or VRE bacteremia from October 21, 2012, to December 13, 2013, were included in the study unless they met one of three exclusion criteria (Figure 1), which included 1) patients who were not admitted and patients who expired or were discharged before blood culture results were available; 2) patients with blood culture reports that were corrected after they were finalized; and 3) patients who did not have the BC-GP done on their blood culture after the test had been implemented (these samples were inadvertently omitted). The BC-GP went live on June 25, 2013. Patients who had blood cultures prior to the implementation of the BC-GP were in the pre-BC-GP group; those whose blood cultures occurred after implementation were in the post-BC-GP group. This study was approved by the BUMC institutional review board.

Patients were identified by searching the laboratory’s database for the target organisms. Patients were included more than once if they had two separate bacteraemic episodes, which was defined as >1 month from the last positive blood culture or a separate admission that occurred >30 days after discharge from the previous admission. Clinical data were obtained from the patient’s electronic health record (EHR). Data collected included demographic characteristics, intensive care unit (ICU) admission, and antibiotic therapy. Comorbidities were identified if they were documented in the problem list section of

From the Department of Pathology and Laboratory Medicine (Beal, Thomas, Dekmezian, Benavides) and the Department of Pharmacy (Nguyen, Njoku), Baylor University Medical Center at Dallas; med fusion Laboratory, Lewisville, Texas (Beal, Thomas, Dhiman, Dekmezian, Benavides); the Department of Quantitative Science, Baylor Health Care System, Dallas, Texas (Qin); and Baylor Research Institute, Dallas, Texas (Hawkins). Dr. Beal is now affiliated with the University of Florida Health Shands, Gainesville, Florida.

Corresponding author: Raul Benavides, MD, Department of Pathology, Baylor University Medical Center at Dallas, 3500 Gaston Avenue, Dallas, TX 75246 (e-mail: raulbena@baylorhealth.edu).
the EHR. For patients admitted to the ICU for some or all of their hospital stay, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated based on the characteristics during the 24 hours following ICU admission.

Times were documented from blood culture collection to the following: Gram stain, BC-GP result (in the postimplementation group), traditional identification and susceptibilities, and the first dose of optimal antibiotics. Fourteen patients were already receiving the optimal antimicrobials at the time of the Gram stain and were not included in the time to optimal antibiotic analysis. Patients who received the optimal antibiotic >200 hours from the blood culture draw were also not included, as we believed that this change was likely not in response to the blood culture result. Patients who died during their hospital admission were not included in the length of hospital stay analysis.

Antibiotics were documented based on the date and time that the dose was given as recorded in the medication administration record. For MSSA, optimal antimicrobials were considered to be oxacillin, nafcillin, or cefazolin. For VRE, optimal antimicrobials included daptomycin or linezolid.
Blood cultures during the pre-BC-GP and post-BC-GP periods were processed identically. Blood was collected in a BacTAlert FA (30 mL) and/or FN (40 mL) bottle (bioMérieux, Durham, NC) and transported via courier to med fusion. Couriers picked up specimens from BUMC every 2 hours, and the time to drive from BUMC to med fusion was 30 to 60 minutes. Upon arrival at med fusion, bottles were incubated on the BacTAlert automated blood culture system for up to 5 days. When the aerobic or anaerobic bottle was identified as positive, a Gram stain was performed, and the media were inoculated on appropriate solid agar media. Plates were read after approximately 24 hours of incubation, at which time rapid biochemical tests, such as coagulase, catalase, and pyrrolidonyl arylamidase (PYR, Remel, Lenexa, KS), were performed and the identification was released in the EHR. Identification and susceptibility testing were performed using traditional phenotypic methods and the VITEK®2, (bioMérieux). During the post-BC-GP period, the first bottle per bacteremic episode that showed gram-positive cocci was tested using the BC-GP according to the package insert (2). The BC-GP was also run if the Gram stain showed gram-positive cocci mixed with organisms of other Gram morphologies. The BC-GP was run 24 hours a day, 7 days a week.

Reporting occurred per routine protocol, as described below, with modification during the post-BC-GP period. Critical calls from med fusion to BUMC are required to take place within 30 minutes from the time the result is available. BUMC’s critical call procedure for inpatients consists of calling the nurse on the ward within 15 minutes, who is responsible for telling the physician. Before implementation of the BC-GP (pre-BC-GP), critical calls were made at the time of the Gram stain. Blood cultures that were identified as VRE were also called as critical values. These results were also released in the EHR.

In the post-BC-GP period, the above procedure continued. In addition to calling in the BC-GP results as a critical value to the nurse on the floor (who was responsible for telling the physician), the results were released in the EHR. In the EHR, the BC-GP result for MSSA was accompanied by an interpretive comment describing a recommendation for treatment. The comment stated, “Staphylococcus aureus. MSSA—consider switching to oxacillin or cefazolin if no severe beta-lactam allergy. Recommended by BUMC Stewardship. Tested by Verigene Molecular Assay.” There was no comment for VRE. The comment for MSSA and other organisms tested by the BC-GP underwent a rigorous approval process by the Antimicrobial Stewardship Program (ASP), infectious disease physicians, and laboratory staff.

Patient characteristics and clinical outcomes were compared between the pre- and post-BC-GP groups. Student’s t test was used for comparison of continuous variables. The chi-square test and Fisher’s exact test were used for categorical variables.

RESULTS

A total of 168 episodes of bacteremia were screened, including 126 with MSSA and 42 with VRE. Eleven patients in the pre-BC-GP group and 10 in the post-BC-GP group met exclusion criteria (Figure 1). Eighty episodes of bacteremia (59 with MSSA and 21 with VRE) were included in the analysis in the pre-BC-GP group; 67 (51 with MSSA and 16 with VRE) were included in the post-BC-GP group (Figure 1). There were no statistically significant differences in the pre and post groups with regards to demographic data (Table 1). There were 14 polymicrobial cultures (8 pre- and 6 post-BC-GP).

### Table 1. Demographics and baseline characteristics for patients in the pre- and post–gram-positive blood culture study groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before (n = 80)</th>
<th>After (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSA</td>
<td>59 (74%)</td>
<td>51 (76%)</td>
</tr>
<tr>
<td>VRE</td>
<td>21 (26%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16 (24%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>53.2 ± 17.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>55.5 ± 16.2</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>47 (59%)</td>
<td>41 (61%)</td>
</tr>
<tr>
<td><strong>Allergies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>15 (19%)</td>
<td>15 (22%)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>4 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td><strong>Comorbid conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>34 (43%)</td>
<td>21 (31%)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>7 (9%)</td>
<td>13 (19%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>7 (9%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>7 (9%)</td>
<td>13 (19%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>9 (11%)</td>
<td>14 (21%)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>5 (6%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>10 (13%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Surgery in previous 30 days</td>
<td>5 (6%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>3 (4%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Bone marrow transplant</td>
<td>5 (6%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid tumor</td>
<td>5 (6%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>6 (8%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>ICU admission&lt;sup&gt;d&lt;/sup&gt;</td>
<td>30 (38%)</td>
<td>31 (46%)</td>
</tr>
<tr>
<td>APACHE II score, mean</td>
<td>20.5 ± 7.8</td>
<td>20.8 ± 7.3</td>
</tr>
<tr>
<td>Days in ICU</td>
<td>10.5 ± 10.1</td>
<td>11.6 ± 12.3</td>
</tr>
<tr>
<td>Polymicrobial infections</td>
<td>8 (10%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>46 (58%)</td>
<td>44 (66%)</td>
</tr>
<tr>
<td>Black</td>
<td>22 (28%)</td>
<td>16 (24%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (9%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (6%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Includes 18 vancomycin-resistant *Enterococcus faecium* and 3 vancomycin-resistant *E. faecalis*.

<sup>b</sup>Includes 15 monomicrobial vancomycin-resistant *E. faecium* and 1 polymicrobial vancomycin-resistant *E. faecalis* found with *E. faecium* and other organisms.

<sup>c</sup>All ± values are means plus/minus the standard deviation.

<sup>d</sup>Includes patients with ICU admission any time during the index hospital admission.

The APACHE II score was calculated based on the characteristics during the initial 24 hours following ICU admission. Missing variables were considered normal. MSSA indicates meticillin-sensitive *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit.
From the time of the blood draw, the Gram stain was reported an average of 23.4 ± 10.0 hours in the pre-BC-GP group and 22.3 ± 10.0 hours in the post-BC-GP group (Figure 2). In the pre-BC-GP group, the preliminary identification was reported at 41.0 ± 13.4 hours, and the final identification and susceptibility results were reported at an average of 61.7 ± 17.0 hours. In the post-BC-GP group, the BC-GP result was called to the floor and released in the EHR an average of 25.3 ± 10.1 hours following the blood draw, which was an average of 3.1 ± 1.1 hours following the Gram stain result. Seventy patients (88%, 70/80) in the pre-BC-GP group and 54 patients in the post-BC-GP group (81%, 54/67) were on empiric vancomycin. The percent of these patients that were later placed on optimal antibiotics after the Gram stain result and during the bacteremic episode (within 200 hours from the blood draw) increased from 64% (45/70) pre-BC-GP to 80% (43/54, \( P = 0.011 \)) post-BC-GP.

For patients who were not on optimal antibiotics (regardless of empiric vancomycin use) by the time of the Gram stain, the average time from blood culture collection to the first dose of optimal antibiotics was 66.2 ± 29.35 hours pre-BC-GP (n = 54) and 47.3 ± 36.0 hours post-BC-GP (n = 51). For MSSA, the average times were 71.9 ± 23.2 hours pre-BC-GP (n = 34) and 51.3 ± 38.9 post-BC-GP (n = 38). For VRE, the average times were 56.3 ± 26.2 hours pre-BC-GP (n = 20) and 35.6 ± 23.0 post-BC-GP (n = 13). The mean time from collection to the first dose of optimal antibiotics was reduced overall in the post-BC-GP group by 18.9 hours (\( P = 0.004 \)), with a 20.6-hour reduction (\( P = 0.009 \)) for patients with MSSA and a 20.7-hour reduction (\( P = 0.08 \)) for patients with VRE.

In-hospital mortality rates during the index admission were 16.3% (13/80) for the pre-BC-GP group and 26.9% (18/67) for the post-BC-GP group (\( P = 0.16 \)). Patients who died during their hospital admission were not included in the length of stay analysis. For survivors, the average length of stay was 19.7 ± 21.8 days pre-BC-GP (n = 67) and 17.6 ± 14.1 days post-BC-GP (n = 49, \( P = 0.56 \)). For MSSA survivors, the average length of stay was 14.6 ± 13.7 days (n = 52) in the pre-BC-GP group and 15.1 ± 12.6 days in the post-BC-GP group (n = 41, \( P = 0.88 \)). For VRE survivors, the average length of stay was 37.3 ± 33.7 days (n = 15) in the pre-BC-GP group and 30.8 ± 14.9 in the post-BC-GP group (n = 8, \( P = 0.61 \)).

**DISCUSSION**

Our study found a decrease in time from blood draw to identification and susceptibility results of 36 hours (\( P < 0.001 \)) after implementation of the BC-GP. Overall, we found that patients in the post-BC-GP group obtained the first dose of optimal antibiotics 19 hours faster; additionally, more of these patients received optimal antibiotics. Other studies have shown that rapid identification of organisms in blood cultures has many benefits, such as faster time to optimal antimicrobials (5–7), decreased length of hospital stay (7), and decreased overall hospital costs (5, 7, 8).

Current literature suggests that the benefits of a faster time to antibiotic therapy with decreased time to identification rely on real-time involvement, most commonly by a clinical pharmacist or another member of an active ASP (5–9). Frye et al (9) reported that following implementation of a rapid blood culture test, there was no reduction in the time to optimal antibiotics for patients with MSSA in spite of a decrease in time to result. The authors attributed this to the fact that results were only passively released into their EHR and no additional interventions were made at the time of identification of MSSA. On the contrary, Bauer et al (8) showed that patients with MSSA received nafcillin or cefazolin 1.7 days (\( P = 0.002 \)) sooner with the use of a rapid polymerase chain reaction and an active ASP. In their study, the microbiology laboratory notified both the...
physician and an infectious disease pharmacist with the assay result. However, the pharmacist was only contacted between 8:00 am and 5:00 pm Monday through Friday. In our study, we showed that patients received optimal antibiotics about 1 day earlier, without the need for a real-time, active intervention by a pharmacist. Our use of antimicrobial recommendation comments accompanying the BC-GP result demonstrated that up-front planning and communication among infectious disease physicians, the ASP, and the lab had benefits that equalled other institutions' use of real-time interventions. Finally, the use of these comments was not restricted to any day or time, nor were they subject to any particular person's ability and availability to communicate with care providers.

Although other studies about rapid blood cultures have shown a decrease in the length of stay (7), our study did not find a statistically significant difference. Our study included patients with infections in other organ systems and polymicrobial infections and patients with serious comorbidities; other studies have excluded these patients.

The in-hospital mortality rates in each group were not statistically different. The pre-BC-GP group was hospitalized in the winter and spring (December to June) and the post-BC-GP group was hospitalized in the summer and fall (June to December); seasonal differences could have affected the underlying disease. Polymicrobial infections accounted for 9.5% of bacteraemic episodes included in the study. Pavlaki et al (10) showed that polymicrobial infection is a significant contributor to 28-day mortality.

Numerous studies have shown that delayed time to or lack of optimal antibiotic use increases morbidity and mortality. Lodise et al (11) reported that delayed treatment (>44.75 hours from the time the culture result was available) of *Staphylococcus aureus* bacteremia led to a 7-day longer hospital stay (20.2 days vs. 14.3 days; *P* = 0.05) and was an independent predictor of infection-related mortality. Ibrahim et al (12) showed that in-hospital mortality was greater in ICU patients who received inadequate antimicrobial therapy (61.9% vs. 28.4%, *P* < 0.001). Inadequate antibiotic use was an independent determinant of hospital mortality. In their study, the organisms with the highest rates of inappropriate antimicrobial therapy included VRE (n = 17; 100%), *Candida* species (n = 41; 95.1%), and MRSA (n = 46; 32.6%). Although statistically significant changes in length of stay and mortality were not seen in our study, we can presume that the patients who received optimal antibiotics faster would have better clinical outcomes.

One limitation of this study is that it looked at only 2 of the 12 organisms that are detected by the BC-GP. Furthermore, our study was not powered to assess long-term outcomes such as crude mortality or readmission rates. Our study attempted to reflect real life, so patients with polymicrobial bloodstream infections and other infections were included. We did not exclude patients with comorbidities that are often associated with a long length of stay. We also did not exclude or differentiate among patients with allergies to any of the antibiotics referred to in the study, as patients with documented allergies to those antibiotics are sometimes still treated with them based on the care provider's clinical judgment. Our study calculations utilized the time that the medication was administered and not the time that the medication was ordered.

**Acknowledgments**

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The SUCCESS model for laboratory performance and execution of rapid molecular diagnostics in patients with sepsis

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Successful performance and execution of rapid diagnostics in a clinical laboratory hinges heavily on careful validation, accurate and timely communication of results, and real-time quality monitoring. Laboratories must develop strategies to integrate diagnostics with stewardship and evidence-based clinical practice guidelines. We present a collaborative SUCCESS model for execution and monitoring of rapid sepsis diagnostics to facilitate timely treatment. Six months after execution of the Verigene Gram-Positive Blood Culture (BC-GP) and the AdvanDx PNA-FISH assays, data were collected on 579 and 28 episodes of bacteremia and fungemia, respectively. Clinical testing was executed using a SUCCESS model comprising the following components: stewardship, utilization of resources, core strategies, concierge services, education, support, and surveillance. Stewardship needs were identified by evaluating the specialty services benefiting from new testing. Utilization of resources was optimized by reviewing current treatment strategies and antibiogram and formulary options. Core strategies consisted of input from infectious disease leadership, pharmacy, and laboratory staff. Concierge services included automated Micro-eUpdate and physician-friendly actionable reports. Education modules were user-specific, and support was provided through a dedicated 24/7 microbiology hotline. Surveillance was performed by daily audit by the director. Using the SUCCESS model, the turnaround time for the detailed report with actionable guidelines to the physician was ~3 hours from the time of culture positivity. The overall correlation between rapid methods and culture was 94% (546/579). Discrepant results were predominantly contaminants such as a coagulase-negative staphylococci or viridans streptococci in mixed cultures. SUCCESS is a cost-effective and easily adaptable model for clinical laboratories with limited stewardship resources.

Bacteremia is a major cause of severe sepsis and septic shock, accounting for 30% to 40% of cases, with an estimate of about 250,000 cases occurring annually in the United States (1). A significant proportion of causative organisms are gram-positive bacteria, most commonly Staphylococcus species (2). Multiple studies have established that timely administration of appropriate antibiotics significantly reduces the mortality of severe sepsis and septic shock. Use of inappropriate empiric antibiotics is a common factor associated with mortality rates as high as 75% (3, 4). Delays in initiating antimicrobial treatment are correlated with a progressive increase in mortality (5). The choice of initial antibiotics for treatment of bacteremia must currently be determined empirically. A reduction in time to an accurate identification and susceptibility results may lead to improved patient outcomes, although literature on the magnitude of such an effect is mixed (6, 7).

Current standard blood culture procedures consist of inoculating a blood culture bottle and placing it on an automated continuous monitoring and alert platform (8). Upon positivity, the contents are Gram stained, plated on appropriate media, and allowed to grow for 18 to 42 hours or longer, with subsequent subcultures and susceptibility testing as appropriate. The temporal delay between collection of a blood sample from a patient and availability of traditional identification and susceptibility results has obvious implications regarding patient care.

Newer technologies such as nucleic acid amplification tests, fluorescence in situ hybridization (FISH), and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) provide rapid identification of pathogens and co-detection of key resistance markers directly from positive blood cultures. The Verigene Gram-Positive (BC-GP) and Gram-Negative (BC-GN) blood culture assays are approved by the Food and Drug Administration (FDA) to detect common gram-positive and gram-negative organisms, respectively, and associated resistance markers within 3 hours from positive blood cultures (9). The Verigene assays are nonamplified tests that rely on nucleic acid extraction from positive blood cultures followed by microarray-based detection using capture and detection probes. BC-GP is specific for 12 gram-positive bacterial identification targets and 3 associated resistance markers (mecA, vanA, and vanB), while BC-GN is specific for 8 gram-negative bacterial identification targets and 6 resistance markers (blaCTX-M, blaKPC, blaNDM, blaVIM, blaIMP, and blaOXA). The turnaround time from positive blood culture to results can be markedly reduced compared with traditional methods, potentially providing

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clinically useful data hours or days before traditional methods. Peptide nucleic acid (PNA) FISH is also an FDA-approved technology that uses a PNA probe that hybridizes to the target rRNA when present in the sample and allows visualization of bacteria (such as *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus faecalis*/other enterococci, *Escherichia coli*, *Klebsiella* and *Pseudomonas* spp.) and yeasts (*Candida* spp.) in positive blood cultures within 1.5 hours of positivity (10). Rapid identification and resistance reporting may allow de-escalation of empiric coverage to appropriate targeted therapy and reduction in length of hospital stay.

In this prospective study, we evaluated the laboratory performance of two rapid molecular tests, Verigene BC-GP and Yeast Traffic Light PNA FISH, on a cohort of inpatients from Baylor University Medical Center at Dallas and regional hospitals in Dallas, Texas. In addition, we developed a logical execution protocol to ensure clinical “SUCCESS” of the laboratory testing.

**MATERIALS AND METHODS**

Laboratory performance and execution of rapid diagnostics was based on seven key components of the SUCCESS model (Figure 1). Standardized treatment guidelines were developed by a collaborative team of infectious disease specialists, pharmacists, and laboratory directors. To support an antimicrobial stewardship program team with limited financial and personnel resources, a strategy to bypass pharmacy intervention and include treatment recommendations on the report was chosen for timely and effective communication of the results to the users. Stewardship recommendations and algorithms for possible test result scenarios were formulated after the review of institutional treatment strategies, practices and interventions based on conventional microbiology testing results, and antibiogram and formulary options. In addition, comments were developed to address possible limitations of the assay to avoid adverse patient outcomes. Extensive materials were developed for training and education. Electronic tools were developed for daily updates, surveillance, and audit of results.

For monitoring the performance of the executed tests in routine three-shift microbiology laboratories, results were audited for a period of 6 months after the go-live date. A total of 15,793 blood cultures were performed during this period. Blood cultures with positive alerts from the BacT/ALERT system (bioMérieux, Inc., Durham, NC) containing gram-positive coccis (n = 579) and/or yeast (n = 28) were tested according

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**Figure 1.** The seven key components of the SUCCESS model.
to manufacturer procedures using the FDA-approved BC-GP (Nanosphere, Northbrook, IL) and Yeast PNA FISH assay (Advanced, Woburn, MA), respectively. Any results indicating no organisms detected or an internal control failure were reflexively repeated. Concurrent with the BC-GP and PNA-FISH testing, traditional laboratory procedures were also used to identify causative organisms, including plating on appropriate media and the routine biochemical and antibiotic susceptibility tests.

Results from rapid testing were compared with biochemical testing for concordance in identification and antibiotic susceptibility. Turnaround time analysis was measured from the time of Gram stain following culture bottle positivity to the availability of rapid assay results.

RESULTS

The execution model was direct communication of a detailed report with actionable guidelines to the physicians within 3 hours from the time of culture positivity using the laboratory and hospital information systems in addition to critical calls. Tables 1 and 2 outline the comments that were incorporated in the Verigene and PNA-FISH reports, respectively. Briefly, the initial Gram stain was reported with a critical call as routine. The report was updated with the Verigene or PNA-FISH results and the applicable stewardship comment within 1.5 hours for yeasts and 3 hours for bacteria. A second critical call was initiated at this time to communicate the result update to the physicians. Subsequently, the identification by conventional methods from culture and susceptibility results was communicated when available. Careful consideration was given to communicate the limitations of the assay with appropriate canned comments. For example, in an event of codetection of S. aureus, S. epidermidis, and mecA targets, a comment was added to specify that methicillin resistance was detected but could not be assigned to either S. aureus or S. epidermidis. The recommendation was made to refer to the final pathogen identification and sensitivities to prevent premature change in management. Similarly, a comment was added to address the cross-reactivity of S. pneumoniae with other members of the S. mitis group. All not-detect calls also went out with a recommendation to refer to final ID and sensitivities.

### Table 1. Stewardship guidance for Verigene reportinga

<table>
<thead>
<tr>
<th>Verigene result</th>
<th>Reported organism</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>S. aureus</td>
<td>Methicillin susceptible. Consider de-escalating to oxacillin or cefazolin if no severe allergy.</td>
</tr>
<tr>
<td>S. epidermidis ± mecA</td>
<td>S. epidermidis (1 of 2 sets)</td>
<td>Common contaminant, often does not require treatment.</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>Coagulase-negative staphylococcus, NOT S. epidermidis or S. lugdunensis (1 of 2 sets)</td>
<td>Methicillin resistance detected but cannot be assigned to either S. aureus or S. epidermidis. Refer to final ID and sensitivities.</td>
</tr>
<tr>
<td>S. aureus + S. epidermidis + mecA</td>
<td>S. aureus, S. epidermidis</td>
<td>Consider de-escalating to ampicillin, ampicillin/sulbactam or piperacillin/tazobactam; synergistic gentamicin may be required with ampicillin in some circumstances.</td>
</tr>
<tr>
<td>E. faecalis + vanA and/or vanB</td>
<td>E. faecalis, vancomycin resistant; initiate VRE contact precaution</td>
<td></td>
</tr>
<tr>
<td>E. faecalis</td>
<td>E. faecalis</td>
<td>Initiate VRE contact precaution. Consider daptomycin or linezolid.</td>
</tr>
<tr>
<td>E. faecium + vanA and/or vanB</td>
<td>E. faecium, vancomycin resistant</td>
<td>Consider de-escalating to oxacillin, cefazolin, or other penicillin if no severe allergy.</td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>β-hemolytic strep group A</td>
<td>Other members of Streptococcus mitis group may also give a positive result.</td>
</tr>
<tr>
<td>S. agalactiae</td>
<td>β-hemolytic strep group B</td>
<td>Amoxicillin is the preferred drug therapy. Consider switching to ampicillin if no severe allergy. For severe beta-lactam allergy, consider trimethoprim-sulfamethoxazole.</td>
</tr>
<tr>
<td>S. anginosus</td>
<td>S. anginosus</td>
<td></td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>S. pneumoniae</td>
<td>The Gram-positive organism(s) seen on Gram stain will be identified by routine culture and susceptibility methods. The organism(s) could not be identified by the Verigene Molecular Assay.</td>
</tr>
<tr>
<td>Listeria spp.</td>
<td>Listeria spp.</td>
<td></td>
</tr>
</tbody>
</table>

Not-detect

<table>
<thead>
<tr>
<th>Verigene culture discordant result</th>
<th>Corrected report</th>
</tr>
</thead>
<tbody>
<tr>
<td>This isolate was originally Not Detected by Verigene Molecular Assay.</td>
<td></td>
</tr>
</tbody>
</table>

---

aThe stewardship guidance is based on institutional practice and guidelines and may not be generalizable.

bRemove comment if second bottle turns positive for same morphology.

cRemove comment when culture results are updated.

dVRE indicates vancomycin-resistant enterococci.

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The report was updated with the Verigene or PNA-FISH results and the applicable stewardship comment within 1.5 hours for yeasts and 3 hours for bacteria. A second critical call was initiated at this time to communicate the result update to the physicians. Subsequently, the identification by conventional methods from culture and susceptibility results was communicated when available. Careful consideration was given to communicate the limitations of the assay with appropriate canned comments. For example, in an event of codetection of S. aureus, S. epidermidis, and mecA targets, a comment was added to specify that methicillin resistance was detected but could not be assigned to either S. aureus or S. epidermidis. The recommendation was made to refer to the final pathogen identification and sensitivities to prevent premature change in management. Similarly, a comment was added to address the cross-reactivity of S. pneumoniae with other members of the S. mitis group. All not-detect calls also went out with a recommendation to refer to final identification and sensitivities to prevent misinterpreting a not-detect call as negative for targets that were not present on the BC-GP panel (Table 1).

For periodic cumulative updates to the physicians, an automated personalized Micro eUpdate service was provided. This service sent a summary of updated microbiology results by physician/physician group every 6 hours via a secure email. This provided easy access to results when the electronic medical
A cumulative electronic report on Verigene and PNA-FISH results from the prior 24 hours was also sent to the pharmacist every morning. This allowed the pharmacist to monitor compliance with treatment recommendations and identify and target “nonadopters” for additional education. Using this approach, we were able to target 64% uptake at execution and ∼80% uptake after 3 months of execution after additional education (data not shown).

Performance of the tests was evaluated by daily audit and correlation with the conventional results. During the 6-month period, 579 blood cultures were assayed, of which 525 were monomicrobial and 54 were polymicrobial in culture. The correlation between the results by conventional methods and the Verigene BC-GP assay were 97% (508/525) for monomicrobial (Table 3) and 70% (38/54) for polymicrobial cultures (Table 4), with an overall correlation rate of 94% (546/579). The average turnaround time from Gram stain to Verigene reporting was 3.1 ± 1.1 hours.

There were seven errors with major clinical impact in the monomicrobial cultures, which included miscalling *S. aureus* as coagulase-negative staphylococci (*n* = 3), failure to identify the *mecA* marker in an *S. aureus* isolate (*n* = 1), and miscalling

### Table 2. Stewardship guidance for PNA-FISH reportinga

<table>
<thead>
<tr>
<th>PNA-FISH result</th>
<th>Reported organism</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em>/<em>parapsilosis</em></td>
<td><em>C. albicans</em>/<em>parapsilosis</em></td>
<td>Unable to differentiate between <em>C. albicans</em> and <em>C. parapsilosis</em>. Both organisms are typically susceptible to fluconazole.</td>
</tr>
<tr>
<td><em>C. glabrata</em>/<em>kruiser</em></td>
<td><em>C. glabrata</em>/<em>kruiser</em></td>
<td>Unable to differentiate between <em>C. glabrata</em> and <em>K. kruiser</em>. Culture identification to follow.b</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td><em>C. tropicalis</em></td>
<td>Typically susceptible to fluconazole.</td>
</tr>
<tr>
<td>Not-detect</td>
<td></td>
<td>The Yeast seen on Gram stain will be identified by routine culture. The yeast could not be identified by the PNA FISH.b</td>
</tr>
<tr>
<td>PNA-FISH culture discordant result</td>
<td>Corrected report</td>
<td>This isolate was originally Not Detected by the PNA FISH.</td>
</tr>
</tbody>
</table>

aThe stewardship guidance is based on institutional practice and guidelines and may not be generalizable.

bRemove comment when culture results are updated.

cRemove comment when sensitivity results are updated. *C. kruiser* is intrinsically resistant to fluconazole.

PNA indicates peptide nucleic acid; FISH, fluorescence in situ hybridization.

### Table 3. Concordance between monomicrobial cultures and the isolates detected by BC-GP assay

<table>
<thead>
<tr>
<th>Monomicrobial culture results</th>
<th>No. (%) of isolates</th>
<th>Discrepant results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Correct calls</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>14 (2.7%)</td>
<td>14 (100%)</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em>, vancomycin resistant</td>
<td>1 (0.2%)</td>
<td>1 (100%)</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus faecium</em></td>
<td>2 (0.4%)</td>
<td>2 (100%)</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus faecium</em>, vancomycin resistant</td>
<td>15 (2.9%)</td>
<td>15 (100%)</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>51 (9.7%)</td>
<td>48 (94.1%)</td>
<td>3 <em>S. epidermidis</em>, 1 <em>Staphylococcus</em> spp.</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em>, methicillin resistant</td>
<td>51 (9.7%)</td>
<td>50 (98.0%)</td>
<td>1 Missed <em>mecA</em></td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>193 (36.8%)</td>
<td>192 (98.9%)</td>
<td>1 <em>Staphylococcus</em> spp.</td>
</tr>
<tr>
<td><em>Staphylococcus lugdunensis</em></td>
<td>1 (0.2%)</td>
<td>1 (100%)</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus spp.</em> NOT <em>S. epidermidis</em> or <em>S. lugdunensis</em></td>
<td>105 (20.0%)</td>
<td>102 (97.1%)</td>
<td>3 <em>S. epidermidis</em></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>15 (2.9%)</td>
<td>15 (100%)</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus anginosus group</em></td>
<td>7 (1.3%)</td>
<td>7 (100%)</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus spp.</em> NOT <em>S. pyogenes</em>, <em>S. agalactiae</em>, <em>S. pneumoniae</em>, or <em>S. anginosus group</em></td>
<td>38 (7.2%)</td>
<td>32 (84.2%)</td>
<td>6 5 not detected, 1 <em>S. pneumoniae</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>1 (0.2%)</td>
<td>1 (100%)</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td>6 (1.1%)</td>
<td>3 (50%)</td>
<td>3 3 IC failure</td>
</tr>
<tr>
<td>Non–BC-GP target</td>
<td>25 (4.8%)</td>
<td>25 (100%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>525</td>
<td>508</td>
<td>17</td>
</tr>
</tbody>
</table>

Sensitivity: 96.8%. BC-GP indicates gram-positive blood culture; IC, internal control.
Table 4. Concordance between polymicrobial cultures and BC-GP assay

<table>
<thead>
<tr>
<th>Verigene BC-GP call</th>
<th>No. of isolates</th>
<th>Correct reads</th>
<th>Discrepant results</th>
<th>Culture results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not detected</td>
<td>16</td>
<td>11</td>
<td>3</td>
<td>CoNS + 1 or 2 non–BC-GP targets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Viridans streptococci + CoNS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Viridans streptococci + 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>or 2 non–BC-GP targets</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>CoNS + 1 or 2 non–BC-GP targets</td>
</tr>
<tr>
<td>NOT S. epidermidis or S. lugdunensis</td>
<td></td>
<td></td>
<td></td>
<td>CoNS multiple morphotypes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Viridans streptococci + 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>or 2 non–BC-GP targets</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>15</td>
<td>11</td>
<td>4</td>
<td>S. epidermidis + CoNS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>S. epidermidis + 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>or 2 non–BC-GP targets</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>5</td>
<td>2</td>
<td></td>
<td>Streptococcus spp. + 1</td>
</tr>
<tr>
<td>NOT S. pyogenes, S. agalactiae, S.</td>
<td></td>
<td></td>
<td></td>
<td>or 2 non–BC-GP targets</td>
</tr>
<tr>
<td>pneumoniae, or S. anginosus group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Streptococcus spp. + CoNS</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Streptococcus spp. + MRSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
<td>1</td>
<td></td>
<td>MSSA + 1 or 2 non–BC-GP targets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus + mecA</td>
<td>4</td>
<td>2</td>
<td></td>
<td>MRSA + MSSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MSSA + CoNS</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>1</td>
<td>1</td>
<td></td>
<td>S. pneumoniae + MSSA + 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>or 2 non–BC-GP targets</td>
</tr>
<tr>
<td>Enterococcus faecalis + vanA</td>
<td>1</td>
<td>1</td>
<td></td>
<td>E. faecalis (not VRE) + 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>or 2 non–BC-GP targets</td>
</tr>
</tbody>
</table>

Sensitivity: 70.4%. BC-GP indicates gram-positive blood culture; CoNS, coagulase-negative Staphylococcus; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-sensitive Staphylococcus aureus; VRE, vancomycin-resistant enterococci.

in a mix of E. faecalis and a non–BC-GP target, Enterobacter cloacae (Table 4).

In 41 instances the BC-GP molecular assay failed to identify any organisms, including the non–BC-GP targets such as Abiotrophia spp., Bacillus spp., Aerococcus spp., Actinomyces spp., Acinetobacter spp., anaerobic gram-positive cocci, Corynebacterium spp., Clostridium perfringens, Escherichia coli, Enterococcus casseliflavus, E. gallinarum, and Micrococcus spp. The most common organism associated with the not-detected call was Micrococcus spp. (n = 25).

PNA FISH analysis of 28 blood cultures containing yeast on Gram stain yielded identification of C. albicans/parapsilosis (n = 21), C. glabrata/kruusei (n = 4), and C. tropicalis (n = 1). Two specimens were not-detect call by PNA-FISH and were identified as Cryptococcus neoformans after routine laboratory culture and identification methods. PNA-FISH gave accurate results for the two specimens mixed with bacterial targets. The average turnaround time from Gram stain to PNA-FISH reporting was ~1.5 hours.

**DISCUSSION**

The validation of newer techniques is a vital component in the endless process of laboratory improvement. There is substantial data in the literature to support the superior laboratory performance and better turnaround time of new diagnostics such as Verigene and PNA-FISH compared to conventional methods for sepsis (11–15). However, limited guidance is available for integration of such techniques into the laboratory workflow, and the subsequent introduction to the clinical setting reveals a separate set of challenges. In this study, we sought to evaluate both the validity of the laboratory portion of the molecular assay in a true clinical setting along with the execution and uptake of the results by the end users.

The laboratory performance for BC-GP in our study was comparable to that of published reports. The overall concordance between the Verigene BC-GP assay and the expected results (i.e., correct identification of targeted organisms and susceptibility) using conventional testing was 94%. Many of the discrepancies were related to organisms of little relative clinical significance, such as S. epidermidis or another coagulase-negative staphylococcus in a single blood culture set, or where there was another accurately reported pathogenically dominant organism in a mixed culture (such as pneumococcus alongside coagulase-negative staphylococcus). Other discrepancies included clinically relevant gram-positive rods, which were not the targets of the molecular assay. One notable discrepancy in our study was
a 50% (3 of 6 cultures) failure rate of the BC-GP assay to detect Group A streptococcus. This was realized as a limitation of the assay. Group A streptococcus harbors cell-wall–located DNase, which serves as an important virulence factor in pathogenesis (16). The DNases are also known to degrade the internal processing control that comprises a nontarget organism, Bacillus subtilis, which invalidated the result.

Despite significant literature on analytical and laboratory validation of rapid diagnostics, there are a handful of reports in the literature that have looked at the clinical and economic outcomes for patients after successful execution. Sango et al (17) evaluated the impact of Enterococcus identification and resistance detection using Verigene BC-GP. The intervention by an infectious disease and/or critical care pharmacist on 74 patients with enterococcal bacteremia led to a significant decrease in the mean time to appropriate antimicrobial therapy in the postintervention group (23.4 h; \( P = 0.005 \)) compared with the preintervention group. Alby et al (18) developed a treatment algorithm for streptococci and enterococci identified with the Verigene BC-GP assay in collaboration with their institutional antimicrobial stewardship program. However, the execution plan and algorithm utilization still relied on effective manual communication of the BC-GP results directly to an on-call pharmacist, who in turn used the treatment algorithm as a guide when recommending therapy at the bedside. Bauer et al (19) also used direct phone contact with the infectious diseases pharmacist as an effective mode of communication with results of the rapid PCR for methicillin-resistant S. aureus/S. aureus bacteremia. Clinical and economic outcome evaluation on 156 patients showed that the mean time to switch from empiric vancomycin to cefazolin or nafcillin in patients with methicillin-susceptible S. aureus/S. epidermidis, and mecA are concurrently detected. A resolution by conventional testing is required for such cases. Lastly, the assay cannot differentiate between S. pneumoniae and the S. mitis/oralis group. False-positive S. pneumoniae does not limit the utility of the assay, as treatment algorithms can be developed around this limitation by effective communication of the results and assay limitations (18).

Acknowledgments

We would like to thank all the lab personnel that helped to collect this data.


Impact of the DASH diet on endothelial function, exercise capacity, and quality of life in patients with heart failure

Luay Rifai, MD, Carol Pisano, RN, Janel Hayden, RD, Suela Sulo, PhD, and Marc A. Silver, MD

Endothelial dysfunction has been recognized as a pathophysiologic mechanism in the progression of heart failure (HF). However, little attention has been given to the ability of dietary approaches to improve endothelial function. This study examined the effects of the Dietary Approaches to Stop Hypertension (DASH) diet on endothelial function, exercise capacity, and quality of life in patients with chronic symptomatic (stage C) HF. Forty-eight patients were randomized to follow the DASH diet (n = 24) or the general HF dietary recommendations (n = 24). Endothelial function was assessed by measuring large and small arterial elasticity (LAE and SAE) at rest. Exercise capacity (measured with the 6-minute walk test) and quality of life (measured with the Minnesota Living with Heart Failure Questionnaire) at baseline and 3 months were also evaluated. Patients were older adults with an average HF duration of 5 years. LAE at 1 month improved significantly in the DASH diet group (P < 0.01). Overall LAE and SAE scores at 3 months also improved; however, the net changes were not statistically significant. The DASH group had better exercise capacity (292 m vs 197 m; P = 0.018) and quality of life scores (21 vs 39; P = 0.006) over time, while sodium intake levels at 1, 2, and 3 months were comparable between the groups. Adhering to the DASH diet improved arterial compliance initially and improved exercise capacity and quality of life scores at 3 months. The DASH diet may be an important adjunctive therapy for patients with symptomatic HF.

Heart failure (HF) remains a leading illness responsible for significant morbidity and mortality in the United States. Current HF treatment guidelines provide no specific recommendations for dietary intake. Patients with HF typically follow dietary guidelines for prevention of coronary heart disease (1). The Dietary Approaches to Stop Hypertension (DASH), a carbohydrate-rich and low-fat diet that emphasizes fruits and vegetables, has been formally adopted into the 2013 dietary guidelines for cardiovascular risk prevention (2, 3). Endothelial dysfunction underlies pathophysiologic mechanisms in the progression of HF and may be an important therapeutic tool in the management and prevention of HF. Several components of the DASH diet may be partly responsible for its salutary effects and influence on endothelial function (4–8). This study examined the effects of the DASH diet on endothelial function, exercise capacity, and quality of life in patients with chronic symptomatic (stage C) HF.

METHODS

A single-center randomized controlled study was conducted. Patients were randomly assigned via a computerized assignment log into the DASH diet regiment or the comparison group, which required patients to follow the general HF dietary recommendations for 3 months. The study comprised 48 stable patients with chronic symptomatic (stage C) HF from the outpatient adult HF clinic at Advocate Christ Medical Center between February and July 2013. Institutional review board approval was obtained in January 2013. The study duration was 6 months. Inclusion criteria included adults over 18 years of age with stage C/New York Heart Association (NYHA) functional classes I–III and systolic or diastolic HF for at least 6 months. The patients were taking recommended medications for HF. Exclusion criteria included serum creatinine >3 mg/dL, allergy or intolerance to components of the DASH diet, chronic inflammatory bowel disease affecting gastrointestinal absorption, inability to perform the 6-minute walk test due to severe musculoskeletal disease, and dependency on using a walker or a cane for ambulation.

After written informed consent was obtained, patients were randomized, using a block-randomization algorithm, to be in the DASH group (n = 24) or the comparison group (n = 24) for 3 months in addition to receiving their standard HF medical therapy. Patients in the DASH group were provided with an educational packet consisting of a copy of the US Department of Health and Human Services DASH eating plan guidebook (9); a DASH shopping list (10), containing various DASH diet components from which patients could choose and a reference

From the Department of Cardiology, Advocate Lutheran General Hospital, Park Ridge, IL (Rifai); Heart Failure Institute, Advocate Christ Medical Center, Oak Lawn, IL (Rifai, Pisano, Hayden, Silver); James R. & Helen D. Russell Institute for Research & Innovation, Advocate Lutheran General Hospital, Park Ridge, IL (Sulo); and the Department of Medicine, Advocate Christ Medical Center, Oak Lawn, IL (Silver).

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for the dietary components they were encouraged to consume for the duration of the study; and a daily and weekly food diary. Patients in the comparison group had no changes to their dietary habits other than the current general admonitions for diet in HF.

At the initial visit, all patients received further education regarding their diet from our outpatient dietitian. The same dietitian conducted monthly in-person visits and weekly or biweekly phone calls to counsel patients and reinforce their respective diets. In-person sessions were approximately 15 minutes in duration, in a one-on-one setting, and tailored to the individual patient’s comorbidities. To more accurately assess the degree of concordance with the DASH diet, patients were assessed monthly using a DASH diet index developed by Folsom et al (11). The scoring system was based on the premise that each of the major DASH diet guidelines should contribute equally to the total index score. The index has 11 items, and the score ranges from 0 to 11, with higher scores indicating higher levels of concordance. During the interview with the dietitian, the reported intake of sodium was estimated from the patients’ corresponding food diaries and included in a food frequency questionnaire. Baseline data included demographic characteristics, clinical history, physical exam, NYHA functional class, body mass index, quality of life as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (12), ejection fraction available from recent transthoracic echocardiogram, and serum markers known to influence HF: electrolyte measurements (sodium, potassium, magnesium), creatinine, B-type natriuretic peptide (BNP), galectin-3, and peripheral (SpO2) and cerebral (ScrO2) oxygen saturations.

Data collected throughout the study included exercise capacity as measured by the 6-minute walk test (13), weight, and DASH diet index score for compliance. To assess endothelial function, large and small arterial elasticity (LAE and SAE) at rest, a power analysis was performed with the Student t test to account for differences in endothelial function between the groups. Based on the results of Fuentes et al (5), and assuming a mean change in endothelial function of 0.5 to 3.0 mL/mm Hg, estimated group standard deviations of 2.0 and 2.3, and α of 0.05, a minimum of 11 patients in each group was required to achieve 80% power to detect a difference of 3.5 between the groups. To account for potential differences in the secondary outcomes of interest and for the attrition rate throughout the 3-month period, the sample was increased to 24 patients in each group.

Descriptive analyses were calculated on all variables as appropriate. LAE and SAE were compared with baseline values using repeated-measures analysis of variance. The baseline characteristics and secondary outcomes of interest were compared using Student’s t test, chi-square or Fisher’s exact test, Mann-Whitney U test, or Wilcoxon signed rank test depending on variable type and distribution. All data were analyzed using the SPSS software package, version 20.0 (SPSS Inc., Chicago, IL), and a P value of 0.05 was defined as statistically significant.

