Baylor Scott & White Medical Center Proceedings
The peer-reviewed journal of Baylor Scott & White Health

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Clinical research studies enrolling patients through Baylor Scott & White Research Institute

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<thead>
<tr>
<th>Research area</th>
<th>Specific disease/condition</th>
<th>Contact information (name, phone number, and e-mail address)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesiology</td>
<td>Various device trials, measuring oxygenation levels, EEG algorithms of sedation, SpO2 and fluid volume levels, delivery of various anesthesia medications</td>
<td>Zhang Zhang 214-865-3128 <a href="mailto:Zhang.Zhang@BSWHealth.org">Zhang.Zhang@BSWHealth.org</a></td>
</tr>
<tr>
<td>Asthma and pulmonary disease</td>
<td>Chronic obstructive pulmonary disease, asthma (adult), lung transplant, pulmonary hypertension, diaphragm impairment, nebulizer, inhalation</td>
<td>Jessica Propps 214-820-1821 <a href="mailto:Jessica.Propps@BSWHealth.org">Jessica.Propps@BSWHealth.org</a></td>
</tr>
<tr>
<td>Cancer</td>
<td>Breast, ovarian, endometrial, prostate, brain, lung, bladder, colorectal, pancreatic, and head and neck cancer, hematological malignancies, leukemia, multiple myeloma, non-Hodgkin’s lymphoma, bone marrow transplant</td>
<td>Laura Schrum-Breen 214-865-4994 <a href="mailto:Laura.Schrum-Breen@BSWHealth.org">Laura.Schrum-Breen@BSWHealth.org</a></td>
</tr>
<tr>
<td>Central Texas</td>
<td>Cancer,cardiology, family medicine, gastroenterology, infectious disease, kidney, neurology, ob/gyn, ophthalmology, orthopedics, pathology, pediatrics, plastic surgery, pediatrics, psychiatry, pulmonary, radiology, rheumatology, surgery, transplant, urology</td>
<td>Vanessa Hoeftsher 1-888-863-3675 <a href="mailto:Vanessa.hoeftsher@bswhealth.org">Vanessa.hoeftsher@bswhealth.org</a></td>
</tr>
<tr>
<td>Diabetes (Dallas)</td>
<td>Type 1 and type 2 diabetes, cardiovascular events</td>
<td>Lisa Mamo, RN 214-818-7974 <a href="mailto:Lisa.Mamo@BSWHealth.org">Lisa.Mamo@BSWHealth.org</a></td>
</tr>
<tr>
<td>Diabetes (Plano)</td>
<td>Pancreatic islet cell transplantation for type I diabetics, who either have or have not had a kidney transplant</td>
<td>Anne Marie Jones 214-818-7823 <a href="mailto:Anne.Jones@BSWHealth.org">Anne.Jones@BSWHealth.org</a></td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>Traumatic brain injury</td>
<td>Jon Thammavong 214-818-9687 <a href="mailto:Jon.Thammavong@BSWHealth.org">Jon.Thammavong@BSWHealth.org</a></td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>Inflammatory bowel disease</td>
<td>Sandra Kirby, RN 214-818-9792 <a href="mailto:Sandra.Kirby@BSWHealth.org">Sandra.Kirby@BSWHealth.org</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Dallas)</td>
<td>Aortic aneurysm, coronary artery disease, hypertension, poor left 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</td>
<td>Michele Boatman 214-820-2273 <a href="mailto:Michele.Boatman@BSWHealth.org">Michele.Boatman@BSWHealth.org</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Legacy Heart)</td>
<td>All risk for heart attack/stroke; previous heart attack/stroke/PAD; cholesterol disorders; atrial fibrillation; overweight/diet; other heart-related conditions</td>
<td>Lisa Marsh 214-865-2271 <a href="mailto:Lisa.March@BSWHealth.org">Lisa.March@BSWHealth.org</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Plano)</td>
<td>Aortic aneurysm; coronary artery disease; renal diet for uncontrolled hypertension; poor left 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</td>
<td>Lisa Marsh 214-865-2271 <a href="mailto:Lisa.March@BSWHealth.org">Lisa.March@BSWHealth.org</a></td>
</tr>
<tr>
<td>Hepatology</td>
<td>Liver disease</td>
<td>Niecelle Lloyd 214-820-1710 <a href="mailto:Niecelle.Lloyd@BSWHealth.org">Niecelle.Lloyd@BSWHealth.org</a></td>
</tr>
<tr>
<td>Infectious disease</td>
<td>HIV/AIDS</td>
<td>Bryan King, LVN 214-823-2533 <a href="mailto:Bryan.King@lvnicdc.org">Bryan.King@lvnicdc.org</a></td>
</tr>
<tr>
<td>Infectional disease</td>
<td>Hepatitis B</td>
<td>Niecelle Lloyd 214-820-1710 <a href="mailto:Niecelle.Lloyd@bswhealth.org">Niecelle.Lloyd@bswhealth.org</a></td>
</tr>
<tr>
<td>Nephrology</td>
<td>Type 2 diabetes with chronic kidney disease</td>
<td>Veronie Simak 214-820-4628 <a href="mailto:Veronie.Simak@BSWHealth.org">Veronie.Simak@BSWHealth.org</a></td>
</tr>
<tr>
<td>Neurology</td>
<td>Stroke, migraine</td>
<td>Guynh Lam Doan 214-818-2522 <a href="mailto:Guynh.Lam.Doan@BSWHealth.org">Guynh.Lam.Doan@BSWHealth.org</a></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>Multiple sclerosis, stroke</td>
<td>Vicki Staines, RN 214-820-2528 <a href="mailto:victoria.staines@BSWHealth.org">victoria.staines@BSWHealth.org</a></td>
</tr>
<tr>
<td>NICU</td>
<td>Cerebral aneurysm</td>
<td>Mary Wallace 214-820-4752 <a href="mailto:Mary.Wallace@BSWHealth.org">Mary.Wallace@BSWHealth.org</a></td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>Intermittent stroke therapy</td>
<td>Tonia Harrison 214-820-2615 <a href="mailto:tiona.harrison@BSWHealth.org">tiona.harrison@BSWHealth.org</a></td>
</tr>
<tr>
<td>Rheumatology (9900 N. Central Expressway)</td>
<td>Rheumatoid arthritis, psoriatic arthritis, lupus, gout, ankylosing spondylitis</td>
<td>Elizabeth Venincasa, RN, BSN 214-987-1253 <a href="mailto:Elizabeth.Venincasa@BSWHealth.org">Elizabeth.Venincasa@BSWHealth.org</a></td>
</tr>
<tr>
<td>Surgery</td>
<td>Chronic limb ischemia, pain management with chest tubes, colon polyps, diaphragm stimulators, and surgery as it pertains to GERD, breast cancer, esophageal, colon, colon cancer, pancreas, lung, hernias, dysautonomia, per-oral endoscopic myotomy (POEM), thoracic outlet syndrome</td>
<td>Tammy Fisher, RN, MSN, MBA 214-820-7221 <a href="mailto:Tammy.Fisher@BSWHealth.org">Tammy.Fisher@BSWHealth.org</a></td>
</tr>
<tr>
<td>Transplantation</td>
<td>Bone marrow, blood stem cells</td>
<td>Grace Townsend 214-818-8472 <a href="mailto:Grace.Townsend@BSWHealth.org">Grace.Townsend@BSWHealth.org</a></td>
</tr>
<tr>
<td>Trauma and critical care</td>
<td>Patient outcomes, PTSD, pain management with chest tubes, damage control surgery, readmission, trauma activation, critical care, acute care surgery</td>
<td>Evan Elizabeth Rainey 214-865-2410 <a href="mailto:Evan.Ellis@BSWHealth.org">Evan.Ellis@BSWHealth.org</a></td>
</tr>
<tr>
<td>Waco</td>
<td>Diabetes, chronic kidney disease, CO2, hypertension; prevention of second cardiac event, atopic dermatitis</td>
<td>Michele Richardson, BA, CCR 254-202-2645 mrichardson@illcm cosmetics.net</td>
</tr>
<tr>
<td>Weight management</td>
<td>Obesity</td>
<td>Lisa Mamo, RN 214-818-7974 <a href="mailto:Lisa.Mamo@BSWHealth.org">Lisa.Mamo@BSWHealth.org</a></td>
</tr>
<tr>
<td>Women’s Health (Fort Worth)</td>
<td>Uterus fibroids</td>
<td>Theresa Cheyne 817-922-2579 <a href="mailto:Theresa.Cheyne@BSWHealth.org">Theresa.Cheyne@BSWHealth.org</a></td>
</tr>
</tbody>
</table>

Baylor Scott & White Research Institute is dedicated to providing the support and tools needed for successful clinical research. For more information, please contact Megan Jacob at Megan.Jacob@BSWHealth.org.
Clinical uptake of antimicrobial stewardship recommendations following Nanosphere Verigene Blood Culture Gram-negative reporting

Aaron Belknap, MD, Daniel S. Grosser, MD, Daniel A. Hale, MD, Benjamin J. Lang, MD, Peter Colley, PharmD, Raul Benavides, MD, and Neelam Dhiman, PhD

We performed a retrospective chart review of patients to determine if the Verigene Gram-negative blood culture (BC-GN) results would lead to earlier deescalation of empiric therapy for inpatients with GN bacteremia with *Citrobacter* spp., *Enterobacter* spp., *Klebsiella* spp., and *Escherichia coli* to appropriate targeted coverage. A total of 899 records were reviewed from April 2014 to February 2016 from three institutions within the Baylor Scott & White Health network. The cases were reviewed for initial antibiotic coverage, timing of Verigene results, change in antibiotic coverage, and how these changes related to the timing of Verigene results. The lab reported the BC-GN results and final conventional susceptibility results within 2.5 ± 1.3 and 73.6 ± 40.0 hours from the Gram stain, respectively. Overall, 29.1% of patients were transitioned from empiric to targeted therapy at 12.2 ± 13.5 hours in response to BC-GN results, which was significantly earlier (P < 0.001) than results by conventional methods. After accounting for patients already on targeted therapy, polymicrobial infections, and patients deceased or lost to follow-up, we identified antibiotic stewardship opportunities in ~28% of GN infections. Further subanalysis demonstrated site-specific differences in the uptake of stewardship recommendations, whereby 32.4%, 50.5%, and 15.0% of cases at different hospitals demonstrated the expected change in antibiotics. These results suggest that Verigene had the expected impact in a third of the cases and the results reporting algorithm minimized the real-time involvement of the pharmacist while maintaining optimal patient management. However, this impact varied substantially by clinical site and was tempered by variable initial antibiotic coverage and clinician response.

Effective and prompt antimicrobial therapy is crucial for the survival of patients with sepsis (1–3). Rapid molecular technologies aimed at decreasing the time to identification and susceptibility results have recently entered the market (4, 5). The Verigene Gram-Negative Blood Culture (BC-GN) assay is one such rapid panel that detects seven genera, four species, and six resistance markers directly from positive blood cultures (6). We adopted the BC-GN assay in our laboratory to serve the needs of the multisite Baylor Scott and White Health network. For effective implementation, we worked with the Antimicrobial Stewardship Program (ASP) to provide recommended changes to antibiotic therapy based on the species identification and local pathogen susceptibility patterns in the result comments. The goal was to improve patient outcomes by guiding transition of the empiric treatment (vancomycin and piperacillin/tazobactam) to targeted therapy, while simultaneously preventing antibiotic overuse and the development of antibiotic resistance. This study aimed to determine if decreasing the time to blood culture result using the BC-GN system paired with well-defined ASP-recommended therapy changes would impact clinical outcomes. The primary objective was to evaluate the clinical uptake and utilization of the BC-GN results by measuring the reduction in time from positive blood culture to the deescalation of empiric therapy and the switch to the first dose of appropriate antibiotics per the resulting algorithm. As previously published, an algorithm designed using electronic communications and minimum pharmacist intervention was used (7, 8). We also determined if there were any site-specific differences in the uptake of stewardship recommendations within the network.

METHODS

This was a multisite, retrospective chart review of patients admitted with Gram-negative (GN) bacteremia to Baylor University Medical Center, a 1079-bed tertiary referral center in Dallas, Texas, and two smaller acute care hospitals also within the Baylor Scott and White Health network, 574-bed Baylor All Saints and 296-bed Baylor Irving. Blood cultures were performed at the affiliated reference laboratory, med fusion, in Lewisville, Texas. Molecular testing on the positive blood cultures was performed using Verigene BC-GN panel (Nanosphere, Inc., Northbrook, IL). This study was approved by the institutional review board.

Medical records were reviewed from April 2014 to February 2016 from three sites for initial antibiotic coverage, timing of the appearance of Verigene results in the electronic health record (EHR), change in antibiotic therapy (if any), and how these changes compared to the timing of Verigene results. Times were

From the Departments of Pathology and Laboratory Medicine (Belknap, Grosser, Hale, Lang, Benavides) and Pharmacy (Colley), Baylor University Medical Center at Dallas; and med fusion Laboratory, Lewisville, Texas (Dhiman).

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documented for blood culture collection, Gram stain, BC-GN result, conventional identification and susceptibilities, and the first dose of appropriate antibiotic. For this study, we chose a subset of GN organisms—Citrobacter spp., Enterobacter spp., Klebsiella spp. and Escherichia coli—as the recommended change in antibiotics was most different from empiric therapy and was predicted to have a maximum impact upon change in antibiotics in response to stewardship recommendations. Other GN bacteria such as Pseudomonas aeruginosa, Proteus spp., and Acinetobacter spp. were also detected in the assay but were not considered because of the likelihood of minimal impact on empirical antibiotic usage. Appropriate adjustment was defined as deescalation of empiric therapy (vancomycin and piperacillin/tazobactam) to the appropriate targeted coverage such as third- or fourth-generation cephalosporins within 24 hours in response to the stewardship recommendations on the Verigene report. Antibiotics were documented based on the date and time that the dose was given as recorded in the EHR. Patients who died during their hospital admission or were discharged before Verigene results were available were excluded.