RESULTS
Table 1 describes patients’ demographic and clinical characteristics. Overall, they were older adults, with an average HF duration of 5 years. No significant differences in demographic and clinical characteristics were found between the groups (P values > 0.05). Table 2 compares the results of the groups’ outcomes. Although patients in the DASH group reported better LAE and SAE scores over time, the net changes did not reach statistical significance (P values > 0.05). The dietary compliance (as reported by the DASH index score) improved over time, but this improvement was not statistically significant (P > 0.05). The LAE and SAE measurements over time for both groups are also summarized in Figure 1. No statistically significant differences were reported for 6-minute walk test scores at baseline. However, patients in the DASH group achieved better distances over time than those in the comparison group (Figure 2). MLHFQ scores at baseline were similar between the groups (P = 0.056); however, patients in the DASH group reported improved MLHFQ scores at 3-month follow-up (21 vs. 39; P = 0.006) (Figure 3). Although more patients in the comparison group had sodium intake levels >1500 mg/day at baseline, groups were comparable regarding the changes in sodium intake levels at 1, 2, and 3 months (P values > 0.05). No statistically significant differences between the DASH and comparison groups were found for weight, body mass index, BNP, or SctO2 at baseline or for hemodynamic parameters, SctO2, or BNP at any time during the study. The DASH dietary plan was well tolerated in our patients; no serious adverse effects were noted. None of the hemodynamic parameters were also obtained using the HDI/PulseWave™, including mean arterial blood pressure, heart rate, systemic vascular resistance, stroke volume, estimated cardiac output, and estimated cardiac index. The primary endpoint was the impact of the DASH diet on endothelial function, measured by LAE and SAE. The secondary endpoints were changes in hemodynamic parameters, exercise capacity, and quality of life during the 3-month follow-up period.
Table 1. Baseline characteristics of patients in the DASH and comparison group*

<table>
<thead>
<tr>
<th>Variable</th>
<th>DASH (n = 24)</th>
<th>Comparison (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>13 (54%)</td>
<td>16 (67%)</td>
</tr>
<tr>
<td>Women</td>
<td>11 (46%)</td>
<td>8 (33%)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>60 (11)</td>
<td>64 (12)</td>
</tr>
<tr>
<td>Black</td>
<td>9 (38%)</td>
<td>13 (54%)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>112.3 (28.9)</td>
<td>106.4 (27.9)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>37.2 (8.6)</td>
<td>35.1 (8.1)</td>
</tr>
<tr>
<td>Heart failure duration (years), mean (SD)</td>
<td>6.5 (5.3)</td>
<td>4.7 (4.0)</td>
</tr>
<tr>
<td>Etiology/type of heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>15 (63%)</td>
<td>9 (38%)</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>10 (42%)</td>
<td>11 (46%)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>8 (33%)</td>
<td>9 (38%)</td>
</tr>
<tr>
<td>New York Heart Association functional class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>II</td>
<td>7 (29%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>III</td>
<td>16 (67%)</td>
<td>19 (79%)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>21 (88%)</td>
<td>23 (96%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>12 (50%)</td>
<td>17 (71%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>10 (42%)</td>
<td>11 (46%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (67%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>3 (13%)</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>2 (8%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%), mean (SD)</td>
<td>41 (13)</td>
<td>40 (15)</td>
</tr>
<tr>
<td>Peripheral tissue oxygenation (%), mean (SD)</td>
<td>97 (2)</td>
<td>98 (2)</td>
</tr>
<tr>
<td>Cerebral tissue oxygenation (%), mean (SD)</td>
<td>67 (5)</td>
<td>67 (6)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg), mean (SD)</td>
<td>136 (20)</td>
<td>129 (18)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg), mean (SD)</td>
<td>71 (11)</td>
<td>68 (8)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg), mean (SD)</td>
<td>95 (14)</td>
<td>90 (10)</td>
</tr>
<tr>
<td>Sodium (mEq/L), mean (SD)a</td>
<td>137 (3)</td>
<td>136 (4)</td>
</tr>
<tr>
<td>Creatinine (mg/dL), mean (SD)a</td>
<td>1.3 (0.4)</td>
<td>1.6 (0.6)</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/mL), mean (SD)a</td>
<td>102 (97)</td>
<td>253 (472)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL), mean (SD)a</td>
<td>12.9 (1.4)</td>
<td>12.3 (1.5)</td>
</tr>
<tr>
<td>Albumin (g/dL), mean (SD)a</td>
<td>3.4 (1.0)</td>
<td>3.5 (0.3)</td>
</tr>
<tr>
<td>Total protein (g/dL), mean (SD)a</td>
<td>7.5 (0.8)</td>
<td>7.6 (0.4)</td>
</tr>
<tr>
<td>Low-density lipoprotein (mg/dL), mean (SD)a</td>
<td>88 (33)</td>
<td>75 (17)</td>
</tr>
<tr>
<td>High-density lipoprotein (mg/dL), mean (SD)a</td>
<td>52 (20)</td>
<td>41 (10)</td>
</tr>
<tr>
<td>Cholesterol (mg/dL), mean (SD)a</td>
<td>163 (46)</td>
<td>142 (24)</td>
</tr>
<tr>
<td>Triglyceride (mg/dL), mean (SD)a</td>
<td>115 (84)</td>
<td>124 (96)</td>
</tr>
<tr>
<td>Galectin-3 (mg/mL), mean (SD)a</td>
<td>19.1 (5.2)</td>
<td>23.0 (13.8)</td>
</tr>
</tbody>
</table>

*All P values > 0.05. SD indicates standard deviation; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

*Data were missing for <8% of the patients.

*Dyslipidemia was defined as fasting levels of low-density lipoprotein >100 mg/dL, or high-density lipoprotein <40 mg/dL, or triglyceride >150 mg/dL.

DISCUSSION

The clinical practice guidelines for HF endorse with reasonable evidence dietary recommendations for people at risk of HF (stages A and B), while few patients with a diagnosis of HF (stages C and D) meet the general nutritional recommendations (17, 18). Endothelial dysfunction has been recognized as a pathophysiologic mechanism in the progression of HF, and several pharmacologic and nonpharmacologic prevention and treatment strategies have been proposed (19–22). The effects of the DASH diet on endothelial function in patients with chronic symptomatic (stage C) HF using pulse contour analysis were assessed. Significant improvement in LAE was observed in patients who received the DASH diet for 1 month, but the change was less prominent at 2 and 3 months. No significant change in SAE over time was found in either group.

Since dietary patterns are complex mixtures of foods and nutrients, it is not clear whether the salutary effects of DASH on endothelial function are due to the vasodilatory effect of micronutrients (e.g., magnesium) in the DASH diet, the possible mediation of nitric oxide release, direct vasodilation, the interaction between foods and micronutrients, or a combination of these mechanisms. Another possible explanation is the antioxidant properties of components of the DASH diet, conceivably producing protective effects through preservation of endothelial function and antiinflammatory processes. Hummel et al supported the desirable influence of the DASH diet in HF on patients' blood pressure, arterial stiffness, oxidative stress (23), as well as ventricular diastolic function and arterial coupling (24).

Although the change in LAE and SAE in the DASH diet group was more prominent in the short term and was not sustained beyond 1 month, an improvement in clinical parameters of prognostic value in HF (6-minute walk test and MLHFQ) was evident at 3 months. These results are in line with recent studies demonstrating short-term effects of the DASH diet in mechanisms contributing to HF (23,24), thus suggesting that the DASH diet may also improve HF through autonomic and cardiac mechanisms other than improving endothelial function.
Patients with HF continue to consume large quantities of sodium daily. Based on previous recommendations and in accordance with the DASH diet index score for assessment of adherence, the sodium dietary goal for the study was set at 1500 mg/day (11, 25). Although most patients consumed more than 1500 mg/day of sodium, the changes observed in LAE and SAE cannot be attributed to sodium, as no statistically significant changes in estimated sodium intake were found in the groups during the study time. However, more data are needed to support a specific sodium intake level, especially considering that emerging evidence appears to be conflicting (4, 26, 27).

Newer and more reliable means of assessing longer-term sodium intake are needed to replace current measures that are episodic, are prone to recall bias (e.g., food frequency questionnaires), and may not be reflective of the overall sodium intake patterns (e.g., 24-hour urinary sodium measurements) (28).

The DASH index score trended toward greater compliance over time. This may reflect a more realistic expectation of transitioning into a new dietary lifestyle, in addition to implementing proper reinforcement to patient education. The DASH diet index was chosen over other available indexes for its simplicity and to supplement patients’ self-reported food diaries. However, to improve adherence and behavioral modification rates, further exploration is needed to understand how to best implement the DASH dietary recommendations. Also, since the DASH diet is recommended to the public for the prevention of cardiovascular disease, a metric to assess consistency with this diet may be useful in clinical practice.

This study has several limitations. The results are hypothesis generating and cannot be generalized to all patients with HF. No blinding techniques were used, potentially affecting the interpretation of the results, especially the endothelial function levels and 6-minute walk test results. A dietary intervention other than the general dietary recommendations was used to evaluate the effect on endothelial function in HF over time. A limitation of dietary intervention studies is the lack of accurate measurement of individual components. It is unclear which specific DASH components contributed to the observed effects. Although multiple educational and compliance interventions were made available to the patients, they selected and consumed the food at their own discretion, allowing for extraneous variables to influence the study results. Adherence was self-reported rather than confirmed via objective tests, e.g., collection of 24-hour urine to assure equivalence in sodium intake. Food diaries and DASH diet scores, however, indicated good dietary adherence that improved over time from baseline dietary patterns for the DASH group. It is unknown whether our short-term results could be sustained in a cohort with complete freedom of food choice. Although no significant

<table>
<thead>
<tr>
<th>Variable</th>
<th>DASH</th>
<th>Comparison</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute large arterial elasticity (mL/mm Hg × 10), mean (SD)</td>
<td>15.1 (1.4)</td>
<td>14.9 (1.2)</td>
<td>0.905</td>
</tr>
<tr>
<td>Absolute small arterial elasticity (mL/mm Hg × 100), mean (SD)</td>
<td>6.3 (0.8)</td>
<td>5.3 (0.7)</td>
<td>0.366</td>
</tr>
<tr>
<td>Six-minute walk test (meters), mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>254 (119)</td>
<td>202 (77)</td>
<td>0.158</td>
</tr>
<tr>
<td>3 months</td>
<td>292 (124)</td>
<td>197 (81)</td>
<td>0.018</td>
</tr>
<tr>
<td>Minnesota Living with Heart Failure Questionnaire, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29 (20)</td>
<td>38 (4)</td>
<td>0.056</td>
</tr>
<tr>
<td>3 months</td>
<td>21 (15)</td>
<td>39 (22)</td>
<td>0.006</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>110.0 (6.8)</td>
<td>101.1 (6.0)</td>
<td>0.333</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>35.8 (1.8)</td>
<td>33.0 (1.6)</td>
<td>0.256</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/mL), mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>102 (97)</td>
<td>253 (472)</td>
<td>0.138</td>
</tr>
<tr>
<td>3 months</td>
<td>94 (97)</td>
<td>314 (510)</td>
<td>0.081</td>
</tr>
<tr>
<td>Cerebral oxygen saturation (%), mean (SD)</td>
<td>68 (1)</td>
<td>67 (1)</td>
<td>0.984</td>
</tr>
<tr>
<td>DASH Index Score, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>6.8 (2.1)</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>2 month</td>
<td>7.3 (2.5)</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>3 month</td>
<td>7.4 (2.3)</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>Average</td>
<td>6.8 (1.9)</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>Sodium intake (mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>≤1500 5 (21%)</td>
<td>0 (0%)</td>
<td>0.050</td>
</tr>
<tr>
<td></td>
<td>&gt;1500 19 (79%)</td>
<td>24 (100%)</td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>≤1500 4 (14%)</td>
<td>4 (14%)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>&gt;1500 16 (57%)</td>
<td>18 (64%)</td>
<td></td>
</tr>
<tr>
<td>2 months</td>
<td>≤1500 4 (14%)</td>
<td>2 (7%)</td>
<td>0.208</td>
</tr>
<tr>
<td></td>
<td>&gt;1500 9 (32%)</td>
<td>16 (57%)</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>≤1500 5 (21%)</td>
<td>5 (21%)</td>
<td>0.718</td>
</tr>
<tr>
<td></td>
<td>&gt;1500 10 (36%)</td>
<td>14 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are missing for 13% to 30% of the patients. NA indicates not applicable; SD, standard deviation.
differences in demographics were found between the groups, more black patients enrolled in this study compared with previous dietary intervention studies. This is of interest since black patients are especially sensitive to the effects of micronutrients in the DASH diet (29). Finally, a repeat measurement of left ventricular ejection fraction was not part of this study.

In patients with HF, the DASH diet was associated with favorable changes in LAE, exercise capacity, and quality of life scores. Integrating the DASH diet into the dietary patterns of patients with HF could hold potential beneficial effects in decreasing the progression of endothelial dysfunction. To determine whether the particular positive effect on endothelial dysfunction and other possible salutary effects of DASH can be translated to clinical practice merits further investigation. These findings could inform the design of larger studies in the future that could incorporate well-characterized, more rigorous, and individualized nutritional management, while being mindful of the complex pathophysiology of HF. This study is one of the few randomized controlled trials to evaluate a dietary pattern in patients with HF, where little information is available to define optimal nutrient intakes and food patterns.
Acknowledgments

We would like to thank Christopher Blair, Director of Research Services, Advocate Health Care, Oak Brook, IL, for his help with data analysis. We thank Jennifer Swanson for her help with manuscript review and editing. We thank the patients and the nursing staff of the Heart Failure Institute, Oak Lawn, IL, for their cooperation and participation in this study.


A survey-based analysis of symptoms in patients with postural orthostatic tachycardia syndrome

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Postural orthostatic tachycardia syndrome (POTS) is one of the most prevalent presentations of orthostatic intolerance (1, 2) and is defined as an increase in heart rate of 30 beats per minute (bpm) or more occurring within the first 10 minutes of standing or head-up tilt in the absence of orthostatic hypotension. The forms were completed from 2006 to 2014 and comprised 37 questions describing various symptoms. The most frequently reported symptoms included palpitations, lightheadedness, and headache, although sleep disturbances, gastrointestinal complaints, sensitivity to temperature, and rash were also common.

METHODS
Intake forms were given to 39 patients with POTS seen in the Boston Medical Center Autonomic Clinic. All patients had been diagnosed with POTS by a documented increase in heart rate of ≥30 bpm occurring within the first 10 minutes of standing or head-up tilt in the absence of orthostatic hypotension. The forms were completed from 2006 to 2014 and comprised 37 questions describing various symptoms. Patients were asked to answer “yes” or “no” according to the symptoms they experienced often. Data analysis was performed using StatPlus.

RESULTS
Baseline characteristics of 38 of the 39 patients are listed in Table 1 (no demographic data were available for one patient). Autonomic symptoms were among the most common complaints in our population (Table 2). Palpitations were reported by 92% of patients. Other commonly experienced autonomic symptoms included lightheadedness with standing (87%) and worsening of symptoms in the morning (69%).

DISCUSSION
POTS is characterized by a variety of associated symptoms. In this study, 92% of patients experienced palpitations and 77% had facial flushing or rash, supporting the theory of an increase in circulating catecholamines and a hyperadrenergic pathophysiology in these patients. The high frequency

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of tremor further suggests sympathoexcitation. Headaches of various types, including migraine and orthostatic headaches, have been reported in POTS (5, 8–10). In this study, 87% of patients suffered from headaches.

Patients with POTS have sleep abnormalities and fatigue (11–13). Bagai et al showed that POTS patients report poor sleep quality, more daytime sleepiness, and more fatigue than healthy controls (14). Similarly, about half of our patients reported insomnia, nocturnal awakenings, and early morning awakenings, and nearly all (90%) reported fatigue. Recent studies using wrist actigraphy and polysomnography have confirmed that POTS patients have decreased sleep efficiency, increased nocturnal awakenings, and increased REM latency compared to controls (11, 15). The hyperadrenergic state present in POTS patients may account for differences in autonomic functioning during sleep, resulting in less restful sleep and subjective tiredness, but additional mechanisms such as hypovolemia and increased energy expenditure from a hyperadrenergic state may also contribute.

POTS patients often experience chronic gastrointestinal symptoms. Electrical activity of the stomach has been shown to change during upright position in children with POTS, and both increased and decreased gastric emptying has been noted as well (16, 17). Functional gastrointestinal disorders, such as irritable bowel syndrome and functional dyspepsia, are also associated with POTS, suggesting the possibility that increased variability of the gastric pacemaker rhythm and sympathetic

| Table 1. Baseline characteristics of POTS patients (n = 38)* |
|----------------|----------------|
| Variable       | Result         |
| Age, mean ± SD (years) | 35 ± 12 |
| Females        | 34 (89%)       |
| Body mass index, mean ± SD (kg/m²), n = 22 | 25 ± 6 |
| Age at symptom onset (years), n = 34 | |
| <18            | 12 (35%)       |
| 18–25          | 8 (24%)        |
| 26–35          | 10 (29%)       |
| >35            | 4 (12%)        |
| Time to diagnosis (years), n = 26 | |
| <1             | 6 (23%)        |
| 1–10           | 10 (38%)       |
| >10            | 10 (38%)       |
| Highest education level, n = 30 | |
| High school    | 8 (27%)        |
| Associate's degree | 4 (13%)    |
| Undergraduate degree | 9 (30%)    |
| Graduate degree     | 9 (30%)       |
| Hypermobility disorders | |
| Ehlers-Danlos syndrome | 6 (15%)     |
| Joint hypermobility syndrome | 1 (2.6%) |

* n = 38 unless otherwise stated (no demographic data available for one patient).

| Table 2. Symptoms reported by POTS patients (n = 39) |
|----------------|----------------|
| Symptom                     | Frequency |
| Autonomic                   |            |
| Palpitations                | 92%        |
| Lightheadedness             | 87%        |
| Lightheadedness with standing| 87%    |
| Morning exacerbation of symptoms | 69% |
| Lightheadedness with sitting | 64%   |
| Fainting                    | 54%        |
| Lightheadedness with laying  | 36%        |
| Neurological                |            |
| Headache                    | 87%        |
| Concentration difficulty    | 77%        |
| Blurry vision               | 69%        |
| Word-finding difficulty     | 59%        |
| Memory difficulty           | 54%        |
| Tremor                      | 49%        |
| Sleep                       |            |
| Fatigue                     | 90%        |
| Early morning awakenings    | 51%        |
| Nighttime awakenings        | 46%        |
| Insomnia                    | 39%        |
| Gastrointestinal            |            |
| Irritable bowel symptoms    | 46%        |
| Swallowing difficulty       | 41%        |
| Respiratory                 |            |
| Breathing difficulty        | 64%        |
| Autoimmune                  |            |
| Sensitivity to hot or cold temperature | 87% |
| Hands change color in the cold | 74% |
| Medication sensitivity      | 56%        |
| >2 medication allergies     | 33%        |
| Connective tissue           |            |
| Loose joints/double-jointed | 44%        |
| Dermatomal                  |            |
| Facial flushing or rash     | 77%        |
| Pain symptoms               |            |
| Pain                        | 69%        |
| Muscle cramping             | 69%        |
| Joint pain                  | 62%        |
| Leg pain                    | 56%        |
| Miscellaneous               |            |
| Susceptibility to cold or infections | 44% |
| Iron deficiency anemia      | 39%        |
| Hearing loss                | 28%        |
| Family history of low blood pressure | 28% |


nervous system dysfunction in POTS can directly disturb gastrointestinal function (18).

There is still limited data on respiratory symptoms in POTS. In a study of 152 patients with POTS, 42% reported dyspnea as a common symptom (5), and 64% of our patients endorsed difficulty breathing. Del Pozzi et al showed that POTS patients have an initial increase in respiratory rate and a significant increase in minute ventilation during head-up tilt table testing compared to normal controls (19). It is thought that reduction of central blood volume secondary to peripheral pooling in POTS patients may stimulate the carotid body, resulting in sympathetic activation and hyperpnea (19).

POTS has been associated with multiple connective tissue disorders, primarily joint hypermobility syndrome and Ehlers-Danlos syndrome (EDS). Wallman et al showed the prevalence of EDS in patients with POTS (18%) is significantly higher than the suggested prevalence of EDS in the general population (0.02%) and in those with dysautonomia not meeting criteria for POTS (4%) (20). In our cohort, 15% of patients carried a diagnosis of EDS. EDS patients are also significantly more likely to be diagnosed with POTS by tilt-table testing compared to healthy controls (21). Although no cohesive mechanism exists to explain comorbid dysautonomia in hypermobility syndromes, current evidence points to multiple mechanisms, including adrenoreceptor hyperresponsiveness, molecular defects in blood vessel connective tissue, and peripheral neuropathy as likely contributors (22).

Dermatologic changes are common but rarely reported in POTS patients. A recent case report described multiple dermatologic findings in a patient with POTS, including hyperemia of the trunk and extremities and Raynaud’s phenomenon (23). The author speculated that these findings can be explained by excessive vasoconstriction and hypoxia in the cutaneous vasculature secondary to imbalances in local mediators, especially increased angiotensin II and decreased nitrous oxide (23). In our study, 77% of patients reported facial flushing or rashes, likely representing hyperemia, and 74% endorsed symptoms consistent with Raynaud’s phenomenon.

POTS, a common form of orthostatic intolerance seen in young females, remains poorly understood. This analysis of 39 patients at a large medical center was conducted in an attempt to better understand the heterogeneous presentations of POTS patients. Limitations of our study include a small sample size and lack of comparison to a control group. With more patients, it will be easier to differentiate between high-frequency and low-frequency comparisons. Comparison of frequency of symptoms between POTS and healthy controls would eliminate a bias towards symptoms that occur in both. The intake survey format limited interpretation of symptoms with yes-no questions and was not validated. Additional information on each symptom would be useful in terms of symptomatic treatment but also in elucidating pathophysiology. In the future, a survey with more detailed questions regarding each symptom, specifically relating to frequency and severity, would be useful.


Since restricted resident work hours have reduced resident participation in traditional educational activities, we wanted to evaluate e-mail–based education in an internal medicine residency. One internal medicine faculty member sent four clinical case-based questions per week to all internal medicine residents over a 10-month period (132 questions total). The mean percentage of participation on a set of questions was 69% (range, 43% to 97%). The mean percentage of correct answers on all questions for all residents was 70% (range, 15% to 100%). Seventy-three percent of the question sets resulted in an electronic interaction between the residents and the faculty sponsor. Based on an anonymous survey, 96% of the residents found the program useful. The faculty sponsor spent 60 to 150 minutes per week on this activity. We think that this program increased overall reading since it did not replace any traditional activity; further, it provided practice with board-type questions. This approach can supplement the educational curriculum for internal medicine training.

Residency programs now face more challenges in providing quality education in the context of complicated patient care and the duty-hour standards instituted by the Accreditation Council for Graduate Medical Education in July 2003. Electronic or web-based learning can supplement or replace traditional teaching, and several studies have evaluated the efficiency of web-based learning, the ability to retain knowledge from online education, and the impact of computer questions on different learning styles (1–3). Electronic mail offers efficiency and convenience to residents, and its integration into medical education can support adult learning goals by increasing the involvement of the learner in the educational activity through interaction with the faculty and other learners (4, 5). However, recent studies have not always reported positive outcomes, which could reflect different learning styles or different workloads and time constraints (4, 6, 7). Our study objective was to evaluate the feasibility of e-learning in an internal medicine residency program and to determine if residents would participate.

METHODS

The internal medicine residency of Texas Tech University Health Sciences Center of Lubbock, Texas, had 32 categorical residents and two preliminary residents during the time of this project. Most clinical rotations take place at School of Medicine facilities or the adjacent University Medical Center Hospital. The department has daily conferences at 8:00 am and noon. The department rigorously follows work hour rules, and these regulations have reduced the residents’ opportunities to attend conferences and structured learning activities.

One internal medicine faculty member e-mailed two clinical case-based questions to the internal medicine residents twice a week for 8 months. This individual is an American Board of Internal Medicine–certified nephrologist with extensive experience in student, resident, and fellow education. E-mail responses from the residents were due by midnight the same day. These questions had the same format as questions on the American Board of Internal Medicine certification examination and were adapted from several resources after careful review for content, including the Medical Knowledge Self-Assessment program sponsored by the American College of Physicians. After discussion with the residents, the format was changed from two questions twice a week to four questions once a week. These questions were sent on a Tuesday with answers due on Friday. The faculty member coordinated this project and replied to individual residents to stimulate discussion throughout the week. This report covers 132 questions sent over a 10-month period. All questions and responses were saved in an electronic folder and were analyzed weekly to track the percentage of participation, the percentage of correct answers, the frequency of electronic interaction between the residents and the faculty sponsor, and the content areas with low scores. We used an anonymous survey (www.surveymonkey.com) to learn the residents’ opinions about this program, and we administered a learning style inventory based on the Myers-Briggs Type Indicator personality test to determine the distribution of learning styles in our program. The institutional review board at Texas Tech University Health Sciences Center approved the study.

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Table. Examples of questions used in a web-based education project

<table>
<thead>
<tr>
<th>Question</th>
<th>Response options*</th>
</tr>
</thead>
</table>
| 1. You are asked to consult on a 31-year-old male with prolonged bleeding after an oral surgery procedure. He has no prior history of bleeding diathesis or family history of bleeding disorders. The patient’s past medical history is remarkable for infection with the human immunodeficiency virus, with a CD4 count of 51/ml3. The examination is remarkable only for spotty lymphadenopathy. The platelet count is 230,000 cells/ml. His international normalized ratio is 1.5. Activated partial thromboplastin time is 40 s. Peripheral blood smear shows no schistocytes and is otherwise unremarkable. A 1:1 mixing study corrects both conditions immediately and after a 2-h incubation. Fibrinogen level is normal. Thrombin time is prolonged. What is the diagnosis? | a. Disseminated intravascular coagulation (DIC)  
b. Dysfibrinogenemia  
c. Factor V deficiency  
d. Liver disease  
e. Factor XIII deficiency |
| 2. Which of the following statements best describes the function of proteins encoded by the human major histocompatibility complex (MHS) I and II genes? | a. Activation of the complement system  
b. Binding to cell surface receptors on granulocytes and macrophages to initiate phagocytosis  
c. Nonspecific binding of antigen for presentation to T cells  
d. Specific antigen binding in response to B cell activation to promote neutralization and precipitation  
e. Rheumatoid factor |
| 3. A 23-year-old man seeks evaluation for low back pain. He states that when he first awakens there is a dull achin pain in his lower lumbar and gluteal region. When he first noticed the pain about 6 months ago, he thought the pain might be related to his mattress, but it has worsened even after buying a new mattress. Most mornings, it takes about 45-60 min to loosen up after he has awakened, but the pain will recur if he is idle. He is currently in law school and finds it increasingly difficult to remain in classes because of back pain. When he exercises, the pain lessens. There are occasional nights that the pain will awaken him from sleep, and he will have to move around and stretch his back to improve the pain. On physical examination, there is pain with palpation at the iliac crests, ischial tuberosities, greater trochanters, and heels. With maximal inspiration, the chest expands 4 cm, and there is decreased flexion of the lumbar spine. A radiograph of the pelvis shows erosions and sclerosis of the sacroiliac joint bilaterally. Which of the following tests is most likely to be positive in this individual? | a. Alkaline phosphatase  
b. Antibodies directed against cyclic citrullinated peptides (CCP)  
c. Antinuclear antibodies  
d. HLA-B27  
e. Rheumatoid factor |

*Correct answers: 1, b; 2, c; 3, d.

Tech University Health Sciences Center in Lubbock approved the analysis of this project for publication.

RESULTS

The mean percentage of participation on a set of questions was 69% ± 12%, with a range of 43% to 97%. The mean percentage of correct answers on all questions for all residents was 70% ± 22%, with a range of 15% to 100%. There was no significant difference in the percentage of answers correct between the three resident training levels based on chi-square analysis. Seventy-three percent of the question sets resulted in electronic interactions between the residents and the faculty sponsor.

The response rate to the anonymous survey was 72%. Ninety-six percent of the respondents found the program useful, and 78% said they routinely looked up information before submitting their answers. Eighty-seven percent thought that the answers provided by the faculty sponsor stimulated reading. The faculty sponsor spent 60 to 150 minutes per week on this activity. Our residency program had 18 sensing type and 12 intuitive type learners based on the Myers-Briggs test.

DISCUSSION

Most internal medicine residents in our program participated in this web-based project. This supplemental program increased overall reading since it did not replace any traditional activity. It provided practice with board-type questions and stimulated interaction with the faculty sponsor and review of pertinent literature. Overall, this program has been successful and well received and has the potential to distribute 600 questions over a 3-year residency program. In addition, this approach can provide images and figures relevant to patient care. However, the time demands on the faculty sponsor are relatively high, since only one faculty member participated in writing and answering the questions.

Different learning styles of internal medicine residents may influence the outcomes of any educational project. The four learning styles based on Kolb’s 12-item assessment tool include assimilators, convergers, divergers, and accommodators (8). Adesunloye et al found that most internal medicine residents (42%) and attending physicians (55%) were assimilators who prefer lectures, reading, and analytical models (9). In their study, 32% of the residents were convergers, 10% divergers, and 16% accommodators (9). Convergers like to experiment with practical application of new ideas, accommodators prefer “hands-on” experience, and divergers prefer to work in groups (10–12). Consequently, learning styles among internal medicine residents are diverse and likely influence participation in any education project.
We used the Myers-Briggs–based learning style inventory to evaluate the learning style of our residents. Sixty percent of our residents described themselves as sensing types who prefer to give their attention to specifics and details. Their learning is focused in the present on “what is,” and they are uncomfortable with the uncertainty of guessing or prioritizing. The remaining 40% of our residents described themselves as intuitive types who prefer to give their attention only to those details that are needed to construct relationships and patterns. Their learning is focused more on the future using “what if” thinking, and they enjoy using their imagination to address uncertainty and organize relationships. Both the sensing-type and the intuitive-type learning styles can benefit from our approach to e-learning, but for different reasons. The sensing-type learners benefit strongly from the insight gained from understanding the wrong answers. Since all answer choices are rational, they all contain elements of conditional probability and thus a lack of certainty. Some answer choices hinge on very specific combinations or patterns of variables that can be readily perceived by a sensing-type learner. The intuitive-type learners have little difficulty in ruling out wrong answers that don’t fit the patterns that they instinctively see, provided they remember enough facts. They benefit from an increase in the essential fact base on relevant topics in internal medicine, which can be provided through e-learning. However, independent of learning style, residents must learn, and e-learning provides an efficient process relevant to both residents and training programs.

The acute respiratory distress syndrome (ARDS) is a major cause of acute respiratory failure. Its development leads to high rates of mortality, as well as short- and long-term complications, such as physical and cognitive impairment. Therefore, early recognition of this syndrome and application of demonstrated therapeutic interventions are essential to change the natural course of this devastating entity. In this review article, we describe updated concepts in ARDS. Specifically, we discuss the new definition of ARDS, its risk factors and pathophysiology, and current evidence regarding ventilation management, adjunctive therapies, and intervention required in refractory hypoxemia.

During the Vietnam War in 1960s, military physicians encountered a distinctive form of hypoxic respiratory failure involving both lungs simultaneously. During the same period, civilian physicians who came across this form of lung injury called it adult respiratory distress syndrome (1). This term was later modified to acute respiratory distress syndrome (ARDS), when similar cases were reported across all age groups. In the United States, the most recent population-based data estimated an incidence of 190,000 cases per year (2). Mortality from ARDS has been estimated at 26% to 58% (3–6). Advances in supportive care have led to improvements in patient outcomes (7, 8). Nevertheless, the mortality associated with this syndrome remains unacceptably high.

DEFINITION AND DIAGNOSIS

ARDS and what was previously called acute lung injury (ALI) are both characterized by rapid onset of respiratory failure following a variety of direct and indirect lung insults. Since these entities were originally described, multiple definitions or diagnostic criteria have been proposed. In 1988, Murray et al introduced the lung injury score, which included chest radiograph, the ratio of the partial pressure of arterial oxygen and the fraction of inspired oxygen (PaO$_2$/FiO$_2$), total respiratory system compliance, and positive end-expiratory pressure (PEEP). Despite its clinical utility, the score was unable to differentiate between cardiogenic and noncardiogenic edema (9). In 1994, the American and European Consensus Conference established specific clinical criteria for ARDS and ALI (10). There were three diagnostic criteria: 1) PaO$_2$/FiO$_2$ ≤ 200, 2) bilateral infiltrates on chest radiograph, and 3) pulmonary artery occlusion pressure < 18 mm Hg when measured by pulmonary artery catheterization, or no clinical evidence of left atrial hypertension. The term ALI was adopted from the lung injury score to include patients with less severe forms of the same pathological entity. Therefore, patients with a PaO$_2$/FiO$_2$ of 200 to 300 were included within this group.

Since its description, the American and European Consensus Conference definition has been widely used for enrollment of ARDS patients in therapeutic clinical trials (11–15). Nevertheless, the aforementioned definition also presented several shortcomings. First, the reliability in reading chest radiographs was questionable. Second, the definition did not explicitly define the time interval for “acute.” Third, the level of PEEP utilized during ventilation was not incorporated in the definition. Last, the use of pulmonary artery catheters has been decreasing over the last few years, precluding measurements of pulmonary artery occlusion pressures.

Based on the aforementioned limitations, and after reviewing current epidemiologic evidence and results of clinical trials, in 2011 the European Society of Intensive Care Medicine proposed the Berlin ARDS definition (16), which considered the factors of timing, chest imaging, origin of edema, and oxygenation:

- **Timing**: Within 1 week of a known clinical insult or new or worsening respiratory symptoms
- **Imaging**: A chest radiograph or computed tomography scan showing bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
- **Origin of edema**: Respiratory failure not fully explained by cardiac failure or fluid overload; objective assessment (e.g., echocardiography) needed to exclude hydrostatic edema if no risk factor present

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Oxygenation: Divided into mild (\(\text{PaO}_2/\text{FiO}_2 > 200\) to \(\leq 300\) mm Hg with PEEP or continuous positive airway pressure \(\geq 5\) cm H\(_2\)O), moderate (\(\text{PaO}_2/\text{FiO}_2 > 100\) to \(\leq 200\) mm Hg with PEEP \(\geq 5\) cm H\(_2\)O) or severe (\(\text{PaO}_2/\text{FiO}_2 \leq 100\) mm Hg with PEEP \(\geq 5\) cm H\(_2\)O).

Of note, the term ALI has been eliminated. The categories of mild, moderate, and severe correlate with mortalities of 27%, 32%, and 45%, respectively (16).

Risk Factors

Multiple conditions may cause ARDS (Table 1). Sepsis remains the most common cause of ARDS, with 46% of the cases triggered by pulmonary entities (2). Mortality also varies according to the cause. Particularly, mortality in patients with ARDS due to severe trauma (injury severity score > 15) is 24.1%, whereas mortality in patients with severe sepsis with a pulmonary source is 40.6% (2). Notably, certain patient-related variables have been associated with the risk of developing ARDS and with mortality. Among these risk factors, age (2, 17–19), male gender, African American race (20), and history of alcoholism are associated with a higher incidence and mortality (21–23). Active and passive smoking exposure increases the incidence of ARDS as well (24, 25). Patients with a higher body-mass index have an increased incidence of ARDS, but its association with mortality is not clearly defined (26–28). Both diabetes mellitus and prehospital antiplatelet therapy seem to have a protective effect on development of ARDS (29–31).

Interestingly, the Acute Lung Injury Verification of Epidemiology (ALIVE) study (32) reported that ALI occurred in 16.1% of patients who were mechanically ventilated for other reasons. Hence, several groups have investigated a variety of methods to predict ARDS. Particularly, Gajic et al described the Lung Injury Prediction Score (LIPS, Table 2) using a prospective cohort study of 5584 patients (33). A LIPS score higher than 4 was associated with risk of developing ARDS within a median time of 2 days. The score has a sensitivity of 69% and a specificity of 78%, with a positive predictive value of 18% and a negative predictive value of 97%.

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### Table 1. Common risk factors for acute respiratory distress syndrome/acute lung injury

<table>
<thead>
<tr>
<th>Direct</th>
<th>Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pneumonia</td>
<td>• Nonpulmonary sepsis</td>
</tr>
<tr>
<td>• Aspiration of gastric contents</td>
<td>• Major trauma</td>
</tr>
<tr>
<td>• Inhalation injury</td>
<td>• Pancreatitis</td>
</tr>
<tr>
<td>• Pulmonary contusion</td>
<td>• Severe burns</td>
</tr>
<tr>
<td>• Pulmonary vasculitis</td>
<td>• Noncardiogenic shock</td>
</tr>
<tr>
<td>• Drowning</td>
<td>• Drug overdose</td>
</tr>
<tr>
<td>• Fat embolism</td>
<td>• Multiple transfusions (&gt;15 units blood in 24 h) or transfusion-related acute lung injury</td>
</tr>
<tr>
<td>• Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy</td>
<td>• Neurogenic pulmonary edema</td>
</tr>
<tr>
<td></td>
<td>• Amniotic fluid embolism</td>
</tr>
<tr>
<td></td>
<td>• Following bone marrow transplantation</td>
</tr>
</tbody>
</table>

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### Table 2. Lung Injury Prediction Score calculation worksheet

<table>
<thead>
<tr>
<th>LIPS points</th>
<th>Predisposing conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Shock</td>
</tr>
<tr>
<td>2</td>
<td>Aspiration</td>
</tr>
<tr>
<td>1</td>
<td>Sepsis</td>
</tr>
<tr>
<td>1.5</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>1</td>
<td>High-risk surgery(^a)</td>
</tr>
<tr>
<td>1</td>
<td>Orthopedic spine</td>
</tr>
<tr>
<td>2</td>
<td>Acute abdomen</td>
</tr>
<tr>
<td>2.5</td>
<td>Cardiac</td>
</tr>
<tr>
<td>3.5</td>
<td>Aortic vascular</td>
</tr>
<tr>
<td>2</td>
<td>High-risk trauma</td>
</tr>
<tr>
<td>2</td>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>2</td>
<td>Smoke inhalation</td>
</tr>
<tr>
<td>2</td>
<td>Near drowning</td>
</tr>
<tr>
<td>1.5</td>
<td>Lung contusion</td>
</tr>
<tr>
<td>1.5</td>
<td>Multiple fractures</td>
</tr>
</tbody>
</table>

**Risk modifiers**

- Alcohol abuse: 1
- Obesity (body mass index >30): 1
- Hypoalbuminemia: 1
- Chemotherapy: 1
- Fraction of inspired oxygen > 0.35 (>4 L/min): 2
- Tachypnea (respiratory rate >30/min): 1.5
- Oxygen saturation < 95%: 1
- Acidosis (pH <7.35): 1.5
- Diabetes mellitus\(^b\): –1

\(^a\) Add 1.5 points if emergency surgery.
\(^b\) Only if sepsis.


**PATHOPHYSIOLOGY OF VENTILATOR-INDUCED LUNG INJURY**

Gattinoni et al (34) described three general regions of the lung: normal lung tissue, a region densely consolidated, and a region that collapses during expiration and is recruitable during inspiration. When these heterogeneous lungs are ventilated at low tidal volumes, in the absence of PEEP, they present a repetitive opening and closing of airways and lung units (35). This type of injury is called “atelectrauma” (35). Conversely, when heterogeneous lungs are ventilated with high tidal volumes, overdistension of alveoli is produced, leading to “barotrauma,” which involves complications such as pneumothorax (36). A third form of ventilator-induced lung injury is called “biotrauma,” which is a systemic inflammatory response syndrome as a consequence of a release of lung cytokines (tumor necrosis factor–alpha, interleukin-6, interleukin-8, matrix metalloproteinase 9, nuclear factor kappa-light-chain-enhancer of activated B cells) (37).

**TREATMENT**

**Standard treatment**

**Low-tidal volume strategy.** The aim of mechanical ventilation in ARDS is to provide oxygenation and ventilation, while reducing the risk of ventilator-induced lung injury. A multicenter National Heart, Lung, and Blood Institute ARDSnet trial randomly assigned 861 patients with ARDS to receive low-tidal volume ventilation (initial tidal volume of 6 mL/kg) or conventional mechanical ventilation (initial tidal volume of 12 mL/kg) (11). Tidal volumes were titrated to keep plateau pressures (alveolar pressure at the end of a paused inspiration) lower than 50 cm H$_2$O in the conventional ventilation group, and lower than 30 cm H$_2$O in the low-tidal volume group. Results showed that the intervention group (low-tidal volume) had a lower mortality rate (31% vs. 40%) and more ventilator-free days (12 days vs. 10 days). A recent meta-analysis of four randomized trials, which included 1149 patients, confirmed these findings with a reduction of hospital mortality from 41% to 34.2% (38). Since the publication of this landmark study, a low-tidal volume strategy, which involves a tidal volume of 6 mL/kg predicted body weight, is considered the standard of care. In certain circumstances, tidal volumes may be further decreased to 4 mL/kg in order to limit inspiratory plateau pressures to levels lower than 30 cm H$_2$O (11).

**Positive end-expiratory pressure.** The utilization of PEEP improves gas exchange and lung function in a number of ways. PEEP recruits collapsed alveoli, improving oxygenation and lung compliance, and reduces cyclic atelectasis, decreasing atelectrauma and biotrauma. Despite these benefits, the appropriate dose of PEEP is still a matter of controversy. In the ARDSnet trial (11), patients using tidal volumes of 4 mL/kg required significantly higher levels of PEEP. Therefore, some have argued that this could have been the reason for the positive outcomes of the study. However, the subsequent Higher vs. Low PEEP in Patients with ARDS (ALVEOLI) study (4), which was a prospective, multicenter trial with 549 patients randomized to either lower or higher levels of PEEP, showed no differences in outcomes among groups. Importantly, the study design of the ALVEOLI trial was highly criticized, as many providers believe that PEEP levels cannot universally be set for all patients, but rather must be individualized based on lung mechanics.

The analysis of the static lung compliance curve has been proposed to titrate PEEP. Both the lower inflection point on the aforementioned curve and the stress index calculated from the pressure-time curve have been employed with varying results (39, 40). However, in ARDS the lung does not function as a single compartment model but rather as a multiple one. Therefore, setting PEEP considering the lower and upper inflection points may not be the most reliable strategy. The stress index has been advocated as a favorable parameter to select PEEP level, avoiding potential hyperinflation (Figure 1) (41). To measure it, the ventilator should be set under conditions of constant flow and volume-limited ventilation. The stress index defines the slope of...
the airway opening pressure during a period of constant flow. Values lower than 1 suggest a continuous decrease in elastance during lung inflation. This is consistent with potential recruitability and, therefore, PEEP can be increased. Values higher than 1 suggest an increase in lung elastance, consistent with lung hyperinflation. In these situations, PEEP should be decreased to avoid overstretching. Even though the stress index represents an interesting physiologic concept, more investigations are needed to validate it as an optimal technique for PEEP titration.

Two other trials have evaluated the optimal level of PEEP in the treatment of ARDS. The Lung Open Ventilation Study (LOVS) was a multicenter randomized controlled trial that included 983 patients (42). The control group was ventilated with low tidal volume, plateau pressures not exceeding 30 cm H2O, and low levels of PEEP. The intervention group used low tidal volumes, plateau pressures not exceeding 40 cm H2O, and higher levels of PEEP. In addition, the intervention group performed recruiting maneuvers (40-sec breath holds at pressures of 40 cm H2O). This last strategy resulted in reduced refractory hypoxemia and lower utilization of rescue techniques for hypoxemia, such as inhaled nitric oxide (iNO), prone ventilation, extracorporeal membrane oxygenation (ECMO), or high-frequency oscillatory ventilation (HFOV). The EXPRESS trial was also a multicenter randomized controlled trial, which included 767 patients from 37 French intensive care units (ICUs) (43). Patients were randomized to a minimal distension group (PEEP 5–9 cm H2O) or a maximal recruitment group (PEEP increased to reach plateau pressure of 28–30 cm H2O). The high PEEP recruitment strategy had no mortality benefit, but resulted in better oxygenation, higher compliance values, and more ventilator-free days (7 vs. 3 days; = 0.04) and organ failure–free days (6 vs. 2 days; = 0.04) in the subgroup of patients with refractory hypoxemia. A recent meta-analysis, which included data from ALVEOLI, LOVS, and EXPRESS trials, revealed that higher levels of PEEP were associated with improved survival among patients with moderate to severe ARDS (44).

Hemodynamic monitoring and fluid management. Avoidance of intrathoracic fluid accumulation is thought to be beneficial in patients with ARDS. Based on this premise, the Comparison of Two Fluid-Management Strategies in ARDS trial (FACTT) evaluated the hemodynamic management of patients with ARDS guided by a pulmonary artery catheter or a central line catheter, plus an explicit hemodynamic management protocol (45, 46). The FACTT study included 1000 patients, who were randomized to 1 of 4 hemodynamic protocols for a period of 7 days. The conservative hemodynamic strategy aimed for a central venous pressure <4 mm Hg or a pulmonary artery occlusion pressure <8 mm Hg. The liberal hemodynamic strategy aimed for a central venous pressure of 10 to 14 mm Hg or pulmonary artery occlusion pressure of 14 to 18 mm Hg. The mean (± standard error [SE]) cumulative fluid balance during the first 7 days was −136 ± 491 mL in the conservative strategy group and 6992 ± 502 mL in the liberal strategy group ( < 0.001). Also, the conservative strategy improved the oxygenation index and increased the number of ventilator-free days (14.6 ± 0.5 vs. 12.1 ± 0.5; < 0.001) during the first 28 days. Interestingly, despite restrictions in the use of fluids in the conservative group, there was no increase in the incidence of shock or need for dialysis during the first 60 days (10% vs. 14%; = 0.06) (46). These results support a conservative fluid strategy in the management of patients with ARDS.

Refractory hypoxemia

In certain situations, in which patients with ARDS do not improve their oxygenation with conventional therapies, other treatment options deemed as “salvage therapies” or “rescue therapies” have been advocated.