Blood was collected at individual sites and transported via courier to med fusion. Upon arrival at med fusion, bottles were incubated on the BacT/ALERT automated blood culture system for up to 5 days. When the aerobic or anaerobic bottle was identified as positive for bacterial growth, a Gram stain was performed, with inoculation on appropriate solid agar media. Plates were read after approximately 24 hours of incubation. Identification and susceptibility testing were performed using conventional phenotypic methods, MALDI-TOF and the VITEK®2 (bioMérieux, Durham, NC). The first bottle per bacteremic episode that showed a GN organism on Gram stain was tested using the BC-GN. The BC-GN was also run if the Gram stain showed mixed organisms with Gram-positive or other Gram stain morphologies.

The BC-GN results were called as a critical value to the floor and were released in the EHR. For Citrobacter spp. and Enterobacter spp., the Verigene report was accompanied by an interpretive comment suggesting the appropriate antimicrobials were fourth-generation cephalosporins and recommending discontinuation of empiric coverage. For Klebsiella spp. and E. coli, appropriate antimicrobials included third-generation cephalosporins and discontinuation of empiric coverage. The stewardship recommendations were developed by a collaborative team of ASP, infectious disease physicians, and laboratory staff.

Student's t-test was used to determine statistical significance in cases where intervention was made in response to the rapid Verigene result vs. the availability of the final report based on conventional methods.

**RESULTS**

The patient demographic and laboratory data are summarized in Table 2. Overall, there was a slight predominance of women (61.2%) in the study cohort. The mean age of women was 56.6 ± 19.4 years, significantly lower ($P < 0.001$) than the mean age of the men (63.6 ± 15.9 years) at the time of the septic episode. This was unlikely to have any clinical significance. From the time of the blood collection, the Gram stain was reported within an average of 20.0 ± 10.4 hours and the BC-GN result was reported within 2.5 ± 1.3 hours of the Gram stain. The time between Gram stain and final identification and susceptibilities using conventional methods was 73.6 ± 40.0 hours.

The distribution of the GN bacterial targets across the three sites evaluated within the Baylor network is shown in Table 3. Across the three sites evaluated, E. coli was the predominant isolate (72.5%), 14.4% of which harbored extended spectrum beta-lactamases (ESBLs). This was followed by Klebsiella spp.,

### Table 1. Targets detected on Verigene Blood Culture Gram-negative panel and associated stewardship comments

<table>
<thead>
<tr>
<th>Verigene target</th>
<th>Stewardship comments added to the Verigene report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrobacter spp., Enterobacter spp.</td>
<td>• Consider discontinuing empiric Gram-positive coverage if appropriate.</td>
</tr>
<tr>
<td></td>
<td>• Consider a fourth-generation cephalosporin if appropriate.</td>
</tr>
<tr>
<td></td>
<td>• Deescalate further when susceptibility results are available.</td>
</tr>
<tr>
<td>Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli</td>
<td>• Consider discontinuing empiric Gram-positive coverage if appropriate.</td>
</tr>
<tr>
<td></td>
<td>• Consider a third-generation cephalosporin if appropriate.</td>
</tr>
<tr>
<td></td>
<td>• Deescalate further when susceptibility results are available.</td>
</tr>
<tr>
<td>ESBL producer (CTX-M)</td>
<td>• Recommend use of meropenem.</td>
</tr>
<tr>
<td></td>
<td>• Deescalate when susceptibility results are available.</td>
</tr>
<tr>
<td>Carbapenemase producer (KPC, OXA, VIM, IMP, NDM)</td>
<td>• Initiate contact precautions.</td>
</tr>
<tr>
<td></td>
<td>• Consider infectious disease consult.</td>
</tr>
</tbody>
</table>

**Table 2. Demographic and laboratory parameters for result reporting (n = 899)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females: Males</td>
<td>550:349</td>
<td></td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>59.3 ± 18.5</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>63.6 ± 15.9</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>56.6 ± 19.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time (hours), mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between draw and Gram stain result</td>
<td>20.0 ± 10.4</td>
<td></td>
</tr>
<tr>
<td>Between Gram stain and Gram-negative blood culture result</td>
<td>2.5 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>Between Gram stain and final report</td>
<td>73.6 ± 40.0</td>
<td></td>
</tr>
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</table>
Rapid diagnosis of Gram-negative bacteremia and outcomes

October 2017

Table 3. Distribution of Gram-negative organisms across three Baylor Scott & White Health hospitals

<table>
<thead>
<tr>
<th>Targets</th>
<th>BUMC</th>
<th>BAS</th>
<th>IRV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>284</td>
<td>133</td>
<td>141</td>
<td>558</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>94</td>
<td>31</td>
<td>26</td>
<td>151</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
<td>37</td>
<td>12</td>
<td>4</td>
<td>53</td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em></td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td><em>Citrobacter</em> spp.</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>ESBL producers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em> (% ESBLs)</td>
<td>55</td>
<td>14</td>
<td>25</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>(19.4%)</td>
<td>(10.5%)</td>
<td>(17.7%)</td>
<td>(16.9%)</td>
</tr>
<tr>
<td><em>K. pneumoniae</em> (% ESBLs)</td>
<td>16</td>
<td>2</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>(17.0%)</td>
<td>(6.5%)</td>
<td>(0%)</td>
<td>(11.9%)</td>
</tr>
<tr>
<td><em>K. oxytoca</em> (% ESBLs)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(12.5%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(7.1%)</td>
</tr>
<tr>
<td>Carbapenemase producers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>(% carbapenemase producers)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2.7%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(1.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>500</td>
<td>199</td>
<td>200</td>
<td>899</td>
</tr>
</tbody>
</table>

BAS indicates Baylor All Saints; BUMC, Baylor University Medical Center; ESBL, extended spectrum beta-lactamases; IRV, Baylor Irving.

which constituted 20.5% of the isolates, with 10.3% of the *Klebsiella* spp. harboring ESBLs.

The timeline of antibiotic adjustment in response to stewardship recommendations on the rapid BC-GN report is shown in Figure 1. Across all three sites combined, 29.1% (262/899) of patients were transitioned from empiric to targeted therapy and made the expected change to antibiotics in response to stewardship recommendations within 24 hours. In the subset where an intervention was made, the switch to appropriate targeted antibiotics was made at 12.2 ± 13.5 hours in response to BC-GN results, which was significantly earlier (*P* < 0.001) than when results by conventional methods became available (73.6 ± 40.0 hours).

After accounting for patients already on recommended targeted therapy, polymicrobial infections, and patients deceased or lost to follow-up, we found antibiotic stewardship opportunities in ~28% of GN infections. Further subanalysis demonstrated site-specific differences in the uptake of stewardship recommendations, whereby 32.4% of cases at Baylor University Medical Center, 50.5% at Baylor All Saints, and 15.0% at Baylor Irving demonstrated the expected change in antibiotics (Table 4). We also noticed overuse of carbapenem/quinolone drug categories (only 9.6% of patients on carbapenem/quinolone were ESBL producers) at the Baylor Irving site.

DISCUSSION

Rapid identification of GN bacteremia and key susceptibility markers can lead to many benefits, such as earlier deescalation of empiric therapy and switch to appropriate targeted antimicrobials that can lead to better patient outcomes, decreased length of hospital stay, and decreased overall hospital costs (9–12). The Verigene BC-GN assay has two major advantages favoring its routine use: a random-access format with very limited hands-on time and the ability to rapidly provide clinically actionable therapeutic information to physicians.

Our study demonstrated that implementation of the BC-GN panel across a multisite facility led to earlier deescalation of empiric therapy and switch to appropriate targeted antibiotics in approximately 29% of the cases. Multiple patients were shown to be on targeted antibiotic therapy from initial dosing (i.e., before organism identification was available by Verigene BC-GN). The initial postulation was that the choice of antibiotics may be driven by order sets in the EHR, for which physicians may be directed to empiric therapy other than vancomycin and
piperacillin/tazobactam, as it is not needed in all cases. However, further subset analysis by order sets demonstrated that there was no association between use of order sets to prescribe antibiotic therapy and changes in therapy in response to BC-GN result. There was also no association of patient location (i.e., within or outside of the intensive care unit) and response to the BC-GN result. No association between use of order sets to prescribe antibiotic further subset analysis by order sets demonstrated that there was no association of patient location (i.e., within or outside of the intensive care unit) and response to the BC-GN result.

We determined that there were site-specific differences in antibiotic stewardship practices. Of interest, we identified high empiric use of carbapenem/quinolone drug classes despite low identification of ESBL on the BC-GN result at the Baylor Irving site. Although carbapenem are active in this setting, these high-cost agents should be reserved for the additional coverage of drug-resistant organisms (13, 14). The outcome of this study will allow concentration of antimicrobial stewardship efforts at this site. Confidence in the rapid results on the BC-GN panel combined with education should minimize the use of carbapenem/quinolone drug categories when not indicated. Further opportunities for discontinuation of empiric coverage and earlier switch to targeted therapy were identified for approximately one-fourth of the cases.

Our study is comparable to previously published outcome studies on BC-GN rapid testing. Hill et al (10) evaluated the performance of the Verigene BC-GN assay and potential impact of rapid antibiotic interventions in 54 patients. BC-GN identified the organism approximately 24 hours faster than conventional methods. Upon retrospective evaluation of medical records by the stewardship team, it was concluded that antibiotic management could have been modified for 31.8% of patients an average of 33 hours sooner. Walker et al (12) did a retrospective review of GN bacteremia cases before (n = 98) and after (n = 97) Verigene BC-GN implementation and demonstrated that rapid implementation of effective therapy was statistically significant for postintervention cases of ESBL-producing organisms (P = 0.049) but not overall (P = 0.12).

The study was limited, as it did not evaluate the economic savings to the hospital in terms of antibiotic usage, length of hospitalization, and mortality. Another limitation is that underlying diagnosis and associated complications were not evaluated. Larger prospective studies are warranted to support the findings of our study and to address other important aspects influencing the routine use of this assay.


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**Table 4. Blood culture Gram-negative report utilization across three Baylor Scott & White Health hospitals**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Category</th>
<th>BUMC (n = 500)</th>
<th>BAS (n = 199)</th>
<th>IRV (n = 200)</th>
<th>Total (n = 899)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected change in antibiotics*</td>
<td></td>
<td>132 (26.4%)</td>
<td>100 (50.5%)</td>
<td>30 (15.0%)</td>
<td>262 (29.1%)</td>
</tr>
<tr>
<td>No change/change other than recommended</td>
<td></td>
<td>368 (73.6%)</td>
<td>99 (49.5%)</td>
<td>170 (85.0%)</td>
<td>637 (70.9%)</td>
</tr>
<tr>
<td>Reasons for no change in GP coverage</td>
<td>Not on dedicated GP coverage</td>
<td>170 (34.0%)</td>
<td>26 (13.0%)</td>
<td>133 (66.5%)</td>
<td>329 (36.6%)</td>
</tr>
<tr>
<td>Died/ED/discharged</td>
<td></td>
<td>35 (7.0%)</td>
<td>4 (2.0%)</td>
<td>0 (0.0%)</td>
<td>39 (4.3%)</td>
</tr>
<tr>
<td>Polymicrobial cultures</td>
<td></td>
<td>31 (6.2%)</td>
<td>1 (0.5%)</td>
<td>2 (1.0%)</td>
<td>34 (3.8%)</td>
</tr>
<tr>
<td>Continued empiric GP</td>
<td></td>
<td>132 (26.4%)</td>
<td>68 (34.0%)</td>
<td>35 (17.5%)</td>
<td>235 (26.1%)</td>
</tr>
</tbody>
</table>

### Notes:

- BAS indicates Baylor All Saints; BUMC, Baylor University Medical Center; ED, emergency department; ESBL, extended spectrum beta-lactamases; GN, Gram-negative; GP, Gram-positive; IRV, Baylor Irving.
- *Expected change was defined as deescalation of empiric therapy (vancomycin and piperacillin/tazobactam) for patients with *Escherichia coli* bacteremia to the appropriate targeted coverage per institutional guidelines within 24 hours in response to the stewardship recommendations on the Verigene report.

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Percutaneous coronary intervention and inpatient mortality in patients with advanced chronic kidney disease presenting with acute coronary syndrome

Brijesh Patel, DO, Mahek Shah, MD, Raman Dusaj, MD, Sharon Maynard, MD, and Nainesh Patel, MD

Chronic kidney disease (CKD) is an important risk factor for coronary artery disease, yet patients with CKD are less likely to undergo coronary angiography and percutaneous coronary intervention (PCI). We retrospectively analyzed the 2006–2012 National Inpatient Sample Database to examine the temporal trends in coronary angiography and PCI among patients without CKD, with advanced CKD (CKD III–V), and with end-stage renal disease (ESRD) presenting with unstable angina/non–ST elevation myocardial infarction (NSTE-ACS) and ST-elevation myocardial infarction (STEMI). A total of 579,747 admissions for NSTE-ACS and 293,950 admissions for STEMI were studied. Patients with NSTE-ACS were less likely to undergo coronary angiography/PCI than those with STEMI, irrespective of CKD. Between 2006 and 2012, performance of PCI saw an uptrend across all CKD groups with NSTE-ACS (no CKD, 29.9%–36.8%; CKD III–V, 18.2%–21.5%; ESRD, 19.8%–27.5%; all \( P_{\text{trends}} < 0.01 \)) and STEMI (no CKD, 57.0%–76.0%; CKD III–V, 33.0%–52.6%; ESRD, 29.9%–42.9%; \( P_{\text{trends}} < 0.01 \)). Multivariate analyses revealed that PCI was associated with a lower risk of hospital mortality across all degrees of CKD in both NSTE-ACS (adjusted odds ratios: no CKD, 0.44; CKD III–V, 0.48; ESRD, 0.46; \( P < 0.01 \)) and STEMI (no CKD, 0.35; CKD III–V, 0.50; ESRD, 0.52; \( P < 0.01 \)). Performance of PCI increased over time among patients presenting with NSTE-ACS and STEMI in the presence of advanced CKD and independently predicted lower in-hospital mortality.