High-frequency oscillatory ventilation. HFOV delivers very low tidal volumes (equal to or less than anatomic dead space) at frequencies of 3 to 15 Hz. It also maintains a high airway pressure to permit recruitment. Ventilation is inversely related to the respiratory frequency and is directly related to the pressure amplitude of oscillation. Ideally, this strategy permits a more homogenous distribution of ventilation by maintaining mean airway pressure (47, 48), but avoiding hyperinflation (49, 50) and ventilator-induced lung injury by minimizing swings in tidal volumes (51).

Several randomized controlled trials have failed to show a mortality benefit with HFOV. Two large multicenter randomized controlled trials were recently published. The OSCILLATE trial was a multicenter randomized controlled trial conducted at 39 ICUs in five countries (52). The study included 548 patients with moderate to severe ARDS who were randomly assigned to HFOV targeting lung recruitment or a conventional low tidal volume–high PEEP ventilation strategy. The HFOV group had increased in-hospital mortality (47% vs. 35%; = 0.005). Also, those in the HFOV group required more sedation, paralytics, and vasopressor agents. The OSCAR trial included nearly 800 patients in 17 United Kingdom ICUs. This study also failed to demonstrate a survival benefit at 30 days (41.7% mortality in the HFOV group and 41.1% mortality in the control group; = 0.85) (53).

Airway pressure release ventilation. Airway pressure release ventilation (APRV) is a pressure-targeted, time-cycled mode of mechanical ventilation that permits spontaneous breathing across the full breathing cycle. It involves a long inspiratory time followed by a very short expiratory time, creating inverse ratio ventilation. By increasing the inflation period, the mean airway pressure is increased without an increase in the peak pressure. The superimposed spontaneous breathing has the advantage of providing more even ventilation distribution as well as augmentation of cardiac filling (54). In a randomized controlled trial, 30 mechanically ventilated trauma patients were randomly assigned to either APRV or pressure-limited ventilation (55). APRV was found to be associated with shorter duration of mechanical ventilation, a shorter ICU length of stay, and use of less sedatives and paralytics. Numerous studies have shown that APRV can decrease the peak airway pressure, improve alveolar recruitment, and improve oxygenation (56–60). Nevertheless, there is no evidence of an improved mortality outcome by using this mode, as compared to other modes of mechanical ventilation.
**Extracorporeal membrane oxygenation.** ECMO is used in ARDS patients with very severe hypoxemia, uncompensated hypercapnia (pH < 7.15), or excessively high end-inspiratory plateau pressures (>35–45 cm H₂O) despite the use of standard-of-care treatments for the management of ARDS (61–64). Despite earlier negative trials (65), the Conventional Ventilator Support vs. ECMO for Severe Adult Respiratory Failure (CESAR) study suggests there may be some benefit with extracorporeal lung support in patients with severe ARDS (66). In this randomized controlled study, 180 patients were randomized to receive veno-venous ECMO (after being transferred to a specialized center) or conventional mechanical ventilation (in regional centers). The former group had a higher 6-month survival than the latter (63% vs. 47%; \( P = 0.03 \)). Nevertheless, it is important to note that the intervention group underwent mechanical ventilation using a lung protective strategy, whereas it was used in only 70% of patients in the control group. Also, despite mortality benefits in the intervention group, only 75% of these patients actually received ECMO upon arrival to the specialized center. Therefore, the CESAR study demonstrated a mortality benefit in a specialized center vs. a regional center, but not necessarily a clear benefit of ECMO.

**Vasodilator therapy.** The rationale for using selective inhaled pulmonary vasodilators is to cause selective vasodilation in normal lung segments and recruit blood flow to these areas, where it can be oxygenated (67). Due to their local action and short half-lives, selective pulmonary vasodilators do not usually have systemic side effects, such as hypotension. Two metaanalyses compared iNO to either placebo or conventional management and found a modest and transient improvement in oxygenation, without improvement in survival, duration of mechanical ventilation, or ventilator-free days (68). It was also noted that patients without sepsis or septic shock responded more frequently to iNO than patients with septic shock (69). Inhaled epoprostenol has also been used in patients with ARDS, and it has similar physiologic effects as iNO. As with iNO, no study has demonstrated a clear survival benefit.

**Recruitment maneuvers.** Recruitment maneuvers can be defined as a strategy to increase transpulmonary pressure transiently with the goal of reexpansion of previously collapsed but recruitable lung alveolar units. This strategy can be performed by using conventional ventilators or oscillators.Gattinoni et al showed that the amount of lung mass that can be recruited averages 9% of the total lung mass, with pressures between 5 and 45 cm H₂O (70). Recruitment maneuvers can increase the aerated lung mass and prevent atelectrauma caused by repeated opening and closing of terminal respiratory units (71). Two commonly used recruitment maneuvers are the sigh and sustained inflation. “Sigh” involves increasing tidal volume or PEEP for one or several breaths per minute to a prespecified plateau pressure. The other form of recruitment maneuver is the sustained inflation method, which consists of pressurizing the airways at a specific level and maintaining it for a given duration. A common combination is the application of 40 cm H₂O of airway pressure for 40 seconds. Despite the physiologic advantages associated with recruitment maneuvers, three randomized controlled trials and one metaanalysis were not able to demonstrate a beneficial effect of recruitment maneuvers on oxygenation. Current evidence does not recommend their routine use, but recruitment maneuvers remain an option as a rescue therapy in severe hypoxemic patients (72–74).

**Prone positioning.** Conceptually, prone position may lead to a more uniform distribution of lung stress and strain, leading to improved ventilation-perfusion matching and regional improvement in lung and chest wall mechanics. However, prior reports indicated that prone positioning was associated with a variety of complications, such as hardware displacement and pressure ulcers. Prior clinical trials showed that prone positioning improved oxygenation in patients with ARDS, without benefits in terms of survival (75–77). In those studies, investigators used either repeated sessions of prone ventilation lasting 6 to 8 hours per day (14, 78) or prolonged prone ventilation lasting 17 to 20 hours (79–81) with similar results. While previous randomized controlled trials had not shown a survival benefit in patients with ARDS (80, 82), some observation studies and metaanalysis revealed a positive signal in a subset of patients with severe ARDS (83, 84). A recent multicenter prospective controlled trial (the PROSEVA study) randomized 466 patients with severe ARDS (\( PaO_2:FiO_2 < 150 \), \( FiO_2 ≥ 0.6 \), PEEP ≥ 5 cm H₂O) to undergo early (within 33 hours of intubation) prone-positioning sessions of at least 16 hours, or to be left in the supine position (79). Prone positioning decreased 28-day mortality (16% vs. 33%; \( P < 0.001 \)), decreased 90-day mortality (24% vs. 41%; \( P < 0.001 \)), increased ventilator–free days (14 vs. 10 days at day 28), and decreased time to extubation. The incidence of complications did not differ significantly between the groups, except for the incidence of cardiac arrests, which was higher in the supine group. Absolute and relative contraindications for prone positioning include spinal instability, elevated intracranial pressure, hemodynamic and cardiac abnormalities, massive hemoptysis, thoracic and abdominal surgeries, anterior chest tubes with leaks, and deep venous thrombosis treated for <2 days.

**Adjunctive therapy**

**Neuromuscular blocking agents.** Lung-protective mechanical ventilation has become the cornerstone management strategy for ARDS (85). However, patients with ARDS are still exposed to the risk ofatelectrauma and barotrauma due to suboptimal ventilator strategies. Neuromuscular blocking agents have been proposed as adjuvant therapy in ARDS, as they may decrease patient-ventilator asynchrony and, potentially, avoid the risk of barotrauma and biotrauma (86).

A recent multicenter double-blinded randomized controlled trial (ACURASYS) was conducted with 340 patients with severe ARDS. The study compared cisatracurium with placebo (13). All patients were sedated, titrating the Ramsay sedation score to 6 (no response on glabellar tap). Muscle paralysis monitoring, using train-of-four testing, was not allowed in order to maintain study blinding. Cisatracurium was associated with decreased adjusted 90-day mortality (31.6% vs. 40.7%; \( P = 0.08 \)). Furthermore, mortality at 28 days was 23.7% in the...
cisatracurium group and 33.3% in the placebo group ($P=0.05$). In this study, there was no difference in the rate of myopathy between the two groups.

**Steroids.** Inflammation is a key component in ARDS. Multiple studies have investigated the role of steroids in the prevention of ARDS and in the treatment of its different phases. Four trials have assessed the use of methylprednisolone for prevention of ARDS in a high-risk group of patients (sepsis/septic shock) (87–90). Specifically, Weigelt et al looked at high-risk surgical ICU patients (90). In this study, methylprednisolone at a dose of 30 mg/kg every 6 hours for 2 days increased the incidence of ARDS (64% vs. 33%), as well as the rate of infections (77% vs. 43%). Similarly, Bone et al demonstrated an increased 14-day mortality in the steroid group compared with a control group (52% vs. 22%) (88).

Multiple controlled studies have evaluated the role of glucocorticoid therapy in early and late ARDS. Bernard et al performed the first multicenter double-blinded prospective randomized controlled trial to assess the role of a short course of steroids given for 24 hours to patients with early ARDS (91). The study showed that there was a small decrease in 45-day mortality (60% vs. 63%) and an increased chance of ARDS reversal (39% vs. 36%) among patients receiving methylprednisolone compared with placebo. A large multicenter randomized controlled trial was conducted by the National Heart, Lung, and Blood Institute ARDSnet group to determine the efficacy and safety of a moderate dose of steroids for a period of 21 days in patients with persistent ARDS (>7 days). The study showed no survival benefit at 60 or 180 days (92). Similar results were reported by Annane et al in the same year (93). Meduri et al performed a multicenter double-blinded randomized controlled trial with 91 patients with ARDS who received steroids within 72 hours of entry into the study (94). The authors used a prolonged course of methylprednisolone (a loading dose of 1 mg/kg, followed by an infusion of 1 mg/kg/day from day 1 to day 14, 0.5 mg/kg/day from day 15 to day 21, 0.25 mg/kg/day from day 22 to day 25, and 0.125 mg/kg/day from day 26 to day 28). This study showed a significant decrease in mortality (20.6% vs. 42.9%; $P=0.03$), reduction in the duration of mechanical ventilation ($P=0.002$), and reduction in ICU stay ($P=0.007$).

The contradictory results of the ARDSnet and Meduri trials are likely due to the rapid taper of steroids in the ARDSnet study and the use of steroids during different phases of the disease. Clinical trials evaluating the effect of a prolonged course of steroids in ARDS have consistently shown a significant improvement in oxygenation ($\text{PaO}_2/\text{FiO}_2$ ratio) (92, 95–97) and a reduction in systemic inflammation (95–97), organ dysfunction score (92, 95–97), duration of mechanical ventilation (95–97), and ICU length of stay (95–97). Data from five recently conducted large trials were analyzed and showed that patients who received corticosteroids early (<14 days after onset of ARDS) had reduced mortality (38% vs. 52.5%; $P=0.02$) (98). Both the ARDSnet group and Meduri showed an increase in the number of ventilator-free days and decreased length of ICU stay. Review of available data shows that the beneficial effect of corticosteroids is seen only when used in the early phase of ARDS and not in the late phase. Therefore, a recent consensus statement recommended early initiation of prolonged glucocorticoid therapy for patients with moderate to severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 200$ mm Hg on PEEP 10 cm H2O), and before day 14 (99).

**CONCLUSION**

ARDS continues to be associated with a high mortality. Despite multiple randomized controlled trials, only lung protective ventilation strategies, neuromuscular blocking agents, and prone ventilation have been shown to decrease mortality. Many trials are underway looking at nebulized heparin, aspirin, stem cell therapy, growth factors, interferon-β, and vascular endothelial growth factor. The new Berlin definition of ARDS may assist future trials of novel therapies by improving diagnostic reliability and allowing more precise stratification of patients according to severity.


The objective of this study was to create an annotated list of textbooks dedicated to teaching the neurologic examination. Monographs focused primarily on the complete neurologic examination published prior to 1960 were reviewed. This analysis was limited to books with the word "examination" in the title, with exceptions for the texts of Robert Wartenberg and Gordon Holmes. Ten manuals met the criteria. Works dedicated primarily to the neurologic examination without a major emphasis on disease description or treatment first appeared in the early 1900s. Georg Monrad-Krohn’s “Blue Book of Neurology” (“Blue Bible”) was the earliest success. These treatises served the important purpose of educating trainees on proper neurologic examination technique. They could make a reputation and be profitable for the author (Monrad-Krohn), highlight how neurology was practiced at individual institutions (McKendree, Denny-Brown, Holmes, DeJong, Mayo Clinic authors), and honor retiring mentors (Mayo Clinic authors).

In the late 1800s, Wilhelm Erb, Joseph Babinski, William Gowers, and others developed the neurologic exam as we know it today. Examination techniques were described in their articles and neurologic texts. Erb was one of the first to emphasize a detailed and systematic neurologic exam (1). Erb and Carl Westphal first reported the muscle stretch reflex in 1875, and it has been an integral part of the neurologic exam since. Babinski focused on finding reliable signs that could differentiate organic from hysterical paralysis and emphasized the exam over the history, unlike his mentor Jean-Martin Charcot (2). Charcot, the father of French neurology, focused primarily on intense observation and “knew how to see” (3). Babinski’s "toe phenomenon" (1896) is the best known of the signs separating organic from hysterical paralysis, but he also chronicled exaggerated flexion of the forearm, combined flexion of the thigh and trunk, and the platysma sign in patients with organic hemiplegia. Concerning Gowers, Spillane noted:

When Gowers took up his pen [1880s] there had been . . . some recent fundamental developments . . . [including] the growing realization of the importance of the physical examination of the patient, particularly stimulated by the discovery of the ophthalmoscope [1851] and the deep reflexes [1875] (4).

Gowers mastered the use of the ophthalmoscope and the tendon hammer shortly after their introductions to medicine, publishing both an important book on medical ophthalmoscopy and an influential article on the muscle stretch reflexes in 1879 (5, 6).

As knowledge of the nervous system and its diseases grew, the complexity and length of the neurologic exam increased. Authors felt the need to share their systematic approaches to the neurologic exam with students and wrote books dedicated to the topic.

RESULTS

The Clinical Examination of the Nervous System

Georg Monrad-Krohn (1884–1964) was a Norwegian neurologist. He qualified in medicine in Norway and trained in neurology at the National Hospital, Queen Square, and the Maida Vale Hospital, both in London, England. While training, he completed his thesis on the abdominal reflexes (7) and also worked out his systematic approach to the neurologic exam (espousing the tenets of the full exam, writing out the findings, and proposing the location and nature of the lesion). Monrad-Krohn

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published *Den Kliniske Undersøkelse av Nervesystemet* in Oslo in 1914 and returned to Norway in 1917. In 1920, a London publishing house asked him to translate his abdominal reflexes thesis into English, but he refused and instead offered his manuscript of *Clinical Examination of the Nervous System*, which was published in 1921 (8). This was an original work in English, not just a translation from the Norwegian. Monrad-Krohn called it an enlarged edition of his Norwegian book in the preface. The guiding motto of the monograph was a quote from Claude Bernard: "Recueillir les faits et ne s'astreindre à les interpréter qu'ensuite est la condition indispensable pour arriver à la vérité" [Collect the facts and force oneself to explain them only then, is the necessary condition for reaching the truth] (8, 9).

The exam book was popular, and in the US it became known as the "Blue Bible" (10). Macdonald Critchley wrote: "Like every British neurologist of my generation, I had studied with approval his Blue Book of Neurology, as Norwegian students called it. . . . It ran to 12 editions and many re-writings, and had been translated into several languages" (11). Per Critchley, the text was a bestseller for the publisher H. K. Lewis (11). Compston wrote in 2009:

His book introduced many components of the examination that survive. There is the recall of prime ministers, recitation of serial digits forwards and in reverse, interpretation of proverbs, mental arithmetic on mythical shopping trips, tongue twisters such as *West Register Street* and the *British Constitution*, and sensory examination—preferably spread over two days (12).

The manual included a section on simulation (malingering). Monrad-Krohn recommended the following:

If the patient pretends not to be able to move a leg or an arm, one lifts it passively for him, and asks him to let it sink slowly, it cannot be paralyzed; it would then fall down unless there be pronounced rigidity (8).

The third edition added a scheme for the routine neurologic exam and was likely the first to use ++/+ to denote a reflex of average strength (13, 14).

A reviewer of the 1921 first edition opined that "if a few thousand practitioners and a few hundred young neurologists of this country would commit its contents to memory, the American neurological level would rise like the Wissahickon in a spring freshet" (15). Another stated that "the outline is sufficiently brief to be practical and sufficiently detailed to save the search of numerous volumes for methods" (16). One critic commented, anachronistically, that the 1964 final edition was quaint, outmoded, out of style, and inefficient, giving as evidence the recommendation to use a lamp or candle for the pupillary light response (17).

**Psychiatric-Neurologic Examination Methods**

August Wimmer (1872–1937) was a Danish psychiatrist and neurologist. He wrote two tomes on epidemic encephalitis. Wimmer helped found clinical psychiatry as a scientific discipline in Denmark (18). He published a psychiatric-neurologic exam book in Danish in 1917. This work was translated into English and released as *Psychiatric-Neurologic Examination Methods, With Special Reference to the Significance of Signs and Symptoms*, in 1919 (19). The translator, Andrew Hoisholt, hoped that "the book would be found useful to the American student in psychiatry, especially in connection with his work in mental clinics" (19). The text included 61 pages on the examination of the psychic state and 86 pages on the somatic state. Wimmer covered the psychiatric exam more thoroughly than Monrad-Krohn did. In addition, the monograph included a scheme of examination for the neurologic patient. He commented that "the subject of simulation has deliberately been omitted. . . . Compendious references to ‘unmasking tricks’ can do mischief in the hands of a ‘nonspecialist’" (19). One reviewer noted that Wimmer’s contribution was "a useful, short and convenient précis of case examination methods for the psychoses, psychoneuroses, and in part for sensorimotor disturbances" (20). Another stated that "hitherto there has been no equivalent for it in English, and thanks are due Dr. Hoisholt for making it available" (21).

**Neurological Examination: An Exposition of Tests with Interpretation of Signs and Symptoms**

Charles McKendree (1886–1954) was a professor of clinical neurology at the College of Physicians and Surgeons, Columbia University, and the Neurological Institute in New York City. He published *Neurological Examination: An Exposition of Tests with Interpretation of Signs and Symptoms* in 1928 (22). It was dedicated to Fred Tilney, with a foreword by Henry Alsop Riley. The author stated:

The method of examination which is described and elaborated is that which has been in use for several years in the Department of Neurology, College of Physicians and Surgeons, Columbia University, and in the Vanderbilt Clinic. It is also employed in routine examinations at the Neurological Institute, New York City (22).

McKendree nicely outlined 24 abnormal associated movements in the text, which was a more thorough review than early editions of Monrad-Krohn’s book. He also showed pictures of a myosthenometer (for muscle power), reflex liminometer (for strength of stimulus applied to the tendon, and reflex threshold), thermophore (for heat sensation), and kinetometer (for position sense), but did not recommend these exam tools for routine use. The book included an examination form from the Neurological Institute of New York (copyrighted 1925) for recording the history and exam in an organized fashion, with reflexes graded from 0 to 5. This form was adapted from a Vanderbilt Clinic (affiliated with Columbia University) neurological examination sheet copyrighted in 1919 (23).

One reviewer commented that "the book is concise and well written. . . . Although not the best of its scope, it may be used to advantage by students" (24), and another that "while the description of the methods of examination for the neurologic status is satisfactory . . . that for the mental status comprises only eleven pages which might better have been omitted" (25).
The Examination of the Central Nervous System

Donald Core (1882–1934) was a neurologist at the University of Manchester and the Manchester Royal Infirmary. He trained in Manchester but also studied in Paris with Babinski (26). Core published The Examination of the Central Nervous System in 1928 (27), after releasing a book in 1922 on functional nervous disorders (28). Core nicely outlined a plan for the routine examination of the nervous system, emphasizing the motor and sensory systems, cranial nerves, speech, and mental state. This monograph did not make much of an impact, possibly because it was narrowly focused on “medical students . . . in particular, for those who have not completed their training in neurology” (27). One reviewer remarked that “this book is of service to students particularly in their junior year” (29), while another was more critical:

When a neurologist includes in his book a chapter of some 20 pages on mental states we ought not, perhaps, to be too critical as to his terminology . . . Nevertheless we must point out that in such expressions as “Delusions may be auditory, visual, or olfactory.” . . . “hallucinations” are referred to and not “delusions” (30).

Introduction to Clinical Neurology

Gordon Holmes (1876–1965) went to medical school in Ireland and then spent 2 years doing research with Edinger and Weigert in Frankfurt. He completed his neurology training at the National Hospital, Queen Square, and eventually became physician and director of research there. Holmes was consultant to the British Expeditionary Force in World War I, editor of the journal Brain, and knighted in 1951. He felt that “the elicitation of scientific data at the bedside required a discipline of method as rigid as that of the laboratory” (31) and was known for his remarkable bedside teaching ability and examination skills (32–35). Critchley noted:

He could coax physical signs out of a patient like Paganini on the violin. Perhaps it is still not generally realized that every neurologist alive today—wherever he works—is unconsciously utilizing the routine clinical examination propagated, perfected, and perpetuated by Gordon Holmes (36).

Residents at National Hospital stated that if personally afflicted with a nervous disorder, they would have Kinnier Wilson take the history, Gordon Holmes carry out the clinical examination, Collier make the diagnosis, and Risien Russell advise treatment (37). McHenry wrote:

The neurological examination as we know it today was conceived during the thirty years between 1870 and 1900 and elaborated into its present form by the clinical neurologists of the first half of this century, particularly Gordon Holmes (1946) (1).

The 1946 noted by McHenry referred to Holmes’ book Introduction to Clinical Neurology, which was published in 1946 (38). The text’s aim was “to discuss the nature and the significance of the symptoms and abnormal signs which a patient with a nervous disorder may present or which may be revealed by clinical examination” (38). In the work he distilled the essence of his teaching at the National Hospital. He hoped the book would be useful to students and “also recall to some of my former helpers and to visitors to the wards our clinical rounds and discussions” (38). Holmes included a scheme for routine exam of neurologic patients in the appendix. Holmes’ routine exam is essentially the one taught to trainees today by the author. The monograph discussed cranial nerves II, III, IV, VI, and VIII in detail, but the others were relatively neglected (39). It is a classic text that went through three editions, the last being revised by Bryan Matthews in 1968 (40). A reviewer in 1946 opined that “no student of neurology will have completed his training or his library who fails to read this book” (41).

Handbook of Neurological Examination and Case Recording

Derek Denny-Brown (1901–1980) went to medical school in New Zealand, did research with Sherrington at Oxford, and then completed neurological training at the National Hospital and Guy’s Hospital in London. He subsequently worked at the National Hospital and St. Bartholomew’s. He next moved to America and became director of the Neurological Unit at Boston City Hospital and James Jackson Putnam Professor of Neurology at Harvard. By the late 1960s, the Neurological Unit had trained 22 of the chairmen of neurology departments in North America (42). Denny-Brown later became president of the American Neurological Association.

He published Handbook of Neurological Examination and Case Recording in 1946 (43). This small wire-bound booklet was first issued in March 1942 in a private printing for the Neurological Unit, and Raymond Adams and Harry Kozol advised the author on its content (43). Concerning the case history, Denny-Brown commented:

Only constant practice brings facility in description, conciseness with relevant detail. Phrases such as ‘tends to’ or ‘is suggestive of’ should be avoided. An ounce of fact is worth ten of guessing (43).

He also wisely noted that “patients often describe in great detail the numerous doctors they have seen, the hospitals they have attended, and what was said or done to them, without mentioning what was happening to their pain or other complaint in this period, and only repeated questions . . . will elicit this more essential information” (43). Denny-Brown described a general approach or scheme for the routine neurologic exam, which is very similar to the neurologic examination taught today, perhaps reflecting his training by Gordon Holmes (44). He strongly felt that “the only absolute reflex sign is the plantar response. . . . Briskness or sluggishness of tendon jerks, or abdominal reflexes, is only of significance in relation to other evidence or when one-sided” (43).

The handbook went through three editions. A reviewer of the first edition stated that “these outlines can hardly replace chapters in standard textbooks available to all students,
residents, and physicians, for they are sketchy and lack the usual tables and illustrations” (45). This was a harsh review, as the handbook was designed to be “small enough to fit into the pocket of a ward jacket” and dealt “with the basic facts of clinical examination and initial approaches to patient problems” (42).

**The Neurologic Examination**

Russell DeJong (1907–1990) went to medical school and completed his neurology training at the University of Michigan. He became chairman of the Department of Neurology at his alma mater, was one of the founding members of the American Academy of Neurology, and was the original editor of the journal Neurology. He was president of the American Board of Psychiatry and Neurology and the American Neurological Association (33).

He published the massive 1079-page *The Neurologic Examination* in 1950 (46). The book was “designed to present, in some detail, the information necessary for a complete neurologic examination” (46) and followed the lectures on the neurologic exam given to students at the University of Michigan Medical School. In contrast to prior works on the subject, neuroanatomy and neurophysiology were covered thoroughly. DeJong noted that “the chief causes for incorrect diagnoses are insufficient examination, inaccurate observations, and, less commonly, false conclusions from correct and sufficient facts” (46). He recommended that the sensory exam “should always be repeated at least once to confirm the findings” and that “since the presence of hair or of hyperhidrosis may interfere with the accuracy of the [sensory] tests, it may be wise to shave or dry the part to be examined” (46). The work was extensively referenced and contained a detailed chapter on the exam of patients with hysteria or malingering, unlike prior exam monographs. He preferred to use the term “hysterical dysbasia” over “astaia-abasia” for the gait disturbance seen in patients with hysteria. His was among the first treatises to include a separate detailed chapter on the clinical examination of coma (47). The name of the book was changed to DeJong’s *The Neurologic Examination* with the 1992 fifth edition (revised minimally by Armin Haerer) (48). The sixth and seventh editions were revised by William Campbell (49, 50). A book reviewer noted that the work “reflects a long, careful preparation by a thoughtful author” and that “if there is any criticism to be leveled, it is that perhaps the volume is too encyclopedic for the average student to use as a textbook. . . . However, as a reference book, as a book for establishing lines for investigation, as a source of material for teachers of neurology, it has no peer” (51).

**Diagnostic Tests in Neurology: A Selection for Office Use**

Robert Wartenberg (1887–1956) was a neurologist, book reviewer/critic, and editor. He trained and worked in Germany, was subsequently a refugee from Nazism, and became clinical professor of neurology at the University of California, San Francisco. Wartenberg was an outstanding teacher who despised mediocrity. He was a thorough book reviewer, and authors would send manuscripts to him before being sent to press to avoid a later rapping over the knuckles (52, 53). His review of Alpers’ *Clinical Neurology* advised:

> There is only one therapy: the book should be withdrawn from the market, ground into pulp, re-written and carefully edited. Then—and only then—will it be a valuable addition to neurological literature (54).

Alpers’ textbook of neurology went through six editions, with the last being published in 1971 (55).

Wartenberg published *Diagnostic Tests in Neurology: A Selection for Office Use* in 1953 (56). The “tests” were neurologic exam maneuvers that could be easily applied in the office or at the bedside. The tests were arranged in the following order: cranial nerves, peripheral nerves, pyramidal system, extrapyramidal system, cerebellar system, sensory system, and vasomotor-trophic system. Mental status testing was not discussed in detail. The audience was said to be general practitioners, although Gordon Holmes clarified in the foreword that the book was useful for neurologists as well. Wartenberg avoided eponyms and supplanted them with physiologic terms (facial nerve tapping test instead of Chvostek’s sign, thumb bending test instead of Froment’s sign). He noted:

> It is well-nigh impossible to attribute a scientific discovery to a single person. It is rare that single eponyms are historically correct. The disavowal of eponyms may discourage the overambitious from mass production of unnecessary signs and reflexes. . . . A fitting physiological name for a test tells more than any proper name can. We need more physiology and fewer eponyms, more understanding of neurology and less memorizing of proper names (56).

The text was unique in that it had two indexes: a general one and one based on the morbid condition with its associated bedside tests. The monograph was translated into several languages and went through three editions in German (and one in English). A reviewer commented that “whether such a disconnected presentation of a group of signs and tests is of value each reader must determine for himself,” and that “although the author has recognized that many so-called pyramidal signs are associated with lesions of the extrapyramidal system, he seems to have promoted this confusion rather than clarified it” (57).

**Examination of the Nervous System: A Student’s Guide**

A. Theodore Steegmann (1902–1992) completed his neurology residency at Cleveland City Hospital (Ohio), a clinical clerkship at the National Hospital, Queen Square, and neuropathology research with Walther Spielmeyer in Munich, Germany (58). He eventually became professor of medicine (neurology) and chair of the Section of Neurology in the Department of Internal Medicine at the University of Kansas. In 1956 he published *Examination of the Nervous System: A Student’s Guide*, which was aimed at medical students, “whose curiosity and questions have taught me more neurology than I have taught them” (59). The book was a practical guide for the beginner, “small enough so that it can be carried on the hospital wards in the pocket of the student’s jacket” (59). Steegmann thanked
Robert Wartenberg for reading the manuscript carefully before it was published and recommended Wartenberg’s *Diagnostic Tests in Neurology* for those wanting more detailed information on the neurologic exam (59). The book included an examination form for recording the exam in an organized fashion, with reflexes graded from 0 to 5. There were also separate muscle strength (graded 0 to 5) and sensory forms. Steegmann included a short section on examination of the comatose patient. The first edition of the book did not cover language or memory testing, but later editions did (59, 60). One reviewer noted that “this is a handy, compact book of 164 pages, which includes a clear explanation of the necessary techniques for bedside examination of some of the functions of the central nervous system,” and added that “one could quarrel over making a statement for student consumption that a complete social history is not necessary for most neurological patients” (61).

**Clinical Examinations in Neurology**

*Clinical Examinations in Neurology* was published in 1956 by members of the Sections of Neurology and Physiology at the Mayo Clinic in Rochester, Minnesota (62). The book was dedicated to Henry Woltman and Fred Moersch (the second and third neurologists in the history of the institution) on their retirements. In addition to honoring Woltman and Moersch, the work was meant to guide the trainees in neurology at the Mayo Clinic, “to facilitate their mastery of the clinical neurologic examination” (62). The authors noted that “since our practice is a group practice, data regarding examination must be recorded in a form intelligible to others in the group. Neurologic record forms have been in use at the Mayo Clinic for approximately 30 years” (62). Forms for quantitatively detailing neurologic findings were included in a pocket attached to the rear paste-down of the book. The pocket contained a sensory chart, a muscle chart, a single history/exam sheet (Figure), and a triple-folded sheet for documenting a more comprehensive history and exam. The monograph included dedicated chapters on the electroencephalogram and electromyography/nerve conduction studies. The chin-chest maneuver to identify nerve root pain was described in this text. Some have referred to the chin-chest maneuver as the “Mayo Clinic sign” (63), although this term has never been used at the institution. Passive flexion of the head on the chest is employed when checking for Brudzinski’s neck sign (46, 56, 64). Wartenberg described this maneuver as the head bending test in 1953 (56).

A reviewer commented that “the well-known Mayo Clinic system of quantitative recording of findings is clearly
expounded” and that “especially noteworthy are the admirably restrained and strictly factual chapters on electroencephalography and electromyography that offer the clinician exactly what he needs to know and, without the extravagance observed in some quarters, set these valuable techniques in their proper places” (65). The reviewer also felt that “the discussion of sensory functions [was] less than sophisticated” and made note of “only six minor biographical references” (65).

**DISCUSSION**

The gross anatomical structure of the nervous system was well established by 1850, and scientific clinical neurophysiology emerged over the next 50 years (39). Neurologic examination findings help localize a lesion through an understanding of this anatomy and clinical neurophysiology. The history of the neurologic exam is therefore a consequence of the history of neuroanatomy and clinical neurophysiology (39).

There was an exponential expansion of knowledge in the anatomy, physiology, pathology, and clinical aspects of the neurosciences in the 1800s (66). This expansion was reflected in comprehensive neurology reference books in the late 1800s (39). Several general neurology textbooks in the late 1800s included chapters or sections on the neurologic examination (Gowers, Oppenheim, Mills, among others) (67–69). Charles Mills’ 1898 work, *The Nervous System and Its Diseases*, was called the “first thorough review of the neurologic examination to appear in textbook form” (66). Being focused on the whole of neurology, these tomes also described disease diagnosis and therapy. In comparison, books dedicated primarily to the neurologic examination without a major emphasis on disease description or treatment did not appear until the early 1900s (*Table*). The audiences of these monographs included medical students, residents, nonneurology practitioners of medicine, and neurologic specialists. The books all explained how to evaluate cerebral, cranial nerve, motor, sensory, and cerebellar/gait function, in varying degrees of detail (3). These volumes helped establish a uniform approach to patients with neurologic disease (39). Modifications in the routine neurologic examination were indicative of cultural, university, or regional allegiances, but the core exam was similar (3).

Most of the texts were small in size (octavo or duodecimo), with the exception of DeJong’s book (quarto, 1079 pages). Monrad-Krohn’s “Blue Book of Neurology”/“Blue Bible” was the earliest success and went through the most editions. The Wartenberg and Monrad-Krohn volumes were translated into the most languages. The McKendree, Steegmann, and Mayo monographs included neurologic exam blanks/sheets/forms. These works served the important purpose of educating trainees on proper neurologic examination technique and how it related to neurologic anatomy and physiology (70). They could make a reputation and be profitable for the author (Monrad-Krohn), highlight how neurology was practiced at individual institutions (McKendree, Denny-Brown, Holmes, DeJong, Mayo), and honor retiring mentors (Mayo).

Modern neurology examination monographs (by Campbell, Biller et al., Fuller, and Lewis, among others) are similar in organization to their predecessors (50, 71–73). According to Amazon Best Sellers Rank (accessed December 7, 2014), the current best-selling neurologic examination book is *The Four-Minute Neurologic Exam* by Goldberg (74). It is considerably shorter that its forebears (54 pages), is written for nonneurologists with limited time, and “is not a substitute for the more formal neurologic evaluation that should follow . . . when the screening exam reveals significant findings” (74).
Holmes would not have been satisfied with this book, as "he examined every patient from top to toe, taking no short cuts . . . even a Parkinsonian was subjected to the most rigorous sensory testing, though the diagnosis had been obvious to him right from the start." (36). Holmes noted in 1936:

"The more common causes of . . . errors are inaccuracy or incompleteness of observation. This is particularly liable to occur in the ordinary examination of patients, in which facts that seem insignificant are neglected, or the student may see only that for which he looks, or routine may blunt the keenness of observation (75)."

Acknowledgment

The author would like to thank Dr. Peter Koehler for translating Claude Bernard's quote from French to English.

58. Albert T. Steegmann, M.D. file. University of Kansas Medical Center Archives, Kansas City, KS.
Intussusception occurs when a proximal segment of intestine invaginates into a distal segment. It is a common cause of intestinal obstruction in children but is infrequent in adults. A 77-year-old woman presented with a 1-month history of intermittent abdominal pain associated with nausea and distended abdomen. Imaging showed a complex elongated sausage-shaped mass in the transverse colon with no obstructive pattern or free air. Surgery confirmed colonic intussusception in addition to a palpable cecal mass requiring a right hemicolectomy. Histologic study demonstrated adenocarcinoma in situ within a tubulovillous adenoma. Surgical excision of the affected intestine is the recommended treatment of choice.

CASE DESCRIPTION

A 77-year-old white woman presented to the emergency department with a 1-month history of intermittent upper abdominal pain associated with nausea. Initially, the pain was infrequent but it progressed and became more severe and regular, each bout lasting about 2 minutes. She denied fever, chills, weight loss, vomiting, hematochezia, constipation, changes in bowel habits, or any other symptom. Vital signs were within normal limits. Examination revealed a soft, distended, nontender abdomen without guarding, rebound tenderness, or palpable masses. During examination, an episode of abdominal pain was witnessed; it lasted 2 minutes and then resolved. A contrast-enhanced abdominopelvic computed tomography (CT) scan showed a complex-appearing and elongated sausage-shaped mass involving the proximal to mid-aspect of the transverse colon with diffuse wall thickening and pericolonic fat stranding (Figure 1). No obstructive pattern or free air was observed.

Due to the chronicity of symptoms, the patient was admitted and optimized for surgery with hydration, electrolyte replacement, and pain control. Elective surgery on hospital day 3 confirmed a colonic intussusception and a palpable cecal mass. A right hemicolectomy with an ileocolic side-to-side anastomosis was performed. The resected colon was opened, and a protruding tumor was found in the cecum. The tumor measured 4.2 × 3.3 × 0.3 cm (Figure 2). Histologic study demonstrated a minute focus of adenocarcinoma in situ within a 4.2 cm tubulovillous adenoma invading the lamina propria with no muscularis mucosa penetration. No lymphovascular invasion was seen. Surgical margins were negative, and 13 benign lymph nodes were harvested. The patient recovered well and was discharged on postoperative day 4.

DISCUSSION

Only about 5% of intussusceptions causing intestinal obstruction occur in adults (1–9). There are multiple types of intussusception, such as gastro-duodenal, jejuno-jejunal, ileo-ileal, ileo-colic, and colo-colic (5–8). In children, 90% of the intussusceptions are ileo-colic and idiopathic (1, 10). In a recent study with 148 adults, 80% of the cases were enteric intussusceptions (1, 6, 8). In adults, 80% of the intussusceptions are secondary to a pathologic process such as tumors, suture lines, or adhesions (2). Benign or malignant tumors act as a lead point in 65% of reported adult cases (2–5, 7, 10). Most of the adult colo-colic intussusceptions are due to malignancy, such as primary adenocarcinoma of the colon, as in our patient (3, 6–8, 10).

The most common symptoms of intussusception in adults are abdominal pain, nausea, and vomiting (1, 3–8). Physical exam rarely discloses an abdominal mass. Plain films usually
show intestinal obstruction (1, 9). CT scan is the most sensitive diagnostic tool due to the pathognomonic target sign and sausage-shaped appearance (2, 3, 5, 6, 10). In a recent study by Lindor et al, 93% of the adults with intussusception had a positive CT scan (1). Even though CT scan diagnoses the intussusception, the etiology is rarely identified (10). Sonography also can be useful in diagnosing intussusception by revealing a target or doughnut sign in transverse view, but this can be limited by obesity or the presence of distended bowel loops (9). A recent retrospective review by Honjo et al showed that ultrasonography had an accuracy of about 50% in the preoperative diagnosis of adult intussusceptions (11).

The treatment for intussusception varies greatly among children and adults due to the different etiologies. In children, the treatment of choice involves reduction of the intussusception with hydrostatic or pneumatic enemas since most are idiopathic in nature. Adults usually present with nonspecific symptoms, and diagnosis can be difficult. When preoperative diagnosis is established in adults, reducing the intussusception is controversial due to the high incidence of malignancy, which can result in perforation, dissemination of microorganisms and malignant cells into the peritoneal cavity, and anastomotic complications of the edematous and inflamed bowel (2, 6, 8, 9). For these reasons, most authors recommend resection of the affected bowel to either prevent recurrence or provide cure, since more than 65% of the adults have a malignant lesion as the lead point (2, 6, 8, 10). Recent studies have proposed preoperative reduction in certain patients with nonischemic small bowel intussusceptions secondary to benign disease. Preoperative reduction permits a more limited resection, in contrast to primary en bloc resection, which is not ideal in patients at risk of short gut syndrome (6, 9).


We present a case of large-volume barium aspiration in a 56-year-old woman with stage IV tongue squamous cell carcinoma and longstanding dysphagia. The patient rapidly developed hypoxemic respiratory failure from the resultant chemical pneumonitis. However, her respiratory status improved with supportive care alone in 48 hours. Barium aspiration is rare and often produces dramatic radiographic findings, but is generally associated with a favorable prognosis.

**CASE DESCRIPTION**

A 56-year-old cachectic woman with longstanding dysphagia and multiple episodes of aspiration pneumonia presented with orthostasis in the setting of poor oral intake, weight loss, and progressive failure to thrive. She had stage IV tongue squamous cell carcinoma and was receiving palliative chemotherapy. In anticipation of a gastric tube placement, barium was administered the night before the planned procedure. The following morning, she acutely developed increased work of breathing and profound hypoxemia.

On examination, her temperature was 100.4°F; pulse, 160 beats per minute; blood pressure, 111/55 mm Hg; respiratory rate, 30 breaths/minute; and oxygen saturation, 70% on room air. Her oxygen saturation improved to 95% on a 100% high-flow set running at 15 L per minute. She coughed frequently. Her breath sounds were coarse at the bilateral bases with mild accessory muscle use. Her extremities were warm and without edema. The white blood cell count was 21.5 × 10³ cells/mm³, which had increased from 4.8 × 10³ cells/mm³ the day before. Her troponin T level was <0.01 ng/mL. A comprehensive metabolic panel was normal. An electrocardiogram showed sinus tachycardia without ischemic changes. A chest radiograph demonstrated aspiration of barium, highlighting her bilateral airways and bronchial tree, most pronounced in the lower lobes (Figure 1a).

In the medical intensive care unit, she required a 100% nonbreather mask initially to maintain adequate oxygenation, but otherwise appeared comfortable without overt respiratory distress. She was provided with supportive management including chest physiotherapy, a percussion vest, and an Acapella device to promote cough and clearance of the barium material. Over the following 48 hours, her respiratory status gradually improved and she no longer required supplemental oxygen. At discharge, her chest radiograph (Figure 1b) showed small quantities of barium, primarily in the left lower lobe.

**DISCUSSION**

Barium studies are often used to evaluate disordered swallowing, despite the risk of aspiration. Aspiration of large quantities of barium sulfate and attendant complications are rare (2). Barium has not been shown to commonly cause chemical pneumonitis (3). In fact, cases have been reported of incidental diagnosis of barium aspiration on chest imaging in patients who were completely asymptomatic after the initial study (4). Before the advent of bronchoscopy, inhalation bronchography with barium contrast was used to identify respiratory pathology without major complications or symptoms in human and nonhuman animals (3).

Mechanical obstruction leading to alveolar dead space as well as uncommon acute inflammatory reactions have been reported (5–7). Cases with severe respiratory complications appear to occur at higher frequency in patients with extensive comorbid diseases. Dysphagia and head and neck malignancy are common risk factors for high-volume aspiration (1, 5, 8), and these risk factors were present in our patient.

Although data are sparse guiding the optimal management of barium aspiration, potential treatment strategies vary based on the quantity of barium aspirated, the patient’s comorbid disease profile, and the presenting symptoms. Many patients are completely asymptomatic after barium swallow, and in these cases, no intervention is required (2). The acute immunologic response seen in gastric content aspiration is not normally seen with barium aspiration alone (9, 10). However, when gastric contents are aspirated with barium and the patient develops...
signs of infection, antibiotics have been used (6). In patients with more progressive clinical courses who develop severe respiratory failure requiring intubation, bronchoscopy and suctioning have been attempted (8). However, complications of bronchoalveolar lavage include the possibility for contrast to spread to initially unaffected areas of the lung (11).

Barium studies should be used judiciously in elderly patients with multiple comorbidities and altered head and neck anatomy. Functional endoscopic evaluation of swallowing may provide a safer alternative to barium studies (12). Furthermore, recent studies have attempted use of a retroesophageal suction catheter to eliminate aspiration in patients with profound dysphagia (13). The use of retropharyngeal suction during the study may also be worthwhile when evaluating high-risk patients to minimize the risk of massive barium aspiration and the ensuing complications.

Limited data exist characterizing the long-term prognoses of patients after isolated barium aspiration events. Most patients appear to have complete recovery given the inert nature of barium; however, high-resolution chest imaging has detected subtle evidence of early fibrosis even 1 year after aspiration (4).

Effect of resection of an orbital arteriovenous malformation on central venous pressure

Victoria S. Starks, MD, Grant Gilliland, MD, Joseph Hise, MD, Ike Thacker, MD, and Kenneth F. Layton, MD

We report the first utilization of intraoperative central venous pressure (CVP) monitoring in the resection of an orbital arteriovenous malformation. A 24-year-old woman with a history of a left orbital mass who had previously undergone resection of a cranio-orbital arteriovenous malformation presented with gradual recurrence in the left orbit. She visited the emergency department with sudden vision loss, which resolved over several hours. This transient vision loss was thought to be due to a steal phenomenon from the ophthalmic artery due to the residual vascular malformation. Further surgical resection was undertaken. A preoperative angiogram identified residual feeding vessels, and the larger vessels were embolized. At the start of the procedure, her CVP was elevated (29 mm Hg), as measured by a central venous line. The remaining feeding vessels were surgically ligated, and an intraoperative arteriogram confirmed their successful ablation. At the conclusion of the procedure, the CVP had decreased to 9 mm Hg.

Arteriovenous malformations (AVM) are congenital lesions composed of direct abnormal connections between the arterial and venous systems. Small lesions may remain asymptomatic, while larger lesions with high flow may manifest with symptoms due to mass effect, vascular steal, or even high-output cardiac failure.

CASE REPORT

A 24-year-old African American woman initially presented at age 15 with an enlarging, nonpainful, left orbital mass, proptosis, and ptosis. Magnetic resonance imaging and magnetic resonance angiography identified the mass as a cranio-orbital AVM with the nidus in the subcutaneous tissue of the left upper eyelid. Feeding vessels from both the internal and external carotids were identified. Shortly after initial presentation, she underwent embolization and staged surgical resection of the AVM, including anterior orbitotomy and frontoorbitozygomatic craniotomy. Histologic study showed a benign AVM.

In the intervening time, the patient noted increasing fullness in her lid and recurrent ptosis, especially during an incidental pregnancy (Figure 1a). She presented to the emergency department with sudden painless vision loss in her left eye. Her visual acuity was 20/20 in the right eye but light perception in the left eye. There was no afferent pupilary defect. Extraocular muscle movements were intact, and she had no pain with eye movement. During the 4 hours she spent in the emergency department, the vision in her left eye improved to 20/40 with no intervention.

The episode of transient vision loss was thought to be related to residual malformation causing a steal phenomenon. The patient elected to undergo exploration and resection of residual AVM. Preoperative angiography revealed a preseptal, palpebral AVM fed by residual branches from the ophthalmic artery distal to the central retinal artery. Feeder vessels were embolized with polyvinyl alcohol particulates. High flow was noted through small distal branches of the internal maxillary artery, which were too small for embolization (Figure 1c).

In the operating room, anesthesia was induced with propofol and fentanyl and maintained with desflurane, sufentanil, and dexmedetomidine. Pressure support with a positive end-expiratory pressure of 5 cm H₂O was utilized throughout the case. After induction, a central venous line was placed in the right internal jugular vein with ultrasound guidance and advanced into the superior vena cava in the standard fashion. At the start of the procedure, the patient’s central venous pressure (CVP) was elevated (29 mm Hg). A Krönlein incision was made and dissection was extended to the lateral orbital rim. Computed tomography–guided navigation with the Stryker navigation system was utilized. The lateral orbital wall was resected en bloc to decompress the orbit. The dissection proceeded along the extraocular muscles from lateral to medial, adhesions were lysed, and vascular contributions to the AVM were ligated (Figure 1b). The plane of dissection was then converted to subperiosteal and again vessels were clipped as they were encountered. At this point, a medial canthal incision was made, and vessels extending over the nasal bridge were clipped, as was the anterior ethmoidal...
artery. An intraoperative angiogram revealed successful ablation of the feeding vessels (Figure 1d). At the conclusion of the procedure, the patient’s CVP was 9 mm Hg. The patient has been followed for a year and has not had any further episodes of vision loss.

**DISCUSSION**

AVMs are abnormal blood vessel conduits between the arterial and venous systems due to the absence of an intervening capillary bed. AVMs result from errors in vascular development between the fourth and sixth weeks of gestation (1). By comparison, arteriovenous fistulas are acquired arteriovenous shunts, occurring, for example, after trauma. As congenital malformations, AVMs are nonmalignant; however, they are dynamic lesions and generally progress if untreated and often recur after resection. The Schobinger staging system is used to classify AVMs and to document progression (2). The earliest stage is applied to cutaneous lesions with detectable shunting on Doppler; the latest stage is reserved for high-output cardiac failure as a result of large AVMs.

Although AVMs are present at birth, they may not become clinically apparent until puberty or adulthood. There is a recognized phenomenon of AVM expansion during puberty in both sexes that is attributed to hormonal effects (1). Pregnancy has been studied in Schobinger stage I lesions and was not found to be associated with AVM progression; however, the effects of pregnancy on larger AVMs is not known. In the case described, the patient experienced AVM progression during puberty and pregnancy. Mechanisms implicated in AVM expansion include angiogenesis and mechanical effects of increased blood flow, such as dilatation, hypertrophy, aneurysm formation, and collateralization (2).

The mechanism of steal is shunting through lower resistance vessels and underperfusion of higher resistance areas. Steal syndrome has been implicated in the dynamic neurological changes noted in 4% to 12% of patients with AVMs (3). Cerebral blood flow, intraarterial pressure, and blood flow velocity are elevated in vessels near the AVM, and normalization of perfusion parameters and resolution of neurological symptoms has been reported after resection (3). Delayed vision loss after external carotid ligation for maxillofacial AVMs has been attributed to steal syndrome, associated with recollateralization of the external carotid from the ophthalmic artery (4). Other mechanisms proposed for vision loss in patients with AVMs, especially those involving the cavernous sinus, are venous hypertension or thrombosis causing impaired venous drainage (4). In the case described here, the transient monocular vision loss may have been secondary to a combination of steal and venous hypertension.
CVP is measured by a pressure transducer in the superior vena cava and correlates with right atrial pressure and cardiac preload. The right atrium and superior vena cava are contiguous systems with nearly equal pressures, even at the extremes of intravascular volume (5). Frequently used to monitor volume resuscitation, CVP is a popular adjunct parameter in the assessment of intravascular volume. CVP is increased in settings of elevated venous volume or decreased venous compliance, including fluid or blood product transfusion, increased intra-thoracic or intra-abdominal pressure, and vasopressors (5).

The draining vein pressure of intracranial AVMs has been shown to decrease after AVM resection (6). The systemic implications of intracranial AVMs have been studied, and CVP has been reported as unaffected or decreased after intracranial AVM resection (6, 7). The lack of effect on CVP by intracranial AVMs may not hold true for extracranial AVMs, as unique autoregulation of the cerebral vasculature prevents direct transmission of intracranial pressure to the systemic circulation and vice versa. There are no reports comparing CVP monitoring before and after extracranial AVM resection.

In the case described, the AVM was acting as a conduit for arterial blood to pass directly into the venous system, thus elevating the pressure in that system, which was recorded by the CVP monitor. Resection of the residual AVM led to correction of venous pressures, which was reflected in a decrease in the CVP. The anesthetic agents utilized during this case were unlikely to be confounders, as these agents are associated with either increased or unaffected CVP (8–10). Placement of a central line is not superfluous in many cases of AVM resection, as these lesions can cause significant blood loss and hemostasis is often difficult to attain, since the abnormal vessels often pass through bone. CVP monitoring may be a useful adjuvant tool to document physiologically significant resection of extracranial AVMs.
Acute myocarditis can be induced by various concomitant disease processes including infections. Most of these cases are viral in origin; however, bacterial infections are also implicated to a lesser degree. Group A streptococcus is a frequent culprit in bacterial-induced myocarditis. Its diagnosis is suspected by the presence of signs and symptoms of rheumatic fever as established by the Jones criteria. The development and refinement of current diagnostic tools has improved our ability to identify specific pathogens. It has been found that group A streptococcus may be responsible for more cases of infection-induced acute myocarditis than previously thought, and often without the clinical features of rheumatic fever. We present the case of a 43-year-old man hospitalized with chest pain that was initially diagnosed as an acute ST-elevation myocardial infarction. Further evaluation confirmed that his chief complaint was due to acute nonrheumatic streptococcal myocarditis.

G

roup A streptococcus (GAS) is rarely reported as a causative pathogen of acute myocarditis without clinical features suggestive of rheumatic fever. The incidence of acute myocarditis is estimated to be 1 in 10 cases per 100,000 persons, with acute viral infections accounting for most of the cases of infectious myocarditis (up to 1% to 5% of all cases). No epidemiological data estimating the incidence of GAS-induced myocarditis exist at this time. Myocardial inflammation and damage is thought to be caused by IgG binding proteins produced by GAS antigens that cross-react with cardiac myosin (1). Despite the advent of new laboratory and imaging tools, the diagnosis of acute myocarditis continues to be a challenge due to its wide variety of clinical presentations. We present the case of a 43-year-old man hospitalized with chest pain that was initially diagnosed as an acute ST-elevation myocardial infarction. Further evaluation confirmed that his chief complaint was due to acute nonrheumatic streptococcal myocarditis.

CASE PRESENTATION

A 43-year-old man presented to the hospital complaining of continuous, nonradiating, retrosternal chest pressure. The pain began at rest approximately 18 to 24 hours prior to his arrival. His pain was 6 on a scale of 1 to 10, without alleviating or aggravating factors. Additionally, the patient reported a 3-day history of sore throat, cough, fever, chills, headache, and epigastric pain. The patient had no significant risk factors for cardiovascular disease.

On admission, his electrocardiogram showed a sinus rhythm with a rate of 75 beats per minute and mild ST elevations in leads I, II, AVF, V4, V5, and V6 (Figure 1). Troponin I and creatine kinase-MB levels were found to be elevated at 15.8 ng/mL and 68.6 ng/mL, respectively. A repeat troponin I level was markedly increased at 45.8 ng/mL. Transthoracic echocardiogram demonstrated preserved left ventricular systolic function with an ejection fraction of 55% and no regional wall motion abnormalities. Trivial mitral regurgitation and mild left atrial dilatation were noted. Percutaneous coronary angiography revealed no evidence of obstructive coronary artery disease, and left ventriculography corroborated our echocardiogram findings.

The patient’s white blood cell count was 15.9 × 10^9 per L and the erythrocyte sedimentation rate was 47 mm/h. The patient reported several instances of elevated oral temperature at home; the highest reading was 102°F. He was afebrile at the time of admission. A rapid streptococcal antigen test was positive. Antistreptolysin O titer (74 IU/mL) and a blood culture were negative. Treatment with amoxicillin and colchicine was initiated. The patient experienced gradual improvement in his symptoms and was discharged 3 days later with complete resolution of his chest pain.

The patient had no further episodes of chest pain, and a repeat electrocardiogram showed improved tracings 7 days after discharge. Tonsillectomy was planned. Cardiac magnetic...
resonance imaging was performed 17 days after his discharge, showing a pattern of abnormal signal intensity (T2 hyperintensity and delay hyperenhancement) involving the subepicardial myocardium, without evidence of associated left ventricular contractile or functional abnormalities (Figure 2).

DISCUSSION

Current published reports contain extensive evidence linking acute carditis (pericarditis, myocarditis, and valvulitis) with acute rheumatic fever. Acute myocarditis associated with GAS pharyngitis without rheumatic fever symptoms is rare, and its incidence has been increasingly reported since Gore and Saphir first described it in 1947 (2). The rise in reported cases is likely related to its strikingly similar clinical presentation to that of an acute myocardial infarction and the present-day availability of diagnostic tools that make the diagnosis of GAS-induced myocarditis more accurate.

Case series published by Talmon et al (3), Mokabberi et al (4), and Upadhay et al (5) provide a constellation of findings that can be useful to the clinician in making a differential diagnosis (Table 1). A diagnosis of GAS-induced myocarditis is to be suspected in young men with a chief complaint of acute chest pain without significant risk factors for premature cardiovascular disease, particularly with evidence of streptococcal pharyngitis or tonsillitis. Electrocardiogram tracings will most likely show ST-segment elevations in conjunction with elevated cardiac enzymes. Coronary arteries are typically angiographically normal. The most common transthoracic echocardiogram findings are left ventricular wall motion abnormalities, mitral regurgitation, and pericardial effusion.
Cardiac magnetic resonance imaging appears to be the imaging modality of choice for confirmation of the diagnosis; however, it remains largely untested. Mavrogeni et al (6) described the largest series of patients evaluated with cardiac magnetic resonance imaging thus far. Unfortunately, their sample size was small (17 patients), and a correlation between cardiac enzymes and cardiac magnetic resonance imaging could not be made. Positive late gadolinium enhancement was identified in 13 patients. Reimaging 3 months later showed normal results in 14 patients.

Another important consideration is the possibility of recurrent episodes of myocarditis secondary to streptococcal infection in previously affected patients. Chikly et al (7) published a case of a 37-year-old man who presented with two separate episodes, 5 years apart from each other. Both episodes began with streptococcal pharyngitis a few days before seeking medical attention for chest pain.

### Table 1. Three reported case series of acute nonrheumatic streptococcal myocarditis

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>Number of reported cases</td>
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<td>9</td>
</tr>
<tr>
<td>Male</td>
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<td>Mean age of onset (years)</td>
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<tr>
<td>Mean latency of pharyngitis or tonsillitis to chest pain (days)</td>
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Invited commentary

What is the definition of SPAM? Even if you cannot define it, you must recognize it!

Chest pain with electrocardiographic ST elevation is managed today with coronary arteriography at a hospital capable of percutaneous coronary intervention (PCI). When no culprit coronary stenosis is found, the angiographic catheter is removed, and it is often the responsibility of another physician to determine the cause of the pain and electrocardiographic changes. Pericarditis is often diagnosed, but it does not explain the elevation in cardiac biomarkers. Treatment with a nonsteroidal antiinflammatory drug with or without colchicine might offer benefit, but in some cases it is not enough. Days of insufficient treatment might pass before the evolution of electrocardiographic changes looks more like myocarditis than pericarditis.

In this issue of BUMC Proceedings, Aguirre and coworkers (1) present a case of streptococcal pharyngitis–associated myocarditis. They describe the presentation in a 43-year-old man and a logical sequence of tests used to diagnose acute myocarditis and its association with group A streptococcal pharyngitis. They deserve special commendation for their tabular collation of the published literature of this disease, including this case.

There are fewer than 50 cases of streptococcal pharyngitis–associated myocarditis in the medical literature. Yet, annually in the US, 11 million patients present to an emergency department or ambulatory care setting with sore throat, and group A streptococcus is responsible for 5% to 15% of sore throats in adults and 20% to 30% in children (2, 3). The incidence of streptococcal pharyngitis–associated myocarditis might be larger than is recognized.

Treatment with penicillin provides clinical improvement in 2 to 3 days and improvement in left ventricular function (4). Delayed diagnosis or failure to diagnose can result in persistent left ventricular dysfunction and recurrence. Is chronic antibiotic suppression of group A streptococcus needed, as is used to prevent recurrent acute rheumatic fever? Is it necessary only when there is persistent exposure to unhygienic carriers like schoolchildren? When is tonsillectomy needed?

A high index of suspicion for streptococcal pharyngitis–associated myocarditis is necessary when a young patient, especially male, with no risk factors for coronary artery disease presents to the emergency department with chest pain, electrocardiographic ST elevation, and elevated cardiac biomarkers and has no culprit coronary stenosis. The next questions must be about close recent exposure to someone with streptococcal pharyngitis and/or a sore throat in the last week. Cultures and serologic testing for streptococcal infection can detect chronic asymptomatic exposure.

What would foster recognition of streptococcal pharyngitis–associated myocarditis? A catchy name might help. I propose an additional dictionary definition of the word spam, with all capital letters:

SPAM (noun)
1. Trademark for spiced ham (1937)
2. Unsolicited or undesired electronic message (1990s)

SPAM might be included in the guidelines for the management of STEMI. When it is diagnosed in greater numbers, controlled trials can be designed to answer these questions about the benefits of chronic antibiotic suppression and of tonsillectomy.

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E-mail: schiavw@ccf.org

A 58-year-old man, who had used cocaine and other illicit drugs in the past, had mild, intermittent exertional chest discomfort for 2 weeks followed by severe, prolonged chest pain, which began while he was dancing and was unrelieved by rest. An electrocardiogram recorded on arrival at the emergency department (Figure 1) showed acute inferoposterior myocardial infarction with some features of right coronary arterial occlusion, i.e., ST elevation lead III > lead II and ST depression in lead I, and some features of left circumflex occlusion, i.e., ST depression in leads V1, V2, and aVR (1). Right-sided chest leads showed no significant ST elevation. The cardiac rhythm was marked sinus arrhythmia that did not meet criteria for type I or type II sinoatrial block. The P-R intervals were at the upper limit of normal (0.18 to 0.22 seconds). Over the next several hours, there was minimal sinus arrhythmia. The PR interval varied from 0.42 to 0.18 seconds, and there was further evolution of the changes of inferoposterior myocardial infarction.

Twelve hours after the first electrocardiogram, the tracing changed dramatically (Figure 2). Marked sinus arrhythmia was completely dissociated from a regular accelerated idioventricular rhythm, so-called block-acceleration dissociation, i.e., the presence of some degree of atrioventricular block with the atrioventricular dissociation probably being accentuated by the accelerated idioventricular rate (2). Accelerated idioventricular rhythm is common in acute myocardial infarction and, unlike ventricular tachycardia, does not worsen prognosis (3).

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Although the electrocardiogram has features of both right and left circumflex coronary arterial occlusion, two facts suggest the right as the culprit. First, the right is the culprit four times as often as the left circumflex in patients with acute inferior myocardial infarction (1). Second, the artery to the atioventricular node arises from the right coronary 90% of the time, and any degree of new atioventricular block suggests the right as the culprit; a caveat here is that inferior myocardial infarction, especially early in its course, often is accompanied by an increase in vagal tone that could be responsible, at least in part, for the atioventricular block, as well as the marked sinus arrhythmia.

Coronary arteriography revealed total occlusion of the right coronary in its mid portion and 90% narrowing of the left circumflex beyond a large first obtuse marginal branch. A bare metal stent was placed in the right coronary artery, and the patient had an uneventful postprocedural course with no further arrhythmia.

Takotsubo cardiomyopathy is an uncommon clinical entity, also called apical ballooning syndrome, characterized by transient systolic dysfunction of the apical and/or mid segments of the left ventricle. We report a case that highlights takotsubo syndrome in the setting of thyrotoxicosis that required thyroidectomy. The association of takotsubo syndrome and hyperthyroidism has been reported before. We found 13 previously reported cases of thyrotoxicosis-induced cardiomyopathy, most associated with Grave’s disease and none treated with thyroidectomy. Awareness of this possible association is important in establishing the diagnosis and instituting proper management.

**CASE PRESENTATION**

A 61-year-old woman presented with dyspnea and palpitations. She denied chest pain or recent emotional stress. Examination disclosed tremors and mild respiratory distress, a blood pressure of 128/76 mm Hg, a heart rate of 126 beat per minute, and a respiratory rate of 24 breaths per minute. The electrocardiogram showed atrial fibrillation with rapid ventricular response and nonspecific ST-T wave changes (Figure 1). Her troponin T level was 0.12 ng/mL and creatine kinase MB, 6 ng/mL. A thyroid function test suggested the presence of thyrotoxicosis, with free T3 of 1.2 pg/mL and creatine kinase MB, 6 ng/mL. A thyroid function test suggested the presence of thyrotoxicosis, with free T3 of 12.8 pg/mL (reference range, 2.0–4.2 pg/mL), free T4 of 5.6 pg/mL (reference range, 0.93–1.70 pg/mL), and thyroid-stimulating hormone of 0.01 uIU/mL (reference range, 0.27–4.2 uIU/mL). An echocardiogram showed moderately decreased left ventricular systolic function with an ejection fraction of 35% to 39% and akinesis of the septal wall and apical region. A coronary angiogram did not show any coronary artery stenosis, but ventriculography showed large apical ballooning (Figure 2). A thyroid ultrasound showed a complex 5 mm nodule in the midinferior pole of the left thyroid gland. Thyroid-stimulating immunoglobulin was highly positive, indicating autoimmune hyperthyroidism (Grave’s disease).

The patient’s heart rate was controlled by a calcium channel blocker drip, and then the patient was started on beta-blockers, methimazole, and prednisone to treat thyrotoxicosis. Due to difficulty controlling her hyperthyroid state, a thyroidectomy was performed. Five days after the operation, the patient’s clinical condition improved significantly, and she was sent home on beta-blockers and levothyroxine supplement. At 3 months of follow-up, the patient remained asymptomatic, and a repeat echocardiogram showed an ejection fraction of about 60% with no abnormal regional wall motion abnormalities.

**DISCUSSION**

Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy, consists of acute reversible nonischemic cardiomyopathy characterized by the hallmark of apical ballooning that leads to transient left ventricular dysfunction. Left ventricular function usually recovers in 1 to 4 weeks in patients who survive the acute episode. It has a presentation that mimics myocardial infarction with both electrocardiographic changes (ST-segment elevation and/or T-wave inversion) and elevated cardiac enzymes but with no coronary obstruction. In the vast majority of patients, coronary catheterization doesn’t show evidence of significant coronary artery disease.

It is estimated that 2% of patients with suspected acute ST-elevation myocardial infarction have the syndrome. This condition can be easily mistaken for ST-segment elevation myocardial infarction. This in turn can lead to a misdiagnosis and hence wrong treatment, especially in a noncardiac center where thrombolysis remains a first-line treatment for acute ST-segment myocardial infarction. The other common presentation...
is congestive cardiac failure, which is fortunately less of an issue, as it has a similar standard treatment (3).

We identified 13 previously reported cases diagnosed as takotsubo cardiomyopathy associated with thyrotoxicosis, most of which were associated with Grave’s disease. Other causes included exogenous levothyroxine intake, Hashimoto’s thyroiditis, and toxic multinodular goiter. In all cases, the patients had a complete recovery of the cardiomyopathy after treatment for thyrotoxicosis. Our case was unique as it did not respond well to medical management and our patient underwent thyroidectomy with complete resolution of her symptoms.

It has been noted that acute medical illness, physical stress, or emotional stress can be the trigger of takotsubo cardiomyopathy. Further, this condition is more common in elderly and postmenopausal women, which suggests that low estrogen levels or a sex-related difference in myocardial sensitivity to catecholamines might play a role in this condition (4, 5). It has even been suggested that takotsubo cardiomyopathy might be related to the autoimmunity of thyroid disease (6). The precise etiology, however, remains unknown. Inflammation and fibrosis have also been suggested as playing a role. A recent study suggested a significant contribution of oxidative stress to the pathogenesis of takotsubo syndrome, which further supports the idea of regional hypokinesis of the myocardium as a sign of inflammation related to stress (7).

Treatment of takotsubo cardiomyopathy is usually supportive, with standard medications for heart failure and treatment of the underlying conditions. Our patient was treated with a beta-blocker, antithyroid medications, and steroids, but due to persistent symptoms, she underwent a thyroidectomy.

A 66-year-old man with a history of coronary artery disease was evaluated due to ventricular tachycardic (VT) storm. The patient continued to have frequent recurrences of VT despite treatment with amiodarone and lidocaine. Since the ventricular arrhythmia could be related to myocardial ischemia related to a chronic total occlusion (CTO) of the right coronary artery, the patient underwent successful percutaneous coronary intervention of the CTO, followed by implantable cardioverter defibrillator implantation. He had no further episodes of VT during his hospital stay. After 9 months of follow-up, he had no further chest pain or clinically apparent recurrent ischemia. Interrogation of his defibrillator has shown brief nonsustained episodes of ventricular tachycardia, but the patient has not required delivery of a shock. The temporal association between treatment of the CTO and resolution of the VT, as well as the lack of recurrence of sustained VT, suggest a causative link between underlying ischemia produced by a chronically occluded coronary artery and provocation of VT and lend supportive evidence to this treatment approach.

Patients with chronic total occlusions (CTOs) of the coronary arteries most commonly present with angina pectoris or exertional dyspnea. The role of a CTO in arrhythmogenesis is less clear. Advanced techniques now exist allowing percutaneous treatment of complex CTOs, which can not only improve patient symptoms but may also decrease arrhythmia.

CASE DESCRIPTION

A 66-year-old man with a history of coronary artery disease, for which he had undergone coronary artery bypass grafting 12 years previously, was transferred to our tertiary care facility due to ventricular tachycardic storm. He had been well until 4 days prior to admission, at which time he presented to an outside facility with syncope. He had spontaneous recovery of consciousness prior to the arrival of emergency medical services. Continuous telemetric monitoring showed no ventricular arrhythmia, an echocardiogram showed normal left ventricular size and normal systolic function, and a nuclear myocardial perfusion study showed a large perfusion defect involving the inferior and inferolateral walls, a mixture of infarction and ischemia. The etiology of syncope was unclear.

Two days after dismissal, he had acute onset of substernal chest discomfort that radiated toward his right shoulder and back. Emergency medical services was again summoned; en route to the hospital he was documented to have multiple episodes of ventricular tachycardia (VT) managed with direct current cardioversion and subsequent initiation of intravenous amiodarone. The patient continued to have frequent recurrences of VT (Figure 1a), which prompted the additional initiation of intravenous lidocaine (bolus and drip). Baseline laboratory results revealed normal serum potassium, magnesium, calcium, and phosphorus. Initial serum troponin levels were below assay limit but eventually climbed to a peak of 3.35 ng/mL (abnormal > 0.10 ng/mL). Baseline electrocardiogram (Figure 1b) showed sinus tachycardia, a right bundle branch block, and Q waves in leads II, III, and aVF, with mild diffuse ST segment depression. Cardiac catheterization revealed a patent left internal mammary artery to his left anterior descending artery and two occluded saphenous vein grafts, one previously anastomosed to the second obtuse marginal branch and one to the distal right coronary artery (RCA). The native mid left circumflex and proximal RCA were occluded. The occluded RCA was unchanged compared to the description of a prior angiogram done 5 years previously (Figures 2a, 2b).

The decision was made that the ventricular arrhythmia could be related to myocardial ischemia related to the CTOs. Due to the findings of thinning and akinesis of the lateral wall, as well as the angiographic nature of the two CTOs, percutaneous coronary intervention (PCI) of the CTO of the RCA was planned, and the patient was transferred to our tertiary care center. The patient underwent successful PCI of the CTO. As all collaterals to the distal RCA were arising from the proximal RCA, a single 8F AL1 guide was used to cannulate the RCA. The proximal “cap” was found to be hard, impenetrable to our workhorse wire, with no evidence of microchannels based on probing with a tapered-tip, polymer-coated wire (Fielder XT, Abbott Vascular, Temecula, CA). The proximal cap was able...
to be penetrated using a Confianza Pro 12 (Abbott Vascular, Temecula, CA) with support of a FineCross (Terumo Medical Somerset, NJ) microcatheter. Once engaged in the occlusion, the Confianza Pro 12 was exchanged for a Pilot 200 (Abbott Vascular, Temecula, CA), which was able to be advanced into a medium-sized right ventricular marginal branch beyond the occlusion (Figure 2c). A small channel was made in the occlusion with an Apex 1.5 mm balloon (Boston Scientific, Natick, MA), after which the pilot wire was able to be moved into the main RCA channel. Angiography confirmed intraluminal placement (Figures 2d, 2e). The pilot wire was exchanged for a standard workhorse wire (Luge, Boston Scientific, Natick, MA), and further angioplasty was performed culminating in placement of a single $2.75 \times 28$ Promus element drug-eluting stent (Boston Scientific, Natick, MA), which was postdilated with a 3.0 mm noncompliant balloon (NC Apex, Boston Scientific, Natick, MA). Subsequent images revealed excellent results, with Thrombolysis in Myocardial Infarction grade 3 flow (Figure 2f). The patient received intravenous unfractionated heparin during the case, with a target activated clotting time of 250 to 300 seconds. He had been loaded with clopidogrel 600 mg a few hours prior to the procedure.

Subsequently, he had no further episodes of VT during his hospital stay. His intravenous amiodarone and lidocaine were discontinued approximately 12 hours after the procedure. Serial troponin I peaked at 3.35 ng/mL. An implantable cardioverter defibrillator (ICD) was placed the following day without complication. He was observed another 24 hours in the hospital, during which no further ventricular arrhythmia was seen, and no complications from either the PCI or ICD implantation.
were present. He was initially discharged on oral amiodarone, but this was stopped shortly after discharge due to concern for potential side effects.

At 9-month follow-up, the patient had no further chest pain or clinically apparent recurrent ischemia. ICD interrogation has shown brief nonsustained episodes of VT, but he has not required delivery of a shock.

DISCUSSION

CTOs can lead to a number of clinical sequelae. The most common scenario that prompts revascularization is the presence of stable, exertional angina pectoris. Many present with dyspnea and decreased exercise tolerance (often attributed to other causes including aging), and reports have documented a higher incidence of left ventricular dysfunction, ventricular arrhythmia, and cardiac death among patients with a CTO. Additionally, retrospective studies of treatment of CTOs have suggested improvements not just in anginal class, but in ventricular performance (1, 2), exercise tolerance (3), tolerance of future ischemic events (4), and even mortality (5–8). While the retrospective nature of these trials limits the conclusions, they nonetheless suggest that treatment of CTOs may benefit the patient beyond simply a reduction in angina.

Elegant studies have shown that virtually all CTOs are ischemic when tested by fractional flow reserve, regardless of the maturity of collateral channels (9, 10). Most are ischemic at rest, even in the absence of vasodilators and hyperemia. Furthermore, there is supportive evidence that a CTO not only produces ischemia in the zone supplied by the CTO, but may also provoke ischemia in the territory of donor collateral vessels (11).

Animal studies have shown that hibernating myocardium can be a focus of ventricular arrhythmia and sudden cardiac death, even in the absence of acute or prior myocardial infarction. Furthermore, even though adaptations may have occurred that allow for normal myocardial functioning, the potential for life-threatening arrhythmia still exists (12).

Prior studies have explored the link between CTOs and ventricular arrhythmia. Nombela-Franco et al studied 162 patients who had received an ICD to prevent sudden cardiac death (13). Among that group, 44% had at least one CTO. Over a 26-month period, appropriate device therapy was delivered to 18% of the patients. The presence of a CTO was found to be associated with higher rates of ventricular arrhythmia and death and was independently associated with appropriate ICD therapy (hazard ratio 3.5).
In conclusion, percutaneous treatment of CTOs may lead not only to relief of angina and dyspnea, but also to resolution of ventricular arrhythmia by minimizing underlying ischemia.


Appropriate sensing is essential for the normal functioning of an implantable cardioverter defibrillator (ICD). T-wave oversensing is a potential clinical problem in ICD patients that may result in inappropriate shocks. Oversensing may have various underlying causes and can be treated with noninvasive or invasive means. We present the case of a 45-year-old man presenting with shock storm as a result of T-wave oversensing. Workup revealed a hemodynamically significant stenosis of the left anterior descending artery treated with percutaneous coronary intervention and drug-eluting stent placement. This resulted in the resolution of T-wave oversensing and restoration of normal ICD functioning.

Myocardial ischemia–induced hyperacute T waves can potentially lead to T-wave oversensing in patients with implantable cardioverter defibrillators (ICD). This may result in the inadvertent delivery of ICD therapies. Our report highlights one such case and discusses differential diagnoses and appropriate treatment strategies.

CASE DESCRIPTION

A 45-year-old man with past coronary artery bypass grafting, ischemic cardiomyopathy, and biventricular ICD presented after experiencing multiple shocks from his ICD. His device (Medtronic Concerto C154DWK, Medtronic, Inc., Minneapolis, MN) was implanted for primary prevention. The patient reported that he was unloading a truck at work just prior to the ICD firing. The associated preceding symptoms were mild lightheadedness, dizziness, and left shoulder heaviness but no chest discomfort or dyspnea. Family history was significant for sudden cardiac death of his father at age 35. He was taken to a local hospital by emergency medical services, where the initial electrocardiogram (ECG) demonstrated sinus rhythm with T-wave inversions in the inferolateral leads and tall amplitude T waves in V1 to V3. He was subsequently transferred to our hospital for further care.

His initial vital signs and physical examination were unremarkable. Laboratory workup revealed a troponin-I level of 1 ng/mL (normal <0.03 ng/mL), creatinine kinase of 88 U/L (normal, 24–173 U/L), and creatinine kinase-MB of 2 ng/mL (normal, 0–6.4 ng/mL). All electrolytes, including potassium, glucose, and magnesium, were within normal limits. The initial 12-lead ECG at our hospital revealed normal sinus rhythm with intermittent biventricular-paced complexes and an increased T-wave amplitude of native QRS complexes (as compared to his prior baseline ECG demonstrating biventricular-paced rhythm) (Figure 1). Initial ICD interrogation revealed 35 episodes of T-wave oversensing (resulting in spurious detection of ventricular fibrillation zone), 9 attempts of overdrive pacing, and 6 episodes of 35J shocks (Figure 2). Shocks were not reproducible by any movement or physical maneuvers. Tachytherapies were turned off and ischemic evaluation was initiated. A transthoracic echocardiogram revealed a left ventricular ejection fraction of 40% with basal inferior and inferolateral akinesia. Positron emission tomography stress nuclear imaging demonstrated a reversible medium-sized anterior defect consistent with left anterior descending artery ischemia. Cardiac catheterization demonstrated mild left main narrowing, 60% to 70% diameter narrowing of the mid left anterior descending artery, and total occlusion of the left circumflex and right coronary arteries. Vein grafts and right internal mammary artery grafts to the diagonal and obtuse marginal arteries were patent. The vein graft to the posterior descending artery was occluded. The left internal mammary artery graft to the left anterior descending artery was atretic and nonfunctional. Fractional flow reserve of the left anterior descending artery revealed a hemodynamically significant stenosis at 0.70. This was treated with a percutaneous coronary intervention and drug-eluting stent placement. The patient tolerated the procedure well.

At a predischarge exercise treadmill stress test, the patient achieved 9 metabolic equivalents without chest pain or ischemic ECG changes. His ECG after coronary intervention showed normal biventricular paced rhythm with a relative decrease in the T-wave amplitude (Figure 3). ICD tachytherapies were turned on. As an additional safety measure to avoid T-wave oversensing, R-wave sensitivity was decreased from 0.3 to 0.6 mV and the ventricular blanking period after ventricular pacing was reprogrammed to 210 ms. The patient followed up in the
ICD clinic at 1, 3, and 6 months and was found to have no further inappropriate tachytherapies.

DISCUSSION
Appropriate sensing is indispensable for proper functioning of the ICD. T-wave oversensing is a common clinical problem, with a reported prevalence as high as 14% (1). It may lead to QRS double-counting and inappropriate tachytherapy. Our patient likely experienced ischemia-induced hyperacute T waves resulting in oversensing by a biventricular ICD. This led to the loss of the essential biventricular pacing and resulted in inappropriate ICD shocks. Other causes of T-wave oversensing were appropriately excluded by a comprehensive workup. Ischemic evaluation revealed hemodynamically significant stenosis of the left anterior descending artery, and percutaneous coronary intervention resulted in resolution of the underlying problem.

Ventricular oversensing is more likely to occur in integrated than in dedicated bipolar leads. Possible causes for T-wave oversensing include either diminution of R-wave amplitude or relative and/or dynamic gain in the T-wave amplitude. Other etiologies of T-wave oversensing may include changes in QT duration (long and short QT syndromes), electrolyte imbalances such as hyperkalemia and hyperglycemia, histamine-2 receptor blockers, low amplitude R waves, exercise, Brugada syndrome, changes in sympathetic tone, an injury current-related increase in the T-wave voltage, alterations in morphology of the intracardiac electrogram, and hyperacute T-wave changes observed during device implantation (2–5).

Over-sensing is typically treated by correcting the underlying problem whenever possible. Correcting any underlying electrolyte abnormalities such as hyperkalemia is usually the first recommended step. Other noninvasive treatment strategies include reprogramming the ICD for lower R-wave sensitivities (provided

Figure 1. (a) Initial 12-lead electrocardiogram at our hospital revealed a normal sinus rhythm with intermittent biventricular-paced complexes. The T-wave amplitude of the QRS complexes (especially the native QRS complexes) was quite high compared with his previous baseline ECG in part (b).
Figure 2. Initial interrogation of the implantable cardioverter defibrillator revealed T-wave oversensing resulting in spurious detection of ventricular fibrillation and spurious shocks.
the R wave is of adequate amplitude), prolonging the postpacing refractory period, increasing the lower-tracking rate limit of the tachycardia detection zone, and administering beta-blockers to slow the heart rate. Some cases may require invasive strategies, which include either repositioning or replacing the ventricular lead or the pulse generator (6). Different algorithms have also been proposed to decrease T-wave oversensing, including the ECG width criterion, threefold programmable parameters with a postsense refractory period, decay delay, linear decay, and the automatic sensitivity control with enhanced T-wave suppression (7).


Figure 3. The electrocardiogram after percutaneous coronary intervention shows a normal biventricular paced rhythm with a relative decrease in the T-wave amplitude. This ECG appears comparable to his prior baseline electrocardiogram illustrated in Figure 1b.
We report a patient with hypoxia secondary to a right-to-left shunt through a patent foramen ovale, following aortic root, valve, and arch replacement due to an aortic dissection in the setting of the Marfan syndrome. Following the operation, he failed extubation twice due to hypoxia. An extensive workup revealed a right-to-left shunt previously not seen. The patent foramen ovale was closed using a percutaneous closure device. Following closure, our patient was extubated without difficulty and has done well postoperatively.

Approximately 25% of the general population is estimated to have a patent foramen ovale (PFO). These small atrial septal defects, present from birth, are usually asymptomatic and found incidentally by echocardiogram or at autopsy (1). We describe the benefit of closure of a PFO for postoperative hypoxia.

**CASE DESCRIPTION**

A 23-year-old Hispanic man with the Marfan syndrome presented with acute chest pain that radiated to his back. The diagnosis of a dilated aortic root and a type B aortic dissection was made quickly by computed tomography scan with contrast. He underwent surgical repair using a two-staged “elephant trunk” procedure. The initial stage of the procedure consists of an aortic valve, root, and arch replacement, including leaving an elephant trunk portion of the graft that hangs down into the descending aorta. Finally the descending thoracic aorta is wrapped at that level of the diaphragm. The second stage of the procedure uses a stent graft, via an endovascular approach, to connect the elephant trunk with the wrapped portion of the aorta. Following the first stage, his postoperative course was complicated by recurrent hypoxia. He underwent two attempted extubations on postoperative days 1 and 7, but the hypoxia persisted. A PFO with a significant right-to-left shunt was found on transesophageal echocardiogram with bubble study (Figure 1).

On postoperative day 9, a percutaneous closure procedure was performed via the right femoral vein. A #25 Amplatzer Cribriform Septal Occluder (AGA Medical Corp., Plymouth, MN) was deployed in the PFO, and placement was confirmed with intracardiac echocardiography and fluoroscopy (Figure 2). A negative echocardiographic bubble study at the conclusion of the procedure confirmed resolution of the right-to-left shunt. On day 10, extubation was successful and normal oxygen saturation was maintained. The patient was discharged from the hospital on postoperative day 22. Five weeks later, he underwent stage 2 of the “elephant trunk” procedure without postoperative respiratory complications. He continues to do well 5 months following the second stage of the procedure.

**DISCUSSION**

Despite the severity of potential consequences of a PFO, hypothesized benefits of closing PFOs, specifically for migraine headaches and strokes, have not resulted in clinical benefit over standard medical management. Three large randomized controlled trials, RESPECT (2), CLOSURE I (3), and PC Trial (4), failed to show a benefit of PFO closure over medical management for the prevention of recurrent paradoxical embolism. The RESPECT trial did, however, demonstrate increased safety and

Usefulness of percutaneous closure of patent foramen ovale for hypoxia

Alyssa G. Munkres, MPH, Timothy N. Ball, MD, Themistokles Chamogeorgakis, MD, Kenneth A. Ausloos, MD, Shelley A. Hall, MD, and James W. Choi, MD

Figure 1. Transesophageal echocardiogram with bubble study, showing right-to-left shunt through a patent foramen ovale. RA indicates right atrium, LA, left atrium; PFO, patent foramen ovale.
efficacy of the Amplatzer PFO Occluder device over the previously used STARFlex Septal Closure System (2, 4). While there is ample evidence through observational studies for the efficacy of PFO closure in prevention of recurrent embolic strokes, no studies have been able to provide evidence for significant benefit over standard anticoagulation. With respect to the treatment of migraines, retrospective studies have shown a significant decrease in severity and frequency with closure of the PFOs (5). Unfortunately, the MIST trial revealed increased morbidity associated with PFO closure for patients with migraine headaches (6).

There is a growing body of evidence for examining the role of PFOs in hypoxia. Classically, patients present with platypnea-orthodeoxia syndrome, positional hypoxia associated with the sensation of difficulty breathing, relieved in a recumbent position. Additionally, there are rare reports of acquired right-to-left shunts following cardiac or pulmonary surgery, detailed in Table 1 (7–22). Hypoxia secondary to PFO is believed to develop from an abnormal anatomic relation between the vena cava and the atrial septum, which directs venous blood flow from the inferior vena cava toward the atrial septum. The change in direction of blood flow can occur with positional changes or following a cardiopulmonary insult or operation, which distort the mediastinum and stretch the atrial septum (23). Acquired shunts have also been described secondary to a dilated aortic root that alters the atrial septum resulting in a shunt (24). As was the case with our patient, closure of the PFO in patients with hypoxia secondary to a right-to-left interatrial shunt has been shown to significantly reduce hypoxemia and associated symptoms.

Although research on the effects of PFO closure for the treatment of hypoxia has been promising, it has been limited to small reports, predominantly case studies. Notably, in all of the cases detailed in Table 1, hypoxia improved immediately following PFO closure. Similarly, the case studies of patients with platypnea–orthodeoxia syndrome undergoing PFO closure report a significant postprocedural increase in blood oxygen saturation and excellent long-term outcomes (23, 25).

### Table 1. Previously published cases discussing closure of patent foramen ovale for hypoxia

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<tr>
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<td>Brugts (22)</td>
<td>Percutaneous—Amplatzer</td>
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*Temporarily.


Mitral stenosis and acute ST elevation myocardial infarction

Joseph Cardoz, MD, DM, K. Jayaprakash, MD, DM, and Raju George, MD, DM

We describe a patient who presented with acute (inferior wall) ST elevation myocardial infarction. Her echocardiogram showed severe mitral stenosis with ball valve thrombus in the left atrial body and thrombus in the left atrial appendage. Coronary angiogram revealed thromboembolic material in the right coronary artery. Mitral valve replacement was scheduled.

Coronary embolization is an infrequent cause of myocardial infarction. We describe a woman with severe rheumatic mitral stenosis who presented initially as acute (inferior wall) ST elevation myocardial infarction (STEMI) due to embolism of thrombus in the left atrium.

CASE DESCRIPTION

A 47-year-old woman presented with progressive exertional and nocturnal dyspnea of 1 year duration. She was hospitalized following a prolonged episode of retrosternal crushing pain of sudden onset on the day of admission. Examination revealed an irregularly irregular pulse at a rate of 120 beats per minute, a blood pressure of 100/70 mm Hg, respiratory rate of 14 breaths per minute, and a temperature of 36.7°C. Precordial examination revealed a tapping apical impulse, loud first heart sound and pulmonary component of second heart sound, opening snap, and a long mid-diastolic rumble over the apex. Other systems were normal.

Baseline laboratory reports were normal. An electrocardiogram showed atrial fibrillation with a fast ventricular rate and about 2 mm ST segment elevation in leads II, III, and aVF (Figure 1). A chest radiograph showed cardiomegaly with radiological signs of pulmonary arterial and venous hypertension and biatrial enlargement (Figure 2). A transthoracic echocardiogram showed severe mitral stenosis with a mitral valve area of 0.9 cm² and a ball valve thrombus of 2.1 cm moving freely within the left atrium and intermittently occluding the mitral valve orifice (Figures 3 and 4). The calculated pulmonary artery systolic pressure was 70 mm Hg. A transesophageal echocardiogram showed the left atrial appendage to be filled with thrombus (Figure 4d). Coronary angiogram showed thrombolysis in myocardial infarction (TIMI) grade 4 thrombus in the mid right coronary artery, with preserved antegrade flow (Figure 5). There were no atherosclerotic plaques or stenotic lesions in either the left or the right coronary systems.

The patient was treated conservatively with intravenous unfractionated heparin, aspirin, clopidogrel, digoxin, furosemide, and spironolactone. With the treatment, the patient experienced symptomatic relief and hemodynamic stability, and she was referred for mitral valve replacement.

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**DISCUSSION**

This case demonstrates a rare and atypical presentation of acute STEMI due to coronary artery embolism in a patient with mitral stenosis. Since the first postmortem description of coronary embolism was published by Virchow in 1856, several such cases have been reported in clinical and postmortem studies. Coronary embolism appears to be the most reasonable explanation for acute myocardial infarction with angiographically normal coronary arteries (1). Wenger and Bauer (2) found 11 cases of coronary artery embolism in 17,469 consecutive autopsy cases at Mount Sinai Hospital, New York, with a general necropsy incidence of 0.06%.

Mitral stenosis is a well-known cause of systemic and pulmonary embolism, and the presence of atrial fibrillation enhances this risk. Scant data are available on the incidence of coronary embolism in patients with mitral stenosis with or without associated atrial fibrillation. Mitral stenosis presenting for the first time as acute STEMI is rare. In the study by Prizel et al (3), coronary artery embolic infarcts comprised 13% of the autopsy-studied infarcts. Underlying diseases predisposing to coronary emboli included valvular heart disease (40%), cardiomyopathy (29%), coronary atherosclerosis (16%), and chronic atrial fibrillation.

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**Figure 2.** Chest radiograph in the posteroanterior view showing several radiological features of mitral stenosis: (1) cephalization ("upturned moustache" sign or Antler sign), (2) widened carinal angle, (3) dilated right descending pulmonary artery, (4) enlarged left atrial appendage with "straightening" of the left heart border, (5) dilated left atrium with a "shadow through shadow," or "double density" appearance, and (6) Kerley B line due to interstitial pulmonary edema.