METHODS

We queried the unweighted 2006–2012 National Inpatient Sample (2) to identify patients aged ≥18 years with a primary diagnosis of acute myocardial infarction (AMI) (ICD-9CM codes 410x and 411.1). Patients were separated into three categories depending on baseline renal function: no CKD, CKD stage III–V, and end-stage renal disease (ESRD) on chronic dialysis (ICD-9CM codes: 585.3-6, 585.9). A chi-square test was used to compare categorical variables. Trend analysis was performed using the Mantel-Haenszel linear test of trend. We created separate multivariable logistic regression models based on the degree of CKD (no CKD, CKD III–V, ESRD) within the group of patients presenting with non–ST elevation myocardial infarction (NSTE–ACS) and ST-elevation myocardial infarction (STEMI) to evaluate the relationship between performance of PCI and in-hospital mortality. Within these models, we adjusted for several risk factors, including patient characteristics (demographics, comorbidities), hospital characteristics (bed size, location, and teaching status), admission characteristics (year, weekend), and primary insurance payer.

RESULTS

A total of 579,747 admissions for NSTE-ACS and 293,950 admissions for STEMI were studied. Patients with advanced stages of CKD had higher proportions of women and comorbidities, but lesser proportions of Caucasians, compared to patients with normal baseline renal function in both the NSTE-ACS and STEMI groups (Tables 1 and 2). As shown in Figure 1, use of both CAG and PCI increased for NSTE-ACS and STEMI during the study duration, irrespective of CKD status. However, patients with CKD and ESRD were less likely to undergo CAG/PCI than those without CKD. By the year 2012, two-thirds of NSTE-ACS patients presenting with NSTE-ACS and STEMI in the presence of advanced CKD independently predicted lower in-hospital mortality.
patients without CKD had CAG, slightly more than half of them received PCI. Higher all-cause hospital mortality was noted among those with an advanced degree of renal dysfunction, with the mortality risk being higher in STEMI than in NSTE patients.

About one-fourth of STEMI patients with ESRD died during hospitalization. The prevalence of in-hospital mortality was nearly double in the STEMI patients than in the NSTE-ACS patients. After adjusting for key variables, performance of PCI in NSTE-ACS was associated with a lower risk of hospital mortality across all degrees of CKD, with adjusted odds ratios of 0.44 for no CKD, 0.48 for CKD III–V, and 0.46 for ESRD. Similarly, PCI in STEMI independently predicted lower in-hospital mortality across the CKD spectrum, with adjusted odds ratios of 0.35 for no CKD, 0.50 for CKD III–V, and 0.52 for ESRD (Table 3).

**DISCUSSION**

Our study showed that an increasing number of patients undergo CAG and PCI for any renal stages, and PCI was associated with marked reduction in mortality risk. Importantly, among patients presenting with STEMI, more underwent CAG and PCI from 2006 to 2012, though there was a disparity between patients with or without CKD. CKD is a known risk factor for increased AMI-related mortality (1). Charytan and colleagues previously reported underperformance of PCI in CKD patients, but the data represented only

<table>
<thead>
<tr>
<th>Variable</th>
<th>No CKD (n = 513,185)</th>
<th>CKD stages III–V (n = 41,999)</th>
<th>ESRD (n = 24,563)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>54.5%</td>
<td>80.0%</td>
<td>56.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caucasian</td>
<td>63.3%</td>
<td>64.5%</td>
<td>43.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>43.4%</td>
<td>43.1%</td>
<td>44.1%</td>
<td>0.004</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>3.0%</td>
<td>1.3%</td>
<td>1.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>21.7%</td>
<td>26.6%</td>
<td>21.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33.1%</td>
<td>54.1%</td>
<td>62.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67.5%</td>
<td>82.0%</td>
<td>87.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>0.9%</td>
<td>0.9%</td>
<td>0.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>12.3%</td>
<td>14.1%</td>
<td>10.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>10.1%</td>
<td>21.7%</td>
<td>23.2%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>No CKD (n = 281,106)</th>
<th>CKD stages III–V (n = 8123)</th>
<th>ESRD (n = 4721)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>42.2%</td>
<td>77%</td>
<td>57.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caucasian</td>
<td>63.9%</td>
<td>65%</td>
<td>45.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>33.6%</td>
<td>41.7%</td>
<td>43.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>3.2%</td>
<td>1.2%</td>
<td>1.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>15.5%</td>
<td>21.6%</td>
<td>17.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25.6%</td>
<td>47.1%</td>
<td>56.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58.2%</td>
<td>81.1%</td>
<td>85.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>0.7%</td>
<td>1%</td>
<td>0.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obesity</td>
<td>10.4%</td>
<td>12.7%</td>
<td>8.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>7%</td>
<td>17.8%</td>
<td>21.2%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Presentation Baseline renal function</th>
<th>Odd ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSTE-ACS</td>
<td>No CKD</td>
<td>0.44 (0.42–0.47)</td>
</tr>
<tr>
<td></td>
<td>CKD III–V</td>
<td>0.48 (0.42–0.56)</td>
</tr>
<tr>
<td></td>
<td>ESRD</td>
<td>0.46 (0.40–0.53)</td>
</tr>
<tr>
<td>STEMI</td>
<td>No CKD</td>
<td>0.35 (0.34–0.36)</td>
</tr>
<tr>
<td></td>
<td>CKD III–V</td>
<td>0.50 (0.43–0.58)</td>
</tr>
<tr>
<td></td>
<td>ESRD</td>
<td>0.52 (0.45–0.61)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; NSTE-ACS, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction. The model is adjusted for age, gender, race, Charlson comorbidity index, weekend and elective admissions, insurance type, alcohol abuse, anemia, arthritic conditions, chronic lung disease, coagulopathy, depression, diabetes, drug abuse, hypertension, hyperthyroidism, Liver disease, fluids and electrolyte disorders, obesity, peripheral vascular disease, pulmonary circulatory disorders, year of admission, bed size and teaching status/location of hospitals, acute kidney injury, lymphoma, metastatic cancer, psychosis, solid tumor without metastases, and percutaneous coronary interventions.
PCI is associated with higher contrast exposure, increasing the risk for CIN and long-term renal impairment. Strategies such as volume expansion reduce the incidence of CIN, allowing clinicians to expand use of PCI among higher-risk populations. Another strategy involves a more selective approach to left ventriculography, thus limiting contrast use with renal dysfunction. Overall reductions in the absolute contrast volume and use of low- to iso-osmolar contrast agents have been associated with a lower risk of CIN. Patient choice plays a significant role in the decision-making process when presented with the higher risk for dialysis among those with increasing severity of CKD. Improvements in practice and evolution in physician and patient attitudes may have contributed to the overall uptrend in performance of CAG and PCI.

Our study has several limitations inherent to its retrospective design, use of an administrative database, and dependence on ICD-9CM coding. We were unable to determine the temporal relationship between acute kidney injury and PCI/CAG which would influence decision making. The overall PCI rate was relatively low, maybe due to revascularization at a separate visit. We chose to exclude patients with an undetermined stage of CKD and did not examine trends in alternative revascularization strategies. We relied on diagnosis codes to stratify the groups, and the database does not provide information on CIN.

In summary, there has been an increase in the use of PCI between 2006 and 2012 among patients with AMI, irrespective of the presence of baseline CKD. Patients with advanced CKD and AMI were less likely to undergo CAG or subsequent PCI and experienced a higher rate of in-hospital mortality compared...
to those with normal baseline renal function. Performance of PCI independently predicted a lower in-hospital mortality among patients presenting with ACS, even in the presence of advanced CKD.


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## Avocations

**DEVOTION**

Hell emptied its belly,  
dropped lava from the sky,  
where once stood a compound  
in a remote village.

Then there were only ruins.  
Barking and sniffing rubble for familiar scents;  
he emerged limping  
from the dense cloud of dust.

Something in there, he sensed,  
in that strange mixture of smells,  
which bound him to the scene.  
He would not break the shackles.

Minutes turned into hours, hours into days.  
His friend and his master  
wasn’t there to fill the bowl.  
Small puddle, next to house also went dry.

Hunger pains slowed him down,  
but he sniffed and he dug,  
till his paws had no pads and his  
bark waned to whimper.

Had no strength to prop his head.  
Ears hung flaccid.  
He curled up in the rubble,  
head resting between legs.

Panting ceased, breathing slowed—then stopped.  
But the eyes remained open, waiting for his master.

© Amanullah Khan, MD, PhD. Dr. Khan (e-mail: aman1963@gmail.com) is vice president of the Poetry Society of Texas (PST) and an oncologist on the medical staff of Baylor Medical Center at McKinney. This poem won first place in PST’s January 2016 contest.
Urinary metabolites in patients undergoing coronary catheterization via the radial versus femoral artery approach

Anupama Vasudevan, BDS, MPH, PhD, Jeffrey M. Schussler, MD, Jane I. Won, BS, Paula Ashcraft, BS, Ivy Bolanos, BS, Matthew Williams, BS, Teodoro Bottiglieri, PhD, Carlos E. Velasco, MD, and Peter A. McCullough, MD, MPH

The transradial approach (TRA) for coronary angiography and percutaneous coronary intervention is associated with lower rates of vascular complications and acute kidney injury when compared to the transfemoral approach (TFA). Urine metabolites and proteins may be useful in identifying the dynamic changes at the vascular endothelial cell level. We attempted to explore the changes in the measurable signals of endothelial and nephron injury within 60 to 90 minutes after catheterization among those with the TRA and TFA approaches. Consecutive patients of a single interventionist who underwent coronary angiography between June 2015 and May 2016 were included. Of the 60 patients included in the analysis, the baseline characteristics were similar between those with a TRA (n = 30) and TFA (n = 30) approach. The values of the biomarkers were natural log transformed for the analysis. We found that the mean values of heat shock protein 27, taurine, and sulfuric acid did not significantly change after the procedure. However, the median value of thioredoxin decreased (P = 0.002) and that of talose increased (P = 0.01) after the procedure. None of the patients in our cohort experienced vascular complications or acute kidney injury. No differences in the values of urinary metabolites (pre, post, and delta) were found between TRA and TFA except for postprocedural thioredoxin. In conclusion, this exploratory study showed no difference in the patterns of acute vascular/renal injury metabolic markers before and after catheterization irrespective of the arterial access site.

METHODS

This was a prospective observational study where consecutive patients of a single interventionalist who underwent coronary angiography by TRA or TFA between June 2015 and May 2016 were invited to participate. Demographic and clinical data were collected for patients enrolled in the study. Two urine samples were collected for these patients: one before the procedure and one 60 to 90 minutes after the last contrast injection. Both were processed for the metabolites and proteins of interest. As TRA patients are released from the hospital the day of the procedure, we focused on the early signaling patterns within very short time frames after the procedure. AKI was defined based on the KDIGO criteria (9).

Talose, taurine, and sulfuric acid were identified in urine samples using a method that involved trimethylsilyl derivatization and separation on a Leco Pegasus 4D two-dimensional gas chromatography (GC×GC)–time of flight mass spectrometry (ToF-MS) (6, 10). D4-Taurine and 13C5-Ribose internal standards were added to 25 μL of the urine specimen and were treated with urease to remove urea; protein precipitation was then performed with ethanol. After drying down, the sample was derivatized to volatile trimethylsilyl for separation by capillary GC×GC with temperature programming and modulation. Detection was performed by ToF-MS with identification of the compounds by their mass spectra and
retention time. Talose and taurine were quantified by ToF-MS with linear standard curves with a lower limit of quantitation of 0.5 nmoles. Urine creatinine was determined by liquid chromatography mass spectrometry (11). Results were reported for talose and taurine in nmoles/mole creatinine. The intraday and interday coefficients of variation for both compounds were <10% for high control and <15% for normal control. Since no labeled internal standard was available for sulfuric acid, the peak areas for the unique mass were reported and the data are considered semiquantitative. Thioredoxin and HSP27 were measured by commercially available enzyme-linked immunosorbent assays obtained from IBL International (Hamburg, Germany) and Invitrogen (Camarillo, CA), respectively.

Categorical variables were reported as proportions and continuous variables as mean ± standard deviation or median (range), if skewed. Comparisons between TRA and TFA were conducted with chi-square/Fisher’s exact test for proportions and Student’s t test or the Wilcoxon rank sum test for continuous variables. Utilizing paired parametric/nonparametric tests, we compared the pre and post values of the natural log-transformed metabolites. We also explored whether the pre, post, and delta (post – pre) measures of the urinary biomarkers differed between the TRA and TFA procedures. With a cohort size of 60, we had 95% observed power to detect a true paired difference of 0.5 pre and post procedure with an alpha of 0.05, two-sided test. Analyses were performed using STATA 14.2. This study was approved by the Baylor Health Care System institutional review board with a waiver of consent. The study was funded by the Baylor Health Care System Foundation.

RESULTS

A total of 69 patients consented to be part of this study, and 60 patients who completed the study were included in the analysis. The demographics and baseline characteristics were similar between the two groups (Table 1). The median preprocedural glucose level was higher among those patients with TFA than TRA (P = 0.001). A larger proportion of TFA patients than TRA patients were found to be admitted to the hospital within 30 days of the procedure (P = 0.02). The median (range) number of catheter exchanges was 3 (1–5) for both TRA and TFA (P = 0.33). The fluoroscopy time was found to be similar between TRA and TFA. Heparin was used in 93% of the radial procedures according to clinical practice guidelines.