**Figure 3.**

(a) Transthoracic echocardiogram parasternal long-axis view showing mitral stenosis with a thickened posterior mitral leaflet and the "hockey stick" or "elbow" sign of the anterior mitral leaflet (red arrow). (b) Parasternal short-axis view at the mitral valve level showing the characteristic "fish-mouth" appearance with a mitral valve area of 0.9 cm². (c) Doppler interrogation of the mitral valve showing the elevated mean and peak transmitral gradients and the pressure half-time. (See also supplementary videos.)
Figure 4. (a, b, and c) Transthoracic echocardiogram apical four-chamber view showing the ball valve thrombus moving freely within the left atrium, intermittently obstructing the mitral valve (red arrows). (d) Transesophageal echocardiogram showing the left atrial appendage filled with clot. (See also supplementary videos.)

Figure 5. Coronary angiogram showing thrombus (arrows) in the (a) mid right coronary artery and (b) normal left coronary artery.

(24%). Mural thrombi were present in 18 (33%).


SUPPLEMENTARY MATERIAL

Three videos are available online. Video 1 (available at http://www.baylorhealth.edu/Documents/BUMC%20Proceedings/2015%20Vol%2028/No_2/28_2_Jayaprakash_Vid1.mp4) is a parasternal long-axis view showing the dilated left atrium and the restricted mobility of the anterior and posterior mitral leaflet with severe mitral stenosis. Video 2 (available at http://www.baylorhealth.edu/Documents/BUMC%20Proceedings/2015%20Vol%2028/No_2/28_2_Jayaprakash_Vid2.mp4) is a parasternal short-axis view showing the “fish-mouth” mitral valve orifice. Video 3 (available at http://www.baylorhealth.edu/Documents/BUMC%20Proceedings/2015%20Vol%2028/No_2/28_2_Jayaprakash_Vid3.mp4) is an apical four-chamber view showing the ball valve thrombus in the dilated left atrium.
Persistent sciatic artery is a rare developmental anomaly. In its complete form, it provides the major arterial supply to the lower leg since the femoral system is hypoplastic. These unique arteries are prone to aneurysm formation and most commonly present with complications related to aneurysm formation, which can lead to limb loss. We encountered a 68-year-old man presenting with bilateral lower-extremity ischemia who was found to have bilateral persistent sciatic artery aneurysms. One aneurysm had already thrombosed, but the other was still patent. We treated this patient with a hybrid open and endovascular repair on the patent side. The aneurysm was excluded with an Amplatzer™ plug (St. Jude Medical, Inc., St. Paul, MN) followed by a femoropopliteal bypass with saphenous vein in situ to revascularize the lower leg. To our knowledge, this is only the second report of a persistent sciatic artery aneurysm successfully treated with Amplatzer plug occlusion.

The sciatic artery is an embryonic continuation of the internal iliac artery that provides the axial blood supply to the lower extremity. In approximately 0.025% to 0.04% of the population, the sciatic artery does not regress in utero and persists to be the major arterial supply to the lower extremity (1). A persistent sciatic artery (PSA) was first described in 1832 (2), and the first death caused by a ruptured sciatic artery aneurysm was reported in 1864 (3). These aberrant arteries are associated with a predisposition for aneurysm formation. Aside from the risk of rupture, sciatic artery aneurysms pose a risk of distal embolization and subsequent limb loss (4). We report a case of acute limb ischemia due to thromboembolism from a sciatic artery aneurysm treated with a combination of open and endovascular techniques. This is the second known reported case of the use of an Amplatzer™ vascular plug (St. Jude Medical, Inc., St. Paul, MN) to exclude a PSA aneurysm.

CASE REPORT

A 68-year-old man presented to the emergency department after experiencing acute onset of bilateral lower-extremity pain while playing golf, with more severe pain in the left leg. He was otherwise healthy and had no prior history of claudication. On examination, he had palpable bilateral femoral and left popliteal pulses. The right popliteal pulse and the bilateral dorsalis pedis and posterior tibial pulses were present by Doppler only. A computed tomographic arteriogram (CTA) demonstrated bilateral PSA aneurysms (Figure 1). The left sciatic artery aneurysm measured 4.5 × 4.0 cm and contained thrombus, but the lumen was patent. The right sciatic aneurysm measured 5.4 × 2.5 cm and was completely occluded by thrombus. The superficial groin pulses were palpable. There was no thrill or bruit. The left calf was cool to touch with blanched on compression. The right calf was warm.

Figure 1. Coronal reconstructed contrast-enhanced CT angiogram demonstrating bilateral persistent sciatic arteries. Note the left persistent sciatic artery (PSA), which begins as a continuation of the internal iliac artery and proceeds caudally exiting the pelvis to course inferiorly into the thigh. The patent PSA aneurysm on the left is marked by the arrow. The sciatic artery aneurysm on the right is thrombosed, and while it is not demonstrated on this reconstructed image, it is easily identified on the original axial CT slices (not shown). Both superficial femoral arteries are hypoplastic, and the PSA supplies both popliteal arteries.

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femoral artery (SFA) was present but incomplete bilaterally, and the popliteal arteries were supplied by the PSAs. The patient was started on a heparin infusion for the presumed thromboembolic event that caused the left leg pain. The leg pain resolved overnight. Ankle brachial indices were 0.84 on the right and 0.89 on the left. Retrograde embolization of his left PSA aneurysm was performed through exposure of the above-knee popliteal artery, which was then accessed with a 45-cm 7 French sheath. The PSA aneurysm was then easily accessed and an angiogram was performed to determine the extent of the aneurysm. A 14-mm Amplatzer plug was placed proximal to the aneurysm, and a 12-mm Amplatzer plug was placed distal to the aneurysm. Platinum and stainless steel coils (Cook Medical, Bloomington, IN) were also placed within the aneurysmal sac (Figures 2a, 2b, 3a). Distal perfusion was then reestablished by femoropopliteal bypass using reversed great saphenous vein. The right-sided aneurysm was not treated, as it was already thrombosed and the patient was no longer symptomatic. The patient did well and was discharged home with palpable pedal pulses on the left. At 6-month follow-up, he continued to be asymptomatic, and thrombosis of the PSA aneurysm was documented on repeat CTA (Figure 3b).

DISCUSSION
In the human embryo, the sciatic artery provides in-line flow to the lower limb buds via the internal iliac artery. The sciatic artery normally involutes by the third month as the femoral artery develops. Remnants of the sciatic artery persist as parts of the internal iliac artery and portions of the popliteal and peroneal arteries (5). Rarely, the sciatic artery persists as the dominant infl ow vessel to the lower extremity. PSAs can be classified as “complete” or “incomplete.” In the complete type (75% of PSAs), the SFA is hypoplastic and the sciatic artery maintains its caliber to provide the major infl ow to the thigh and the popliteal artery (5). In the incomplete type (25% of PSAs), the SFA is still the major infl ow vessel, and the sciatic artery becomes hypoplastic in the thigh (6).

PSAs are usually detected after a vascular complication or incidentally after imaging for another indication. Aneurysm formation occurs in up to 46% of cases (6). Repetitive minor trauma with sitting is thought to contribute to aneurysm formation due to immature elastic properties, but the exact mechanism is unclear (4). Limb ischemia is the most likely complication of PSA and is usually secondary to distal embolization. Buttock pain or a painful pulsatile mass in the buttocks may suggest a sciatic artery aneurysm, and a rapidly expanding mass may be indicative of aneurysm rupture (7). Duplex ultrasound can be useful in confirming a suspected case of a PSA aneurysm if used to investigate a pulsatile gluteal mass. Magnetic resonance angiography, CTA, or arteriography is more helpful in diagnosing the PSA as well as in identifying whether the PSA is complete or incomplete (8).
Treatment generally requires exclusion of the aneurysm and revascularization if the PSA is the dominant inflow vessel to the lower leg (9). Historically, this was done surgically, but currently an endovascular or hybrid approach is used. In addition to being less invasive than open ligation, endovascular embolization is recommended to decrease the risk of sciatic nerve injury. In the incomplete type of PSA, aneurysm exclusion is sufficient (9). Numerous endovascular exclusion approaches have been described in the literature, including femoral, translumpectomy, and open retrograde popliteal access (10–13). In the complete type of PSA, limb revascularization is mandatory, as the blood supply to the lower limb will be entirely dependent on the sciatic artery. Revascularization requires a femoral distal bypass (13). Endovascular approaches to excluding the aneurysm sac with covered stent grafts have been described in the literature; however, the durability of such repairs is yet to be determined and may be a problem in the long term because the stent graft will be in an area that undergoes repetitive trauma with walking and sitting (11, 12). Endovascular treatment of the aneurysm should probably be reserved for patients with prohibitively high operative risk or limited survival.

Multiple cases of therapeutic embolization of PSA aneurysms have been reported, with most using intravascular coils. Amplatzer plugs are self-expanding nitinol mesh devices that are easily delivered with great precision and are capable of occluding large-diameter vessels. They come in a variety of sizes, ranging from 4 mm to 22 mm, and are delivered through sheaths ranging from 4 to 7 French. There are several advantages to using vascular plugs for vessel occlusion. Amplatzer plugs can be deployed more precisely than endovascular coils, which can be difficult to place accurately and can embolize distally. This makes coil embolization challenging in larger-caliber vessels such as PSAs (14). In our previous experience with a similar case of PSA aneurysm, our previous experience with a similar case of PSA aneurysm, combined percutaneous endovascular aneurysm repair and review of the literature (15). At our institution, the larger coils each cost approximately $200, whereas the Amplatzer plugs cost about $800 individually. The break-even point between these two options is exceeded after eight coils have been placed. This estimate does not include the additional 15 to 30 minutes of operating time required for coil embolization. In our case, we did use adjunctive coils. However, in retrospect, this was unnecessary, and in the previously reported case, only two plugs were necessary (16). Another potential benefit of Amplatzer plugs is less scatter on follow-up CT scans, which better renders the follow-up imaging.

**Acknowledgment**

The authors wish to thank Kelli R. Trungale, MLS, ELS, for editorial assistance.


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**Figure 4.** Conventional radiograph of the pelvic region showing endovascular coils within the persistent sciatic artery aneurysm (circle) and distally migrated coils (arrow).
Immune thrombocytopenia associated with consumption of tonic water

F. David Winter Jr., MD, MSc

Thrombocytopenic purpura can develop from an induced antibody response that destroys platelets. Megakaryocyte production may also play a role. Although the inciting antigen is usually not identified, it is important to consider medications. This article presents the case of a man who developed sudden onset of severe thrombocytopenia associated with the ingestion of quinine-containing tonic water.

If any of these few notes on the effects of quinine prove of any use to the profession, or add one drop to the ocean of science, the purpose of the writer will be fully answered. —W. H. Vipan, 1865 (1)

Immune thrombocytopenia can be life threatening with severe complications when platelet counts fall below 25,000/uL. Treatment is directed at suppressing or eliminating the antibody response that destroys the platelets and/or the stimulus that impacts the production of platelets by megakaryocytes. Medications have been implicated in the aberrant antibody response and, in those cases, their identification is important in treatment and prevention of future episodes. The patient discussed herein developed a sudden and dramatic decline in peripheral platelet counts, possibly related to the consumption of tonic water.

CASE PRESENTATION

A 70-year-old man presented with a 2-day history of nosebleeds, mucosal bleeding, painful bruising of his tongue, and diffuse ecchymoses over his arms, legs, and trunk (Figure 1). The previous week he had been seen for a routine checkup. At the time, he felt well, had a platelet count of 151,000/uL, a hemoglobin of 14.1 g/dL, a hematocrit of 42.3%, and no bleeding manifestations. In only 3 days, he developed diffuse bleeding, and his platelet count had dropped to 1000/uL. He was admitted to the hospital. During the 2 days prior to presentation, he had been celebrating with a friend, drinking beverages containing tonic water.

His estimated consumption of the tonic water alone was up to 80 ounces over 2 days. He had indulged in tonic water beverages previously and on a regular basis, though in more moderate quantities. He had a previous history of atrial fibrillation, hypertension, and hyperlipidemia. At age 67, he had replacement of his stenotic aortic valve by a bioprosthesis. There had been no antecedent infectious illnesses. He had stopped warfarin before admission due to the bleeding. Other medications included pravastatin, carvedilol, digoxin, quinapril, vitamin D, montelukast, and fluticasone.

On examination, the patient had diffuse bleeding into his buccal mucosa and posterior pharynx. His tongue was swollen, tender, and bruised. Petechiae and ecchymoses were present over his arms, legs, and trunk. The nasal mucosa was ecchymotic, with dried dark blood. The feces were melanotic and the fecal immunochemical test was positive. Laboratory results are shown in the Table. A peripheral blood smear demonstrated only sparse platelets (Figure 2), and bone marrow biopsy showed megakaryocytes, which were predominantly mature with focally increased cellularity (Figure 3). Flow cytometry showed no evidence of hematopoietic neoplasia, lymphoproliferative disease, or plasma cell dyscrasia.

The patient was treated with dexamethasone 40 mg daily for 4 days. His platelet count promptly rose. His bleeding resolved and ecchymoses subsided by the fourth day of admission. He was discharged. His platelet count at discharge was 67,000/uL and was back in the normal range shortly thereafter. He has since resumed his previous medications, avoided tonic water, and has had no further episodes of thrombocytopenia.

DISCUSSION

Immune thrombocytopenia is defined as a platelet count of <100,000/uL with no evidence of leukopenia or anemia. The condition has been referred to as “idiopathic” but is more frequently called “immune” thrombocytopenic purpura (ITP), even though aspects of the pathogenesis are not always understood. Primary ITP is defined as cases with no clear underlying causation. Secondary ITP is the label affixed when a medication, infection, or other condition accounts for the abnormal
antibody response (2). Various secondary causes of immune thrombocytopenia are listed in Table 2.

A positive test for antibodies would have made for a more convincing diagnosis, although it is known that the absence of such results cannot rule out a diagnosis of drug-induced immune thrombocytopenia (3). There had been a several-week delay in testing for these antibodies, which could have been a factor in the negative report. In addition, problems exist with standardization of testing. Antiplatelet antibodies are known to have low sensitivity and low specificity (4). The ability of laboratories to correctly identify the antibodies has been estimated to be in the range of 20% to 97% (5).

The low haptoglobin level in this patient suggests the possibility of hemolysis, although no significant schistocytes were seen on the peripheral blood smear (Figure 2). The drop in hemoglobin was likely due to gastrointestinal blood loss implied by the positive fecal immunochromatographic test. Hemolytic uremic syndrome has been reported with quinine ingestion (6), although the absence of proteinuria, normal creatinine, and convincing hemolysis makes this diagnosis unlikely.

Thrombocytopenia, when it occurs due to quinine antibodies, is caused by a sensitization to quinine from prior exposure. Upon reexposure, antibodies develop to the drug or to metabolites of the drug. Importantly, and in contrast to primary ITC, platelet levels usually return to normal promptly when quinine is withdrawn. Primary “idiopathic” thrombocytopenia also behaves differently, with a slower onset (7). The rapid onslaught of severe thrombocytopenia in this case favors an antibody response to a medication or substance for which there had been prior sensitization. The patient’s prompt rise in platelet counts and normal platelet counts since initial treatment also favor secondary ITP.

Purpura was first linked with quinine in a report on four patients in 1865 (1). Most cases today are idiopathic, but increasingly medications have been found to play a role. Quinine is reported to be one of the most frequent causes of drug-induced thrombocytopenia. It is thought to be able to bind to platelet membranes and then stimulate IgG antibodies. The antibodies result in destruction of platelets only when the drug is present, and they go away in the absence of the drug. As mentioned above, antibodies to nondrug metabolites can also result in thrombocytopenia and should be included in testing (8). Megakaryocytes may also bind with IgG in the presence of quinine, resulting in apoptosis, a decrease in cell viability and an increase in cell death of the precursor cells (9).

Quinine sulfate is derived from the bark of the Cinchona tree and has been used for centuries as a prophylaxis and treatment for the malaria parasite. Quinine is dissolved in carbonated water to produce tonic water. Sweeteners such as high-fructose corn syrup are often added in contemporary preparations. The taste of tonic water was originally quite bitter, but was more easily tolerated when mixed with gin. A daily “gin ration” was prescribed for the officers of the British East India Company in the 1700s. Winston Churchill, a fan of the gin and tonic drink, once proclaimed, “The gin and tonic has saved more Englishmen’s lives, and minds, than all the doctors in the Empire” (10).

Other drugs were subsequently found to be more effective for malaria, but quinine has remained popular as a treatment for nocturnal leg cramps. At least one study has

Figure 1. (a) Bruising of the patient’s tongue. (b) Ecchymoses and petechiae of lower leg. (c) Ecchymoses and petechiae of upper arm.
Table 1. Laboratory results

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<tr>
<td>Quinine-associated IgM (nondrug)</td>
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demonstrated its effectiveness (11). Others have cautioned its use for such purposes (12). All over-the-counter products containing quinine sulfate were banned by the US Food and Drug Administration on December 12, 2006. The ban included the announcement of “665 reports of adverse events with serious outcomes associated with quinine use, including 93 deaths” (13). A prescription preparation, Qualaquin, remains available in a 324 mg tablet. However, the Food and Drug Administration warned about its use for leg cramps in 2010, stating, “Qualaquin should not be used for night time leg cramps. Qualaquin use may result in serious and life-threatening hematological reactions” (14). With the absence of nonprescription quinine preparations and the strong caution to physicians about prescription Qualaquin, many have resorted to quinine-containing tonic water to ease troublesome leg cramps. This case suggests that tonic water to treat leg cramps, or for celebration, should be used in moderate doses, if at all.

Figure 2. Peripheral blood smear demonstrating a paucity of platelets.

Figure 3. Bone marrow aspirate demonstrating abundant megakaryocytes with a focal increase in cellularity.
Table 2. Causes of thrombocytopenia*

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</table>

*From reference 4, unless otherwise indicated.

Paraneoplastic cerebellar ataxia, also known as paraneoplastic cerebellar degeneration, is one of the wide array of paraneoplastic neurological syndromes in which neurological symptoms are indirectly caused by an underlying malignancy, most commonly gynecological, breast, or lung cancer or Hodgkin’s lymphoma. We describe a patient with severe cerebellar dysfunction attributed to a paraneoplastic neurological syndrome. The case highlights the need to look for paraneoplastic syndromes—both to discover malignancies early, at a treatable stage, and, as in our case, to address very distressing symptoms for the patient’s relief even if the malignancy is not curable.

The neurologic manifestations seen in cancer patients are mostly the consequence of direct tumor invasion of the nervous system or metastases. Other common causes of neurologic symptoms include neurotoxicity from cancer treatment, infections, and vascular or metabolic disorders. In less than 1% of cancer patients, an autoimmune response develops that targets normal neural tissues, which is termed paraneoplastic neurologic syndrome (PNS) (1, 2). Autoimmune neuronal degradation is believed to occur when systemic malignancies express proteins, called onconeural antigens, that are made only in neurons (3). Although no studies to date have conclusively proven that paraneoplastic antibodies are pathogenic, they are still useful markers of autoimmunity that categorize the PNS subtypes (1). We present a case of paraneoplastic cerebellar ataxia (PCA) associated with anti-Yo antibody (anti-Purkinje cell antibody) due to an underlying gynecologic malignancy.

**CASE DESCRIPTION**

A 67-year-old white woman presented with a 3-day history of headache, severe imbalance, nausea, and binocular double vision limiting her mobility. Two weeks earlier, she had been diagnosed with a left 4 cm adnexal mass following a 6-week history of pelvic pain. She was known to have hypertension, coronary artery disease, aortic stenosis (mild), left ear cholesteatoma, and mastoiditis. Neurological examination revealed intact language and cognition, significant bilateral diplopia and nystagmus worse to the right, bilateral dysmetria worse on the left, and broad-based gait ataxia. No focal weakness or change in muscle tone was noted. Deep tendon reflexes were brisk at all sites, and the plantar reflexes were downgoing on the right and upgoing on the left. Routine laboratory work was unremarkable. A biopsy of the recently discovered pelvic mass disclosed a poorly differentiated adenocarcinoma of Mullerian origin. A computed tomography (CT) scan of the chest, abdomen, and pelvis revealed mediastinal lymphadenopathy.

The patient was started on chemotherapy with carboplatin and paclitaxel. A serum paraneoplastic panel was positive for anti-Yo antibody with a high titer (Table 1). Cerebrospinal fluid (CSF) examination showed lymphocytic pleocytosis, high protein, and positive anti-Yo antibodies. Magnetic resonance imaging (MRI) of the head on admission showed no evidence of metastatic disease. MRI done 10 days after admission, however, showed enhancement along the bilateral cerebellar sulci. A diagnosis of anti-Yo–associated PCA was made, and the patient was started on high-dose methylprednisolone.

**Table 1. Laboratory blood work**

<table>
<thead>
<tr>
<th>Result</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraneoplastic antibodies panel: positive results</td>
<td>Purkinje cell cytoplasmic antibody, type 1: 1:61,440</td>
</tr>
<tr>
<td>Paraneoplastic antibodies panel: negative results</td>
<td>ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-2, PCA-Tr, amphiphysin antibody, CRMP-5, striational antibodies, P/Q-type calcium channel antibody, ACHRAb, ganglionic AChR autoantibody, VGKC, NMDA-R Ab</td>
</tr>
<tr>
<td>Other pertinent positive results</td>
<td>EBV IgG</td>
</tr>
<tr>
<td>Other pertinent negative results</td>
<td>Serum Lyme, syphilis, CMV IgM, EBV IgM, HSV-1 PCR, HSV-2 PCR, fungal cultures, bacterial cultures</td>
</tr>
</tbody>
</table>

AchRAb indicates anti-acetylcholine receptor antibody; AGNA, anti-glial/neuronal nuclear antibody; ANNA, anti-neuronal nuclear antibody; CMV, cytomegalovirus; CRMP, collapsin response mediator protein; EBV, Epstein-Barr virus; HSV, herpes simplex virus; Ig, immunoglobulin; NMDA-R Ab, anti-N-methyl D-aspartate receptor antibody; PCA, Purkinje cell cytoplasmic antibody; VGKC, voltage-gated potassium channel.
and intravenous immunoglobulin (IVIG) at 2 g/kg given over a period of 3 days along with her chemotherapy drugs. Her headache resolved, and her diplopia and dysmetria were slightly improved. The patient was transferred to a rehabilitation facility for continuation of palliative chemotherapy.

**DISCUSSION**

PNS are rare neurological syndromes that are not the consequence of direct invasion, metastasis, or side effects of cancer treatment (2). PNS can affect any level of the nervous system (Table 3). They can affect a single site, as in Lambert-Eaton myasthenic syndrome, a single cell type, as in PCA, or multiple areas, as in paraneoplastic encephalomyelitis. The association of many PNS with specific antibodies that recognize onconeural antigens suggests that PNS may be due to an initial autoimmune response against the tumor (1). However, one antibody can be associated with different neurological syndromes, and one syndrome can present with different antibodies as well (1). The antibodies are specific for the malignancy rather than being specific for a neurological syndrome (2).

<table>
<thead>
<tr>
<th>Table 2. Cerebrospinal fluid examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis 1</td>
</tr>
<tr>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Protein (mg/dL) 59</td>
</tr>
<tr>
<td>Glucose (mg/dL) 44</td>
</tr>
<tr>
<td>White blood cell (cells/μL): lymphocytes, neutrophils, monocytes: 41 (86%, 3%, 11%)</td>
</tr>
<tr>
<td>Red blood cell (cells/μL) 0</td>
</tr>
<tr>
<td>Gram stain and cultures negative</td>
</tr>
<tr>
<td>IgG synthesis, cryptococcal Ag, Histoplasma Ag negative</td>
</tr>
<tr>
<td>Cytology for malignant cells negative</td>
</tr>
<tr>
<td>Venereal Disease Research Laboratory</td>
</tr>
<tr>
<td>Paraneoplastic antibodies</td>
</tr>
</tbody>
</table>

IgG indicates immunoglobulin G; PCA-1, Purkinje cell cytoplasmic antibody type 1.

<table>
<thead>
<tr>
<th>Table 3. Paraneoplastic neurologic syndromes and their associated antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndrome</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Lambert-Eaton myasthenic syndrome</td>
</tr>
<tr>
<td>Subacute cerebellar ataxia</td>
</tr>
<tr>
<td>Opsomyoclonus</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
</tr>
<tr>
<td>Limbic encephalitis</td>
</tr>
<tr>
<td>Encephalomyelitis</td>
</tr>
<tr>
<td>Retinopathy (cancer-associated, melanoma-associated, uveitis, optic neuropathy)</td>
</tr>
<tr>
<td>Stiff person syndrome</td>
</tr>
<tr>
<td>Chronic gastrointestinal pseudo-obstruction</td>
</tr>
</tbody>
</table>

Modified with permission from Honnorat J and Cartalat-Carel S, 2004 (1). Ab indicates antibodies; CNS, central nervous system; SCLC, small cell lung cancer; Tr-Ab, thyroid-stimulating hormone receptor antibody; VGCC-Ab, anti-voltage-gated calcium channel antibody.
One of the most common PNS is PCA (4). PCA results in rapid (less than 12 weeks) development of severe pancerellar dysfunction (1, 2). Since it can precede the presentation of neoplasms by several months to a year, a high index of Paraneoplastic cerebellar ataxia and the paraneoplastic syndromes suspicion is required (2). Neurologic symptoms are the first manifestation of the tumor in about 70% of PNS patients (4). The diagnostic possibility should be considered in the setting of a family history of cancer or autoimmune disorder, subacute presentation, neuraxis involvement at multiple levels, and an insidious progression of the neurological condition with no clear alternative diagnosis (2). The hallmark of PCA is severe loss of cerebellar Purkinje cells with relative preservation of other cerebellar neurons and the presence of inflammatory infiltrates in the cerebellar cortex, deep cerebellar nuclei, and inferior olivary nuclei (1, 4–6). Prodromal symptoms, such as viral-like illness, dizziness, nausea, and vomiting, are followed acutely to subacutely by gait unsteadiness progressing rapidly to ataxia, diplopia, often nystagmus, dysarthria, and dysphagia (4, 5). Blurry vision, oscillopsia, transient opsoclonus, and cognitive impairment may be present (4, 5).

CT and MRI studies are initially normal in most cases, although some have transient diffuse cerebellar hemispheric enlargement or cortical meningeal enhancement, with eventual cerebellar atrophy (1, 4). Fluorodeoxyglucose positron emission tomography may show cerebellar hypermetabolism in early stages followed by hypometabolism as cerebellar atrophy develops (4). CSF often shows nonspecific abnormalities, such as mild to moderate lymphocytic pleocytosis, increased protein, a high IgG index, and CSF-specific oligoclonal bands in approximately 60% of PCA patients (2, 4, 5). Intrathecal synthesis of autoantibodies is a frequent finding in PCA patients with anti-Yo antibody (7). Only 60% to 70% will have detectable antibodies in their serum or CSF (2).

### Table 4. Paraneoplastic antibodies in paraneoplastic cerebellar ataxia and their associated malignancies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Neurological syndrome</th>
<th>Associated cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Yo (PCA-1)</td>
<td>Cerebellar ataxia</td>
<td>Ovarian, breast</td>
</tr>
<tr>
<td>Anti-Hu</td>
<td>Cerebellar ataxia, PEM/SN</td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td>Anti-Ri</td>
<td>Cerebellar ataxia, OM</td>
<td>Breast, gynecological, small cell lung cancer</td>
</tr>
<tr>
<td>Anti-Tr</td>
<td>Cerebellar ataxia</td>
<td>Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Anti-VGCC</td>
<td>Cerebellar ataxia, LEMS</td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td>Anti-Ma</td>
<td>Cerebellar ataxia, brainstem dysfunction</td>
<td>Many</td>
</tr>
<tr>
<td>Anti-CRMP5</td>
<td>PEM/SN, cerebellar ataxia</td>
<td>Small cell lung cancer, thymoma, gynecological</td>
</tr>
<tr>
<td>Anti-mGluR1</td>
<td>Cerebellar ataxia</td>
<td>Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Anti-Ta (anti-Ma2)</td>
<td>Limbic encephalopathy, cerebellar ataxia</td>
<td>Testis</td>
</tr>
</tbody>
</table>

Modified from Shams’ili et al, 2003 (6) with permission from Oxford University Press. CRMP5 indicates collapsin response mediator protein 5; LEMS, Lambert-Eaton myasthenic syndrome; mGluR1, metabotropic glutamate receptor 1; OM, opsoclonus/myoclonus; PEM, paraneoplastic encephalomyelitis; SN, sensory neuropathy; VGCC, voltage-gated calcium channels.

**Figure 1.** Paraneoplastic syndrome diagnosis and management flowchart. Modified with permission from Kannoth, 2012 (2).
It is preferable to look for the entire range of paraneoplastic antibodies, as nine specific antineuronal antibodies are associated with PCA (2, 6) (Table 4). Purkinje cell cytoplasmic antibody type 1 (PCA-1), also known as anti-Yo, is highly specific and the most frequently detected autoantibody in PCA (5, 8). The presence of paraneoplastic antibodies can direct the care team towards a tumor search using a CT scan of that region (1) (Figure 1). Most cases of anti-Yo PCA occur in women over 60 years (5).

PCA treatment includes tumor treatment, immunotherapy, and supportive therapy. Treating the tumor as soon as possible is the best approach for stabilization or symptom improvement with or without immunotherapy (2, 4). Immunotherapy includes steroids, IVIG, plasmapheresis, cyclophosphamide, azathioprine, and rituximab (2). In most cases of PCA, the neurological symptom has stabilized by the time treatment is started, meaning that Purkinje cell damage and neuronal loss have most probably already occurred (5). Multiple studies have shown that patients with anti-Yo antibodies have a worse neurologic prognosis, with most becoming bedbound within 3 months of diagnosis, compared with PCA patients with other antibody types (5, 9). However, immunotherapy has been reported to be effective in some cases, and hence a trial of IVIG, steroids, or plasmapheresis is indicated (1). Our patient with anti-Yo–associated PCA experienced clinical improvement in some of her neurological symptoms and stabilization of other symptoms with high-dose steroids and IVIG. However, her relief was partial since her primary cancer was advanced and treatments were limited. Generally, it is the tumor progression and not the neurological disease that causes death in PCA patients (5). Nevertheless, in our patient, the PNS significantly affected her quality of life, while the malignancy was largely asymptomatic. Despite successful treatment of the primary tumor in many cases, paraneoplastic symptoms often continue to negatively impact the patients’ quality of life more so than the underlying tumor (9). This signifies the importance of early diagnosis, as delays in the start of treatment can lead to rapid progression and irreversible neurological damage (2).

Carcinoma of the lungs causing enlarged kidneys

Weeraporn Srisung, MD, Charoen Mankongpaisarnrung, MD, Irfan Warraich, MD, David Sotello, MD, Shannon Yarbrough, MD, and Melvin Laski, MD

Bilateral enlarged kidneys can be caused by a number of conditions. Renal metastasis is included in the differential diagnosis. We report a case of a 67-year-old woman with a 6-month history of productive cough and unintentional weight loss. Cavitary pulmonary lesions and bilateral enlarged kidneys were noted on imaging studies. Hematuria, azotemia, and proteinuria were present. Renal biopsy showed squamous carcinoma cells invading normal-appearing glomeruli and atrophic tubules. The invasive squamous cells stained negative for CK7 and CK 20. Lung biopsy confirmed squamous cell carcinoma. Our case shows that in patients with renal enlargement, even with the absence of a focal mass, renal metastasis should be considered, especially in those with suspected or diagnosed malignancy elsewhere.

Metastasis to the kidney is the most common etiology of intrarenal malignancy (1). We report a case of squamous cell lung carcinoma causing bilateral infiltrative kidney metastasis.

CASE REPORT

A 67-year-old white woman with a 50 pack-year smoking history presented with a 6-month history of productive cough with foul-smelling sputum and a 2-month history of unintentional weight loss of >10 pounds. Breath sounds in the right lung base were diminished. Chest x-ray revealed a right lower lobe cavitary lesion with an air-fluid level, along with right lung base opacity (Figure 1). Computed tomography (CT) showed an 8.6 × 6.2 cm cavitary lesion over the right lower lung with surrounding infiltrate and a 1.6 × 1.4 cm cavitary lesion in the right lower lung. Right-sided pleural effusion and right middle lobe atelectasis were also present. The abdominal CT scan demonstrated enlarged kidneys with smooth outlines, haziness and strandy changes in the perinephric fat, and thickened Gerota’s and lateral conal fasciae on both sides. There were

Figure 1. Chest x-ray showing a right lower-lobe cavitary lesion with an air-fluid level, along with right lung base opacity.

Figure 2. CT of the abdomen demonstrating bilateral enlarged kidneys with multiple poorly circumscribed hypodense foci throughout both kidneys.

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multiple, poorly circumscribed, hypodense foci throughout both kidneys. The right kidney measured 12.5 × 8.7 cm; the left kidney, 13 × 8.1 cm (Figure 2). Adrenal, spinal, and retroperitoneal lymph node metastases were suspected.

Pleural fluid analysis showed an exudative profile with no malignant cells on cytologic examination. The patient’s serum creatinine level was 2.4 mg/dL; 24-hour urine studies showed creatinine clearance of 14 mL/min with 310 mg of protein in 24 hours. Renal ultrasound showed architectural alteration of both kidneys consistent with a diffuse infiltrating process (Figure 3). Amorphous echogenicity, devoid of structural definition of the corticomedullary complex, was present bilaterally. Neither hydronephrosis nor hydroureter was demonstrated.

Renal biopsy demonstrated squamous carcinoma cells interspersed between normal-appearing glomeruli and atrophic tubules. A p63 immunostain was used to highlight squamous carcinoma cells. These cells were negative for CK7 and CK20. (Figure 4a). Electron microscopy of the biopsied tissue showed patchy effacement of foot processes (Figure 4b, 4c). No convincing immune complex deposits were seen. Lung biopsy demonstrated squamous cell carcinoma. Although a small chance remains that the site of origin was carcinoma of the urothelium of the renal pelvis, given the concomitant extensive pulmonary lesions and positive CK20 on immunohistochemistry, squamous cell carcinoma of the lung with renal metastasis is much more likely. Palliative chemotherapy after discharge was planned.

**DISCUSSION**

Bilateral enlarged kidneys may be a result of a number of conditions, in particular diabetic nephropathy, HIV nephropathy, acute glomerulonephritis, and collagen vascular diseases. Renal metastasis and lymphomatous infiltration are also included in the differential diagnosis. Metastasis to the kidney is not rare. In a study of 1000 autopsies, 13% of cases with epithelial-derived malignancies were found to have kidney metastasis (2). This might be explained by the significant percentage of cardiac output received by the kidneys (approximately 25%). The most common site of primary malignancy from which metastatic kidney lesions arise is the lung (3, 4). Renal metastasis from primary lung cancer may be detected at the same time that the primary malignancy is diagnosed, but it may also be found years after the primary cancer is identified (5–7).
Abnormalities found on urinalysis and a basic metabolic panel can lead to detection of metastasis to the kidneys. Our patient is an example in which renal metastasis produced laboratory changes, including hematuria, azotemia, and proteinuria. Renal metastasis can be detected by CT scan, ultrasonography, magnetic resonance imaging, positron emission tomography/CT and, although not usually performed, renal angiography. Lesions may involve one or both kidneys and can either be generally infiltrative or, much more frequently, focal (3, 4, 7, 8). Ultimately, kidney biopsy provides definitive diagnosis of metastatic disease in the kidney.

Mixed epithelial and stromal tumors of the kidney discovered incidentally at autopsy

Varsha Podduturi, MD, and Joseph M. Guileyardo, MD

Mixed epithelial and stromal tumors (MEST) of the kidney are uncommon neoplasms that were added to the World Health Organization’s renal tumor classification in 2004. These entities are biphasic and contain both epithelial and mesenchymal components. MEST most commonly occur in women. Presented are two cases of MEST incidentally discovered at autopsy.

CASE 1

A 42-year-old black woman with a complicated history including bipolar disorder, hypertension, type 2 diabetes mellitus, sarcoidosis, secondary hyperparathyroidism, IgA nephropathy, and dialysis-dependent end-stage renal disease complained of stomach upset and vomiting. En route to her dialysis unit, she became increasingly dyspneic and collapsed. She lost consciousness and became asystolic. Cardiopulmonary resuscitation established a pulse, and she was then transferred to the emergency department. Upon arrival, she experienced cardiac arrest again and resuscitative efforts reestablished a pulse of 30 beats a minute. She was intubated and transferred to the intensive care unit. However, global anoxic encephalopathy proved irreversible, and she died 2 days later. Her body mass index was 35.6 kg/m².

At autopsy, the right and left kidneys weighed 95 and 75 g, respectively. Bilateral renal cortices had finely granular surfaces. Cut sections of the kidneys showed marked cortical thinning. The right kidney had a gray-white, well-demarcated cortical nodule measuring 1.1 × 0.9 × 0.5 cm. Microscopically, the nodule was composed of spindle cells admixed with scattered tubular structures lined by flattened epithelium (Figure 1a).

Areas of fibrosis and cystic change were also present in the adjacent tissue. The stromal portion did not stain by estrogen and progesterone receptor immunohistochemistry. The epithelial component displayed strong immunohistochemical reactivity for low- and high-molecular-weight cytokeratins. No malignant changes were identified. Additional autopsy findings included cardiomegaly (545 g), hypertensive cardiovascular disease, global ischemic-anoxic encephalopathy, and widespread microocclusive intravascular sickling. Heart blood analysis disclosed a hemoglobin A1 of 61.4%, hemoglobin S of 32.4%, hemoglobin A2 of 3%, and hemoglobin F of 0%, all consistent with sickle cell trait.

CASE 2

A 58-year-old white woman with end-stage cryptogenic cirrhosis, Sjogren’s syndrome, and hypothyroidism was discharged from the hospital on oral antibiotics for an atypical pulmonary infection. She presented 1 week later with increasing bilirubin levels and persistent lung infiltrates by computed tomography. Her white blood cell count was 7.1 K/µL; hemoglobin, 11.2 g/dL; hematocrit, 31.2%; platelets, 106 K/µL; albumin, 2.9 g/dL; alkaline phosphatase, 297 U/L; aspartate aminotransferase, 237 U/L; alanine aminotransferase, 107 U/L; and direct bilirubin, 30.9 mg/dL. She was icteric. Chest radiograph showed ground-glass opacities and scattered calcified granulomas in both lungs. Over the next few days, her direct bilirubin level remained elevated (29.8 mg/dL), and her total bilirubin measured 39.1 mg/dL. She developed septic shock, disseminated intravascular coagulopathy, and worsening encephalopathy, and she died.

At necropsy, 2000 mL of clear yellow-green fluid was found in the abdominal cavity. All internal organs were markedly icteric. The right and left kidney each weighed 250 g. A 0.8-cm yellow nodule was in the upper pole of the left kidney. Histologically, the nodule comprised a mixture of spindle cells that resembled ovarian stroma and tubular elements lined by flattened epithelium with eosinophilic cytoplasm (Figure 1b). The areas of fibrosis and cystic change were also present in the adjacent tissue. The stromal portion did not stain by estrogen and progesterone receptor immunohistochemistry. The epithelial component displayed strong immunohistochemical reactivity for low- and high-molecular-weight cytokeratins. No malignant changes were identified. Additional autopsy findings included cardiomegaly (545 g), hypertensive cardiovascular disease, global ischemic-anoxic encephalopathy, and widespread microocclusive intravascular sickling. Heart blood analysis disclosed a hemoglobin A1 of 61.4%, hemoglobin S of 32.4%, hemoglobin A2 of 3%, and hemoglobin F of 0%, all consistent with sickle cell trait.

From the Department of Pathology, Baylor University Medical Center at Dallas.

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stromal portion was highlighted by estrogen and progesterone receptor immunohistochemical stains. The epithelial portion showed similar immunohistochemical reactivity for low- and high-molecular-weight cytokeratins, as in the previous case, and this nodule was also consistent with a MEST. Other significant autopsy findings included end-stage cryptogenic cirrhosis, fibrotic pulmonary granulomas, moderate cardiomegaly (415 g), dural icterus, and chronic thyroiditis. A yellow-black stone obstructed the proximal lumen of the common bile duct near its junction with the hepatic hilum and adjacent to the clip from a previous cholecystectomy. Postmortem cultures were positive for Candida albicans.

**DISCUSSION**

MEST was first described by Michal and Syrucek in 1998 (1), and in 2004 it was included in the World Health Organization’s renal tumor classification (2), accounting for 1.6% of all renal neoplasms (3). These tumors have been reported under various names such as leiomyomatous renal hamartoma, congenital mesoblastic nephroma, cystic hamartoma of the renal pelvis, solitary multilocular cysts of the kidney, multilocular renal cyst with müllerian-like stroma, and adult metanephric stromal tumor (4–12).

Microscopically, the neoplasm is biphasic with both epithelial and spindle cell elements. The epithelial component consists of clusters of tubules lined by flattened to cuboidal epithelium with eosinophilic cytoplasm and a hobnail appearance. The mesenchymal portion usually resembles ovarian stroma, but can range from scar-like fibrous tissue to interlacing fascicles (13). Most of these tumors behave in a benign fashion, but rare cases of metastasis, recurrence (6), and malignant transformation have been reported in the literature (14–16). Malignant features can occur in either component of the tumor and include increased cellularity, nuclear atypia, round to ovoid vacuolated nuclei with prominent nucleoli, and increased mitotic activity (15 to 25 mitotic figures per 10 high-power fields) (17).

These neoplasms are predominantly found in middle-aged, perimenopausal and older women (18), many with a history of long-term estrogen replacement (17). Clinical symptoms may include a palpable abdominal mass, flank pain, and hematuria (19) or can be discovered incidentally. On computed tomography and magnetic resonance imaging scans, MEST appears as a well-circumscribed multiseptate cystic mass with solid components and thick or thin septae (20, 21). Patients usually have an excellent prognosis postoperatively (17).

The mesenchymal element is immunohistochemically reactive for smooth muscle markers such as desmin and smooth muscle actin. The epithelial component is positive for low- and high-molecular-weight cytokeratins and Ulex europaeus (17). The mesenchymal portion also displays reactivity for estrogen and progesterone receptors in many cases (12). Expression of CD10, calretinin, and inhibin has also been described (18); however, morphology remains the most important factor for diagnosis.


Figure 1. Microscopic images of mixed epithelial and stromal tumors. (a) Sections of the tumor showing admixed epithelial and mesenchymal components in Case 1 (hematoxylin and eosin, 100×). (b) Tubules surrounded by a mesenchymal component resembling ovarian stroma in Case 2 (hematoxylin and eosin, 100×).

Avocations

Black Swallowtail Butterfly. Photo copyright © Rolando M. Solis, MD. Dr. Solis (e-mail: rmsolis@mac.com) is an interventional cardiologist with Baylor Scott and White Health and practices at Baylor Medical Center at Garland and The Heart Hospital Baylor Plano.
We describe a 68-year-old man who presented with headaches, nausea, and dizziness and was found to have a superior sagittal sinus venous thrombosis on magnetic resonance imaging. His initial hypercoagulable workup was negative. Computed tomography of the abdomen revealed a large mass originating from the kidney. A radical nephrectomy was performed at an outside hospital, and histological study of the excised mass disclosed clear cell renal carcinoma.

Venous thrombosis in the setting of malignancy is a well-known phenomenon explained by multiple factors that lead to a hypercoagulable state. Thrombotic events are potentially dangerous complications of cancer and can be fatal. We describe a patient who was diagnosed with renal cell carcinoma (RCC) after the initial survey revealed a superior sagittal sinus thrombosis.

CASE DESCRIPTION

A 68-year-old white man with a previous history of hypertension presented to the emergency department with a 6-week history of progressively worsening frontal headache. Magnetic resonance imaging (Figure 1a) at an outside imaging center disclosed a superior sagittal sinus thrombus. He also had recent dizziness, nausea, and headache, all worsened by lying down. A screening colonoscopy 1 year earlier had revealed polyps, which were excised. He had also had recent unspecified outpatient dental sinus surgery. He denied a personal or family history of hypercoagulable disorders. The patient was afebrile, normotensive, and displayed no focal or neurological deficits on physical examination when admitted.

The patient was started on hydrocodone for headache and a heparin drip. Initial laboratory results, including complete blood count, comprehensive metabolic panel, and urinalysis, were within normal limits. A hypercoagulable workup that included lupus anticoagulant, factor V Leiden, prothrombin G20210A mutation, homocysteine, protein C and S deficiency, and antithrombin III deficiency were negative. An evaluation for the JAK2 mutation and paroxysmal nocturnal hemoglobinuria were also negative. Cerebral angiography (Figure 1b) 2 days after admission revealed a partially occlusive thrombus within the middle third of the superior sagittal sinus. Computed tomography of the abdomen (Figure 1c) demonstrated a 10 × 8.6 cm large necrotic mass emanating from the posterior aspect of the left kidney. The renal vein appeared patent with no lymphadenopathy within the retroperitoneum or other organ involvement. A radical nephrectomy was performed at an outside hospital, and the patient was transitioned to low-molecular-weight heparin. Histological study of the excised kidney disclosed clear cell renal carcinoma.