The values of HSP27, thioredoxin, taurine, and sulfuric acid differed significantly by gender. Further, diabetic patients had higher levels of talose than did nondiabetics. The levels of talose were higher in patients who had >3 catheter exchanges during the procedure. The levels of sulfuric acid postprocedure were negatively correlated with the total amount of contrast used during the procedure (Table 2). We found that the values of HSP, taurine, and sulfuric acid did not significantly change following the procedure. Alternatively, the values of thioredoxin decreased and talose increased postprocedure (Figures 1 and 2). The urinary biomarker values did not differ according to procedural approach at any time examined. The only exception was postprocedural thioredoxin, for which significantly higher levels were found in the TFA group. The rates of change of these
Table 1. Characteristics of study patients undergoing coronary catheterization via the radial or femoral artery approach

<table>
<thead>
<tr>
<th>Variable</th>
<th>Femoral (n = 30)</th>
<th>Radial (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (73%)</td>
<td>22 (73%)</td>
<td>19 (63%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Age (years): mean ± SD</td>
<td>65.2 ± 9.6</td>
<td>63.6 ± 13.1</td>
<td>0.6</td>
</tr>
<tr>
<td>BMI (kg/m²): mean ± SD</td>
<td>30.4 ± 5.6</td>
<td>31.4 ± 5.3</td>
<td>0.46</td>
</tr>
<tr>
<td>Black (10%)</td>
<td>3 (10%)</td>
<td>1 (3%)</td>
<td>0.51</td>
</tr>
<tr>
<td>White (83%)</td>
<td>25 (83%)</td>
<td>28 (93%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic (7%)</td>
<td>2 (7%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (10%)</td>
<td>27 (90%)</td>
<td>20 (69%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus (40%)</td>
<td>12 (40%)</td>
<td>6 (20%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Dyslipidemia (90%)</td>
<td>27 (90%)</td>
<td>23 (77%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Peripheral arterial disease (10%)</td>
<td>3 (10%)</td>
<td>1 (3%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Heart failure (23%)</td>
<td>7 (23%)</td>
<td>3 (10%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Atypical chest pain (33%)</td>
<td>10 (33%)</td>
<td>14 (47%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Stable angina pectoris (40%)</td>
<td>12 (40%)</td>
<td>4 (14%)</td>
<td>0.04</td>
</tr>
<tr>
<td>ACS/unstable angina (33%)</td>
<td>10 (33%)</td>
<td>4 (13%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Myocardial infarction (43%)</td>
<td>13 (43%)</td>
<td>6 (20%)</td>
<td>0.05</td>
</tr>
<tr>
<td>TIA/CVA (3%)</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>NA</td>
</tr>
<tr>
<td>Chronic kidney disease (8%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>NA</td>
</tr>
<tr>
<td>Severe valvular disease (3%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Prior PCI (55%)</td>
<td>16 (55%)</td>
<td>11 (39%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Prior coronary bypass (37%)</td>
<td>11 (37%)</td>
<td>1 (4%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Never smoked (35%)</td>
<td>10 (35%)</td>
<td>3 (13%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Ex-smoker (48%)</td>
<td>14 (48%)</td>
<td>16 (70%)</td>
<td></td>
</tr>
<tr>
<td>Current smoker (17%)</td>
<td>5 (17%)</td>
<td>4 (17%)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization in the past 30 days</td>
<td>11 (38%)</td>
<td>3 (10%)</td>
<td>0.02</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²): mean ± SD</td>
<td>75.3 ± 20.9</td>
<td>72.9 ± 20.5</td>
<td>0.67</td>
</tr>
<tr>
<td>BUN (mg/dL): median (range)</td>
<td>18.5 (4–55)</td>
<td>17 (7–27)</td>
<td>0.32</td>
</tr>
<tr>
<td>Glucose (mg/dL): median (range)</td>
<td>115.5 (91–292)</td>
<td>104 (80–157)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL): mean ± SD</td>
<td>13.2 ± 1.7</td>
<td>13.9 ± 1.4</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Preprocedure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Femoral (n = 30)</th>
<th>Radial (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg): mean ± SD</td>
<td>136.5 ± 19.1</td>
<td>137.6 ± 19.9</td>
<td>0.84</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg): mean ± SD</td>
<td>76.1 ± 10.4</td>
<td>76.6 ± 17.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Heart rate (bpm): median (range)</td>
<td>71.5 (51–104)</td>
<td>64.5 (40–120)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Intraprocedure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Femoral (n = 30)</th>
<th>Radial (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventriculogram (86%)</td>
<td>25 (86%)</td>
<td>22 (73%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Sinus rhythm (77%)</td>
<td>23 (77%)</td>
<td>21 (72%)</td>
<td>0.71</td>
</tr>
<tr>
<td>IABP (0%)</td>
<td>0 (0%)</td>
<td>1 (4%)</td>
<td>NA</td>
</tr>
<tr>
<td>Pacing device (16%)</td>
<td>4 (16%)</td>
<td>4 (13%)</td>
<td>NA</td>
</tr>
<tr>
<td>Aspirin (60%)</td>
<td>18 (60%)</td>
<td>16 (55%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Bivalirudin (3%)</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Heparin (60%)</td>
<td>18 (60%)</td>
<td>26 (93%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Isovue (0%)</td>
<td>0 (0%)</td>
<td>4 (13%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Omnipaque (100%)</td>
<td>30 (100%)</td>
<td>26 (87%)</td>
<td></td>
</tr>
<tr>
<td>Total contrast used (cc): median (range)</td>
<td>120 (55–300)</td>
<td>97.5 (36–250)</td>
<td>0.04</td>
</tr>
<tr>
<td>Fluoroscopy time (min): median (range)</td>
<td>10.35 (1.2–90)</td>
<td>7.5 (2.4–20.4)</td>
<td>0.59</td>
</tr>
<tr>
<td>Fluoroscopy dose (mGy): median (range)</td>
<td>946.5 (240–3272)</td>
<td>712.3 (122–2291)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

DISCUSSION

Our study demonstrated that preprocedural values of urinary biomarkers (HSP27, thioredoxin, taurine, talose, sulfuric acid) did not vary between TFA and TRA. All postprocedural values except for thioredoxin were similar between the approaches. However, we also found that irrespective of the arterial access, the postprocedural values of thioredoxin were lower and the postprocedural values of talose were higher than their preprocedural measures. The baseline values differed by gender for some of these metabolites; higher levels of talose were evident in diabetic patients.

Biomarkers are useful in identifying the physiological, pharmacological, and/or pathological processes in the human system. Metabolite and protein profiling are the primary methods employed to identify specific biomarkers in clinical medicine. Precision medicine has benefited from the discovery of several biomarkers, which have been utilized in the identification of disease, prediction of prognosis, and management of medications (12). The intensity of the pattern changes of metabolites and proteins is based on the extent of injury and the degree of cell damage. Systematic analysis of urine has led to a better understanding of the changes in disease states of renal, cardiac, bladder, and ovarian diseases. Urine samples are easy to obtain and are likely to be rich in biomarkers arising from the kidneys (13). PCI and balloon coronary angioplasty have been associated with increases in oxidative stress and the inflammatory processes. C-reactive protein and various cytokines have been identified as potential biomarkers for prediction of coronary artery disease (14). Neutrophil gelatinase-associated lipocalin, IL-18, kidney injury molecule-1, and liver-type fatty acid binding protein have been identified as potential markers of AKI and as a predictor of contrast-induced nephropathy (15).

HSP27 plays a protective role in minimizing the damaging effect of oxidative and chemical stress. It is found to be overexpressed in conditions such as renal injury, diabetes, and cancer (7). Animal studies have shown that HSP27 is values did not differ between the two approaches (Table 3).

Eight patients (13.3%) were readmitted within 30 days of the procedure (4 femoral, 4 radial). Reasons for readmission included coronary artery bypass, heart failure, aortic valve replacement, aortic stenosis, gastrointestinal procedure, cystoprostatectomy, neck surgery, and fever. None of the patients in our cohort experienced an AKI.
associated with protecting the myocardium from ischemic injury as well as in reducing infarct size (16). Further, a positive association has been found between HSP27 and medullary perfusion in patients with kidney allografts, and HSP27 has been identified as a diagnostic marker for renal cell carcinoma (17). In our study, we found higher levels of HSP27 in women than in men. Studies have reported higher levels of urinary thioredoxin in women and have noted that the increased urinary excretion is influenced by an estrogen-mediated mechanism (8). Increased urinary thioredoxin has further been identified as a potential marker for diabetic nephropathy (8) and AKI (18). In our study, the exploratory analysis showed higher levels of thioredoxin in women than in men ($P = 0.0002$ preprocedure; $P = 0.0008$ postprocedure). We also found a significant decrease in the levels of thioredoxin postprocedure, irrespective of approach.

Taurine has been identified to be involved in neuronal modulation, osmoregulation, and protection against oxidative stress (19). Taurine was found to be excreted in excess following surgery, peaking on the second or third day postsurgery.

### Table 2. Urinary metabolites by baseline characteristics and demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Heat shock protein 27</th>
<th>Thioredoxin</th>
<th>Taurine</th>
<th>Talose</th>
<th>Sulfuric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>Gender</td>
<td>0.0001</td>
<td>&lt;0.001</td>
<td>0.0002</td>
<td>0.0008</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.42</td>
<td>0.66</td>
<td>0.62</td>
<td>0.28</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.97</td>
<td>0.18</td>
<td>0.64</td>
<td>0.48</td>
<td>0.13</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.03</td>
<td>0.12</td>
<td>0.03</td>
<td>0.07</td>
<td>0.54</td>
</tr>
<tr>
<td>PAD</td>
<td>0.49</td>
<td>0.11</td>
<td>0.78</td>
<td>0.24</td>
<td>0.25</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.65</td>
<td>0.34</td>
<td>0.39</td>
<td>0.73</td>
<td>0.26</td>
</tr>
<tr>
<td>Catheter exchange &gt;3</td>
<td>0.78</td>
<td>0.52</td>
<td>0.17</td>
<td>0.47</td>
<td>0.89</td>
</tr>
<tr>
<td>Arterial sheath &gt;6</td>
<td>0.76</td>
<td>0.32</td>
<td>0.4</td>
<td>0.45</td>
<td>0.8</td>
</tr>
<tr>
<td>Age</td>
<td>−0.005</td>
<td>0.07</td>
<td>0.003</td>
<td>0.09</td>
<td>0.21</td>
</tr>
<tr>
<td>(rho, $P$ value)</td>
<td>(0.97)</td>
<td>(0.62)</td>
<td>(0.98)</td>
<td>(0.49)</td>
<td>(0.10)</td>
</tr>
<tr>
<td>Total contrast used</td>
<td>−0.078</td>
<td>−0.03</td>
<td>−0.16</td>
<td>−0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>(rho, $P$ value)</td>
<td>(0.56)</td>
<td>(0.80)</td>
<td>(0.24)</td>
<td>(0.09)</td>
<td>(0.86)</td>
</tr>
<tr>
<td>Fluoroscopy time</td>
<td>−0.08</td>
<td>0.08</td>
<td>0.12</td>
<td>−0.15</td>
<td>−0.02</td>
</tr>
<tr>
<td>(rho, $P$ value)</td>
<td>(0.51)</td>
<td>(0.56)</td>
<td>(0.44)</td>
<td>(0.25)</td>
<td>(0.87)</td>
</tr>
<tr>
<td>Total fluoroscopy dose</td>
<td>−0.22</td>
<td>−0.21</td>
<td>−0.21</td>
<td>−0.25</td>
<td>−0.04</td>
</tr>
<tr>
<td>(rho, $P$ value)</td>
<td>(0.09)</td>
<td>(0.11)</td>
<td>(0.12)</td>
<td>(0.05)</td>
<td>(0.74)</td>
</tr>
<tr>
<td>BMI</td>
<td>−0.03</td>
<td>−0.12</td>
<td>−0.07</td>
<td>0.09</td>
<td>−0.08</td>
</tr>
<tr>
<td>(rho, $P$ value)</td>
<td>(0.85)</td>
<td>(0.37)</td>
<td>(0.59)</td>
<td>(0.47)</td>
<td>(0.54)</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.25</td>
<td>0.16</td>
<td>−0.03</td>
<td>0.16</td>
<td>−0.13</td>
</tr>
<tr>
<td>(rho, $P$ value)</td>
<td>(0.09)</td>
<td>(0.28)</td>
<td>(0.84)</td>
<td>(0.27)</td>
<td>(0.40)</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.08</td>
<td>0.26</td>
<td>−0.13</td>
<td>0.17</td>
<td>0.15</td>
</tr>
<tr>
<td>(rho, $P$ value)</td>
<td>(0.57)</td>
<td>(0.06)</td>
<td>(0.35)</td>
<td>(0.22)</td>
<td>(0.26)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PAD, peripheral arterial disease.
Acute infections and diseases of the liver and biliary tree were also noted to increase the production of taurine (20). It was reported that increased urinary excretion of taurine is found in patients with poorly controlled diabetes or ketoacidosis (21). In our study, we did not find any significant differences in the levels of taurine before and after the procedure; however, we did identify gender-specific differences, with higher values of taurine in men. By a partial least squares-discriminant analysis, an exploratory study indicated that increased excretion of talose was associated with renal injury in heart failure patients. Increased excretion of sulfuric acid in heart failure was believed to be due to the oxidative stress in patients’ renal tubules (20). We found a significant increase in talose postprocedure, with higher levels among diabetics. In our study, patients with dyslipidemia had increased levels of sulfuric acid in their urine preprocedure. However, no differences in their levels were found before and after the procedure between the two arterial approaches.

This was a prospective study in which urine was collected at specified time intervals and patients were followed diligently for 30 days postprocedure. However, this study included patients of a single interventionist from one facility, and almost all of the patients included in the study were admitted for an elective procedure. We also did not attempt to randomize the patients to the radial or femoral access route. We acknowledge this as a limitation of the study, as this could have introduced a selection bias and prevents generalizability. We recognize that this was not a study on established AKI biomarkers but an exploratory effort focusing on novel metabolites of vascular injury and renal damage.

Urinary biomarkers of acute vascular injury are a future tool to detect dynamic changes occurring at the cellular level. Despite very different patterns of arterial puncture and wire exchanges involving different lengths and regions of the aorta, we were unable to find significant differences in the molecules chosen between TRA and TFA approaches. Given the differences in clinical outcomes between these methods, future studies should consider broader arrays of markers with the aim of discovering new diagnostic or therapeutic targets for vascular or kidney injury.

Table 3. Urinary metabolites by arterial access

<table>
<thead>
<tr>
<th></th>
<th>Femoral</th>
<th>Radial</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprocedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSP27: mean ± SD</td>
<td>0.71 ± 1.20</td>
<td>0.67 ± 1.12</td>
<td>0.89</td>
</tr>
<tr>
<td>Thioredoxin: median (range)</td>
<td>–2.30 (–2.30 to +4.35)</td>
<td>0.55 (–2.30 to +3.74)</td>
<td>0.25</td>
</tr>
<tr>
<td>Taurine: mean ± SD</td>
<td>4.69 ± 1.31</td>
<td>4.48 ± 1.22</td>
<td>0.54</td>
</tr>
<tr>
<td>Talose: median (range)</td>
<td>6.29 (5.21 to 9.69)</td>
<td>6.06 (4.07 to 6.89)</td>
<td>0.07</td>
</tr>
<tr>
<td>Sulfuric acid: mean ± SD</td>
<td>8.80 ± 0.78</td>
<td>8.41 ± 1.07</td>
<td>0.11</td>
</tr>
<tr>
<td>Postprocedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSP27: mean ± SD</td>
<td>0.99 ± 0.93</td>
<td>0.83 ± 0.87</td>
<td>0.48</td>
</tr>
<tr>
<td>Thioredoxin: median (range)</td>
<td>–2.30 (–2.30 to +4.45)</td>
<td>–2.30 (–2.30 to +3.62)</td>
<td>0.01</td>
</tr>
<tr>
<td>Taurine: mean ± SD</td>
<td>4.82 ± 1.35</td>
<td>4.56 ± 1.12</td>
<td>0.41</td>
</tr>
<tr>
<td>Talose: median (range)</td>
<td>6.49 (5.58 to 11.70)</td>
<td>6.24 (4.52 to 9.62)</td>
<td>0.12</td>
</tr>
<tr>
<td>Sulfuric acid: mean ± SD</td>
<td>8.58 ± 0.68</td>
<td>8.44 ± 0.71</td>
<td>0.44</td>
</tr>
<tr>
<td>Delta (post – pre)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSP27: mean ± SD</td>
<td>0.29 ± 1.08</td>
<td>0.16 ± 0.80</td>
<td>0.61</td>
</tr>
<tr>
<td>Thioredoxin: median (range)</td>
<td>0 (–6.17 to +3.29)</td>
<td>0 (–5.99 to +5.92)</td>
<td>0.33</td>
</tr>
<tr>
<td>Taurine: mean ± SD</td>
<td>0.14 ± 0.89</td>
<td>0.08 ± 0.63</td>
<td>0.76</td>
</tr>
<tr>
<td>Talose: median (range)</td>
<td>0.19 (–2.14 to +5.20)</td>
<td>0.11 (–0.84 to +2.89)</td>
<td>0.72</td>
</tr>
<tr>
<td>Sulfuric acid: mean ± SD</td>
<td>0.22 ± 0.84</td>
<td>0.04 ± 1.19</td>
<td>0.34</td>
</tr>
</tbody>
</table>

HSP indicates heat shock protein. The values presented in the table are natural logarithmic values.

Evaluation of medication compliance for secondary prevention of acute coronary syndrome

Dalvir Gill, MD, Elizabeth A. Feldman, PharmD, and Kan Liu, MD, PhD

To prevent recurrence of acute coronary syndrome (ACS), national practice guidelines recommend use of five-drug combination therapy. Our study assessed the proportion of patients discharged on all five medications following ACS and determined reasons for nonadherence. A retrospective, single-center chart review was conducted at a tertiary academic medical center. Patients 18 years and older who were admitted to the cardiac care unit with a diagnosis of ACS between January 2013 and January 2015 were included. Overall, 200 patients were screened and 155 were included in the study. Half of the patients received all guideline-recommended classes of pharmacological agents at discharge. The other half—78 patients—did not receive the five-drug combination, of whom 48 (62%) had reasons documented for nonadherence. Our study’s findings suggest that rates of adherence need to improve given the clear benefits of these medications.

Acutely coronary syndrome (ACS) remains a major cause of mortality worldwide due to recurrent cardiovascular events. This study aimed to review and document the current utilization and prescribing practices of pharmacotherapy for the secondary prevention of ACS in patients discharged from a cardiac care unit in a tertiary academic medical center.

METHODS

A retrospective, single-center chart review was conducted at State University of New York Upstate University Hospital. Patients 18 years and older who were admitted to the cardiac care unit with a diagnosis of ACS between January 2013 and January 2015 were included. Patients were excluded if they died during the hospitalization, transferred care to another hospital, or had a diagnosis other than ACS. Due to the retrospective retrieval of the data, informed consent was not obtained. The study did not offer any risks to the patients’ confidentiality and privacy.

Using a standardized collection form, the following demographic information was obtained: age at hospital admission, sex, and past medical history including hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, and tobacco use. Reasons for nonadherence were also collected.

Statistical analyses were performed using SPSS version 23.0 (IBM Corp, Chicago, IL). Data were presented using descriptive statistics (mean ± standard deviation, median with interquartile range, or number with percentage). Categorical variables were compared using chi-square test for independence or Fisher exact test. Continuous variables were compared using the Student t test or Mann-Whitney U test. Odds ratios and 95% confidence intervals were calculated when applicable. All tests were two-tailed, and a P value < 0.05 was considered statistically significant.

RESULTS

A total of 200 patients were initially screened, of whom 45 were excluded due to diagnoses other than ACS, transfer to other hospitals for higher level of care, or death during hospitalization (Figure 1). Baseline demographic and clinical characteristics are shown in Table 1. No statistically significant differences were noted between the adherent and nonadherent groups with respect to age, male gender, or past medical history.

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Among the 155 ACS patients, 77 (50%) received all five guideline-recommended medications at discharge. Overall, 95% of the study patients were prescribed aspirin; 92%, thienopyridine inhibitors; 67%, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs); 92%, beta-blockers; and 69%, high-intensity statins. Seventy-eight patients (50%) did not receive the five-drug combination therapy at discharge. The absence of one of the five agents does not necessarily imply lack of optimal treatment. A reason behind the nonadherence was documented for 48 patients (62.0%), as summarized in Table 2.

### Table 2. Reasons for nonadherence to five-drug combination therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Not prescribed the drug</th>
<th>Reason</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARBs</td>
<td>52 (34%)</td>
<td>Hypotension</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kidney disease</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not documented</td>
<td>23</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>12 (8%)</td>
<td>Bradycardia</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotension</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heart block</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cocaine use</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not documented</td>
<td>2</td>
</tr>
<tr>
<td>Statin</td>
<td>54 (69%)</td>
<td>Active liver disease</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myalgia</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allergies</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inappropriate statin intensity</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not documented</td>
<td>5</td>
</tr>
<tr>
<td>Thienopyridine inhibitors</td>
<td>13 (8%)</td>
<td>Gl bleeding</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allergy</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not documented</td>
<td>9</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4 (3%)</td>
<td>Gl bleeding</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not documented</td>
<td>4</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; GI, gastrointestinal.

### DISCUSSION

This study demonstrates that the five-drug regimen was provided to only half of the patients, leaving substantial room for improvement. However, it is also important to note that the individual prescription rates of the medications were encouraging. Observational studies provide valuable insight into treatment effectiveness and generalizability in routine practice (1). This study has demonstrated that these lifesaving medications are being prescribed at suboptimal rates. Other studies have examined the proportion of hospitalized cardiac patients discharged on secondary prevention medications. One study conducted by Yetgin et al showed patients received aspirin, thienopyridine inhibitors, ACEI/ARBs, beta-blockers, statins, and combination therapy at rates of 94%, 100%, 80%, 87%, 96%, and 65%, respectively (2). Another study demonstrated that only 27% of the patients received the combination of all five agents (3).

Although 50% of the patients were not on all of the five medications at discharge, this does not necessarily imply that the patients were treated suboptimally. In the present study, only 62.0% patients had a reasonable explanation for nonadherence. Documented reasons for nonadherence included hypotension, kidney disease, bradycardia, heart block, cocaine use, active liver disease, myalgia, gastrointestinal bleeding, and drug allergies. Beta-blockers have historically been underprescribed, likely due to adverse effects. One study with a rate of nonadherence to beta-blocker therapy similar to ours (6.8% vs 8%) documented the following reasons for nonadherence: sinus node disease/bradycardia (24.2%), hypotension (20.3%), airway disease (14.8%), congestive heart failure (11.7%), unknown (11.7%), other (7%), illicit drug use (6.2%), atrioventricular block (5.5%), depressed mood (0.8%), lightheadedness (0.8%), and fatigue (0.8%) (4). In order to overcome this barrier, patient education and outpatient follow-up to initiate beta-blocker therapy should be considered in all patients who do not have absolute contraindications.

Another underlying problem is compliance. Many studies have shown that patients are nonadherent to the prescribed regimens (1, 5, 6). Premature discontinuation of therapy and prescription nonrenewals have been documented at rates of 33.3% and 75%, respectively (7). Although a compliance rate of 100% would be ideal, certain preclusions exist. Inappropriate prescribing by physicians, adverse effects, contraindications, cost, and nonadherence in addition to other patient-specific factors must also be considered. The use of reinforcement programs to help aid in application of the guidelines, such as the CHAMP program, have been shown to improve prescription rates at discharge and demonstrated treatment persistence at 1-year follow-up (8). Implementation of such programs may be beneficial to ensure proper prescribing and help increase adherence rates.

One interesting finding of our study is the rate of prescribing inappropriate statin intensity. We believe this finding can be explained by changes in guidelines followed by a lag in physician response to such changes, such that some physicians may have still been targeting low-density lipoprotein levels based on...
previous recommendations. One study reviewed treatments at discharge and after 1 year in 6748 patients with a myocardial infarction and found that only 1 in 3 patients were prescribed an appropriate intensity statin and only 25% of patients were prescribed an increase in dosage after discharge (9). The incidence of statin myopathy and transaminitis has been reported at rates of 1.5% to 5.0% (10) and 2% to 3%, respectively (11). Although side effects may be a barrier to statin adherence, a number of physicians clearly are underprescribing statins at the correct dose. We would advise increasing the dose during patient follow-up; if a patient cannot tolerate a statin due to side effects, dose reductions or alternative nonstatin therapies should be considered rather than no treatment.

Our study had multiple limitations, including the small sample size and single center design. Evaluation of patients with reduced ejection fraction may have been beneficial to assess appropriateness of noncompliance rates with ACEI therapy; however, the 2014 guidelines suggest there is evidence that ACEIs may be reasonable in all patients with cardiac or vascular disease (class IIb, level B) (12). The external validity of the results may be limited, and caution must be taken when generalizing the findings of our study. However, in order to better generalize the results, it is crucial to conduct more studies, including those in hospitals from areas all over the US. Furthermore, to meet benchmarks of quality care, management can be compared between different institutions.


Invited Commentary

Turning guidelines into outcomes

Compliance with guideline-based treatment of acute coronary syndromes improves long-term patient outcomes, including survival (1). The most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines for non–ST-elevation acute coronary syndromes were published in 2014 (2), with additional recommendations published in 2015 (3) and 2016 (4). These guidelines are comprehensive, comprising 150 pages and 363 referenced citations. Changes to the ACC/AHA guidelines are not uncommon, and as many as 20% of all class I recommendations are downgraded or omitted in subsequent versions. Downgrades, reversals, and omissions are most common among recommendations not supported by multiple randomized clinical trials (RCTs) (5).

In this issue of Baylor University Medical Center Proceedings, Gill and colleagues report on their center’s compliance with recommended medical therapy following acute coronary syndromes/acute myocardial infarction (6). They assessed whether, at discharge, patients received the five drug classes recommended by current ACC/AHA guidelines: 1) aspirin, 2) thienopyridine inhibitors, 3) beta-blockers, 4) angiotensin-converting enzyme inhibitors/angiotensin receptor blocking agents (ACEIs/ARBs), and 5) high-intensity HMG-CoA reductase inhibitors (statins). All drug classes carry class I indications, meaning that they are recommended and should be administered. The level of evidence for aspirin, thienopyridine inhibitors, and high statin therapy is strong, with level of evidence A, meaning that there is evidence from multiple RCTs that use improves patient outcomes. Gill and colleagues found that >90% of patients left the hospital with prescriptions for aspirin, thienopyridine inhibitors, beta-blockers, and statins.

Of interest, only 69% of patients were prescribed high-intensity statins. This is disappointing given that high-intensity therapy is safe and is associated with better patient outcomes than low- or moderate-intensity therapy (2). Both physicians and patients appear to remain cautious and may worry about perceived side effects, especially myalgias. My hope is that future guidelines will refocus on reduction of low-density lipoprotein (LDL). The use of additional agents such as ezetimibe and PCSK-9 inhibitors to achieve the lowest possible serum LDL offers an opportunity to improve patient outcomes beyond what can be achieved with statin therapy alone.