DISCUSSION

Venous thromboses are found in up to 10% of patients with cancer, with varying rates of occurrence based on tumor type and location (1). Venous thromboembolism is nearly seven times more likely to occur in certain cohorts of cancer patients and acts as a potential cause of mortality (1, 2). The pathogenesis of the hypercoagulable state of malignancy involves multiple factors (3). Tissue factor expression by tumor cells has been implicated as a cause of hypercoagulability due to its role in the extrinsic pathway of coagulation (3, 4). Normal host cell tissue response to tumor cells can also induce procoagulant activity by the effect of tumor necrosis factor stimulation on monocytes, platelets, and endothelial cells (3). The presence of a venous thrombosis can have diagnostic implications in patients with previously undiagnosed malignancy.

Many patients with RCC are asymptomatic at diagnosis and the cancer is discovered incidentally on imaging (5). Studies have shown that only 9% of patients present with the classic triad of RCC (flank pain, palpable renal mass, hematuria), with hematuria being the most common presenting symptom (50%–60% of patients) (6). Secondary symptoms of malignancy, including anemia, cachexia, venous thrombosis, and hepatic dysfunction, may provide the only clues of an underlying
malignancy. Hematologic and electrolyte abnormalities may also present as nonspecific signs in patients with RCC via paraneoplastic mechanisms that include but are not limited to hypercalcemia, anemia, amyloidosis, hepatic dysfunction, and anemia (6, 7). In the setting of undiagnosed cancer, seemingly unrelated symptomatology may point to a malignancy when all other diagnostics are negative.

This initial presentation of undiagnosed malignancy demonstrates the diverse manifestations of cancer. Hypercoagulability in cancer can range from abnormal coagulation studies to clinically evident venous thromboembolism (3). Thromboses to the superior vena cava and internal jugular vein have been reported in patients with metastatic RCC (8, 9). There have been no reported cases of superior sagittal sinus thrombosis in the setting of nonmetastatic RCC.

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide and is often associated with cirrhosis of the liver. These tumors are quite vascular. We present a case of a patient without known cirrhosis who presented with intracardiac extension of HCC inferior vena cava invasion.

CASE PRESENTATION

A 76-year-old white man with hypertension, asymptomatic carotid disease, and type II diabetes mellitus presented for routine follow-up. He was asymptomatic. His social history was negative for alcohol use, tattoos, travel, illicit drug use, blood transfusions, or chemical exposures in the past. His body mass index was 27 kg/m². Examination disclosed no scleral icterus, ascites, organomegaly, asterixis, or spider angiomata. Complete blood counts, basic chemistries, bilirubin, albumin, and coagulation studies were normal. Table 1 notes additional studies. Abdominal ultrasound revealed an 8 cm right hepatic lobe mass. A triple-phase computed tomography (CT) scan of the abdomen revealed a 12 × 8 cm hepatic mass and inferior vena cava compression, but no evidence of cirrhosis (Figure 1). Repeat CT 1 month later revealed an 11 × 13 cm mass with inferior vena cava tumor infiltration and extension to the right atrium, where a 4 × 4 cm mass consistent with tumor infiltration was noted (Figure 2). Liver biopsy noted some hepatocytes with mild fatty changes and no evidence of hemosiderosis or cirrhosis, consistent with moderately differentiated HCC. An echocardiogram showed an ejection fraction of 55% to 60% and a 2.5 × 2.5 cm fixed mass in the right atrium. The patient was started on sorafenib. He tolerated treatment well with only minimal side effects, such as hand-foot syndrome, for approximately 10 months after the diagnosis. He later developed fatigue, dyspnea, and weight loss. Repeat CT noted disease progression. He died approximately 14 months after diagnosis.

DISCUSSION

HCC has a 5-year survival of 5% in nontransplant candidates (1–3). Approximately 80% of cases worldwide are attributable to viral hepatitis (4). Nonviral factors that lead to HCC include obesity and diabetes mellitus (causing nonalcoholic fatty liver disease). Alcohol abuse and tobacco use, hemochromatosis, oral contraceptives, aflatoxin, pesticides, and cirrhosis of any cause can also cause HCC (1–3). Most HCC cases (80% to 90%) are associated with cirrhosis and are caused by viral hepatitis or alcoholic abuse. Most cases of HCC in noncirrhotics

Table 1. Notable laboratory results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline phosphatase, fractionated as biliary origin (IU/L)</td>
<td>249 (38–126)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>51 (15–41)</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>42 (15–41)</td>
</tr>
<tr>
<td>Low-density-lipoprotein cholesterol (mg/dL)</td>
<td>86</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>68</td>
</tr>
<tr>
<td>Hemoglobin A1C</td>
<td>6.8%</td>
</tr>
<tr>
<td>HIV</td>
<td>Negative</td>
</tr>
<tr>
<td>Hepatitis panel</td>
<td>Negative</td>
</tr>
<tr>
<td>Alpha-fetoprotein (ng/mL)</td>
<td>4.1</td>
</tr>
</tbody>
</table>

From the Department of Internal Medicine (Oncale) and the Department of Hematology and Medical Oncology (Lewis), Tulane University Hospitals and Clinics, New Orleans, Louisiana. Dr. Oncale is now affiliated with Oschner Health System. Corresponding author: Melody Oncale, MD, 1514 Jefferson Highway, New Orleans, LA 70121 (e-mail: melodybecnel@yahoo.com; mbecnel@tulane.edu; melody.oncale@ochsner.org).
cardiac surgery can be used in cases of cardiac obstruction (8, 9). Palliative transarterial chemoembolization, or systemic chemotherapy (4, 7). There may be a modest benefit with radiation, or right atrium extension is 1 to 4 months regardless of treatment (4, 5). Local invasion is more common in cirrhotic patients (5). In the rare cases of HCC with tumor extension to the right atrium and inferior vena cava, most patients were either asymptomatic, had cirrhosis, or both (4–9).

The mean survival in HCC patients with inferior vena cava or right atrium extension is 1 to 4 months regardless of treatment (4, 7). There may be a modest benefit with radiation, transarterial chemoembolization, or systemic chemotherapy with sorafenib, depending on the size of the lesions (6). Palliative cardiac surgery can be used in cases of cardiac obstruction (8, 9).

In recent years, HCC has been treated with sorafenib, an oral chemotherapeutic agent that targets several tyrosine kinase–dependent molecular pathways, such as vascular endothelial growth factor and platelet-derived growth factor-beta. These pathways allow for proliferation of HCC; therefore, sorafenib has been associated with reduced angiogenesis and increased apoptosis of tumor cells in HCC. The SHARP (Sorafenib HCC Assessment Randomized Protocol) trial randomized patients with advanced HCC who were Child-Pugh Class A and had good performance scores (Eastern Cooperative Oncology Group scores of 2 or less) to sorafenib versus placebo. There was an increase in overall survival of approximately 3 months in the sorafenib-treated group (median survival of 10.7 months in the treated group compared with 7.9 months in the placebo group) with only minimal side effects of hypertension, hand-foot syndrome, hypertension, and diarrhea (10).

To our knowledge, this is the first patient without evidence of viral hepatitis or cirrhosis to present asymptptomatically with HCC and cardiac involvement. Our case is also unique in that the etiology of this patient’s HCC remains largely cryptogenic. Most importantly, our patient greatly exceeded survival expectations based on currently reported survival data of patients with extensive intracardiac tumor burden (the median survival is 4 months, and our patient survived >14 months). It should be noted, however, that most of the available survival data regarding intracardiac HCC did not involve patients treated with sorafenib. Our patient’s increased survival further underscores the importance of targeted chemotherapeutic agents such as sorafenib in the treatment of patients with advanced HCC.

A 69-year-old man from Texas with an unremarkable past medical history presented with a 2-year history of a diffuse, spreading annular eruption involving most of his trunk. He noticed progressive numbness of his hands and feet but no other systemic symptoms. He had never traveled outside of the United States. Skin biopsy confirmed a diagnosis of leprosy, and he was initiated on appropriate therapy.

Leprosy, also known as Hansen’s disease, is a chronic granulomatous disease of the peripheral nerves and superficial tissues. The diagnosis is challenging, as the incidence is relatively low in the United States. Only about 200 new cases are reported annually to the Centers for Disease Control and Prevention, with about 10% of those occurring in Texas. This report reminds practitioners of the clinical-pathological presentation of leprosy so that prompt treatment can be started.

CASE REPORT
A 69-year-old white man from Texas presented to our dermatology clinic for an annular eruption that had been spreading for the past 2 years. It began as an isolated lesion on his back and presented after he had been deer hunting and processed his own deer meat. It then spread to involve most of his trunk and arms. He denied any itching or burning associated with the eruption; however, he noted a worsening tingling and numbness sensation with intermittent pain in his hands and feet. Over 2 years, he was treated with antihistamines and intramuscular steroid injections. He did note some clearance with steroids, but the rash then quickly recurred. His daily medications were cetirizine, ranitidine, fexofenadine, and montelukast. No other family members were affected. He denied any travel outside of the United States or direct contact with armadillos.

Examination revealed diffuse erythematous, edematous annular plaques coalescing to cover most of his trunk and upper arms to the elbows (Figure 1). Islands of sparing, particularly in the axilla, were noted. He had no involvement of his face, lower extremities, or arms distal to the elbows. Punch biopsy from the edge of an indurated plaque demonstrated granulomatous inflammation with numerous acid-fast bacilli and Fite-positive organisms consistent with leprosy (Figure 2). Periodic acid Schiff stain was negative for fungal organisms. The patient was started on dapsone 100 mg daily, rifampin 600 mg monthly, clofazimine 50 mg daily, and clofazimine 300 mg monthly for 12 months.

DISCUSSION
Leprosy is a chronic granulomatous disease of the peripheral nerves and superficial tissues that is caused by Mycobacterium leprae, an acid-fast bacillus (1). About 90% of patients with documented manifestations of infection with this organism reside in Africa, Asia, and South America, most commonly India, Brazil, Indonesia, and Nepal (2, 3). Most cases have occurred in India (2, 3).

*M. leprae* is an obligate intracellular parasite primarily multiplying within macrophages and Schwann cells (4). It is known that *M. leprae* grows at 30° to 33°C, which may be why it preferentially targets the lips, forehead, ears, and other acral areas (5). *M. leprae* causes a spectrum of illness with forms that are classified as either tuberculoid or lepromatous (6). In the tuberculoid form...
form, lesions are granulomatous with few organisms, extensive epithelioid cells, giant cells, and lymphocytic infiltration (7). In the more disfiguring and widely recognized lepromatous form, lesions show dense infiltration with acid-fast bacilli (8). Bacilli often spread systematically and invade the peripheral sensory nerves which, when damaged, result in peripheral neuropathies that predispose patients to accidental trauma and subsequent nonhealing ulcers (9, 10). As exemplified by our patient, leprosy is characterized by a long and variable incubation period that may take up to 5 to 7 years from inoculation to presentation of clinical disease (11).

Leprosy may be diagnosed clinically and, in the case of the lepromatous form, confirmed by demonstrating the presence of acid-fast bacilli in stained biopsies or scrapings of infected tissue (12). Due to the paucity of organisms in the tuberculoid form, biopsies are often unable to localize any bacilli within the dermis (13). Treatment consists of multidrug therapy, often a combination of dapsone and rifampin, whereas in cases of lepromatous leprosy, clofazimine in addition to both is treated with 6 months of dapsone and rifampin, whereas in cases of lepromatous leprosy, clofazimine in addition to both dapsone and rifampin is used for 12 months (14).

Tuberculoid leprosy is not highly contagious, and both tuberculoid and lepromatous forms are rare in the United States (15). Studies suggest that aerosolized droplets from untreated lepromatous leprosy patients, who are often undiagnosed for several years, are the main source of infection (16). Another natural host for M. leprae is the 9-handed armadillo (Dasypus novemcinctus) which is found in the central Gulf Coast area, particularly in Louisiana and Texas (17). The exact relation between armadillos and human infection with M. leprae is unclear, as many patients deny having ever had contact with armadillos (18).

Baylor Scott & White Health launches alliance with America’s No. 1 heart hospital, Cleveland Clinic

Baylor Scott & White Health announced an alliance with Cleveland Clinic’s Sydell and Arnold Miller Family Heart & Vascular Institute. The alliance creates a collaboration involving the academic, clinical, and research components of Cleveland Clinic and three Baylor Scott & White Health hospitals: Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Baylor University Medical Center at Dallas, and The Heart Hospital Baylor Plano. The three Baylor Scott & White Health hospitals will be the exclusive providers for Texas and Oklahoma cardiac patient referrals from the Cleveland Clinic’s Cardiovascular Specialty Network, which allows patients to seek Cleveland Clinic–directed care closer to home.

Baylor Scott & White Health joins two other alliances in Cleveland Clinic’s Cardiovascular Specialty Network: North Shore–Long Island Jewish Health System in New York and MedStar Heart Institute in Washington, DC. Under the agreement, Cleveland Clinic and the three Baylor Scott & White Health hospitals will share best practices, coordinate care, and develop programs to improve quality and patient safety.

“With so much talk of consolidation and collaboration in health care today, this is an example of the types of collaborations of the future,” said Joel Allison, CEO of Baylor Scott & White Health. “We are honored to be selected for this cardiovascular specialty network, and we’re excited to welcome patients from throughout Texas and Oklahoma.”

Baylor Scott & White accountable care organization lowers costs in first 2 years

Baylor Scott & White Quality Alliance (BSWQA), the system’s accountable care organization, lowered the cost of employee health plan medical costs by nearly $14 million for its members in its first 2 years, compared to the targeted amount. The reduction in costs represented a 7% savings. Among the BSWQA’s other results for its 34,000 covered lives, hospital admissions per thousand were reduced by 4.3%; 30-day readmissions were down 15%; and the prescribing rate for generic medicine increased.

BSWQA President Carl Couch, MD, said, “Successfully accomplishing the mission of the BSWQA will be measured by achieving high performance in accepted quality measures and lowering costs. We are pleased that in our first 2 years managing the health of Baylor Scott & White Health North Texas division employees, we have had very positive performance in both areas. Reductions in unnecessary admissions, readmissions, and emergency department visits not only lower cost, but prevent hardship for patients.”

Since it began in 2011, the BSWQA has grown to more than 3500 physicians (including over 900 physicians from the Baylor Scott & White Health Central Texas division), 49 hospitals, 48 post-acute care facilities, and other stakeholders across the health care continuum. In addition, its collaboration with Walgreens offers simple nonacute care services, in network, for BSWQA’s covered members in 13 clinics opening throughout the Dallas/Fort Worth area in 2014 and 2015.

BSWQA enters into managed care contract agreements that offer shared savings opportunities to participating BSWQA physicians for providing high-quality care at a reduced cost. BSWQA physicians sign contracts committing to improving outcomes, measuring themselves against their peers, collaborating to develop new standards of care, and spreading best practices. Providers use more than 100 evidence-based protocols and metrics for which improvements in care can be compared and monitored.

Baylor Scott & White Health and the Star—home of the Dallas Cowboys—announce preparations to build Center of Excellence in Sports Medicine

Baylor Scott & White Health is working towards the construction of a 200,000-square-foot center of excellence for sports medicine at The Star—Home of the Dallas Cowboys in Frisco, Texas. The initial phase of the project will include an ambulatory surgery center, a diagnostic imaging center, physical therapy, a preventive care program for athletes, and several other health care offerings. The center is scheduled to be operational in the fall of 2016.

“We are working to build a center of excellence in sports medicine not just for professional athletes, but for student-athletes and weekend warriors of all ages,” said Joel Allison, CEO, Baylor Scott & White Health. “We are constantly looking for new ways to promote health and wellness in the communities we serve and believe this is an exciting opportunity to create a medical destination offering everything from urgent care to innovative sports performance training.”

Baylor Scott & White Medical Center—Waxahachie opens with expanded women’s health services and Ellis County’s newest dedicated cancer center

Baylor Scott & White Medical Center—Waxahachie opened in December 2014 as one of the latest major investments Baylor Scott & White Health has made toward the health and wellness of Texans. The $175-million medical center—the first to be built under the Baylor Scott & White Health name—is a replacement facility for the nearby Baylor Medical Center at Waxahachie, which has served Ellis County and the surrounding area for 100 years. The new hospital is located at 2400 N I-35E in Waxahachie and features a dedicated cancer center and expanded women’s health services, including labor and delivery.

A dedicated cancer center, Baylor Charles A. Sammons Cancer Center at Waxahachie, is an important part of the new facility, allowing patients to receive quality cancer treatment close to home. Patients are able to receive the full spectrum of cancer care, including imaging, radiation therapy, chemotherapy, as well as support services. The team paid special attention to the design of the cancer center, with a focus on comfort and privacy. “Our hope is that patients feel as comfortable and relaxed as possible while they are undergoing treatment,” said Chris York, president of Baylor Waxahachie. “We are trying to create a moment of peace in what can be a turbulent time.”

The new hospital also features a dedicated women’s health center offering growing families advanced obstetrical care in a warm, caring environment. With spacious patient suites and waiting areas, the women’s health center team is excited to bring a wide range of amenities and services to Ellis County’s mothers and their families.

Baylor researchers develop biomarker for high-risk colon cancer metastases

A new study from the Center for Gastrointestinal Cancer Research and the
Individualized treatment—and, ultimately, start are successful, the results could help establish best treat those stages. If Dr. Goel and his team develop markers for identifying different stages test and metastasis-specific microRNA study to researchers will take the results from the blood laboratory’s work is currently under way. cancer in patients.

Overtreating—or undertreating—colorectal patients need more extensive treatment to avoid distant metastases, of which liver metastasis cancer patients have a high risk of developing the study can help determine which colorectal of the National Cancer Institute. Results from published on January 30, 2015, in the Journal of the National Cancer Institute. Results from the study can help determine which colorectal cancer patients have a high risk of developing distant metastases, of which liver metastasis is the most common manifestation. With these findings, oncologists can better predict which patients need more extensive treatment to avoid overtreating—or undertreating—colorectal cancer in patients.

Prior to this study, the research team, directed by Ajay Goel, PhD, developed a blood test for finding cancer-related microRNA before a tumor develops in the colon. A third phase of the laboratory’s work is currently under way. Researchers will take the results from the blood test and metastasis-specific microRNA study to develop markers for identifying different stages of colorectal cancer and determine which drugs best treat those stages. If Dr. Goel and his team are successful, the results could help establish individualized treatment—and, ultimately, start treating the right type of cancer with the right type of drug.

- Baylor research findings could eliminate need for 12 injections in preemies

A premature baby’s outcome has more to do with the birth site than a pharmacologic supplement, according to new research from Baylor University Medical Center at Dallas. Because of those conclusions, which were recently published in *JAMA Pediatrics*, researchers expect a shift in the way neonatal care is delivered.

The findings come from a research study involving 6200 premature infants born between 2010 and 2012 at US hospitals. In looking at the data retrospectively, researchers set out to determine if the absence of vitamin A, a...
PHILANTHROPY NOTES

Memory Center named in honor of AT&T

Baylor Health Care System Foundation is pleased to announce that the Baylor Memory Center has been named in honor of AT&T. AT&T’s lead gift was the catalyst for the most recent expansion of Baylor’s dementia and Alzheimer’s services. The Baylor AT&T Memory Center opened in renovated and expanded space in August. It offers additional diagnostic and treatment options along with enhanced programs and services for patients and families challenged with a diagnosis of dementia, including Alzheimer’s disease.

In addition to the lead gift from AT&T, additional support for the new Baylor AT&T Memory Center included grants from Denny Alberts and Cynthia Comparin, Hal and Diane Brierley, and the Donor-Advised Fund at the Communities Foundation of Texas supported by Anne and Harris Clark and The David B. Miller Family Foundation. These gifts totaled nearly $3 million toward the Foundation’s $10 million fundraising goal.

The gifts from AT&T and other generous donors have allowed the Memory Center to double its space on the second floor of The Pyramids at Park Lane building on the northwest corner of Park Lane and N. Central Expressway. This convenient location is directly across from NorthPark Center. In the summer of 2015, the Baylor AT&T Memory Center plans to add another full-time physician to its medical staff. In addition to expanding services for patients and their families, this new physician will coordinate research and clinical trials.

Baylor establishes gastroenterology fellowship in honor of Dr. Daniel DeMarco

Baylor Health Care System Foundation celebrated a new milestone with the completion of a $1.5 million fundraising campaign to establish a gastroenterology fellowship in honor of Daniel DeMarco, MD, medical director of digestive disease technology, Baylor Health Care System. The fellowship was made possible by significant gifts from donors including Dr. DeMarco, his wife, Cara East, MD, medical director, BRI’s Clinical Cardiovascular Research Center, and many of their colleagues and patients.

Dr. DeMarco spoke at the celebration and expressed his gratitude for the philanthropic support shown to make this dream a reality. Dr. DeMarco shared that gastroenterology physicians often have a special bond with their patients because of the connection they make through their comprehensive course of treatment, focusing on the mind, body, and soul.

Funds from the endowment will be used to support one of six gastroenterology fellows each year for 3 years at Baylor.

G. R. White Trust grant supports grieving children of seriously ill adults

Olivia, Nola, Alexander, and Rowan Carroll loved spending special time each week with their “Mimi.” The children knew Mimi was sick and in the hospital; however, they did not know how serious her illness was. Their parents, fighting to manage their own grief, were unable to find the right words to share the honest and difficult reality that Mimi was losing her battle with ovarian cancer. They called on the compassionate expertise of Emily Mulkey, a child life specialist at Baylor Scott & White Health, to help them break the news. As expected, the children were devastated by the news; however, they spent the next 3 hours with Emily, crying, laughing, and sharing their favorite memories of Mimi.

The illness or death of a parent, grandparent, or other important adult in a child’s life can be incredibly difficult for a child to comprehend. Specialists trained in helping children process grief, such as Emily, are common in pediatric hospitals where they help sick children adjust to illness. Baylor Scott & White Health is translating this critical support to the adult hospital environment by pioneering the provision of child life services for the children of seriously ill adults. First meeting with the adults, Baylor’s child life specialists offer age-appropriate explanations to the children when a family member is newly diagnosed with a life-limiting condition, seriously injured, or facing imminent death.

The program’s success would not have been possible without the support of friends like the G. R. White Trust. Earlier this year, the G. R. White Trust awarded a generous grant to help fund the salaries of one social worker and two child life specialists. In addition to expanding the program from two to five Baylor Scott & White Health hospitals, the grant made a meaningful difference in the lives of patients, children, and families who were enduring some of the darkest and most frightening hours of their lives.

For information on how you can support these or other initiatives at Baylor, please contact the Foundation at 214.820.3136.
Dr. Tolia and his team will continue their research to identify what impacts the caliber of neonatal care. “What is very exciting is that our research program at Baylor is addressing this question of quality at both national and local levels,” he said. “We have presented Baylor Research’s quality improvement work nationally, and we have three current projects focused extensively at how quality of care drives outcomes.”

● New research at Baylor could give alternatives for children’s eye exams

Research from the Baylor Visual Function Testing Center, published in *JAMA Ophthalmology*, showed that a new noninvasive technology, spectral-domain optical coherence tomographic imaging (SD-OCT), can help pediatric ophthalmologists detect achromatopsia by studying retinal thickness. This noninvasive approach, which can be used from a distance, is a step up from previous methods, when specialists diagnosed based on age, family history, and the standard eye exam.

As part of the research, investigators studied 18 patients, each of them about 4 years old. Half of the participants suffered from achromatopsia and the other half (control) had normal visual function. By using the SD-OCT, researchers produced three-dimensional high-definition imaging of the children’s retinas. Through those images, they found that the achromatopsia patients had significantly thinner retinas, as much as 17% thinner than those of the control participants. The findings imply the importance of studying a child’s retinal thickness when looking for achromatopsia. Researchers also noted that, in young children, those retinal qualities seemed milder than in older patients with the same achromatopsia diagnosis. This could mean a possible therapeutic window to help patients while they’re still young.

“We think that retinal thickness measurement is a more reliable predictor than age alone or genotype alone,” said Yuquan Wen, PhD, scientific director of the Baylor Visual Function Testing Center. “With the knowledge of retinal thickness in young children with achromatopsia, smarter clinical studies could be designed and monitored based on real structural changes of the retina in conjunction with the visual function change.”

● Baylor Research Institute enters license agreement for anakinra in treating systemic onset juvenile idiopathic arthritis

BRI, the research arm of Baylor Scott & White Health, announced that it has signed an agreement with Swedish Orphan Biovitrum AB (SOBI) to nonexclusively license Baylor’s patents pertaining to the treatment of systemic onset juvenile idiopathic arthritis (SJIA) using interleukin-1 (IL-1) beta antagonists.

“The agreement between BRI and SOBI enhances the reputation of the research scientists and the scientific platform at Baylor Research Institute,” said Dr. Michael A. E. Ramsay, president of BRI. “The institute is a world-class center for human immunology research, and this is an excellent example of that.”

At BRI, Virginia Pascual, MD, and colleagues have shown that overexpression of IL-1 beta plays a critical role in SJIA and that blocking IL-1 beta activity with anakinra is clinically beneficial in these patients. “It is very rewarding to learn that our research has found an effective treatment for an otherwise devastating disease,” Dr. Pascual said. “Now it can benefit children around the world.”

● Laser and surgical robot combine to stop patient’s chest pain

Using a medical laser and a robotic surgical system, a cardiothoracic surgeon on the medical staff at The Heart Hospital Baylor Plano (THHBP) created 30 new holes, or channels, in the heart of a 58-year-old Dallas-area man. The new channels relieved the angina endured by the patient for many years.

“These new channels created by the Holmium: YAG Laser System laser in the heart muscle allow more blood flow to the heart, eliminating some or all angina pain,” explained Dr. Kim Jett, medical director, thoracic robotics, THHBP. The procedure, transmyocardial laser revascularization, can improve a patient’s quality of life when the intense chest pain can’t be treated by medications, stents, or open heart surgery. THHBP clinicians believe this is the first robotic transmyocardial laser revascularization performed in Texas.
Dr. Alan Miller (Figure 1) was born in New York City in 1950. His early life was in the New York City boroughs of the Bronx and Queens and then Long Island. He received a bachelor’s degree from The State University of New York at Buffalo in 1972, a master’s degree in physiology from Roswell Park Division, State University of New York at Buffalo in 1974, and a PhD in physiology from the same institution in 1976. He then did a postdoctoral fellowship followed by a faculty appointment at the University of Miami School of Medicine. While an assistant professor, he entered the PhD to MD program, graduating with an MD in 1983. His training in internal medicine and oncology was at the University of Florida in Gainesville (1983–1987). After completing his training, he held various positions at the University of Florida until 1993, when he moved to New Orleans, Louisiana, where among other responsibilities he directed the bone marrow transplantation program at Tulane University. By 1998, he was professor of medicine and pediatrics and adjunct professor of pharmacology at Tulane University School of Medicine. His administrative roles rapidly accelerated, and by 1996 he was deputy director of the Tulane Cancer Center and by 1999, associate dean for clinical affairs. In 2008, Dr. Miller and his family moved to Dallas, where he became director of the Charles A. Sammons Cancer Center at Baylor University Medical Center (BUMC) and the chief of oncology of Baylor Health Care System. In 2011, he was made professor of internal medicine of the Texas A&M College of Medicine.

Dr. Miller has been a researcher from his early days in college and has continued his investigations to the present time. He has received numerous grants from regional and national organizations, including the National Cancer Institute. His first publication was in 1974, and he has continued to publish throughout his career. During Dr. Miller’s 6 years here in Dallas, he has had a major impact on oncology at BUMC and the entire Baylor Health Care System. He and his wife, Ellen, are the proud parents of three successful offspring. Alan and Ellen are kind and gracious folks and fine additions to the Baylor family.

William Clifford Roberts, MD (hereafter, Roberts): It is January 7, 2015, and Dr. Alan Miller has come to my house for this discussion. Dr. Miller, to start, could you talk about your early life in New York and your parents and siblings?
aunts, and their children also lived close by. There were a lot of family gatherings. My dad was 7 years older than my mom.

Roberts: What was his name?

Miller: Herbert R. Miller and my mom, Charlotte (Figure 3). My father lived from 1924 to 1983; my mom, from 1931 to 1992. My father fought in World War II as a radio man on the flights that went over the Hump (China-Burma-India). He was part of the crew under pilot Randolph “Randy” Apperson Hearst of the Hearst publishing world and later the father of the infamous Patty Hearst.

Roberts: Did your father keep up with him?

Miller: He sent him notes during the time that Patty was in the hands of the Symbionese Liberation Army. I don’t think he ever heard back from him. When the flight crew finally came back to the States via the West Coast, they went to the Hearst mansion and hung out for a day. After the war, my father managed a movie theater. At 23, he was one of the youngest managers of movie theaters in the Bronx. His fancy was taken by a young girl whom he would see at the movie theater. He learned that she was only 16 but he wanted to meet her. Her parents were very old-fashioned and strict and she had curfews. He had trouble meeting her. He rigged a contest where the movie theater held a Sweet 16 contest and got some of her friends to talk her into entering. All the contestants got sent to a professional photographer and had their pictures displayed in the movie theater lobby. And, of course, she won. The rest was history.

Roberts: How old was she when they got married?

Miller: She was 18 when she got married and 19 when I was born.

Roberts: And your dad was 25?

Miller: Yes, I have two younger sisters.

Roberts: What are their names?

Miller: Cindy and Marci, the youngest.

Roberts: What are some of your early memories?

Miller: My first real memory was the morning my sister Cindy was born. I woke up, walked into the kitchen expecting to find my mother, and my grandparents were there. They told me that my mother had gone to the hospital to have the baby. My other memory is the TV console, composed of 80% cabinet and 20% screen. When I was 5 years old, approximately 1955, my uncles, aunts, and cousins moved way out to Levittown, thanks to the GI Bill. I thought it was the end of the Earth. That was a planned community of 1,000 single family homes. Near the same time we moved halfway to the Borough of Queens (Floral Park area), where the houses were attached. We were in a second-floor apartment. I lived there from ages 5 to 10 and attended elementary school PS 86. These garden homes formed a cul-de-sac, so there were rows on either side and across the back, and it was open in the front with a big green area in the middle. There were lots of kids, so there were always friends; it was a close community. I didn’t understand whether we did or didn’t have money. We were comfortable. We were fed and had clothes.

My father left the movie theater industry because it involved working mostly nights. He went into sales, which is where he spent the rest of his life. Initially, he worked as a salesman in a neighborhood appliance store. I liked it because he brought
home 45 rpm records. Cindy was born when we were in the Bronx, and Marci was born while we were in Queens. We then moved to Long Island, to the town of Plainview.

**Roberts:** You were how old?

**Miller:** I was 10 years old and in the fifth grade. In those days, the Good Humor ice cream truck came around the neighborhood. During the summer of 1959, our ice cream man, Bill, asked me who I liked in the Baseball World Series. Of course I said the Yankees. He said that the Yankees weren’t in the World Series that year. I was just flabbergasted. During my entire life, the Yankees had always been in the World Series. To actually learn that the Yankees weren’t in the World Series was a childhood revelation. Those were the days of Mickey Mantle, Yogi Berra, and Bobby Brown, who later became a cardiologist in Fort Worth. Bobby was a Tulane graduate and served on our medical center board when I was at Tulane. Fantastic guy. The fact that he went to medical school while playing professional baseball is amazing.

Our home in Plainview was a single-family house with a yard and garage and driveway with a basketball hoop. We were now living the American dream. Dad kept working in sales and Mom kept being a homemaker. When preparing to move to Plainview, she had to learn to drive. It was 1959. She had two kids with another on the way, and she had never driven a car. At age 28 she learned to drive. It was a great neighborhood with a lot of families with young kids. We lived there until I graduated from high school (Figure 5) and went off to college.

**Roberts:** You entered college at what age?

**Miller:** I was 18 and went to The State University of New York at Buffalo.

**Roberts:** How did you choose?

**Miller:** I applied to Tufts and to the four state universities in the New York system. The tuition in the state universities was much less than that of a private university. I applied to two of the four anchor schools, the other one being Albany. I didn’t apply to Stony Brook, which was on the island, because I wanted to go away to college to gain some independence.

**Roberts:** Let me go back a bit. Your parents never went to college?

**Miller:** Correct. My dad went directly from high school into the Armed Service. My mom went directly from high school to being a housewife. I was one of the first ones in our family to go to college. My grandparents came from Eastern Europe and my uncles had no college. My cousin, Craig, was the first, and I was the second to attend college.

**Roberts:** How did you do in high school? Were you a good student from the beginning?

**Miller:** I was a B+ student. I took the advanced courses in high school. I never was in the top tier, partially because I could get by on natural ability and didn’t apply myself as much as I could have.

**Roberts:** Did you participate in sports or other activities in high school?

**Miller:** I participated in swimming and track, although I spent most of the time on the bench. My mom strongly discouraged any contact sports.

**Roberts:** Were you a runner in track?

**Miller:** Yes. I ran the quarter mile. I wasn’t fast enough to be a sprinter and didn’t have enough endurance to do the mile run.
Roberts: Were there any teachers in high school who had a particular influence on you?

Miller: Yes. In the seventh grade I had a biology teacher, Howard Weinstock, who piqued my curiosity in the life sciences. In high school I can’t say there was a particular one.

Roberts: How many students were in your graduating class in high school?

Miller: 381.

Roberts: Do you remember where you ranked?

Miller: Number 89.

Roberts: What was your home like when you got to Long Island? Were there a lot of books around the house? What did your parents do?

Miller: No, there weren’t a lot of books around. My parents weren’t big readers. A lot revolved around television. Television was rising in popularity. We watched the Ed Sullivan Show and the children shows. I got to be part of the audience known as the “Peanut Gallery” on the Howdy Doody Show.

Roberts: Did the family eat together at night?

Miller: Yes. We waited for my dad to come home. Lots of times I waited on the porch looking down the street for his car to hit the exit.

Roberts: Did you have conversations at the dinner table?

Miller: My parents certainly tried to involve the kids in conversations. For a while they tried to make dinner a time of family “counseling,” a less-threatening situation where we were in a safe zone and could talk about things that might be bothering us or causing problems. We all had code names in this organization, which were our names backwards. The organization was called “The Rellim,” hence the Millers, and I was Nala. It was a way to get us to open up and talk without any repercussions.

Roberts: Was your home a happy one?

Miller: Yes, it was a very happy home. Any problems always revolved around finances. My father’s occupation was not a lucrative one. When he became a manufacturer’s representative rather than a store salesman and sold to the stores, finances improved. That also put him on the road more often.

Roberts: Did you take vacations?

Miller: When I was young, vacations were limited. A big vacation consisted of spending a few days up to a week in the Catskill Mountains. Finally, when I was 16, we took a Christmas road trip to Miami. There were six of us in the car: my two sisters, my mom and dad, and my mom’s wig box and me.

Roberts: Until that trip you had essentially not gone out of the state of New York?

Miller: I had probably been into New Jersey but not much farther.

Roberts: How did college hit you?

Miller: I was on my own for the first time with my best friend, Richie Goldman, and several others from our high school. We had each other to rely on. Living in a dorm was different from home. Sharing a dorm room with someone assigned to me other than my friends was challenging at times. I found college very challenging early on. I found that I couldn’t get by like I did in high school without studying a lot. My first 2 years were rough. I was social but not a big party person. I joined a fraternity, hung out with the fraternity brothers, hung out at the student union, and as a consequence school suffered. Mom and Dad weren’t happy with my report cards early in college.

Something clicked in my junior year. I started getting involved in student government. Knowing that I had to budget my time better and the fact that the courses became more interesting helped. Being away from the 200+ student lecture hall classes where no one noticed if you were paying attention or not, I made the dean’s list in both my junior and senior years. In my junior year, I was elected president of the Dorm Student Association, which I served during my senior year. This was the late 1960s and early 1970s, a very political time. Vietnam was at its height. These leadership activities in college focused me for later positions of leadership.

During my senior year as a biology major, I was required to do an independent research project. As background, the summer after my sophomore year, I worked for a researcher at the Waldemar Cancer Research Center. (My mom had worked there as a volunteer and knew several scientists.) They paid me what I thought was a very handsome $2.50 an hour. My research boss was Leo Gross, PhD, who started me at the bottom. To partially fund their cancer research, they took on contract research in antibiotics. One project was to measure the clear- ance of the antibiotics from urine. They had multiple freezers full of frozen bottles of urine. My job was to thaw the bottles, filter the urine, and then wash all the bottles so they could be used again. The filtering of the urine was the most interesting part. I used an Erlenmeyer flask, and on top of the flask was a silver contraption that had a thick filter pad inside, which was
screwed down very tight to secure the filter and then the urine was poured through the top. Rather than a suction, it was driven through by nitrogen hooked up through a hose to the top of this contraption. I got very proficient at it. One day Dr. Gross came in and complained that the filtering was too slow. To show me how to do it faster, he altered the filtering process and then the urine splattered everywhere. Thereafter, he left me to my own devices. The urine was collected from normal volunteers.

The next part was going to be done on patients in a rehabilitation facility located near Nyack, New York, a 1.5-hour drive from Long Island. They gave the test antibiotics to the patients in the rehab facility, and then we collected the urine on catheterized patients and tested it. A young postdoc also worked at the lab, and she got the day shift. I got the night shift. We did this for 7 days. I would leave home about 5:00 pm and drive up to Nyack and start my shift at 7:00 pm. Every 4 hours I would go around with a flashlight and a box of jars and creep up to the beds and collect the urine from the catheter bags. We had big trash cans with dry ice to hold the samples. It was a great experience for me, plus I got double-pay for working the night shift, $5.00 an hour.

After this experience, I wanted to do something more interesting than the other student projects I’d seen. I knew that Dr. Gross had a friend who was head of education at the Roswell Park Cancer Institute in Buffalo. I asked Dr. Gross if he could arrange an introduction for me because I would like to see if I could do my research project at Roswell Park Cancer Institute. He did, and I interviewed with Edwin Mirand, PhD, a distinguished scientist who did a lot of the early work that led to the development of erythropoietin. Dr. Mirand wanted me to talk to one of his colleagues, Michael Patrick McGarry, PhD. Mike is still one of my life-long friends. My first shock when I walked in was realizing that he wasn’t that much older than me. He started talking about the work they were doing and his passion for the eosinophil. I started working on eosinophils. While my fellow students were doing plant phylum in petri dishes, I was doing surgery on mice, implanting the diffusion chambers in their bellies with bone marrow, treating them with tetanus toxoid, and then looking for development of eosinophils in these chambers. It was fascinating stuff.

At that time I was in the process of putting in applications to medical schools. Mike told me that I was pretty good at this research stuff. He asked if I wanted to stay there and go to graduate school. Roswell Park had its own graduate program, which was under the auspices of the University of Buffalo, but Dr. Mirand was in charge. He suggested I do a master’s degree for a year and then decide if I wanted to stay on for a PhD. It sounded like a reasonable approach. Knowing how poorly I’d done my first 2 years of college, it couldn’t hurt my application. So I joined his lab and 3 years later I had a master’s and a PhD at 25 years of age, with publications in Nature and Blood. We defined the fact that there was a soluble factor that was triggered by secondary antigenic challenges that caused the production of eosinophils, called the *eosinophil-stimulating factor*, and the models we used were both the tetanus toxoid model and the schistosomiasis model. Many years later, when the tools to clone proteins were available, work done by others purified eosinophil-stimulating factor, and it is now *interleukin-5*.

I really enjoyed the research. Because I enjoyed working on blood cells and blood cell stimulation, I decided to do a postdoctoral fellowship. I applied for two of them and was offered both. One was at Sloan Kettering in New York City with Malcolm Moore, PhD, who went on to develop the granulocyte colony-stimulating factor. Malcolm took me into the lab and showed me a bench space about 4 feet wide and said that would be my space. I would be my own technician. The other opportunity was at the University of Miami with Adel Yunis, MD. Dr. Yunis was from Lebanon and was a very dynamic fellow. In contrast to the 4 feet of lab bench I would have had in New York, he showed me the full lab that I would use and introduced me to the technician that would be working with me. I accepted Adel’s offer. Adel is most known for defining the mechanism of chloramphenicol bone marrow toxicity. I worked with him on the mechanisms of toxicity as it related to the stem cells in the bone marrow. Plus, I had my own research projects looking at defining subsets of the bone marrow progenitor cells—which ones had fate to become granulocytes or erythrocytes or platelets.

After 1 year in Miami, I went home to visit the family on Long Island. Now I was 26 years old. My baby sister, Marci, mentioned that her friend had a sister, Ellen, who was a med-tech moving to Miami to continue her education at the University of Miami. Marci thought I could give her information on possible jobs as a med-tech and the lay of the land in Miami. I agreed. That afternoon Ellen called and we talked for quite a while. Then Ellen mentioned that she had a book of Marci’s that she needed to return and I told her to come by and drop it off. This was a Saturday evening. (I actually had planned on spending the evening with Marci because I was leaving the next day.) Around 7:00 pm on the porch appears this knock-out, all dressed up, so I assumed that she must be on her way out for the night and was really just dropping off a book. We stood there talking for 45 minutes when finally I realized that maybe she wasn’t going somewhere else. I invited her in. She came...
in and we shared some wine and talked. I went to Marci and asked her if she would mind if we canceled our date. So Ellen and I went out.

I went back to Miami the next day. She was coming down 6 weeks later to move into the dorms. I picked her up at the airport and a little over a month later we were engaged. That following spring we got married (Figure 8). We will be celebrating our 37th anniversary this year!

Our first child, Michelle, was born in 1979. This was during my postdoc in Yunis’ lab. I was a postdoc for 3 years and then in 1979 I was offered an assistant professor position at the University of Miami. Now I had my own lab but still worked with Yunis. I did some hematology teaching at the medical school. The University of Miami had a unique program at that time, the PhD to MD program. If you had a PhD in the biologic sciences you could earn your MD degree in 2 years—so many times, I tell people I only know half as much as the other physicians. It was a very intense program. All of the basic sciences were completed in 9 months. Because of the PhD background, one could test out of some courses (board-style exams). I was able to test out of physiology and microbiology, but took all the other courses—gross anatomy, pharmacology, etc. Then there was 15 months of clinical work. The full junior year had the standard rotations plus 3 months of electives. I graduated with a regular medical class. I entered that program in 1981 and finished with my MD in 1983.

Roberts: If your mother hadn’t have done volunteer work at that hospital where you got a job, you may have turned out differently.

Miller: Exactly. It was a pivotal summer. During medical school, Dr. Yunis let me keep my lab and technician and kept me on as 20% FTE. Basically, I would come in, design experiments, and review results. I had my lab going and was still publishing through medical school. With our daughter at home, Ellen worked two jobs—as a medical technologist and aerobics teacher—to help us get through that period. In the evenings she went to different homeowner clubhouses, something that led to her going into the fitness business. Eventually, she started her own company, Isobreathing, Inc., which designed exercise programs and sold DVDs and books.

Then it came time to apply for residency programs. I knew I was going to do oncology; the only question was whether to do adult or pediatric oncology. I decided that adult was the way to go and internal medicine was my choice. I went into the match applying for internal medicine programs and matched at the University of Florida in Gainesville. One reason I wanted to go to the University of Florida is that I knew the chief of oncology, Roy Weiner, MD. I had met Dr. Weiner a few years earlier when I was applying to the PhD/MD program and he had just begun working at the University of Florida. We met at an experimental hematology meeting and he had mentioned the program and said that if I was interested, I could come and run the bone marrow lab he was developing to support the bone marrow transplant program they were building. I was flattered but I told him I was then applying to the PhD/MD program. He concurred it was a good decision but he wanted me to come see him when I was ready for internship and residency. He was able to work with the leadership of the Department of Medicine and design a program for me where I basically went in and out of my residency and the lab. It followed the old National Institutes of Health (NIH) model for the NIH scientist training program. I did my first 1.5 years of internal medicine uninterrupted and then 6 months in the lab, and then I went back and forth 6 months and 6 months. The later parts of this started counting toward my oncology fellowship. In essence, I went into medical school at 31 years of age and finished medical school, residency, and fellowship by the time I was 37. At that point I joined the faculty at the University of Florida (1987).

In 1984, during my residency, our second daughter, Rebecca, was born. There were many challenges having two children during residency. Ellen was staying home and juggling a lot of things. She was tremendous and a trooper through this whole time. The day she came home from the hospital I had left my hospital, picked her up at her hospital, dropped her off at the house, and went back to work. Our third child, Joshua Lawrence, was born in 1987.

While working on the faculty of the University of Florida, I became more involved in bone marrow transplantation and experienced the clinical side of what I had been doing in the laboratory for the previous 11 years, which was the growth and regulation of human bone marrow. Early on in my position, I had received grants from the NIH, the Veteran’s Administration, and the American Cancer Society. I had a lab where I predominantly lived and did a couple of months of clinical work a year.
with one clinic day a week. It became more challenging to get grants, and the clinic became more fun, so I started moving slowly towards the clinical side.