Gill and colleagues report lower compliance for ACEIs/ARBs at 67%. However, there is debate as to whether or not routine ACEI/ARB use improves patient outcomes. There is good evidence (level A) that use in patients with heart failure or reduced ejection fractions (<0.40) improves outcomes but little evidence of benefit in patients with preserved ejection fractions (level C). If these agents had no side effects, this might be a purely academic point, but their use exposes patients to side effects including hypotension, hyperkalemia, and rare cases of angioedema.

The good news is that while there is some room for improvement, the majority of patients evaluated by Gill et al are being discharged on the agents they investigated. The relatively lower rate of ACEI/ARB prescribing may be appropriate based on current guidelines, and that rate combined with use of low- and moderate-, as opposed to high-intensity, statin therapy is largely responsible for reducing the compliance rate for all five agents to 50%, making overall compliance appear worse than it is. Of interest, the investigators chose to omit analysis of other agents with class I recommendations. There is proven benefit for aldosterone antagonists in select patients with reduced ejection fraction but preserved renal function and normal serum potassium following myocardial infarction. Use carries a class I indication in current guidelines and comes with strong evidence that therapy improves outcomes (level A).

It may surprise some that a prescription for sublingual or nitroglycerine spray also has a class I recommendation, though this is based on weak evidence (level C). Class I recommendations also exist for prescribing nondihydropyridine calcium antagonists for patients with ischemic symptoms, either in addition to or in place of beta-blockers. Again, there is little evidence for improved patient outcomes (level C). There is even a guideline-directed class I indication to use proton pump inhibitors in patients with a history of gastrointestinal bleeding who require triple antithrombotic therapy (level C). This recommendation may be revisited in future guidelines given growing evidence that long-term proton pump inhibitor use can negatively impact patient outcomes (7).

Left out of the study by Gill and colleagues is an analysis of agents thought to either offer no benefit or cause harm (class III recommendations). These include vitamins E, C, B6, and B12, beta-carotene, and folic acid. High-quality data from RCTs has shown no benefit (level A). Of greater concern, it appears that both hormone therapy and nonsteroidal antiinflammatory drugs can worsen outcomes. It is a class III recommendation to hormone therapy should not be initiated and chronic use stopped if feasible (level A). Nonsteroidal antiinflammatory drugs also appear to cause harm, though the supporting evidence is less strong (level B).

Current ACC/AHA guidelines seek to be both thorough and comprehensive. This is an admirable goal but one that may undermine their purpose, which is to improve patient outcomes. How many physicians will read a 150-page guideline? One option would be for future guidelines to only include...
recommendations based on high-quality data (level A). Such guidelines could further limit themselves to making recommendations either for or against (currently class I and III). Class II recommendations might be dispensed with altogether. The resulting guidelines might fit on a single page and be easily referenced. Perhaps we could trust physicians to navigate treatments and therapies of unclear benefit? After all, physicians have done this for years through shared decision-making with their patients. And shared decision-making between physicians and patients is a class I recommendation.

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Efficacy of acute care health care providers in cardiopulmonary resuscitation compressions in normal and obese adult simulation manikins

Alaina Tellson, PhD, RN-BC, NE-BC, Huanying Qin, MS, Kristin Erwin, BA, and Susan Houston, PhD, RN, NEA-BC

Anually, over 350,000 persons require cardiopulmonary resuscitation (CPR), either in or outside of the hospital. With obesity a rising health issue in the United States, concerns exist regarding the efficacy of quality compressions for CPR in obese patients. The aims of this study were to determine if the compressions for three adult simulation manikins (normal, obese, and morbidly obese) met quality guidelines; to examine any differences in quality of chest compressions performed by health care providers between the three manikins; and to examine the effect of participant characteristics on the quality of chest compressions in obese and morbidly obese manikins. A randomized controlled design was used. Sixty-one health care providers performed chest compressions on the three simulation manikins. Results showed that performance on the normal-sized manikin was significantly better than that on both obese and morbidly obese manikins. Participant characteristics were significantly associated with quality of chest compressions. The effectiveness of compressions in obese and morbidly obese CPR recipients has yet to be determined.

Obesity, defined as a body mass index (BMI) ≥30.0 kg/m², has been recognized for hundreds of years as a health hazard (1). An estimated 79 million people are obese in the US, and roughly 70% of US adults are considered overweight (2, 3). Obesity increases the risk of cardiovascular dysfunction and sudden cardiac arrest (4–7). There are concerns regarding the efficacy of resuscitation in obese patients related to the quality of chest compressions. In a 2015 study by Lee and colleagues, researchers found that during cardiopulmonary resuscitation (CPR) chest compression, depth decreased as patients’ BMI increased, suggesting that the recommended depth of 5 cm may need to be reevaluated for obese patients (8). The first aim of this study was to determine if the quality of chest compression for three adult simulation manikins (normal, obese, and morbidly obese) met the American Heart Association (AHA) guideline for quality chest compressions (28 compressions out of 30 at the appropriate depth of at least 5 cm) as determined by an electronic skills reporter. The second aim was to examine any differences in quality of chest compressions performed between the three adult simulation manikins. The third aim was to examine the contribution of participant characteristics of height, weight, gender, and upper body strength to the quality of chest compressions in obese and morbidly obese manikins.

METHODS

A randomized controlled design was used for this study, wherein the order of performing CPR on normal, obese, and morbidly obese manikins was randomized using a randomization table. Each participant performed CPR in one of six orders (123, 132, 213, 231, 312, 321), where 1 represented a normal manikin; 2, an obese manikin; and 3, a morbidly obese manikin. Obesity was defined as a BMI ≥30 kg/m² and morbid obesity, as a BMI ≥40 kg/m². The order was an issue since studies have shown that rescuers become fatigued during CPR and the quality of their compressions can decrease (9).

This study was conducted in a 116-bed for-profit cardiovascular specialty hospital located in North Texas. After obtaining institutional review board approval, all employees of this hospital who provide direct patient care and were certified in basic life support were invited to participate in the study. Only those with any current impairment preventing the administration of CPR were excluded. A power analysis yielded a sample size of 112. The study was discontinued early with a sample of 61, as preliminary data analysis yielded obvious statistically significant results related to the research questions addressing quality of compressions.

Adult simulation manikins with an electronic skill reporter were used to determine chest compression quality. The electronic skill reporter contains lights that provide feedback on compression depth and hand position. A printout was obtained containing the same information. Since immediate feedback has been shown to improve the quality of CPR (10), only the research team could see the feedback indicator lights during the trial. A standard adult CPR manikin with an electronic skill reporter was used as the “normal-sized” manikin. This manikin closely mimics the average size of an adult female of normal

From Professional Practice, The Heart Hospital Baylor Plano, Plano, Texas, and The Heart Hospital Baylor Denton, Denton, Texas (Telson); and the Departments of Quantitative Sciences (Qin) and Nursing Research (Erwin, Houston), Baylor Scott & White Health – North Texas, Dallas, Texas.

Corresponding author: Alaina Tellson, PhD, RN-BC, NE-BC, 3953 Wisteria Lane, Haltom City, TX 76137 (e-mail: alaina@tellson.net).
weight (11). Only adult manikins were utilized for this study since the majority of cardiac arrests occur in adults (12). Baubin and associates studied the compression characteristics of CPR manikins and found that the standard CPR manikin used in this study was consistent 100% of the time in the amount of pressure it took to perform an adequate chest compression (11). The standard CPR manikin used in this study had a 16 cm diameter with a moderate thorax resistance similar to that in humans (11).

Based on BMI guidelines, manikins to mimic an obese and a morbidly obese adult were created, manufactured, and tested by a professional in the field of manikin design and manufacturing. The manikins were manufactured by taking molds of the standard manikin and adding the calculated amount of a foam substance of a consistency similar to adipose tissue to obtain the proportional equivalent of an obese person and morbidly obese person based on body casts of two individuals matching the BMI criteria for obese and morbidly obese. The body casts of the two individuals were also used to make the “skin.” The thorax framework and the sensors from a standard CPR manikin were in the correct anatomical position in the new manikins. The new manikins were tested for consistency in measuring adequate chest compression by the research team.

The participants were asked to perform two cycles of chest compressions (15 compressions per cycle) on each size manikin at a rate of 100 per minute at a depth of at least 2 inches per current AHA guidelines, with a 5-second pause between the cycles of chest compressions (12). Manikins were placed on hospital beds with backboards under the manikin to replicate an in-hospital scenario. The quality of compressions for each manikin was recorded. At the time of the study, a member of the research team recorded the number of times the electronic skill reporter indicated an adequate compression. These were verified by a printout obtained from the electronic skill reporter by another member of the research team. The quality of chest compressions was measured as the number of successful compressions out of 30 attempts. For each participant, demographic data were also collected, including age, ethnicity, height, weight, BMI, and upper body strength. All participants’ heights and weights were obtained on a calibrated medical scale at the time of participation in the study. Upper body strength was measured using a handheld dynamometer using the manufacturer’s protocol for strength testing.

SAS Enterprise Guide 6.1 (SAS Institute, Cary, NC) was used for data analysis. A P value < 0.05 was considered statistically significant. Descriptive statistics were summarized on participants’ demographics. The outcome, the number of successful compressions out of 30 trials on each manikin, was compared to the AHA standard (28 out of 30) using Wilcoxon rank sum test. Comparison was performed on the outcome between the three manikins using Wilcoxon signed rank test. The Bonferroni method was used for multiple comparison correction for both the Wilcoxon rank sum test and the Wilcoxon signed rank test. The relationship between the outcome and participants’ demographic variables was assessed using a generalized linear model with Poisson as the link function.

### RESULTS

Sixty-one health care professionals were recruited and agreed to participate as “rescuers.” Their characteristics (age, gender, ethnicity, height, weight, BMI, and upper body strength) were recorded (Table 1). The age range of participants was 22 to 62 years old. Their height ranged from 150 to 188 cm. Eighty-two percent of participants were female, which was anticipated since most health care workers are female. Their BMI ranged from 18.38 to 43.49, and their upper body strength ranged from 40 to 140 psi.

When the number of successful compressions performed by rescuers was compared to the AHA guidelines, performance on the normal-sized manikin was not significantly different from the AHA standard (P = 0.09), but performance on the other two manikins was significantly lower than the standard (P = 0.0001) (Table 2). Pairwise comparison in the number of successful compressions among these three manikins was performed. The performance on the normal-sized manikin was significantly better than that on both obese and morbidly obese manikins, with P = 0.0001 for each comparison. There was no significant difference in performance between the two obese manikins (P = 0.10).

A multivariate regression analysis was performed on the data from the normal manikin and rescuer characteristics.

### Table 1. Demographic and personal characteristics of the 61 participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42 ± 10</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>162 ± 37</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 ± 8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27 ± 6</td>
</tr>
<tr>
<td>Upper body strength (lb)</td>
<td>74 ± 24</td>
</tr>
<tr>
<td>Female</td>
<td>50 (82%)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Asian</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>White</td>
<td>41 (68%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (7%)</td>
</tr>
</tbody>
</table>

*Presented as mean ± standard deviation for continuous variables and n (%) for categorical variables.

### Table 2. Comparison of successful compressions by manikin size

<table>
<thead>
<tr>
<th>Manikin</th>
<th>Successful compressions after 30 attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Normal</td>
<td>23</td>
</tr>
<tr>
<td>Obese</td>
<td>0</td>
</tr>
<tr>
<td>Morbidly obese</td>
<td>0</td>
</tr>
</tbody>
</table>

*Compared to the American Heart Association guideline of 28/30 attempts, Wilcoxon rank sum test.

†Statistically significant after Bonferroni correction for multiple comparisons.
As shown in Table 3, age, BMI, upper body strength, ethnicity, and manikin order were all significantly associated with the number of successful compressions. The performance of black, Asian, and white participants was significantly better than that of Hispanics; an increase in age by 1 year was associated with a decrease in the number of successful compressions by 0.0167; an increase in BMI by one unit was associated with an increase in the number of successful compressions by 0.0159; and a one unit increase in upper body strength was associated with an increase in number of successful compressions by 0.0038.

The order of performing CPR on normal, obese, and morbidly obese manikins was randomized using a randomization table where 1 represented a normal manikin; 2, an obese manikin; and 3, a morbidly obese manikin. Regarding the randomization order, the orders 213 and 231 were associated with a lower number of successful compressions than the order 321, which was the reference point.

**DISCUSSION**

High-quality, effective compressions are vital to successful CPR (9, 12). Results of this study indicate that compression quality is lower when performed on obese and morbidly obese adult simulation manikins. Only a few other studies have explored the relation between obesity and quality CPR. Edelson and associates found that morbid obesity was associated with poor outcomes in comparison to subjects who were not morbidly obese (13). They also found that morbidly obese patients received shallower chest compressions. Hamilton concluded that CPR training for individuals working in a hospital should be representative of potential situations that they may encounter (14), and it is likely that health care workers will encounter obese or morbidly obese patients. Implications for healthcare workers include maintaining competency of basic life support skills and being prepared to deliver CPR on obese patients.

A literature search on the impact of rescuer characteristics such as height, weight, gender, and upper body strength yielded no results. However, the potential effect of these characteristics should be considered. Our study showed that significant relationships exist between certain demographic and personal variables and quality of chest compressions.

While our study was limited by its approach of using simulation manikins as a surrogate for obese and morbidly obese CPR recipients, its results regarding effective CPR on obese and morbidly obese patients clearly warrant further investigation. One area to investigate is the use of mechanical compression devices and feedback devices that are now available to assist in administering quality compressions. The prevalence of survival to discharge after in-hospital CPR in obese and morbidly obese patients should be studied. Finally, research is needed to examine outcomes and effectiveness of compressions in combination with rescuer characteristics, with the aim of increasing quality of compressions among individual providers. Innovative methods need to be developed to aid in performing successful CPR on obese and morbidly obese patients. Otherwise, the mortality rate in this population will remain at an unacceptable level.

**Acknowledgments**

This study was supported by a grant from the Cardiovascular Research Review Committee of Baylor Scott & White Health. Special thanks to the research team who assisted with this study: Erin Weaver, BSN, RN, Randy Marcel, MD, Kristi Verschelden, RN, and Julie Dunagan.


Reader Comments

Facts and ideas

I love your "Facts and ideas from anywhere" columns. The July 2017 column (1) deserves some comment. On page 387, you mention Dr. Starzl. In 1966 or thereabout, I was aware that he was planning a liver transplant in an infant. I was unaware then of the 1963 attempt. I sent him an infant with biliary atresia, named Paula. Starzl, whom I talked to several times, planned to do the transplant in Paula as his first infant. While waiting for a donor, the staff got very attached to Paula, he told me. He knew that he would lose the first case and did not want to demoralize the staff excessively. He decided to do another transplant first in an infant with a large liver tumor. He later performed the transplant in Paula and had all sorts of technical problems, and she died.

Russian leeches: I was a guest of Professor Stan Doletski in Moscow in 1979. My family was in the operating room when he corrected an esophageal atresia. We toured the premier children’s hospital with him. It was like the USA in 1890. No money!

Climate change, p. 387: I think that guy Tom Snyder is on drugs. . . . We do have climate change that even rabid anti-CO2 people agree that we cannot affect regardless of what we do. I remember the 1970s when we were told that another ice age was upon us. I am not sure that the planet is now warming. Mount St. Helen got more CO2 into the air than all of the coal-burning power plants in China can do in 100+ years.

Cost of pets, p. 386: I am a dog lover, but not a cat lover. I shudder at the way people spend time and money on dogs. Worst, they substitute them for human infants. You know the demographics. We had three, but it should have been five. We had several poodles also.

Your other items were well discussed. Thank you.

—Dick Ellis, MD
Fort Worth, Texas

Achalasia is a rare disorder that has several treatment options. The gold standard of treatment is a surgical myotomy called a laparoscopic Heller myotomy (LHM). More recently, an endoscopic myotomy has become an option as well, called per-oral endoscopic myotomy (POEM). An achalasia registry was queried for patients undergoing either LHM or POEM at Baylor University Medical Center at Dallas. Patient demographics, preoperative and postoperative data points, and Eckardt scores were collected. The patients were further stratified into their follow-up intervals, immediate postoperative and long-term follow-up, to assess surgical success. A subset analysis was done for success of treatment for patients who had redo surgery versus those undergoing the procedure for the first time. There were 12 patients in the POEM group and 11 patients in the LHM group. Both groups demonstrated mean lower esophageal sphincter pressures with failure to relax. Procedure length and hospital length of stay were similar between the two groups. There were three adverse events in each group, but none altered the patient’s postoperative clinical course. Eckardt scores, used to assess success of the surgery, were 82% for POEM patients and 66% for LHM patients after 6 months. The outcomes for POEM and LHM in our early experience are similar to those reported in the literature for high-volume centers managing achalasia.

Achalasia is a rare disorder of the esophagus that results in aperistalsis and incomplete, or failed, relaxation of the lower esophageal sphincter (LES) muscle (1). The treatments for achalasia consist of disruption of the LES muscle fibers, relieving the outflow obstruction, which include laparoscopic Heller myotomy (LHM), per-oral endoscopic myotomy (POEM), pneumatic dilation, and temporary relief using botulinum toxin injection (2). It has been shown that LHM and pneumatic dilation have similar outcomes at 2 years with regard to symptom relief (3, 4), but meta-analyses and systematic reviews favor LHM as the procedure of choice for its superior response rates long term (5–7). The introduction of POEM has provided another option for management of achalasia; with POEM, an endoscopic submucosal tunnel is created in the wall of the esophagus to access the LES muscle fibers without making incisions for laparoscopic instruments. The endoscopic approach to the LES muscle fibers was originally characterized with a full thickness endoscopic exit of the lumen (8), but was refined with a submucosal tunnel to prevent full thickness leak in a porcine model (9).

Comparison of outcomes of laparoscopic Heller myotomy versus per-oral endoscopic myotomy for management of achalasia

Steven G. Leeds, MD, J. S. Burdick, MD, Gerald O. Ogola, PhD, and Estrellita Ontiveros, MA

Achalasia is a rare disorder that has several treatment options. The gold standard of treatment is a surgical myotomy called a laparoscopic Heller myotomy (LHM). More recently, an endoscopic myotomy has become an option as well, called per-oral endoscopic myotomy (POEM). An achalasia registry was queried for patients undergoing either LHM or POEM at Baylor University Medical Center at Dallas. Patient demographics, preoperative and postoperative data points, and Eckardt scores were collected. The patients were further stratified into their follow-up intervals, immediate postoperative and long-term follow-up, to assess surgical success. A subset analysis was done for success of treatment for patients who had redo surgery versus those undergoing the procedure for the first time. There were 12 patients in the POEM group and 11 patients in the LHM group. Both groups demonstrated mean lower esophageal sphincter pressures with failure to relax. Procedure length and hospital length of stay were similar between the two groups. There were three adverse events in each group, but none altered the patient’s postoperative clinical course. Eckardt scores, used to assess success of the surgery, were 82% for POEM patients and 66% for LHM patients after 6 months. The outcomes for POEM and LHM in our early experience are similar to those reported in the literature for high-volume centers managing achalasia.

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Data on patient characteristics were collected, including gender, age, body mass index, LES basal pressure, LES residual pressures with failure to relax. Procedure length and hospital length of stay were similar between the two groups. There were three adverse events in each group, but none altered the patient’s postoperative clinical course. Eckardt scores, used to assess success of the surgery, were 82% for POEM patients and 66% for LHM patients after 6 months. The outcomes for POEM and LHM in our early experience are similar to those reported in the literature for high-volume centers managing achalasia.

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pressure, percentage of patients with aperistalsis, and type of achalasia based on Chicago classification. Data on the operations included length of procedure and hospital length of stay. Adverse events were noted as any event that was a deviation from the normal expected course. Eckardt scores were collected preoperatively and postoperatively. The postoperative collection was done at an interval of immediately after surgery (<1 month) and long-term follow up (>6 months). The Eckardt score is a validated scoring system to grade symptoms of achalasia patients on a scale of 0 to 12. There are four components: regurgitation, chest pain, dysphagia, and weight loss. The first three receive a score of 0 for none, 1 for occasionally, 2 for daily, and 3 for each meal. Weight loss receives a score of 0 for no weight loss, 1 for <5 lb, 2 for 5–10 lb, and 3 for >10 lb (22). Success of myotomy is based on a total Eckardt score of ≤3 at follow-up (23).

Information on all complications for the procedures was also collected. There were no definite criteria to determine the surgical intervention for each patient. Most patients were offered POEM and LHM and were allowed to choose. However, in some cases insurance reimbursement prevented POEM and patients defaulted to LHM. The redo LHM cohort was not offered POEM because their recurrent symptoms appeared to possibly be related to the fundoplication on preoperative workup as well as inadequate myotomy.

We compared characteristics and outcomes of patients who underwent POEM versus LHM using independent sample t test, Wilcoxon two-sample test, and Fisher's exact test. Paired t test was used to assess changes in Eckardt score between preoperative and postoperative data within procedure groups. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Two-tailed P values < 0.05 were considered statistically significant.

**Figure 1.** Patients enrolled in the achalasia registry. POEM indicates per-oral endoscopic myotomy; LHM, laparoscopic Heller myotomy.
cross the thin remaining longitudinal muscle layer to enter the peritoneal cavity below the phrenoesophageal ligament when making the myotomy. Patients can get significant subcutaneous emphysema for the same reason above the phrenoesophageal ligament. Because CO₂ is used, this will dissipate in the early postoperative phase.

The patient is admitted postoperatively and undergoes an esophagram the following morning, where leak and passage of contrast through the LES is assessed. A liquid diet is started after the esophagram is cleared and the patient is discharged. The patient undergoes another esophagram 1 week later to assess for a healed mucosotomy, and the diet is advanced as tolerated. The patient follows up 3 to 4 weeks postoperatively and at 6 to 12 months. Eckardt scores are taken at both follow-up visits.

The laparoscopic Heller myotomy procedure

The patient is taken to the operating room and placed in supine position with a footboard in place. Laparoscopic access is obtained with a liver retractor elevating the left lobe of the liver. In the primary surgery group, the gastrohepatic ligament is incised to expose the mediastinum. The anterior vagus nerve is identified and preserved. The anterior phrenoesophageal ligament is incised to access the lesser sac. The caudate lobe is identified and the gastrohepatic ligament is taken down following the edge of the caudate lobe until the right crus is seen. The anterior phrenoesophageal ligament is incised to access the mediastinum. Extension of the myotomy is then performed to identify the high pressure zone, outlining the exact location of the hypertensive LES.

A 6 to 8 cm myotomy is completed, with the extent of the myotomy starting 2 cm distal to the LES on the stomach and extending up the esophagus. Using the harmonic scalpel, the muscle fibers are incised down to the mucosa of the stomach. The submucosal plane is then accessed and the myotomy is created measuring 6 cm cephalad. If a mucosal injury is made, a 4-0 vicryl suture is used in a figure-of-eight fashion to approximate the edges of the mucosa. Once the myotomy is complete, an upper endoscopy is done to perform a leak test and verify the patency of the LES. Short gastric vessels are then taken down to mobilize the fundus. Anterior fundoplications are created using 0-Ethibond sutures, tacking the greater curvature of the fundus to the hiatus and laying the fundus over the myotomy, creating an approximate 90 degree fundoplication. Three total sutures are used to create the fundoplication by suturing the greater curvature of the fundus to the hiatus. No drains are used. The capnonperitoneum is released, and the liver retractor and all trocars are removed. Skin closure is done with 4-0 monocryl sutures and then dermabond.

The patient is admitted postoperatively for an esophagram to assess for leak and passage of contrast through the stomach. A liquid diet is started after the esophagram is cleared and the patient is discharged. The patient follows up 3 to 4 weeks postoperatively and 6 to 12 months postoperatively. Eckardt scores are taken at both follow-up visits.

In redo surgery, the procedure is similar except that the enterolysis is performed with the harmonic scalpel, blunt dissection, and sharp dissection to return the stomach to its anatomical position and to evaluate the myotomy. Extension of the myotomy is performed if it appears inadequate. Upper endoscopy is used to guide the dissection and further myotomy. Postoperative management is the same as with the primary LHM cohort.

RESULTS

A total of 12 patients underwent POEM (4 men and 8 women) and 11 patients underwent LHM (6 men and 5 women). The demographic and clinical characteristics of the two groups are compared in Table 1: no differences were statistically significant. Patients’ mean age was similar between the groups: 52 in the POEM group and 53 in the LHM group. Those in the LHM group had a higher mean body mass index than those in the POEM group (28.8 vs 25.7 kg/m²). In the LHM group, 8 patients (73%) had type 1 achalasia, 2 patients (18%) had type 2 achalasia, and 1 patient (9%) had type 3 achalasia; in the POEM group, 10 patients (83%) had type 1 achalasia, 1 (8%) had type 2 achalasia, and 1 (8%) had esophagogastric junction outflow obstruction. The mean procedure time was shorter in the POEM group, at 136 minutes compared with 154 minutes in the LHM group. The postoperative length of stay was a mean of 1.6 days for the POEM group and 2.0 days for the LHM group.

As shown in Table 2, mucosal injury occurred in 1 patient in the POEM group and 3 patients in the LHM group. For the POEM mucosal injury, a hemoclip was placed when it was

<table>
<thead>
<tr>
<th>Achalasia type</th>
<th>POEM (N = 12)</th>
<th>LHM (N = 11)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>10</td>
<td>8</td>
<td>N/A</td>
</tr>
<tr>
<td>Type 2</td>
<td>1</td>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>Type 3</td>
<td>0</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>EGJOO</td>
<td>1</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Procedure length (min), mean ± SD</td>
<td>136 ± 64</td>
<td>154 ± 37</td>
<td>0.43‡</td>
</tr>
<tr>
<td>Hospital LOS (days), mean ± SD</td>
<td>1.6 ± 1.2</td>
<td>2.0 ± 1.9</td>
<td>0.53‡</td>
</tr>
</tbody>
</table>

P value based on *Fisher’s exact test; †Student t test.
BMI indicates body mass index; EGJOO, esophagogastric junction outflow obstruction; LES, lower esophageal sphincter; LHM, laparoscopic Heller myotomy; LOS, length of stay; POEM, per-oral endoscopic myotomy.
noticed intraoperatively immediately distal to the LES on the gastric mucosa. The three mucosal injuries in the LHM group were noticed at the time of surgery and were repaired with a figure-of-eight 4-0 vicryl suture. There was one area of necrosis of the mucosa in the POEM group. The creation of the submucosal tunnel compromised the perfusion of the overlying mucosa. No perforation was seen, and nothing was done at the time of surgery. Follow-up esophagram did not show a leak. One contained leak was seen on the postoperative esophagram in the POEM group. The mucosal approximation with hemoclips was not adequate, and a small amount of contrast leaked into the submucosal tunnel. The patient was immediately taken to the endoscopy suite for an additional hemoclip to be placed. Once the hemoclip was placed, a follow-up esophagram showed resolution of the contained leak. The patient never experienced tachycardia or fever. No clinical difference was seen from the rest of the cohort. No patients needed to return to the operating room. No patients were readmitted within 30 days of their procedure.