In 1993, Dr. Weiner was offered a position at Tulane University in New Orleans to start a cancer center there. I was encouraged by the University of Florida to stay and take on a bigger leadership role. I was already in a leadership role in the bone marrow transplant program but Dr. Weiner strongly recruited me to go with him to Tulane and start a bone marrow transplant program and help him build a cancer center. In the end, I made the choice to go with him. For the next 15 years I was at Tulane. At Tulane my position changed over the years. I started off as director of the bone marrow transplant program and associate director of the cancer center. Around 2001, a vacancy opened for a vice president for clinical affairs. That position ran the group medical practice of close to 400 physicians in all specialties. They decided to fill it with an internal search and when I thought about who the candidates might be, I decided I was better suited for that job than they were. I got the job.

Paul Whelton, MD, MSc, a nephrologist and previously dean of the School of Public Health at Hopkins, was the senior vice president for health sciences at Tulane and I reported to him. He taught me a lot about leadership and administration. I ran the practice and then Dr. Whelton promoted me to associate senior vice president for health sciences. Health sciences at Tulane included the medical school, school of public health, and the Tulane National Primate Research Center, which is one of seven national primate centers. I helped Paul with the oversight of those entities as well as continuing to have the oversight of the clinical operation of the medical school. Everything was going nicely. We were working on some very interesting partnerships with Louisiana State University, which was down the street, with a joint goal of building a combined cancer center and going for National Cancer Institute designation.

In 2005, along came Katrina, which rocked the world of New Orleans, and certainly the world of Tulane and all of us who worked there. (I could spend another hour talking about what happened to us during the rebuilding of the university, medical school, and hospital.) We all had to do some interesting things, and one of my most interesting tasks was to find a cruise ship and bring it back to New Orleans to provide housing for those who had lost their homes when we reopened the university. It was for faculty, staff, and students. We had to fly around to locate a cruise ship, and we did. Less than 6 months after the hurricane, we reopened the medical school, hospital, and university. I think Tulane is as good as or stronger than it was before.

My thoughts had been that when Joshua graduated from high school, I would look for my next opportunity. But with Katrina, there was a need for people not to jump ship and stick around to help rebuild the school and the city of New Orleans. I sat down with the president of the university and he asked for a commitment to stay for a while until things were back to a more normal situation. We agreed on some terms and I stuck around until 2008. Things were moving very well at Tulane. Paul Whelton had accepted a position at Loyola Medical Center in Chicago. I served for a while at the interim senior vice president for health sciences, but the goal for Tulane at the time was to have a bit more consolidation and no longer have health sciences as a separate fiscal unit and bring it more into the university. I started looking at other opportunities and was on the short list for several positions. I was looking at department chairs and dean jobs.

I got a call from a recruiter whom I had heard from about a year earlier. At that time I wasn’t interested in hearing about positions, but she called back and asked if I was on the market yet because that position was still available. I asked her to tell me about it. She said there was an institution called Baylor University Medical Center in Dallas, Texas, and they were going to make a major investment in cancer. I asked, “How major?” She said in the neighborhood of $350 million. They are building a 400,000+-square-foot cancer center and a cancer hospital and are expanding programs (Figure 10). They have a health care system and want oncology developed for the health care system and they are looking for someone to lead it. I was interested. This was June 2008. We initially did a video interview and then a visit to Dallas and BUMC. I...
also talked to the administrator for the cancer center, Donna Bowers. Donna and I had a great conversation. In August 2008, I came and met with many interviewers, saw the plans, and liked what I saw. I went home and told the family that this could be a good opportunity. A couple of weeks later another hurricane was on its way to New Orleans, and Ellen suggested that we go to Dallas. I called the recruiter to let her know that we would be in town if BUMC had any questions. We got to Dallas and meetings were scheduled. By the time that week was over, it was pretty much settled on my part and BUMC’s part that I was coming. Although normally academic appointments take months, my first visit was in August 2008 and I started at BUMC in November 2008. Both sides felt that this was a good combination. I have had the joy of watching this cancer center grow over the last 6 years.

Roberts: What’s been the biggest challenge to get this off the ground?

Miller: The biggest challenge here is that the physicians that we rely on for most of the success are independent private practitioners in different groups. Unlike having faculty report to department chairs, who then report to a dean, here you have to sell your program and get people to want to come on board. We have an incredible wealth of talent. Getting everyone to work for common goals is the challenge.

Roberts: What are your plans now?

Miller: Our oldest daughter, Michelle, is married (Figure 11) and has two children, and they live in Pennsylvania; Rebecca is in Jacksonville, Florida; and Joshua is currently in San Diego but soon will be moving to New York City.

Roberts: What does he do?

Miller: He is a consultant for a firm that helps health care companies launch new products. He has his master’s degree in business and in bioscience. He has a great combination of skills.

Roberts: Do your daughters work?

Miller: Yes. Both are partners in a company that makes all natural healthy dog treats. In addition, Michelle does some fitness work, following in Ellen’s footsteps, and now is over Ellen’s Isobreathing company. Rebecca works in a law office.

The plans at Baylor are to continue to grow our programs by focusing on different cancers and developing “research and treatment” centers. Right now we are focusing on the pancreatic cancer research and treatment center. We build the treatment options and the research opportunities and work to gain recognition for our team as the leaders, if not in our region, in the country, for treatment and research for that type of cancer. We are building these centers one cancer at a time, building on the strengths that we have and bringing in staff where we need them. We are building many around the new molecular dimensions of cancer, targeting molecular abnormalities in the cancer so that the treatment is much more focused than our traditional treatments.

Roberts: What is your day-to-day life like? For example, what time do you get up in the morning?

Miller: I get up around 5:00 am. I’ll either start the day with one of our tumor conferences at 6:30 am or, if there is no conference that day, I’ll go to the Landry Center at 6:00 and work out for an hour.

Roberts: What time do you leave the hospital usually?

Miller: I leave at 6:00 pm unless there is a late meeting.

Roberts: So you work half day? 12 hours?

Miller: Yes.

Roberts: What does your day look like after the conference?

Miller: My time is predominantly spent in meetings—whether it’s meetings to develop the research and treatment centers or about the hospital. Our meetings have multiplied and magnified with the Baylor Scott and White combination. I spend a lot of time figuring out how to integrate oncology between the North Texas and Central Texas branches of our new larger organization. I’m involved in a few clinical research projects, so I review data or other necessary paperwork involving them. I meet with faculty, helping them develop their areas. I’ve put together a solid leadership team to develop all the areas. A lot of my time is now spent with the administrative oncology leader, JaNeene Jones, who took over when Donna Bowers left.

Roberts: Do you see private patients anymore?

Miller: I see patients in the context of the research studies. I will see a patient who goes into one of the trials that I’m involved in, but I don’t have a general open practice.

Roberts: Do you do any bone marrow transplants anymore?

Miller: No.

Roberts: Are you going to work forever, or what are your plans?

Figure 11. At Michelle and Stephen’s wedding, March 17, 2007: Josh, Rebecca, Ellen, Alan, Michelle, Steve.
Miller: I won’t work forever, but right now I don’t see a stop point that would be designated by a particular age or year. I think it’s all going to depend on how long I’m doing things that I enjoy and how those around me feel about my contributions. It’s one of those things that I may recognize it when I see it, but I don’t see it yet.

Roberts: Do you have any hobbies or interests outside of medicine?

Miller: I write. In October 2014, my debut novel came out (Figure 13). Called Reform, it is speculative fiction of what health care might look like in 75 years based on what is happening now. I actually started writing this book over 20 years ago. The idea back then was that technology was changing so much that it was creating a gap between the physician and the patient. A lot of it was technology—robotic—so many things have already come to pass.

When I moved to Dallas, I decided I really wanted to get serious about my writing. I enrolled in the creative writing course at Southern Methodist University at night. I went through the whole cycle of classes, which took about 3 years, and this drove me to write this book. An assignment occurred with each class. Along with that, all the changes in health care reform started coming down, and that plus current technology could lead to a corporate world of medicine where a physician has basically been replaced by machines and technicians. The book is set 75 years in the future, when there are no more medical schools and the only physicians are trained through apprenticeship by a group called The Hippocratin Society. A medical crisis occurs around 2089, and there is a need for the physicians to come to the fore for things to work out. But the medical corporate giant, MED-MET, does everything in its power to suppress the physicians. So there’s intrigue, dirty tricks, romance. Now I am working on a sequel.

Roberts: What’s that one going to be called?
Miller: Corridor A.

Roberts: When do you do your writing?
Miller: On weekends or late at night or whenever the mood hits me.

Roberts: What time do you go to bed at night?
Miller: About 10:00 pm.

Roberts: Seven hours of sleep are sufficient for you? What have been the comments on your book?

Miller: Yes, I’m good with 7 hours. Comments have been “page-turner,” “exciting,” “thought provoking.”

Roberts: Your wife likes it?
Miller: She loved it. She’s the one driving me to write the sequel. She wants to find out what happens.

Roberts: How much time do you take off a year?
Miller: I take off 2 to 3 weeks.

Roberts: Do you have a place you go to?
Miller: We have a lake house on Lake Cypress Springs, near Mount Vernon.

Roberts: How far is that?
Miller: About 1½ hours.

Roberts: Do you go there often?
Miller: When the weather is right, not too cold or not too hot.

Roberts: What do you do there?
Miller: We have canoes and kayaks. My wife is big on standup paddle boarding. We have bicycles.

Roberts: When you go on vacation out of this area, where do you like to go?
Miller: We either go to visit our kids—spending time with each of them or having them all meet somewhere like a beach house—or Ellen and I go to places we haven’t seen before (Figures 14 and 15). This coming May we are going to Africa in a photo safari trip that we are very excited about.

Roberts: You like taking photographs?

Miller: I love taking photos. It’s a hobby and I don’t do it as much as I’d like to. Some of my favorites I’ve taken over the years are hanging in the house. One of Ellen’s hobbies is painting, so many times she’ll take my photo and use it as the model for her painting.

Roberts: What is your house like?

Miller: It’s too big for the two of us. We live in North Dallas just north of I-635. It’s a relatively new house, about 12 years old. It has a lot of space and a mixture of furnishings from when we first got married to things we’ve picked up around here.

Roberts: When you get home at night, do you have a glass of wine or cocktail?

Miller: I did up until about 6 months ago. I didn’t give up drinking but just gave up having a drink every night, and between that and desserts and other things, I’ve managed to shed 30 pounds since July 2014. I’ll have a glass of wine on the weekends. I’ll get home and have dinner, which has changed now in that we have a huge salad. Ellen is also a potter, so she’s made some large bowls so we’ll fill them up with salad. Usually, unless she gets home early, we’ll share time cutting up ingredients for the salad.

Roberts: Do you feel much better after losing the weight?

Miller: My energy is higher. I didn’t realize how much better I would feel.

Roberts: How tall are you?

Miller: A little under 6 feet.

Roberts: Is there anything we haven’t talked about that you’d like to mention?

Miller: I think we’ve covered just about everything.

Roberts: Many thanks, Alan, for your openness!
In medicine, and in life in general, uncertainty is unavoidable. Throughout history, man has tried to bring order to a chaotic world by predicting future events based on past experiences. However, physicians in training are often surprised by the subjectivity and lack of certainty involved in the practice of medicine. Helpful advice is available—and Sir William Osler had much to say about this problem. This article reviews some of Osler’s writings regarding medical uncertainty, provides an outline of the classification currently used by the courts to evaluate medical testimony, and offers some historical notes on probability theory and evidence-based medicine.

OSLER ON UNCERTAINTY

Sir William told medical students:

A distressing feature in the life you are about to enter, a feature which will press hardly upon the finer spirits among you and ruffle their equanimity, is the uncertainty which pertains, not alone to our science and art, but to the very hopes and fears which make us men. In seeking absolute truth, we aim at the unattainable, and must be content with finding broken portions (3).

The practice of medicine is an art based on science, but Osler believed that this was one of the most difficult arts in the world to acquire. He further stated the extremely critical point that “errors in judgment are inevitable in the practicing of an art which consists largely of balancing probabilities” (2). This balancing of probabilities is integral to the day-to-day activities of the physician who produces a differential diagnosis and then systematically confirms or eliminates the various hypotheses. However, as Osler pointed out, “Variability is the law of life and no two bodies are exactly alike, and no two individuals react alike under the abnormal conditions which we know as disease. This is the fundamental difficulty in the education of the physician” (2).

Such a statement is surprisingly timely in our era of personalized or precision medicine, in which targeted therapies are tailored to the individual genetics of a patient at the molecular level. This variability among patients also is why experienced physicians, like William C. Roberts, MD, approach every case with the question: “What is unusual about this case?”

Osler also stated, “Probability guides us when certainty fails,” but he emphasized that uncertainty is unavoidable. He further stated, “There is no discredit, though much discomfort at times in the everlasting perhaps which must preface so much connected with the practice of our art.” Therefore, physicians in training should not be surprised that opinion (not full knowledge) “must be their stay and prop” (2).

UNCERTAINTY AND THE COURTS

Expressing medical opinions under oath is a common activity of the forensic pathologist, and the degree of certainty required depends on the actions and claims that rest on them. The following discussion provides a general outline of the various categories and levels of certainty as used by the courts (1).

Proof beyond the shadow of a doubt is a concept derived from written and televised fiction dealing with the law. Nevertheless, “absolute diagnostic certainty” can be considered to represent the highest level of probability. This is certainty beyond a possible doubt where the likelihood is 100%. One must hold that every other imaginable contingency is impossible. In reality, the law requires lesser degrees of proof, depending on the type of proceeding.

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A “reasonable degree of medical certainty” is the level of proof required in criminal proceedings. In this category, the conclusion is beyond any “reasonable” doubt. This category has no formal definition of numerical probability, but the opinion is generally considered as significantly exceeding 50% likelihood.

A “reasonable degree of medical probability” is the next lower level of proof as used by the courts. In this category, the conclusion is defined as having a probability greater, but not significantly higher, than 50%. This is the degree of probability or burden of proof required in most civil (tort) proceedings, such as medical malpractice cases. This is also the level of certainty required for opinions given on death certificates. In this category, any contingency having a likelihood exceeding 50% may be considered probable or more likely than not. For example, in a medical malpractice case, it must usually be established by expert testimony that a deviation from the standard of care, more likely than not, occurred and led to the patient’s injury. Adherence to the “standard of care” simply means the physician did what a “reasonably prudent” physician would have done under similar circumstances. In such cases, the opposing experts often disagree, and the jury must decide which expert or argument is most credible.

Interestingly, this level of certainty is essentially the same burden of proof used by grand juries who determine whether probable cause exists. A fact has been committed and whether an indictment (true bill) should be returned against a defendant. Probable cause simply means “having more evidence for than against.” If a true bill of indictment is returned by the grand jury, the case enters criminal proceedings where a higher burden of proof (beyond a reasonable doubt) is necessary for conviction.

A “reasonable possibility” involves an opinion or conclusion whose probability is less than 50%. This generally means that the hypothesis does not defy the laws of nature. Such a standard has negligible evidential importance in court; however, a medical witness may be asked if some scenario is “possible” or “conceivable” in order to establish that he or she is not entirely excluding the opinion given by the opposing expert, even though he believes that it is unlikely. Quasi-judicial proceedings such as workmen’s compensation boards may be satisfied with this degree of certainty in a case where the presumption ordinarily favors the worker.

“Speculation” involves a possibility that is so remote that it has no basis in reason. In court, this is usually considered to represent “a guess.” Generally, speculation is not allowed in civil or criminal testimony. Furthermore, if a witness wants to generate some excitement in court, he may preface an opinion with “I would speculate that . . . .” This is guaranteed to generate a forceful objection by one of the attorneys, and often an admonition from the judge to refrain from speculation.

One caveat regarding the above categories is that medical opinions are based on facts as they are known at the time the opinion is rendered. If the facts change (such as when new testimony is given by witnesses), the opinions are likely to change as well. Some experts state in their reports: “These opinions are based on a standard of reasonable medical probability, using the currently available information; I reserve the right to supplement or amend this report if warranted by additional information.” Although somewhat obvious, this statement may cause a judge to allow a second report to be submitted if the facts change.

**STATISTICS AND CERTAINTY**

Physicians must also understand that the statistical definition of “probable” used in medical research or evidence-based medicine applies only to data numerous enough to permit statistical analysis. A P value less than .05 merely indicates that the likelihood of a difference between two data sets being due to chance is less than 5% (1 chance in 20). This is an incorrect and inappropriate standard to require when rendering a medicolegal opinion in a single case, because a single datum is not amenable to statistical analysis. However, the use of statistical probability in general and the $P$ value in particular are so important to conclusions regarding evidence-based medicine that a brief look at their origin and history is warranted.

Much of the mathematical foundations of probability theory and combinatorial algebra began with questions relating to certain gambling problems posed to French mathematicians Blaise Pascal and Pierre de Fermat in 1654 by Antoine Gombaud, the Chevalier de Méré. Subsequent developments, including the production of gambling manuals by other workers, led to mathematical formulas and methods that generate the bell-shaped curve, or normal distribution. Subsequently, in 1894, Karl Pearson coined the term standard deviation, and in 1925 Sir Ronald Fisher, in his book *Statistical Methods for Research Workers*, appeared to be the first to mention $P = .05$ as a level determining statistical significance.

Sir Ronald stated:

> It is convenient to take this point as a limit in judging whether a deviation is to be considered significant or not. Deviations exceeding twice the standard deviation are thus formally regarded as significant. If one in twenty does not seem high enough odds, we may, if we prefer it, draw the line at one in fifty (the 2 percent point), or one in a hundred (the 1 percent point). Personally, the writer [Fisher] prefers to set a low standard of significance at the 5 percent point, and ignore entirely all results which fail to reach this level. A scientific fact should be regarded as experimentally established only if a properly designed experiment rarely fails to give this level of significance.

Therefore, the selection of a cut-off for significance is somewhat arbitrary and raises philosophical questions such as whether people (scientists and nonscientists alike) generally feel that an event that occurs 5% of the time or less (when multiple trials are executed) is a rare event. If the answer is yes, then the adoption of this level as a criterion for judging outcomes is justifiable. Therefore, selection of a threshold depends on subjective interpretations, and, as a formal statement, the level has a more complex history than is generally appreciated.

The theories of probability that originated in a gambler’s dispute are now at the base of many enterprises that we consider more important than gambling, including all kinds of insurance, mathematical statistics, and their application to biology, medi-
cine, educational measurements, and much of modern theoretical physics. We no longer think of an electron being “at” a given place at a given instant, but we do calculate its probability of being in a given region. A little reflection will show that even the simplest measurements we make (blood pressure, etc.) are statistical in nature (5).

Definitions of probability are most frequently based on formal mathematical theory, but what often eludes precise definition (the level of “acceptable” uncertainty) is the subjective probability involved in the personal cognition of individuals whereby past experience aids in the formation of expectations for future events. Furthermore, our need to use mathematical probability theory, in a sense, reflects a need to bridge the reality of events in everyday life and the philosophy of logic (4).

CONCLUSION

The above discussions are intended to illustrate that uncertainty is unavoidable and should be expected in the practice of medicine (and in life as well), but useful guidelines are available. In the words of Sir William Osler:

We must collect facts in order to establish general principles. But in the practice of medicine, where our strength should be, lies our greatest weakness. Our study is man, as the subject of accidents or diseases. Were he always, inside and outside, cast in the same mold, instead of differing from his fellow man as much in constitution and in his reaction to stimulus as in feature, we should ere this have reached some settled principles in our art (2).

Still, he advised that probability guides us when knowledge fails.

In conclusion, the subtle theories of subjective and mathematical probability lie at the very roots of human knowledge and form the basis of much of scientific knowledge as we attempt to predict outcomes from scientific research and day-to-day experiences. Most agree that Pascal and Fermat stated and solved a genuine problem, that of bringing the superficial lawlessness of pure chance under the domination of law, order, and regularity (5). And, to our physicians in training, don’t be surprised by diagnostic uncertainty, especially considering today’s complex patient populations. Remain courageous and heed Dr. Osler’s advice regarding life’s challenges in general and difficult diagnostic and therapeutic choices in particular: “If the fight is for principle and justice, even when failure seems certain, where many have failed before, cling to your ideal, set the horn to your lips, sound the challenge, and calmly await the conflict” (2).

After a hiatus of 8 years, in November 2014, the Commissioner’s office resurrected the series of Major League Baseball (MLB) games against Japanese professional teams. (They were stopped after the World Baseball Series began in 2006.) I was selected to be the medical team physician, out of nine candidates, partly based on my longevity (39 years) as a team physician for the Atlanta Braves. (It may have also helped that I listed Hank Aaron as a reference.) Charles Bush-Joseph (White Sox) was the orthopedist. Each player and physician could bring one guest, so my wife, Marilyn, got to accompany me. Several players invited their dads, which was nice. Seven games were scheduled in four Japanese locations (Osaka, Tokyo, Sapporo, and Okinawa), with two of the seven being exhibitions.

HISTORICAL VIEW OF BASEBALL IN JAPAN

For over two centuries, Japan was isolated from the West. The penalty for a Japanese citizen who left the country and tried to reenter was death. That all changed in 1853 when American Commander Matthew Perry and his four black warships appeared in the Tokyo harbor. A truce was arranged without warfare, and it became possible for Americans to enter the country. American school teachers in Japan, Horace Wilson and Albert Bates, introduced the game of baseball to the Japanese in the 1870s (1). Hiroshi Hiraoka, who had studied in Boston (and was a fan of the Red Sox), established the first baseball team in Japan in 1878.

The first game involving Japanese and American players was in 1896. Several Japanese college baseball teams toured the western coast of the United States, competing against teams from Stanford, the University of Southern California, and Washington. The first American professional team (the Reach All-Americans) to play in Japan in 1908 comprised MLB reserve players and those from the Pacific Coast League. In 1913, as part of a world tour, the New York Giants and the Chicago White Sox played in Japan. In 1922, a team including Waite Hoyt, Herb Pennock, and Casey Stengel became the first to lose to the locals. Ty Cobb did a brief coaching stint in Japan in 1930. The next year a powerful American team, featuring Gehrig, Grove, Cochrane, Frisch, Maranville, O’Doul, and Simmons, won all 17 games against Japanese amateur opponents.

The sport really took off in Japan in 1934 when Gehrig returned, joined by Ruth, Gehringer, Foxx, and Moe Berg, again winning all 17 games. A crowd of 75,000 saw the game in Osaka’s Koshien Stadium. One fan was said to have walked 80 miles in the rain to attend the games and to present a treasured ceremonial sword to the first American (Earl Averill) to hit a home run. Later, a bust of Babe Ruth was placed outside the main gate (Figure 1). Japanese professional teams were started in 1936. Through the ensuing years, many great American stars competed in Japan, including Joe DiMaggio (1951), Mickey Mantle (1955), Stan Musial (1958), Willie Mays (1960), Hank Aaron (1974), Pete Rose (1979), Cal Ripken (1984), Dale Murphy (1986), Ken Griffey Jr. (1990), and Ryan Howard (2006).

Figure 1. Bust of Babe Ruth, at Osaka’s Koshien Stadium.
FORMER JAPANESE STARS

Teenage amateur pitcher Eiji Sawamura struck out Gehriger, Ruth, Gehrig, and Foxx in succession in 1934 (1). He was later killed during World War II when his ship was torpedoed. The Japanese equivalent to our Cy Young Award was named in his honor. Tetsuharu Kawamura was called the “Japanese Ted Williams.” Sachio Kinugasa once played in 2215 consecutive games, despite suffering five broken bones. Third baseman Hiromitsu Ochiai won three triple crowns. Twenty-game-winning pitcher Shinichi Ishimaru played catch before leaving on a kamikaze mission and insisted on throwing 10 consecutive strikes before entering the plane. Infielder Shigeru Mizuura was in a Siberian prisoner-of-war camp and proceeded to teach the game of baseball to his Russian captors. Shigeo Nagashima and Sadaharu Oh were infielders and teammates on the legendary Tokyo Yomiuri Giants, leading them to nine consecutive championships. The extremely popular Nagashima won six batting titles (versus five for Oh), but Oh excelled in home runs, hitting 868 between 1959 and 1980. In a home run–hitting contest against 40-year-old Hank Aaron in 1974, the 34-year-old Oh narrowly lost, 10 to 9 (1).

MOE BERG

One of the most intriguing MLB players to play in Japan was catcher Moe Berg, a 15-year veteran who played on five different teams (2). A graduate of Princeton, Berg was said to be fluent in 12 languages (and unable to hit in any one according to one coach). Casey Stengel once said Berg “was the strangest man ever to play baseball” (2). Berg played in Japan in 1932 and returned with Ruth, Gehrig, et al in 1934, carrying a hidden movie camera, as he was also a spy for the Office of Strategic Services (OSS, a forerunner to the CIA). He snuck into St. Luke’s Hospital in Tokyo and filmed the Tokyo skyline and bay from the rooftop. The film “may have helped Lt. Col. Jimmy Doolittle plan his famous Doolittle Raid” (2). During World War II, Berg parachuted into occupied Yugoslavia (to assess the relative strengths of anti-Nazi resistance groups) and later concealed a weapon to possibly assassinate German physicist Werner Heisenberg (lecturing in neutral Switzerland) if he was convinced Heisenberg was very close to perfecting the atomic bomb (he wasn’t).

JOE DIMAGGIO AND MARILYN MONROE

As mentioned earlier, Joe DiMaggio had played in Japan in 1951. In the spring of 1954, he was romantically involved with Marilyn Monroe. According to Joe’s friend and former teammate, Bobby Brown, “Marilyn was making a movie called ‘Pink Tights’ and didn’t like the script and rebelled” (3). She was suspended and decided to accept Joe’s marriage proposal.

Lefty O’Doul, then manager of the San Francisco Seals, had given baseball clinics in Japan and convinced Joe to go there for his honeymoon, stating that “it’s a foreign country, they will leave you alone” (3). DiMaggio was looking forward to walking about Tokyo without being pestered. Little did Joe know that “the two biggest items in Japan life were ball players and movie stars” (3). Joe had called Bobby Brown (then a doctor stationed in Tokyo) from the airport, stating he would meet him at the hotel within an hour. Seven hours later, the newlyweds finally arrived at the Imperial Hotel. An estimated 5 million Japanese had lined the streets “all the way from the airport to the hotel just to get a glimpse of them” (3). Joe and Bobby subsequently conducted baseball clinics in Tokyo, Osaka, and Fukuoka, while Marilyn flew up to Korea to entertain the US troops.

THE MAJOR LEAGUE BASEBALL ALL-STAR TEAM

The MLB team (Figure 2) featured the two leading batters in the leagues, Justin Morneau (Colorado) and diminutive Jose Altuve (Houston) (Figure 3a, 3b). Perennial all-stars Robinson Cano and Evan Longoria (Figure 4) were joined by three regulars from the World Series runner-ups, Kansas City (pitcher Jeremy Guthrie, shortstop Alcides Escobar, and catcher SalvadorFORMER JAPANESE STARS

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Perez). Hyperkinetic Yasiel Puig (Figure 3c) of the Dodgers added youthful spark to the outfield. The top pitchers included rookie-of-the-year runner-up Matt Shoemaker (Angels) and Chris Capuano of the Yankees (Figure 3d). Both Chris and his wife, Sarah, were fellow Duke University alumni; Sarah had tried out in the Olympic pentathlon.

THE SERIES

The first game, an exhibition against the combined Hanshin Tigers and Yomiuri Giants, was held in the 90-year-old Koshien Stadium, where Babe Ruth performed in 1934. The MLB team, powered by home runs by Perez and Dexter Fowler (Houston) and a grand slam by Evan Longoria, built an 8-0 lead and almost lost it in the 9th when the Japanese team, new trailing only 8-7, had the bases loaded before Jeff Beliveau (Tampa Bay) shut them down.

We moved to the Osaka Dome for the official start of the five-game series. MLB lost 2-0 and we got the first look at future Japanese superstar pitcher, 20-year-old Shohei Otani. We took the bullet train to Tokyo where Ambassador Caroline Kennedy and Sadaharu Oh (Figure 5) threw the ceremonial first pitches. Ambassador Kennedy graciously hosted the team the next day at an embassy luncheon and included Japanese
Special Olympians and youth baseball players. MLB lost again, the second game, 8-4, as the Japanese roughed up their former teammate, Hisashi Iwakuma. In the third official game, four Japanese pitchers combined on a no-hit 3-0 victory, clinching the series for Japan—only the second time in an 80-year period involving Japanese professional teams. We won game four in Tokyo, 6-1, as Capuano pitched well and Morneau and Longoria homered. We also won game five in Sapporo, 3-1, as Shoemaker outpitched Otani and Altuve had three more hits.

The last game, another exhibition, was in Okinawa, a 6-4 loss for MLB. I was more interested in visiting the underground Japanese Naval headquarters, the final battle site of the Pacific War (Figure 6), an 83-day struggle that cost the lives of over 200,000 participants and civilians. Now a mere 70 years after the end of the war, Okinawa is one of a handful of “Blue Zones” in the world where inhabitants live unusually long, healthy lives. The Okinawans’ secrets include hara hachi bu (eating good foods only until they are 80% full), a lifetime of working and gardening, a respect of elders, and a strong social network (4).

MEDICAL ISSUES

Medical problems throughout the 13-day trip were few. At our gathering hotel in Los Angeles, a physician friend developed paroxysmal atrial fibrillation overnight after several alcoholic drinks. I used the “pill-in-pocket” approach (beta-blocker followed by propafenone), and he converted within an hour. Two players were hit by pitches during games, one resulting in a fractured toe and the other in inflammation of the wrist. Ice and compression bandages helped the latter, and the player hit a home run in the next game. Three individuals had skin conditions, one a likely staphylococcal infection on the lateral aspect of the great toe, treated successfully with a cephalosporin. Another had tiny vesicular lesions on his hands, small macular red spots in the palate, and symptoms of a mild sore throat. When he didn’t respond to simple measures, we gave him an azithromycin dose pack, which seemed to accelerate the healing process. A rapid strep test was not available. The traveling secretary had several days of intermittent chills and a periodic low-grade fever. His examination was normal. He responded to acetaminophen and nonsteriodals.

SUMMARY

An MLB all-star team played a Japanese all-star team and lost the five-game series, 3-2, for only the second time in 80 years of periodic competition. Medical problems were few, allowing the physicians and trainers ample time to enjoy the beauty of Japan, including side trips to Kyoto and Nara and a wonderful buffet reception at the American Embassy, hosted by Ambassador Caroline Kennedy (Figure 7).

Acknowledgments

Special thanks to Stacie Waddell for helping with the figures.

Directions to a lost place: a parable for modern times

Michael Davis, ThM

“...I’m lost,” he sighed to himself. Then, just ahead he noticed the little postal truck idling under a timeless elm. A woman in a blue toboggan—all bundled up against the cold—hustled back to her truck. She’d just made a delivery. Pulling alongside, he rolled down the passenger’s window. “Ma’am,” he said, getting her attention. “Can you tell me how to get to Gratitude Street?” She brightened. “Sure. You got a pen?”

When he was ready, she spoke, pointing ahead. “So, at the end of this street, go left. That’s Family. You’ll know Family because every house is wildly different. You’d swear each one had a different Builder. But actually, the same Builder designed every house. It looks like a mess: there’s a treehouse, an igloo, a tent, and a Victorian. Every house and every person on Family look so different they seem out of place. But here’s the amazing surprise: despite all the differences, every house has some small elements exactly—and I mean exactly—the same as all the others.

“Here’s how they discovered it,” she said, warming up. “A long time ago, some angry owners—the homeowners association—drew up rules to make the houses look more alike. Some wanted the igloo removed. Move the teepee, said others. A group felt the treehouse was a terrible eyesore. Then, one day the igloo’s heater just died. The Inuit went door to door: Do you have a part that looks like this? she asked. Before you know it, everyone on the street was in an uproar! Everyone’s house had exactly the same heater! Exactly! House, teepee, igloo, tent: Whatever your part that looks like this?

They realized that even with their differences, many things were the same. Nowadays, tourist vans go up and down Family, telling how two houses can be very different but in some ways are still just like each other. The Igloo’s Heater is their favorite story. “It’s a remarkable place,” she said, wistfully.

She refocused. “Sorry, I do get off track. Back to your directions. Go 10 blocks on Family and then turn left onto Can’t Do It Alone. Pay attention here or you’ll get stuck. Whatever the time of day, people are doing things for others. Somebody’s always on a ladder washing a neighbor’s windows, or baking a shut-in a loaf of bread or chopping them firewood. Everyone is always helping somebody. Funniest thing, too. Once you’re on Can’t Do It Alone, you may end up staying!

“Take Can’t Do It Alone 1 mile. You turn right onto Unexpected just after the railroad tracks. Now, Unexpected seems kind of scary. Some houses are terribly beat up. You’ll see folks just hanging out, lurking. Shady characters, you’d think. Lock your doors and windows, be respectful, and have courage. But, the thing about Unexpected is that just when you think the folks around there are all one thing, they aren’t!"

“One time, a fella’s car broke down on Unexpected in the worst place possible. He saw a man walking toward him. The man wore a big, long coat, the hood pulled up over his head. The traveler’s heart started racing. The figure kept coming, determined. The stranded fella was filled with dread. Then, an insistent knock on his window. Then another, unrelenting. Finally, summoning all his courage, he barely cracked his window, hoping this crazy person couldn’t get in.” The postal lady paused dramatically. “The hood came off the top of a head—just a little—revealing a grizzled Old Man. He spoke in a gruff but reassuring voice, ‘Stay out here any longer and you’re going to catch your death of cold. Come on in, let’s get you warmed up and on your way.’” Now, remember that. When you cross the tracks, Unexpected is just beyond. Unexpected can be scary: unfamiliar and unknown things usually are. But, trust me, the folks and experiences on Unexpected are often just what you need, just when you need it.

“After Unexpected, go about 13 blocks. Life is on your right. Turn there. Now, sometimes you think this Life ain’t going to ever end. So far, this trip’s had lots of surprises: so many twists and turns you feel utterly lost. Now, though, it seems every house is exactly the same. Same trees. Same hedges. Same roofs. You think, ‘Get me out of here! I don’t want this. It’s the same thing all the time.’ Will I ever get where I’m going? you wonder. I’m bored. You gotta look harder when you think like that. Trust me, I know. There are lots of little differences all along the way, small reminders to look and listen. Seriously. Keep your eyes open. Look real hard. Don’t focus on the sameness. Anticipate surprise. Train your eyes to spot details you usually ignore. Believe me, that’s the only way to get through Life. Don’t give up, either. As soon as you think, ‘That’s it. I’m done. I can’t take it anymore,’ you
come up to a big Hill. It’s really tough to get up that Hill. Just keep going. Eventually, at the very top, there’s a Park.

“When you get to the Park, take a break. Look around. It’s the highest point in this here part of the world. It’s so high, it’s hard to catch your breath. But, let your senses steep in the beauty of your surroundings. The air is clear and crisp. The only sounds are birds, leaves rustling, and tree branches soothing one another. Soak it in! Trust me, every day after that, you’re going to try to remember just how it felt. So, take your time. Make a picture in your mind.

“Oh,” she paused. “When you make it up the Hill, it’s tradition to leave a little reminder you were there. Maybe it’s a special rock in a hidden place. Or, a paper tucked into a tree’s hollow. Or, an initial in the dirt or sand. If you have time, do something like that, okay? From there on, you coast gently downhill until you intersect with the most beautiful spot there ever was. If you’ve followed my directions, you can’t miss it. Right there is Gratitude.”

With that, she bid farewell. “More holiday deliveries,” she said.

What happened to the Lost Man who asked for directions? No one’s quite certain. Once you’ve started following these directions, it’s for sure you’ll end up at Gratitude. But, it’s unknown how many stops you’ll make along the way.

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**Reader comments**

**LUPUS ERYTHEMATOSUS FLARE-UP AND MYOPERICARDITIS AS TRIGGERS AND COMORBIDITIES OF TAKOTSUBO SYNDROME**

The interesting case report by Chhabra et al (1) published in the October 2014 issue of *Baylor University Medical Center Proceedings* about a 51-year-old woman with a flare-up of systemic lupus erythematosus who presented with clinical and electrocardiographic evidence of myopericarditis, both of which triggered takotsubo syndrome, suggests that we should broaden our views in diagnosing takotsubo syndrome beyond the confines of the old and revised Mayo Clinic criteria (1, 2) and accept that takotsubo syndrome often emerges along with other pathologies (e.g., pericarditis, myopericarditis, and even acute myocardial infarction) in a pattern of comorbidities. Comparison of the three electrocardiograms recorded in the span of 30 hours reveals marked attenuation of the QRS complexes in leads I, III, aVR, aVF, and V3, in keeping with that recently described in takotsubo syndrome (3), attributed to myocardial edema, as diagnosed by cardiac magnetic resonance imaging. It is unlikely that this was due to pericardial effusion, since an echocardiogram recorded 2 days after catheterization did not disclose such a finding. One wonders whether in this case we are witnessing the “tip of the iceberg” effect, and milder atypical forms of takotsubo syndrome (without apical or apical/midventricular “ballooning”) in association with pericarditis or myopericarditis are quite common in the form of transient left and/or right regional wall motion abnormalities (4), but remain undiagnosed. The authors provide a succinct but comprehensive commentary on the diagnostic intricacies of takotsubo syndrome, acute myocardial infarction, pericarditis, myopericarditis, and Dressler’s syndrome, which all clinicians might read and contemplate.

—John E. Madias, MD

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Users’ Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice, 3rd ed., edited by Gordon Guyatt, MD, Drummond Rennie, MD, Maureen O. Meade, MD, and Deborah J. Cook, MD

Reviewed by Beverlee Warren, MA, MS

abeled by one reviewer as the “bible” of evidence-based medicine (EBM), the third edition of this book lives up to the reputation of its previous versions. Considering its prestigious pedigree, the reader will appreciate the value of this book to medical research. These guides grew out of a collaboration between McMaster University and JAMA when a series of articles was published, between 1993 and 2000, advising clinicians on how to read medical literature. The Evidence-Based Medicine Working Group then aggregated these articles into the first edition of Users’ Guide to the Medical Literature. In the preface to the third edition, editor Gordon Guyatt explained,

By the time of the book’s publication in 2002, EBM had already undergone its first fundamental evolution, the realization that evidence was never sufficient for clinical decision making. Rather, management decisions always involve trade-offs between desirable and undesirable consequences and thus require value and preference judgments (pp. xxiii-xxiv).

By the second edition, published in 2008, EBM had evolved to embrace two additional principles. Guyatt explained,

First, we had realized that only a few clinicians would become skilled at critically appraising original journal articles and that preappraised evidence would be crucial for evidence-based clinical practice. Second, our knowledge of how best to ensure that clinical decisions were consistent with patient values and preferences was rudimentary and would require extensive study (p. xxiv).

This third edition emphasizes preappraised resources, particularly in electronic format, which are able to provide more continuous current data. To that end, purchasers of the book have access to an updated web version of the Users’ Guides to the Medical Literature along with the online edition of The Rational Clinical Examination: Evidence-Based Clinical Diagnosis. Resources in the third edition include interactive calculators and worksheets, downloadable PowerPoint presentations, and podcasts. This edition includes six completely new chapters: Evidence-Based Medicine and the Theory of Knowledge; How to Use a Noninferiority Trial; How to Use an Article About Quality Improvement; How to Use an Article About Genetic Association; Understanding and Applying the Results of a Systematic Review and Meta-analysis; and Network Meta-analysis.

In the foreword to this book, editor Drummond Rennie clearly sets forth the aims of this edition:

To free the clinician from practicing medicine by rote, by guesswork, and by their variably integrated experience. To put a stop to clinicians being ambushed by drug company representatives, or by their patients, telling them of new therapies the clinicians are unable to evaluate. To end their dependence on out-of-date authority. To enable the practitioner to work from the patient and use the literature as a tool to solve the patient’s problems. To provide the clinician access to what is relevant and the ability to assess its validity and whether it applies to a specific patient. In other words, to put the clinician in charge of the single most powerful resource in medicine (p. xix).

What lofty goals! What patient would want anything less? If this book moves every clinician just a step further along on the continuum of competency, then it certainly is worth the time and effort to use the information in the way the authors intended—as a “guide.”

A synopsis of contents at the beginning of each chapter is particularly helpful, as it is presented in terms we commonly use during discovery of any process. These include statements like, “searching for . . .,” “how to . . .,” “when to . . .,” “improving your . . .,” “beware . . .,” and “an illustration of . . ..” The book is replete with helpful figures and tables to enhance understanding of the text.

This publication is no stranger to collaboration. As I mentioned previously, the project grew out of and has expanded in a collaborative environment. McMaster University is noted for its collaborative efforts in evidence-based research and in its generous sharing of tools and guidelines for the enhancement of evidence-based knowledge in my profession, library and information science. A quick perusal of the contributors to this edition shows international participation, including the departments of clinical epidemiology and biostatistics, medicine, public health, neonatology, surgery, dentistry, anesthesia, internal medicine, ethics and the law in medicine, pediatrics, statistics and actuarial science, health economics, education, critical care medicine, cardiology, human behavior, pharmacy, research, family medicine, primary care health sciences, insurance medicine, community health sciences, gastroenterology,
preventive medicine, physical medicine and rehabilitation, laboratory medicine, neurology, molecular medicine, emergency medicine, and health sciences. The experts required to deliver this text illustrate the popular saying, “It takes a village.”

The majority of my professional hours have been spent in literature searching. Databases, search tools, search strategies, and nuances to tease out and refine the specific references that have the right balance of precision (retrieving what you need) and recall (retrieving all you need) for the needs of a particular client change weekly. Vendors of electronic subscription databases change interfaces, new products become available requiring a search learning curve, medical terminology changes and refines along with the profession, and information specialists create and share new tools for expert searching. Here at Baylor, the Baylor Health Sciences Library has such expertise available for literature searches, systematic reviews, and much more. Use them along with statisticians, content specialists, database designers, and others to assist in your development of a systematic approach to reading medical literature and applying it to patient care. Use this book as a reference guide to the scope and depth of the task and take advantage of all the resources—human, electronic, and print—available.

The reviewer, Beverlee Warren, MA, MS, is a medical librarian at the Baylor Heart and Vascular Institute, Dallas, Texas.
Facts and ideas from anywhere

SERUM LOW-DENSITY-LIPOPROTEIN CHOLESTEROL <50 MG/DL

Boekholdt and associates (1) from multiple medical centers did a meta-analysis from 8 randomized controlled statin trials in which conventional lipids and apolipoproteins were determined in all study participants at baseline and at 1-year follow-up. Among the 38,153 patients allocated to statin therapy, 6286 major cardiovascular events occurred in 5387 studied participants during follow-up. The authors found that >40% of the participants in these trials did not reach a low-density lipoprotein (LDL) cholesterol level <70 mg/dL despite being prescribed rosuvastatin 20 mg or atorvastatin 20 mg. There was a clear relation between LDL cholesterol level attained and cardiovascular risks, with the major cardiovascular event rate at 1 year increasing incrementally from 4.4% in those with LDL levels <50 mg/dL, 10.9% for those with LDL of 50 to <70 mg/dL, 16% for those with LDL of 70 to <100 mg/dL, and up to 34% in those with LDL >190 mg/dL. This relation, of course, supports the premise that "lower is better" when it comes to LDL goals.

US DEPARTMENT OF AGRICULTURE’S DIETARY GUIDELINES

Every 5 years our government has been issuing guidelines about healthy eating choices (2, 3). A panel that advises the Department of Agriculture submitted its latest draft recommendations in December 2014, and they include what foods are better not only for our health, but also for our environment. That means that when the latest version of the government’s dietary guidelines come out (near the end of 2015), they may push even harder than in the past for people to choose more fruits, vegetables, nuts, whole grains, and other plant-based foods at the expense of meat. The study, as shown in Table 1, indicates that compared with other popular animal proteins, beef produces the most heat-trapping gases per calorie, produces the most water-polluting nitrogen, needs the most water for irrigation, and requires the most land. Once the recommendations of the advisory panel are finalized, they will be submitted to the Departments of Agriculture and Health and Human Services, which will craft the final dietary guidelines. The guidelines are the basis for the US Department of Agriculture’s “My Plate” icon that replaced the food pyramid in 2010 and is designed to help Americans with healthy eating. Guidelines also will be integrated into school lunch meal patterns and other federal eating programs.

Of course, the meat industry has fought for years to ensure that the dietary guidelines do not call for eating less meat. The present guidelines now recommend eating lean meats instead of reducing meat altogether. The new guideline recommendations featured in the December 2014 draft recommend fewer “red and processed meats.”

The government’s first food guide came in 1916 and established guidance based on food groups. Since then, the guide has come in many forms. The latest one is the circle broken into roughly 4 parts, named fruit, vegetables, grains, and protein, with a small circle for dairy on the side. A growing body of research has found that meat animals, and cattle in particular, with their belching of greenhouse gases, trampling of the landscape, and need for massive amounts of water, are a major factor in global warming.

Administration officials are already enmeshed in bitter fights with Republicans over coal-fired power plants, methane emissions from oil and gas production, and regulation of automobiles. Whether they have the stomach for adding a food fight to the list remains uncertain. The possibility that climate change

<table>
<thead>
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<th>From</th>
<th>Land needed (square feet)</th>
<th>Water needed (gallons)</th>
<th>Greenhouse gases generated (pounds)</th>
<th>Nitrogen generated (ounces)</th>
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</thead>
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<td>6</td>
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<td>2</td>
</tr>
<tr>
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<td>44</td>
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<td>1</td>
</tr>
<tr>
<td>Eggs</td>
<td>32</td>
<td>28</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dairy</td>
<td>94</td>
<td>45</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*Source: Dallas Morning News (2, 3).
politics could affect nutrition guidelines serves as a reminder of how many parts of daily life the struggle to limit global warming can reach.

A revamp of the food pyramid to take climate into account would be a bold step. Despite a major push by the United Nations for countries to rework dietary policies with an eye on climate impact, no country has done so. The Netherlands is expected to be the first when it releases a new chart illustrating food guidelines this year.

This antimeat bandwagon has recently been rebuffed by Nicolette Hahn Niman, the author of Defending Beef: The Case for Sustainable Meat Production (4). Ms. Niman writes: “People who advocate eating less beef often argue that producing it hurts the environment. Cattle . . . have an outsized ecological footprint: they guzzle water, trample plants and soils, and consume precious grains that should be nourishing hungry humans. Lately, critics have blamed bovine burps, flatulence, and even breath for climate change.” Ms. Niman, a long-time vegetarian and environmental lawyer, once bought into these claims. Her husband, Bill, founded Niman Ranch but left it in 2007, and they now have a grass-fed beef company. As a consequence, she has come to the opposite view. She claims that raising beef cattle, especially on grass, is an environmental gain for the planet.

Her arguments are as follows: she indicates that the Environmental Protection Agency argues that all of US agriculture accounts for just 8% of our greenhouse emissions, with by far the largest share owing to soil management—that is, crop farming. A Union of Concerned Scientists report concluded that about 2% of US greenhouse gases can be linked to cattle and that good management would diminish it further. The primary concern is methane, a potent greenhouse gas, but if cattle were fed certain nutritional supplements, the methane from cattle could be cut by half. She further argues that cattle are key to the world’s most promising strategy to counter global warming: restoring carbon to the soil. One-tenth of all human-caused carbon emissions since 1850 has come from the soil, according to certain ecologists. This, she argues, is due to tillage, which releases carbon and strips the earth of protective vegetation, and to farming practices that fail to return nutrients and organic matter to the Earth. Plant-covered land that is never plowed is ideal for recapturing carbon through photosynthesis and for holding it in stable forms.

She further argues that most of the world’s beef cattle are raised on grass. Their pruning mouths stimulate vegetative growth as their trampling hoofs and digestive tracts foster seed germination and nutrient recycling. These beneficial disturbances, like those once caused by wild grazing herds, prevent the encroachment of woody shrubs and are necessary for the functioning of grassland ecosystems. She states that research by the Soil Association in the United Kingdom showed that if cattle were raised primarily on grass and if good farming practices were followed, enough carbon could be sequestered to offset the methane emissions of all US beef cattle and half its dairy herd. Similarly, in the US, the Union of Concerned Scientists estimated that as much as 2% of all greenhouse gases (slightly less than what’s attributed to cattle) could be eliminated by sequestering carbon in the soils of grazing operations. She indicates that grass is also one of the best ways to generate and safeguard soil and to protect water. Grass blades shield soil from erosive wind and water, while its roots form a net that holds soil and water in place.

Niman also argues that cattle are not voracious consumers of water. Some environmental critics of cattle assert that 2500 gallons of water are required for every pound of beef produced. But this figure (or the even higher ones often cited by advocates of veganism) are based on the most water-intensive situations.

Finally, she questions the thought that eating beef worsens world hunger. She indicates that this is ironic since a billion of the world’s poorest people depend on livestock. Most of the world’s cattle live on land that cannot be used for crop cultivation, and in the US, 85% of the land grazed by cattle cannot be farmed, according to the US Beef Board. She mentions that the bovine’s most striking attribute is that it can live on a simple diet of grass, which it forages for itself. And for protecting land, water, soil, and climate, there is nothing better than dense grass.

A major concern of mine would be the fattening cattle farms where cows are placed when they weigh about 700 pounds and are fattened up to 1100 pounds. The ground is trampled, there is no grass around, and the feces slide off into the various water drainage sites.

**FAST FOOD AND TEST SCORES**

Some researchers at Ohio State University used data from a nationally representative sample of about 11,700 children to measure how fast food might be affecting classroom performance (5). This study measured how much fast food the children ate at age 10 and then compared the consumption levels with test results in reading, math, and science 3 years later. They found that even small increases in the frequency in which the students ate fast food were associated with poor academic test results. Habitual fast-food eaters—those who ate fast food daily—had test scores about 20% lower than those who didn’t eat any fast food. The connection held true even after the researchers took into account more than a dozen other factors about the children’s habits and backgrounds, including fitness, broader eating habits, socioeconomic status, and characteristics of their neighborhoods and schools. More than half the fifth graders ate fast food 1 to 3 times a week and nearly three-quarters of them ate fast food at least once a week. Nearly one-third of American children between the ages of 2 and 11—and nearly half of those aged 12 to 19—eat or drink something from a fast food restaurant every day according to a study published in 2008. Fast food still accounts for about 13% of total calories eaten by children and teenagers aged 2 to 18 in the USA.

**GLOBESITY**

Nearly a third of the world’s population is overweight or obese, a percentage that is set to hit 50% by 2030 according to a recent report on “Globesity and Health and Wellness” by Sarbjit Nahal, head of thematic investing at Bank of America Merrill Lynch (6). He estimates the global impact of obesity is
$2 trillion, or 2.8% of global gross domestic product—on par with smoking, armed violence, war, and terrorism. US generals are calling the problem the biggest security threat facing the US today, since overweight recruits cannot pass the fitness requirements. Car makers have been forced to revamp the size of crash-test dummies because the safety implications are so fundamentally different. Although the US, China, and India are the countries with the greatest share of the world’s obese, Greece and Italy have higher percentages of overweight and obese people than the US. It is not just a problem in the developed world. In the developing world, the lower rungs of the socioeconomic ladder have less time for physical activity and eat more processed food. Increasingly in emerging markets, people who are well off are eating fresh and healthy foods and going to the gym.

THE ANNUAL PHYSICAL EXAMINATION

In 2012, the Cochrane Collaboration, an international group of medical researchers who systematically review the world’s biomedical research, analyzed 14 randomized controlled trials with over 182,000 people followed for a median of 9 years that sought to evaluate the benefits of routine, general health checkups, i.e., visits to the physician for general health and not prompted by any particular symptom or complaint (7). The conclusion was that checkups were unlikely to be beneficial. Regardless of which screenings and tests were administered, studies of annual health exams dating from 1963 to 1999 showed that the annual physical did not reduce mortality overall or for specific causes of death from cancer or heart disease. And the checkups consumed billions of dollars, although no one is sure exactly how many billions because of the challenge of measuring the additional screenings and follow-up tests. This lack of evidence is the main reason the US Preventive Services Task Force—an independent group of experts making evidence-based recommendations about the use of preventive services—does not have a recommendation on routine annual health checkups. The Canadian guidelines have recommended against these exams since 1979.

According to Ezekiel J. Emanuel, one explanation for the ineffectiveness of the annual exam in reducing the death rate is that it does little to avert death or disability from acute problems. Unintentional injuries and suicides are, respectively, the fourth and tenth leading cause of death among Americans. And, the annual physical does little for chronic conditions without significantly useful interventions, such as Alzheimer’s, the fifth leading cause of death among older people.

TANNING BEDS

Twenty minutes in a tanning bed costs $7.00 (8). A publication in 2014 estimated that tanning beds account for as many as 400,000 cases of skin cancer in the USA each year, including 6000 cases of melanoma. The incidence in women <40 has risen by one-third since the early 1990s. In 2014, the US Food and Drug Administration (FDA) invoked its most serious risk warning, lifting tanning beds from a category that included Band-Aids to that of potentially harmful medical devices. The Obama administration’s 2010 health care law imposed a 10% tax on tanning salons. More than 40 states now have some restrictions on the use of tanning salons by minors. The use of indoor tanning among teenage girls dropped from 25% to 20% from 2009 to 2013. Stay away.

RUNNING AND MORTALITY

Lee and associates (9, 10), from a 15-year follow-up of 55,137 adults at the Cooper Clinic in Dallas, found that running as little as 5 to 10 minutes per day was associated with reduced mortality from all causes (30%) and from cardiovascular disease (45%) and could add 3 years of life expectancy (Figure 1). This minimal amount, half of that recommended in the guideline, is similar to the 15-minute per day of brisk walking reported in the Lancet in 2011 by Wen et al, one-half of the currently recommended 150 minutes per week, or 30 minutes per day. Both showed a 3-year extension of life expectancy, and both are good news of course to the sedentary, because finding 5 to 15 minutes per day to exercise is much easier than finding 30 minutes. Prior to these two studies, no conclusive timeline had been identified with sufficient statistical power to show definite health benefit.

DALLAS MURDER RATE

In 2014, the murder rate in Dallas was its lowest since 1930, the year that Bonnie and Clyde met (11). A total of 116 murders occurred in Dallas in 2014. That is also a drop from the 143 murders in 2013, and it’s less than half the murders recorded in 2004. The number of murders in Chicago in 2014 was 407, and in Philadelphia, 248, both slight drops from the 2 previous years. For every 100,000 Dallasites, the city recorded just over 9 murders in 2014, slightly above the 2013 national average for cities of >1 million people. In contrast, in murder havens Flint and Detroit, Michigan, 48 and 45 people, respectively, of every 100,000 were murdered. The murder number does not include justifiable homicides, such as shootings by police or homeowners who shoot burglars. The City of Dallas peaked at 500 murders in 1991. The number of aggravated assaults in 2014 increased in Dallas compared to the previous year.
OUR HOTTEST YEAR

The Earth’s hottest year on record was 2014 (12). Both the National Oceanic and Atmospheric Administration (NOAA) and NASA calculated that in 2014 the world had its hottest year in 135 years of recordkeeping. Earlier, the Japanese Weather Agency and an independent group from the University of California at Berkeley also measured 2014 as the hottest on record. Thus, the globe is warmer now than it has been in the last 100 years and, as one scientist mentioned, probably 5000 years. Furthermore, 9 of the 10 hottest years in NOAA global records have occurred since 2000, a reflection of the relentless planetary warming that scientists say is a consequence of human emissions and that has posed profound long-term risks to civilization and to the natural world.

NOAA indicated that 2014 averaged 58.24°F, 1.24° above the 20th century average. NASA, which calculates temperatures slightly differently, put 2014’s average temperature at 58.42°F; 1.22° above the average of the years 1951 to 1980. Earth broke NOAA records for heat in 2010 and in 2005. The last time the Earth set an annual NOAA record for cold was in 1911. February 1985 was the last time global temperatures fell below the 20th century average for a given month, meaning that no one <30 years of age has ever lived through a below-average month.

The heat of 2014 was driven by record warmth in the world’s oceans, and it did not just break old marks, it shattered them. Record warmth spread across far-eastern Russia, the western part of the US, interior South America, much of Europe, Northern Africa, and parts of Australia. One of the few colder spots was in the central and eastern US. Climate scientists indicated the most significant part of 2014’s record is that it happened during a year when there was no El Niño weather isolation. During an El Niño when a specific area of the Central Pacific Ocean warms unusually and influences weather worldwide, global temperatures tend to spike. Previous records, especially in 1998, happened during El Niño years. The planet is warming and it is as simple as that.

SEA RISING

According to an article in the January 2015 issue of Nature, the current rise in sea level is 2.5 times faster than it was from 1900 to 1990 (13). The faster pace apparently is due to the melting of ice sheets in Greenland and Antarctica and shrinking glaciers, triggered by human-made global warming. Previous research had shown that between 1900 and 1990 the seas rose about two-thirds of an inch each decade. The new study recalculates that rate to less than half an inch a decade. While hundreds of tide gauges around the world have been measuring sea levels since 1900, they have mostly been in Europe and North America. Thus, estimates of 20th century sea level rise gave an incomplete picture of the global effect. The new method uses statistical analysis and computer models to better simulate the areas in the gap. The implications are that more and more sea level rise will occur in the future, perhaps at a faster rate than previously thought.

THE CASE FOR FOSSIL FUELS

Alex Epstein in a book entitled The Moral Case for Fossil Fuels argues that plentiful, reliable, affordable energy is necessary for human flourishing and, indeed, for human life, and at this point, that energy can best be provided by fossil fuels: coal, petroleum, and natural gas (14). The author drives home the idea that the crusade against fossil fuels stems less from a desire to ensure clean air and water for human use than from an idealization of “untouched” nature—the view that human nonimpact on the planet is to be striven for above all else. Epstein argues that if one is concerned about sea level rises or destructive hurricanes, one should cheer on industrialization all the more loudly. Prosperous economies are best able to manage the challenges Earth’s climate throws our way. “It is only thanks to cheap, plentiful, reliable energy that we live in an environment where the water we drink and the food we eat will not make us sick and where we can cope with the often hostile climate of Mother Nature.”

From air-conditioning to desalinization, it is industrial society—enabled by affordable and abundant energy—that allows humans to transform their environment and thrive in otherwise unpleasant climates. Epstein further emphasizes that climate crusaders who thwart developing world access to coal-fired power plants perpetuate the misery. Cheap, 24/7 electricity is critical to economic development. While coal has become enemy #1 in large swaths of the West, access to cheap electricity from coal-fired power plants vastly improves the length and quality of life of the world’s poor. The vast numbers of people on this planet who do not have access to sufficient energy to cook 2 meals a day spend a significant portion of their waking hours gathering sticks and dung to burn for heat and cooking. They would benefit tremendously if they were connected to a large coal-fired power plant. Indeed, the quality of the very air they breathe would improve; every year millions of people die prematurely due to the inhalation of contaminants from indoor cooking fires.

STEVEN BRILL ON HEALTH CARE COSTS

Steven Brill is the author of Time’s “Trailblazing Special Report on Medical Bills.” His book, America’s Bitter Pill, is a sweeping inside account of how Obamacare happened and what it does and does not do to curb the abuses (15). Brill’s piece in Time was published in January 2015 and was adapted from his book.

Brill indicates the following: America’s total health care bill for 2014 was $3 trillion. That’s more than the next 10 biggest spenders combined: Japan, Germany, France, China, the UK, Italy, Canada, Brazil, Spain, and Australia. All that extra money produces no better results, and in many cases, worse results. There are 31.5 magnetic resonance imaging (MRI) machines per 1 million people in the US, and 5.9 per 1 million in the UK. We spend $86 billion treating back pain, which is as much as is spent on all the countries’ state, city, county, and town police forces. Possibly half of that is unnecessary. We spend $17 billion a year on artificial knees and hips, which is 55% more than Hollywood takes in at the box office each year. We have
created a system in which 1.5 million people work in the health insurance industry, while barely half as many physicians provide the actual care. And all those high-tech advances—pacemakers, MRIs, 3-D mammograms, etc.—have produced an ironically upside-down health care marketplace. Health care is the only industry in which technological advances have increased costs instead of lowering them.

Health care is America’s largest industry by far, employing a sixth of the country’s workforce. It is average Americans’ largest single expense, whether paid out of their pockets or through taxes and insurance premiums. The health care industry spends four times as much on lobbying as the #2 Beltway spender, the military industrial complex.

Brill’s solution includes cutting out the middleman, the insurance companies, which now account for 15% to 20% of private health care costs. As hospitals consolidate, something that is happening all over the country, they need to become their own insurance companies so they can cut out the middleman and align the incentives. The insurance company, then, would have not only every incentive to control the doctors’ and hospitals’ costs, but also the means to do so.

### PERCENT OF INCOME SPENT ON HEALTH INSURANCE

The US average in 2013 was 9.6%, nearly double that in 2003. The percentage of income spent on insurance premiums and deductibles in 2013 was highest in Florida at 12.4% and second highest in Texas at 12.3% (16). The cost of the average employer-sponsored family health insurance plan was $16,049, or 27% of the annual income of working Texans in 2013! Many Texas companies have shifted more of the cost of these plans to their workers. Deductibles, the amount a worker has to spend on health care before insurance kicks in, went up sharply in Texas between 2003 and 2013. Single workers paid deductibles averaging $624 in 2003, and the average in 2013 was $1,543. While employers once paid 80% of premiums, now companies typically pay a little over two-thirds of the premium cost for a family plan in 2013, leaving the workers with the other 31%. Health insurance premiums in Texas increased by 6.1% a year between 2003 and 2009, but slowed to 2.4% annually between 2010 and 2013. Premium hikes for workers during those 3 years, however, and deductibles went up by 7.4% annually. With median income at $49,500 in 2013, the average Texas family with a workplace insurance plan spent $6,088 on premiums and deductibles. In 2003, the cost was $2,960, or 7.4% of income. The result is that out-of-pocket costs are consuming a greater share of employee incomes.

### MEDICARE PATIENT MALADIES

The most common chronic ailments in patients ≥65 years who are enrolled in Medicare are listed in Table 2 (17). About two-thirds of Medicare beneficiaries have two or more chronic conditions, and they tend to visit different doctors for different diseases. Often, a single overseeing physician is not involved. Beginning in January 2015, Medicare will pay primary care physicians a monthly fee to better coordinate care for the most vulnerable seniors, those with multiple chronic illnesses, even if they don’t have a face-to-face encounter. The goal is to help patients stay healthier between doctor visits and avoid hospitalization and nursing homes, which of course are quite expensive. Medicare’s new fee is about $40 a month per qualified patient. Previously, the program paid only for services provided in the physician’s office. To earn the new fee, physicians must come up with a care plan for qualified patients and spend time each month on such activities as coordinating their care with other health providers and monitoring their medications. Also, patients must have a way to reach someone in the care team who can access their health records 24 hours a day for proper evaluation of an after-hours complaint. The new fee could enable physicians to hire extra nurses or care managers to do more of the preventive work. Patients must agree to care coordination; the fee is subject to Medicare’s standard deductible and co-insurance.

Being a care coordinator is like being a quarterback. Dr. Matthew Press described in a piece in the New England Journal of Medicine (18) the 80 days between diagnosing a man’s liver cancer and his surgery. The internists sent 32 e-mails and had 8 phone calls with the patient’s 11 other physicians. (This article was supplied to me by Dr. Joseph Rothstein.) The chronic care management fee is one of multiple projects Medicare has underway in hopes of strengthening primary care and, in turn, saving money.

### AFGHAN OPIUM POPPY CULTIVATION

The United Nations estimates that the land area used to cultivate poppies in Afghanistan increased 7% in 2014 to 554,000 acres (19). The profits from opium and heroin are huge, and the UN Office of Drugs and Crime reported that in 2014, Afghan poppy farmers took in about $850 million, more than twice as much as 5 years earlier. Processing labs have sprung up there in several border provinces, and street sales of refined powder have become a major business in Kabul and several provincial

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<td>Osteoporosis</td>
<td>7%</td>
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*Source: Centers for Medicare and Medicaid Services, 2012 data, as it appeared in Dallas Morning News (17).
CANINE OVERPOPULATION

Melinda Beck in a piece in The Wall Street Journal indicates that there are an estimated 375 million stray dogs worldwide (20). She discusses methods of sterilization and suggests that the fastest and least expensive method of neutering male dogs is a quick injection of calcium chloride into the testicles, which makes them sterile. The dogs get a light sedative but no general anesthesia or incisions. They can be up and running again in minutes. The cost: about $1 per dog. Calcium chloride could be a boon to animal shelters in many impoverished areas, many of which lack the funds and facilities to sterilize dogs surgically. More than 3 million dogs and cats are euthanized in US shelters every year. But few veterinarians and shelter operators even know about calcium chloride. It has been stalled in a regulatory catch-22 that illustrates how products that do not have much profit potential can languish unused. Inexpensive, nonsurgical sterilization would be a godsend to countries like India, where packs of dogs run wild. And the stray dogs terrorize some neighborhoods, fighting over food and reproducing exponentially.

Research on calcium chloride goes back to the 1970s when it was tested as a sterilizing agent in calves, colts, and other animals. A number of studies now have described a variety of doses and solutions of calcium chloride and concluded that a 20% solution of calcium chloride in ethyl alcohol was optimal, rendering dogs “azoospermic” and reducing testosterone levels by 70%, with no adverse effects. Calcium chloride is not approved by the FDA and probably never will be. It is such a common chemical that it cannot be patented. As a result, drug companies are not interested in investing the $10 million or more needed to run the required clinical trials. Without FDA approval, most veterinarians and animal welfare groups are leery of endorsing it.

Nevertheless, finding safe, nonsurgical ways to control animal reproduction has been a goal of animal researchers for decades, but progress has been slow. One nonprofit foundation that works to advance neglected medical research tried to start the FDA approval process for the use of calcium chloride in male cats in 2014 but the bid for a “barrier to innovation” waiver of the $87,000 application fee was denied on the grounds that the research was not “innovative” enough. I suspect that calcium chloride will slowly be adapted as an inexpensive, quick, relatively painless procedure that could make a big dent in canine overpopulation.

PLANNING FOR THE INEVITABLE

Jane Bryant Quinn, author of Making the Most of Your Money Now, described what to tell your adult offspring about your money (21). She strongly advised telling your offspring where to find your will, health care directive, financial records, and any life insurance policies. If the will leaves them uneven shares, explain that decision, either orally or by a thoughtful explanatory letter. Tell all of the offspring who has the power of attorney or is the executor of your will. She advises not telling the offspring exactly what you are worth, in case your assets get depleted later in life. The offspring shouldn’t be planning on an inheritance they might not get. Conversely, up-front disclosure about your intentions can help prevent siblings’ dishonesty in handling family assets, if that is a risk. Families manage better when one leaves no big surprises behind.

To prevent your family’s scrambling to find documents during an emergency, she advises the following. 1) Inventory your assets and their location. Include the name of your physician, accountant, insurance agent, and financial advisor. 2) Make a list of passwords for your computer, mobile devices, and accounts. 3) Compile a list of the medications you take. 4) Prepare an advance directive, which often consists of two parts: a power of attorney that names someone to make medical decisions for you if you are incapacitated and a living will that details the life-sustaining measures you want if you are unlikely to recover. 5) Execute a durable power of attorney so someone can make financial decisions on your behalf if you are unable. 6) Don’t put a will or advance directive solely in a safe deposit box, where family members might not have access to it. Give copies to trusted relatives.

COSTS OF MEDICAL CARE PER CAPITA IN VARIOUS DEVELOPED COUNTRIES IN 2013

When the costs of medical care per capita were compared in 12 developed countries, the USA led the list, with $2.91 trillion for health care in 2013, or $9,255 per American (22) (Table 3). The increase in the US from 2012 to 2013, namely 3.6%, was the lowest since the government started counting medical expenses in 1960. In part, the US spends more because our prices are so much higher—for hospitals, drugs, medical devices, and medical salaries. Over 44 million US consumers have uncollected medical debt on their credit reports. The US also spends more than the other countries because our citizens as a whole are in worse shape than the citizens of most other countries, with obesity, high cholesterol levels, heavy salt and sugar in our diets, and smoking (although down to 17% presently). After Mexico, the US is the fattest country in the world. About 25% of our population doesn’t exercise whatsoever. Indolence, of course, leads to diabetes mellitus, some cancers, elevated blood cholesterol levels, and other chronic conditions that drain the nation’s wealth. The care for patients with chronic disease in the US accounts for $3 of every $4 spent on our health care.

PRACTICAL WISDOM FROM JOHN W. GARDNER

John Gardner (1912–2002), a great civic leader and Secretary of Health, Education, and Welfare under President Lyndon
Johnson, delivered the commencement address in June 1991 at Stanford University’s 100th commencement ceremony. The speech is full of practical wisdom (23).

As you settle into your adult lives, you cannot write off the danger of complacency, boredom, growing rigidity, imprisonment by your own comfortable habits and opinions. A famous French writer once said, “There are people whose clocks stop at a certain point in their lives.” I could without any trouble name a half dozen national figures resident in Washington, DC, whom you would recognize, and I could tell you roughly the year their clock stopped.

If you are conscious of the danger of going to seed, you can resort to countervailing measures. At any age. You can keep your zest until the day you die. If I may offer you a simple maxim, “Be interested.” Everyone wants to be interesting, but the vitalizing thing is to be interested. Keep your curiosity, your sense of wonder. Discover new things. Care. Risk. Reach out.

Learn all your life. Learn from your failures, from your successes. . . . We learn from our jobs, from our friends and families. We learn by accepting the commitments of life, by playing the roles that life hands us (not necessarily the roles we would have chosen). We learn by taking risks, by suffering, by enjoying, by loving, by bearing life’s indignities with dignity.

The lessons of maturity aren’t simple things such as acquiring information and skills. You learn not to engage in self-destructive behavior, not to burn up energy in anxiety. You learn to manage your tensions, if you have any, which you do. You find that self-pity and resentment are among the most toxic of drugs. You conclude that the world loves talent but pays off on character. You discover that no matter how hard you try to please, some people in this world are not going to love you, a lesson that is at first troubling, and then really quite relaxing. . . .

You bear with the things you can’t change. You come to terms with yourself. As Jim Whitaker, who climbed Mount Everest, said: “You never conquer the mountain. You only conquer yourself.” You master the arts of mutual dependence, meeting the needs of loved ones and letting yourself need them. You can even be unaffected—a quality that often takes years to acquire. You can achieve the simplicity that lies beyond sophistication. . . .

One of the enemies of sound, lifelong motivation is a rather childish conception we have of the kind of concrete, describable goal toward which all of our efforts drive us. We want to believe that there is a point at which we can feel that we have arrived. We want a scoring system that tells us when we’ve piled up enough points to count ourselves successful. So you scramble and sweat and climb to reach what you thought was the goal. And when you get there, you stand up and look around and chances are you feel a little empty. . . .

You wonder whether you climbed the wrong mountain. But . . . life isn’t a mountain that has a summit. Nor is it . . . a riddle that has an answer. Nor a game that has a final score. Life is an endless unfolding and . . . an endless process of self-discovery, an endless and unpredictable dialogue between our own potentialities and the life situations in which we find ourselves. By potentialities I mean not just intellectual gifts but the full range of one’s capacities for learning, sensing, wondering, understanding, loving and aspiring. . . . It is my hope that you will keep on growing, and that you will be the cause of growth in others.

Table 3. Per capital cost of health care in various developed countries in 2013*

<table>
<thead>
<tr>
<th>Country</th>
<th>Cost (US dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>$9,255</td>
</tr>
<tr>
<td>Norway</td>
<td>$6,758</td>
</tr>
<tr>
<td>Switzerland</td>
<td>$6,080</td>
</tr>
<tr>
<td>Netherlands</td>
<td>$5,178</td>
</tr>
<tr>
<td>Germany</td>
<td>$4,884</td>
</tr>
<tr>
<td>Canada</td>
<td>$4,602</td>
</tr>
<tr>
<td>Finland</td>
<td>$3,686</td>
</tr>
<tr>
<td>Iceland</td>
<td>$3,642</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>$3,289</td>
</tr>
<tr>
<td>Italy</td>
<td>$3,183</td>
</tr>
<tr>
<td>South Korea</td>
<td>$2,411</td>
</tr>
<tr>
<td>Hungary</td>
<td>$1,803</td>
</tr>
</tbody>
</table>

*Source: Dallas Morning News (22).
21. Quinn JB. Kids and your money: It’s important to have ‘the talk.’ *AARP Bulletin/Real Possibilities*, January-February 2015.
ANESTHESIOLOGY AND PAIN MANAGEMENT

CARDIOLOGY/CARDIAC, VASCULAR, AND THORACIC SURGERY


without dietary intervention in overweight or obese insulin-naïve individuals with type 2 diabetes: results from the DIET trial. *Diabetes Obes Metab* 2014;16(2):186–192.


**GASTROENTEROLOGY**

Note: See also Oncology for research on colon cancer.


**GERONTOLOGY**


**HEALTH CARE RESEARCH AND IMPROVEMENT**


IMMUNOLOGY/BASIC SCIENCES


**NURSING/ALLIED HEALTH**


Shigeysu K, Tazawa H, Hashimoto T, Mori Y, Nishizaki M, Kishimoto H, Nagasaka T, Kuroda S, Urata Y, Goel A, Kagawa S, Fujitowa T. Fluorescence virus-guided capturing system of human colorectal circulating...


ORAL AND MAXILLOFACIAL SURGERY


ORTHOPEDIC SURGERY


527. Tenenbaum S, Stockton KG, Bariteau JT, Brodsky JW. Salvage of avascular necrosis of the talus by combined ankle and hindfoot arthrodesis without structural bone graft. Foot Ankle Int 2014 Nov 6 [Epub ahead of print].

OTOLARYNGOLOGY


PATHOLOGY


PHYSICAL MEDICINE AND REHABILITATION
Note: See also Trauma.


PULMONOLOGY/INTENSIVE CARE/SLEEP MEDICINE


RADIOLOGY
Note: See also Oncology, Neurology, and other departments in which radiologists were first authors or coauthors.


RHEUMATOLOGY


SURGERY
Note: Most surgery articles are subclassified by specialty, even if general surgeons were first authors or coauthors.


TRANSPLANTATION (ORGAN AND PANCREATIC CELLS)


had right ventricular hypertrophy. Ventricular cavities and only the patient with chronic cor pulmonale 3 patients had dilated right ventricular cavities and non-dilated left nor the subacute patient had chronic pulmonary vascular changes. All indicative of irreversible pulmonary hypertension. Neither the acute patient with chronic cor pulmonale had plexiform pulmonary lesions.

Background: The result of primary or idiopathic pulmonary hypertension almost certainly present from birth because the pattern of elastic fibers in the pulmonary trunk was that seen in newborns where the pressure in the pulmonary trunk and ascending aorta are similar. The patient with chronic cor pulmonale had pleuropulmonary lesions indicative of irreversible pulmonary hypertension. Neither the acute nor the subacute patient had chronic pulmonary vascular changes. All 3 patients had dilated right ventricular cavities and non-dilated left ventricular cavities and only the patient with chronic cor pulmonale had right ventricular hypertrophy.

Described are certain clinical and morphologic features of one patient with acute, another with subacute, and one with chronic cor pulmonale. All 3 had evidence of severe pulmonary hypertension. The patient with acute cor pulmonale 4 days after coronary bypass for unstable angina pectoris suddenly developed severe breathlessness with cyanosis and had fatal cardiac arrest and necropsy disclosed massive pulmonary embolism. The patient with subacute cor pulmonale had severe right-sided heart failure for 5 weeks and necropsy disclosed microscopic-sized neoplastic pulmonary emboli from a gastric carcinoma without parenchymal pulmonary metastases. The patient with chronic cor pulmonale had evidence of right-sided heart failure for years, the result of primary or idiopathic pulmonary hypertension.


Cannula-assisted flap elevation (CAFE): a novel technique for developing flaps during skin-sparing mastectomies
Grant MD

Background: One of the most challenging procedures in breast surgery is the skin-sparing mastectomy (SSM). Various techniques and incisions have evolved that characterize this procedure; however, what is common in all of them is the smaller the incision, the more difficult it is to develop the skin flaps.

Methods: A procedure was developed that incorporates the use of liposuction cannulas (without suction) to create the skin flaps. The technique and results are described in this manuscript.

Results: From October of 2012 to April 2014, 289 mastectomies (171 patients) were performed using the CAFE procedure on women of all shapes and sizes. Postoperatively, no problems were experienced with flap viability using this technique. The main difference in side effects between the CAFE technique and other standard techniques for developing flaps in SSMs was more bruising than normal, but this resolved rapidly. The results for use of this technique were consistently impressive. The learning curve for this procedure is very short, especially for those who perform SSMs using sharp technique (scissors). Residents and fellows became proficient with the CAFE technique in a relatively short amount of time. Plastic surgeons were pleased with the cosmetic outcomes of their reconstructions that follow this type of mastectomy. Patients were extremely satisfied with their reconstructions as well.

Conclusions: Incorporating the use of liposuction cannulas (without suction) makes the creation of flaps for SSM a relatively simple and rapid method. It is especially useful to assist in developing skin flaps with even the smallest of skin incisions.

Curcumin mediates chemosensitization to 5-fluorouracil through miRNA-induced suppression of epithelial-to-mesenchymal transition in chemoresistant colorectal cancer
Toden S, Okugawa Y, Jascur T, Wodarz D, Komarova NL, Buhrmann C, Shakhbaei M, Boland CR, Goel A

Resistance to cytotoxic chemotherapy is a major cause of mortality in colorectal cancer (CRC) patients. Chemoresistance has been linked primarily to a subset of cancer cells undergoing epithelial-mesenchymal transition (EMT). Curcumin, a botanical with anti-tumorigenic properties, has been shown to enhance sensitivity of cancer cells to chemotherapeutic drugs, but the molecular mechanisms underlying this phenomenon remain unclear.
Effects of curcumin and 5-fluorouracil (5FU) individually, and in combination, were examined in parental and 5FU resistant (5FUR) cell lines. We performed a series of growth proliferation and apoptosis assays in 2D and 3D cell cultures. Furthermore, we identified and analyzed the expression pattern of a subset of putative EMT-suppressive microRNAs (miRNAs) and their downstream target genes regulated by curcumin. Chemosensitizing effects of curcumin were validated in a xenograft mouse model. Combined treatment with curcumin and 5FU enhanced cellular apoptosis and inhibited proliferation in both parental and 5FUR cells, while 5FU alone was ineffective in 5FUR cells. A group of EMT-suppressive miRNAs were upregulated by curcumin treatment in 5FUR cells. Curcumin suppressed EMT in 5FUR cells by downregulating BM11, SUZ12 and EZH2 transcripts, key mediators of cancer stemness-related polycomb repressive complex subunits. Using a xenograft and mathematical models we further demonstrated that curcumin sensitized 5FU to suppress tumor growth. We provide novel mechanistic evidence for curcumin-mediated sensitization to 5FU-related chemoresistance through suppression of EMT in 5FUR cells via upregulation of EMT-suppressive miRNAs. This study highlights the potential therapeutic usefulness of curcumin as an adjunct in patients with chemoresistant advanced CRC.

**CLINICAL TRANSPLANTATION**

Skin cancer evaluation in transplant patients: a physician opinion survey with recommendations

Lloyd A, Klintmalm G, Qin H, Menter A


**Background:** Non-melanoma skin cancer is the most common malignancy in transplant patients. However, routine skin cancer evaluation is currently not the standard of care.

**Objective:** To investigate the current barriers among transplant physicians to skin cancer screening in their patients. To provide recommendations for appropriate routine skin surveillance.

**Methods:** A web-based survey was conducted among Baylor Dallas transplant physicians. Thirty-seven of 46 responses were received, and 13 physicians (28%) were classified as “high screeners.”

**Results:** The univariate analysis revealed three main barriers including the perception of difficulty in seeing a dermatologist ($P = 0.017$), skin cancer evaluation is not an important aspect of transplant care ($P = 0.038$), and thirdly, the belief that there is insufficient evidence to warrant universal skin cancer screening in transplant patients ($P = 0.013$). The fully adjusted multivariable analysis resulted in two significant conclusions; the most important predictor was the perceived lack of medical evidence for skin cancer screening.

**Limitations:** The small sample size and all responses being from the same institution in Texas.

**Conclusion:** The dermatologic evidence for regular skin cancer screening in transplant patients needs dissemination to our transplant colleagues. This is a significant practice gap which can be appropriately closed by integrating dermatologists into the transplant team.

**GENOME MEDICINE**

Transcriptional fingerprints of antigen-presenting cell subsets in the human vaginal mucosa and skin reflect tissue-specific immune microenvironments


*Genome Med* 2014;6(11):98. Reprinted with permission from BioMed Central Ltd.

**Background:** Dendritic cells localize throughout the body, where they can sense and capture invading pathogens to induce protective immunity. Hence, harnessing the biology of tissue-resident dendritic cells is fundamental for the rational design of vaccines against pathogens.

**Methods:** Herein, we characterized the transcriptomes of four antigen-presenting cell subsets from the human vagina (Langerhans cells, CD14+ and CD14- dendritic cells, macrophages) by microarray, at both the transcript and network level, and compared them to those of three skin dendritic cell subsets and blood myeloid dendritic cells.

**Results:** We found that genomic fingerprints of antigen-presenting cells are significantly influenced by the tissue of origin as well as by individual subsets. Nonetheless, CD14+ populations from both vagina and skin are geared towards innate immunity and pro-inflammatory responses, whereas CD14- populations, particularly skin and vaginal Langerhans cells, and vaginal CD14- dendritic cells, display both Th2-inducing and regulatory phenotypes. We also identified new phenotypic and functional biomarkers of vaginal antigen-presenting cell subsets.

**Conclusions:** We provide a transcriptional database of 87 microarray samples spanning eight antigen-presenting cell populations in the human vagina, skin and blood. Altogether, these data provide molecular information that will further help characterize human tissue antigen-presenting cell lineages and their functions. Data from this study can guide the design of mucosal vaccines against sexually transmitted pathogens.

**JOURNAL OF FORENSIC SCIENCE**

Sickle cell trait as a contributory cause of death in natural disease

Podduturi V, Guileyardo JM


Sickle cell trait (SCT) affects 300 million people globally, and awareness is growing that SCT is not an entirely benign condition; however, most reported cases have been non-natural deaths. Autopsy records from the Baylor University Medical Center (BUMC) in Dallas, Texas, contained seven natural deaths from January 2007 to October 2013 in which micro-occlusive sickling was identified at autopsy and SCT confirmed by postmortem hemoglobin fractionation. Sickle crisis was never diagnosed clinically. These cases illustrate the importance of red cell morphology in autopsy material. When sickling is suspected, hemoglobin fractionation should be performed. If confirmed, SCT should be listed as an autopsy finding and the severity and distribution of sickling documented. Extensive micro-occlusive sickling should be considered contributory to death; however, its relative importance...
depends on all facts of the case. Accurate reporting should facilitate further research and the development of evidence-based preventative and supportive strategies for these patients.

MEDICINE

Increasing the supply of kidneys for transplantation by making living donors the preferred source of donor kidneys

Testa G, Siegler M


At the present time, increasing the use of living donors offers the best solution to the organ shortage problem. The clinical questions raised when the first living donor kidney transplant was performed, involving donor risk, informed consent, donor protection, and organ quality, have been largely answered. We strongly encourage a wider utilization of living donation and recommend that living donation, rather than deceased donation, become the first choice for kidney transplantation. We believe that it is ethically sound to have living kidney donation as the primary source for organs when the mortality and morbidity risks to the donor are known and kept extremely low, when the donor is properly informed and protected from coercion, and when accepted national and local guidelines for living donation are followed.

ORPHANET JOURNAL OF RARE DISEASES

Agalsidase alfa in pediatric patients with Fabry disease: a 6.5-year open-label follow-up study


Orphanet J Rare Dis 2014;9(1):169. Reprinted with permission from BioMed Central Ltd.

Background: Signs and symptoms of the X-linked disorder, Fabry disease (FD), can occur early during childhood with heterogeneous clinical manifestations including potential cardiac and renal dysfunction. Several studies support the efficacy of the enzyme replacement therapy (ERT) agalsidase alfa in adults with FD, though published data on the long-term safety and efficacy of agalsidase alfa in children are limited. As early treatment with ERT has the potential to reduce complications arising from disease progression, children in particular could benefit. The objective of this study was to evaluate the safety and efficacy of long-term agalsidase alfa ERT in children with FD.

Methods: TKT029 was a 6.5-year open-label, multicenter, extension study of children who completed TKT023 (26-week, open-label, every-other-week, intravenous 0.2 mg/kg agalsidase alfa). TKT029 was divided into two phases (before and after an agalsidase alfa manufacturing process change); only patients who participated in both phases were included in the analysis. Primary endpoints included safety, tolerability, and heart rate variability (HRV). Additional efficacy parameters included left ventricular mass index (LVMI), estimated glomerular filtration rate (eGFR), and plasma/urine globotriaosylceramide (Gb3).

Results: Eleven patients participated (phase 1 baseline median [range] age: 10.8 [8.6–17.3] years; 10 [90.9%] males). During TKT029 (6.5 years), all patients experienced ≥1 treatment-emergent adverse event (AE); eight patients had ≥1 possibly/probably drug-related AE. Six patients experienced infusion-related AEs, but none discontinued due to AEs. Eight serious AEs arose (two patients); none were deemed drug-related. No deaths occurred. Three patients developed anti-agalsidase alfa antibodies, with IgG antibodies in one patient that were agalsidase alfa neutralizing, but without apparent clinical impact. Renal (eGFR) endpoints remained generally in normal range. Cardiac endpoints remained stable within normal range for LVMI and a trend towards improved HRV, although some patients experienced a reduction in heart rate. Plasma and urinary Gb3 reductions were maintained.

Conclusions: TKT029 represents the longest assessment of ERT in children with FD in a clinical trial setting. Overall, agalsidase alfa was well tolerated and demonstrated a stabilizing clinical effect. Agalsidase alfa may be a useful clinical therapeutic option for long-term treatment initiated during childhood in patients with FD.

If you are a Baylor researcher and would like your published abstract to be included in this section, please e-mail the PubMed citation to Cynthia. Orticio@BaylorHealth.edu.
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Original Research
130 Antibiotic utilization improvement with the Nanosphere Verigene Gram-Positive Blood Culture assay by S. G. Beal et al
144 The SUCCESS model for laboratory performance and execution of rapid molecular diagnostics in patients with sepsis by M. Debenham et al
151 Impact of the DASH diet on endothelial function, exercise capacity, and quality of life in patients with heart failure by J. L. Aguirre et al
157 A survey-based analysis of symptoms in patients with postural orthostatic tachycardia syndrome by A. Deb et al
160 An interactive web-based project to stimulate internal medicine resident reading using board-type questions by M. Turcik-Kara et al

Review Article
163 The acute respiratory distress syndrome by A. M. Modrykamien and P. Gupta

Historical Study
172 History of neurologic examination books by C. J. Boes

Case Studies
180 Cecal adenocarcinoma presenting as colonic intussusception in adulthood by J. Gonzalez-Hernandez et al
183 Large-volume barium aspiration by G. L. Hundemer et al
185 Effect of resection of an orbital arteriovenous malformation on central venous pressure by V. S. Starks et al
188 Acute nonrheumatic streptococcal myocarditis resembling ST-elevation acute myocardial infarction in a young patient by J. L. Aguirre et al
191 Invited commentary: What is the definition of SPAM? Even if you cannot define it, you must recognize it! by A. M. Miller and W. C. Roberts
192 Cardiac arrhythmias during myocardial infarction by D. L. Glancy et al
194 Takotsubo cardiomyopathy associated with hyperthyroidism treated with thyroidec-tomy by S. Omar et al
196 Ventricular tachycardia storm with a chronic total coronary artery occlusion treated with percutaneous coronary intervention by T. A. Mixon
199 Myocardial ischemic hypertensive T-wave oversensing leading to a defibrillator shock storm by L. Chhabra et al
204 Usefulness of percutaneous closure of patent foramen ovale for hypoxia by A. M. Modrykamien et al

Miscellaneous
207 Mitral stenosis and acute ST elevation myocardial infarction by J. Cardoz et al
210 Effectiveness of exclusion of a persistent sciotic artery aneurysm with an Amplatzer™ plug by A. Lee et al
213 Immune thrombocytopenia associated with consumption of tonic water by F. D. Winter Jr.
217 Paraneoplastic cerebellar ataxia and the paraneoplastic syndromes by S. Atif et al
221 Carcinoma of the lungs causing enlarged kidneys by W. Shiung et al
224 Mixed epithelial and stromal tumors of the kidney discovered incidentally at autopsy by V. Podduturi and J. M. Guileyardo
227 Superior sagittal sinus thrombosis as the initial presentation of renal cell carcinoma by M. F. Reddy et al
229 Hepatocellular carcinoma with extension to the heart via the inferior vena cava by M. Oncale and B. Lewis
231 Leprosy in a Texan by G. L. Vick et al

Interview, Editorials, and Book Review
237 Alan Marshall Miller, MD, PhD: a conversation with the editor by A. M. Miller and W. C. Roberts
247 Probability and uncertainty in clinical and forensic medicine by J. M. Guileyardo
250 Experience as a physician to the Major League Baseball All-Stars series against Japan by J. D. Cantwell
254 Directions to a lost place: a parable for modern times by M. Davis
256 Book review: Users’ Guides to the Medical Literature by B. Warren

From the Editor
258 Facts and ideas from anywhere by W. C. Roberts

224 Baylor news
255 Reader comments: Lupus erythematosus flare-up and myopericarditis as triggers and comorbidities of takotsubo syndrome (J. E. Madras)
266 2014 publications of the Baylor medical and scientific staff
286 Selected published abstracts of Baylor researchers

The largest not-for-profit health care system in Texas, and one of the largest in the United States, Baylor Scott & White Health was born from the 2013 combination of Baylor Health Care System and Scott & White Healthcare. For more information on our 43 hospitals and more than 500 patient care sites, please visit www.BaylorScottandWhite.com and www.sw.org.

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