Postoperative outcomes were evaluated with Eckardt scores to indicate the success of the procedure (Table 2). In the immediate postoperative period, Eckardt scores significantly improved to a mean of 1.3 ± 1.0 (P < 0.0001) in 7 of 12 patients in the POEM group and 0.7 ± 1.2 (P = 0.03) in 3 of 11 patients in the LHM group. The other patients failed to follow up in the immediate phase due to distance from the facility. In follow-up at least 6 months after surgery, patients were called to obtain Eckardt scores. The mean score in the POEM group was 1.2 ± 1.6 for 11 of 12 patients at a mean of 483 days, and 3.0 ± 0.7 for 9 of 11 patients in the LHM group with a mean of 273 days. The remaining patients did not have 6 months elapse from the operation to report a score. Success of the procedure with Eckardt scores ≤3 after 6 months was 82% in the POEM group and 66% in the LHM group (P = 0.62).

A subset analysis was done for patients who had the procedure as a primary surgery versus a redo surgery. One patient in the POEM group had a prior LHM and reported an Eckardt score of 2, indicating success. Three patients in the LHM group had prior LHM, and only one reported a successful score of 3. The other 2 patients reported scores of 5 and 6. No significant differences were observed in the success rate between the two groups (Table 2).

**Table 2. Outcomes of patients undergoing POEM vs LHM for management of achalasia**

<table>
<thead>
<tr>
<th>Complications (n)</th>
<th>POEM (N = 12)</th>
<th>LHM (N = 11)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal injury during surgery</td>
<td>1</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>Mucosal necrosis</td>
<td>1</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Postoperative leak</td>
<td>1</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Return to operating room</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>30-day readmission</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Eckardt scores (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative</td>
<td>8.3 ± 1.8</td>
<td>6.9 ± 3.2</td>
<td>0.20</td>
</tr>
<tr>
<td>Immediate postoperative</td>
<td>1.3 ± 1.0</td>
<td>0.7 ± 1.2</td>
<td>0.39</td>
</tr>
<tr>
<td>Late postoperative</td>
<td>1.2 ± 1.6</td>
<td>3.0 ± 0.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Follow-up days, median (IQR)</td>
<td>385 (274–500)</td>
<td>285 (217–473)</td>
<td>0.59†</td>
</tr>
<tr>
<td>Success after 6 months</td>
<td>82% (9/11)</td>
<td>66% (6/9)</td>
<td>0.62*</td>
</tr>
<tr>
<td>In primary surgery group</td>
<td>80% (8/10)</td>
<td>83% (5/6)</td>
<td>0.99*</td>
</tr>
<tr>
<td>In redo group</td>
<td>100% (1/1)</td>
<td>33% (1/3)</td>
<td>0.99*</td>
</tr>
</tbody>
</table>

P value based on *Fisher’s exact test; †Wilcoxon two-sample test.

IQR indicates interquartile range; LHM, laparoscopic Heller myotomy; POEM, per-oral endoscopic myotomy; SD, standard deviation.

**DISCUSSION**

These results indicate a favorable success rate in our institution’s early experience with POEM and LHM. The success rate was 82% for POEM and 66% for LHM at a follow-up of at least 6 months. There were no complications related to either procedure that altered the patient’s postoperative course, except for one patient with a contained leak in the POEM group. This was identified with an immediate postoperative esophagram without further morbidity.

POEM has become more widespread, and a significant amount of data has been reported on its efficacy and outcomes. Inoue et al reported their 500-patient experience with an adverse event rate of 3.2% (14), and Sharata et al showed a 6% morbidity rate in 100 patients (15). We show a 25% adverse event incidence in our 12 patients with no Clavien Dindo grade IV or V and only one grade III event. This is a much higher rate but related to our early experience and low patient numbers. This rate is much more comparable to other reports of early experiences, such as Hungness et al (20), who reported an approximate 18% adverse event rate. We anticipate this rate will decrease once the number of procedures increases. Despite the high adverse event rate, there was very little alteration in the patients’ postoperative clinical courses. The hospital length of stay was 1.6 days in our data, which is similar to other reports noting a length of stay of 1 to 3 days (15, 24, 25) in high-volume analysis.

A large meta-analysis by Marano et al compared POEM and LHM (26). It revealed that POEM has a slightly better maintenance of a lower Eckardt score than LHM, but the difference didn’t reach statistical significance. Our data reflect the same trend (Figure 2). There was also no significant difference between operative times in the meta-analysis. Our data reflect the same finding, with 136 minutes for POEM and 153 minutes for LHM. We did see a difference in our complication rates for POEM and LHM, where the meta-analysis showed no difference. Finally, POEM has produced Eckardt scores of ≤3 in 90% to 98% of patients in several studies (18, 24, 27, 28). These success rates seem to surpass the success of LHM and pneumatic dilation (86% and 76%, respectively) (7). Overall, our data, showing success rates of 82% for POEM and 66% for LHM, follow the trend reported in the literature.

A major limitation to this study is statistical power due to the low numbers of patients for each procedure. Even though the cohort numbers were low, they could adequately illustrate our early experience with POEM and LHM for evaluation.
In conclusion, POEM and LHM have been shown to be acceptable procedures to treat achalasia. This small cohort shows endpoints and outcomes consistent with larger published series. We have attempted to overcome the learning curve based on operative time and should expect outcomes to be consistent with those of larger-volume centers with a longer experience.


Usefulness of radium-223 in patients with bone metastases

Nishant Gupta, MD, Arushi Devgan, MBBS, Itisha Bansal, MD, Thomas D. Olsavsky, MD, Shuo Li, MD, Ahmed Abdelbaki, MD, and Yogesh Kumar, MD

Castration-resistant prostate osseous metastases can be challenging to treat. There is a new era of clinical advancement with the Food and Drug Administration approval of radium-223 for use in these patients. Radium-223 is the only clinically used therapeutic radiopharmaceutical that emits alpha particles, making it extremely safe for therapeutic purposes for the patient as well as close contacts. This review discusses radium-223’s mechanism of action, pharmacokinetics, indications, and safety profile, as well as findings of concluded clinical trials.

Prostate cancer is the most common malignancy in men in the United States and Europe and is the third leading cause of cancer-related death in men. Nearly 14% of men will be diagnosed with prostate cancer at some point in their life. In 2014, prostate cancer accounted for 24% and 27% of all new male cancer cases in Canada and the US, respectively (1, 2). About 85% of cases present with localized disease, but nearly 40% progress to metastatic cancer. Bone metastases can be present in more than 90% of patients with advanced prostate cancer, leading to significant morbidity and mortality (3, 4). Patients are initially treated with either chemical or surgical androgen deprivation therapies. However, there is inevitable progression to castration-resistant prostate cancer (CRPC), which develops despite castration levels of testosterone. When this disease presents with detectable macroscopic metastases, patients are considered to have metastatic CRPC (mCRPC), which has a poor prognosis and an expected survival of 18 to 20 months. Complications include significant bone pain, skeletal-related complications such as pathologic fractures, malignant hypercalcemia, bone marrow suppression, and spinal cord compression (5–7).

MECHANISM OF ACTION AND RADIObIOLOGY OF RADIUM-223

Radium 223 dichloride (radium-223), an alpha-emitting radionuclide, was the first agent of its kind to be approved by the US Food and Drug Administration (FDA) following the 2013 ALSYMPCA trial for treatment of bone pain in patients with mCRPC. It has a half-life of 11.4 days. Radium-223 decays to 4 alpha particles for every atom. It is a calcium mimic that binds to hydroxyapatite and induces double-stranded breaks in DNA (8, 9). The short range of particles emitted and the high linear energy transfer lead to intensive killing in a small tissue volume, thereby sparing more of the normal bone (10). Its effect is a combination of decreased pathologic bone turnover and tumor irradiation (11). Other bone-seeking radiopharmaceuticals like the beta-emitting strontium-89 and samarium-153 ethylenediamine tetramethylene phosphonic acid have also been used for bone therapy, but have not been found to increase overall survival (12, 13).

PHARMACOKINETICS

Radium-223 is taken up primarily by bone tissue and bone metastases rapidly after intravenous injection. Most of the agent (95%) is eliminated from the body by the fecal route; ~5% is excreted in urine. Therefore, any changes in intestinal transit can affect the elimination rate of radium-223. It is not metabolized by the liver (1).

SAFETY PROFILE

Data collected from more than 1000 patients in phase 2 and 3 trials comprise the basis for the drug’s safety profile (1). Data from a 3-year follow-up study have also shown that radium-223 therapy is both safe and well tolerated (14). However, combining radium-223 with chemotherapy is not recommended because of potential additive effects of bone marrow suppression.

The most common adverse reactions observed were nausea, vomiting, diarrhea, and peripheral edema. Radium-223 can cause hematologic abnormalities like anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Anemia and thrombocytopenia were the most common reasons for discontinuation of the drug (15). Concurrent administration of...
radium-223 with antiandrogen therapies such as enzalutamide or abiraterone is well tolerated (16).

CLINICAL TRIALS

The first-in-human trial was conducted in 2000 by Nilsson et al to study the safety and tolerability of radium-223. They concluded that radium-223 was tolerated well at therapeutic dosages, with pain relief and positive effects on serum markers as indications of its anticancer effect (17).

The BC1-02 was the second clinical study conducted in 2002. It was a randomized double-blind placebo-controlled multicenter phase 2 trial. This study showed that adverse events, including serious adverse events, were more common when patients were not treated with radium-223 (18). Two additional randomized, double-blinded phase 2 trials were conducted (BC1-03 and BC1-04) before starting the ALSYMPCA (ALpharadin in SYMptomatic Prostate Cancer) trial (19). The ALSYMPCA trial, which concluded in 2013, was a randomized, double-blind, multinational phase 3 trial. Testing a total of six injections of radium-223 per patient, the trial showed a significant improvement in overall survival rates and improved quality of life with treatment (20). The trial also showed delayed development of skeletal complications and a significant reduction of the risks of spinal cord compression and requirement for external beam radiation therapy (4). There were no clinically significant differences in hematologic adverse events with radium-223 treatment (4).

INDICATIONS

Radium-223 is indicated for use in the management of adult men with CRPC with symptomatic metastases to the bone and no other visceral metastases. It is given intravenously over 1 minute at 50 kBq/kg body weight every 4 weeks for a total of 6 injections. There is no need for dose adjustment in the elderly and those with renal or hepatic impairment (1). The main adverse event to look for after administration is bone marrow suppression. This requires a baseline hematological investigation, with follow-up studies before and after each dose (1). Interval investigation of hematologic abnormalities is typically done 1 week before each injection. The gap between each injection can be extended up to 8 weeks if laboratory values are abnormal, to allow for repeat evaluation. If at 8 weeks the patient continues to experience a hematologic abnormality, treatment is halted.

DISCUSSION

Current treatment guidelines for mCRPC include hormonal agents like abiraterone acetate and enzalutamide, the chemotherapeutic agent cabazitaxel, the immunotherapeutic agent sipuleucel-T, and radium-223 (19, 21).

Radium-223 has been studied in comparison with other treatment modalities (19). Other bone-targeted therapies, apart from radiopharmaceuticals, include osteoclast inhibitors like the bisphosphonate zoledronic acid and the RANKL inhibitor denosumab. However, neither showed improvement in disease progression or overall survival (2). According to Hoskin et al, radium-223 is well tolerated and effective in patients with symptomatic mCRPC, irrespective of previous docetaxel use (22). Also, chemotherapy following treatment with radium-223 is feasible and appears well tolerated, irrespective of prior docetaxel use (23). According to Finkelstein et al, the hematologic safety profile of radium-223 with concomitant EBRT was similar to that without concomitant EBRT. Therefore, EBRT can be used additionally with radium-223 for pain palliation (24). There were no statistical differences when the treatment was combined with bisphosphonates (4). Trials studying the feasibility and efficacy of combining radium-223 with other endocrine modalities are currently ongoing (19).

CONCLUSION

Radium-223 is a first-of-its-kind FDA-approved bone-targeting therapeutic agent that positively impacts overall survival, delay in symptomatic skeletal events, and quality of life. Various clinical trials and their post hoc analyses have proved its safety and efficacy in treating mCRPC with bone metastases. However, its role in managing micro bone metastases in early mCRPC is still ambiguous. Ongoing research and trials are attempting to address various combination therapies and treatment sequencing strategies. They are also exploring use of radium-223 for treatment of other cancers like breast cancer, renal cancer metastases to bone, and thyroid cancer (1, 19) with osseous metastasis.


24. Finkelstein SE, Michalski JM, O’Sullivan JM, Parker C, Garcia-Vargas JE, Sartor AO. External beam radiation therapy (EBRT) use and safety with radium-223 dichloride (Ra-223) in patients (pts) with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases (mets) from the ALSYMPCA trial. J Clin Oncol 2015;33(7 Suppl):182.
We report a 67-year-old woman who presented with adrenal crisis as a manifestation of autoimmune polyglandular syndrome 2, a polygenic disorder characterized by concurrent primary adrenal insufficiency and either autoimmune thyroid disease or type 1 diabetes mellitus.

CASE REPORT
A 67-year-old woman with primary adrenal insufficiency (AI), hypothyroidism, non–insulin-dependent diabetes mellitus (DM), and dyslipidemia presented to our emergency department with symptomatic hypotension and presyncope associated with a 2-week history of postprandial nausea, vomiting, diarrhea, and abdominal cramping and a 20-pound unintentional weight loss. Her initial diagnosis of AI was made by a cosyntropin stimulation test during a hospital admission for hypotension and volume depletion 6 years earlier. She was discharged on hydrocortisone, and later fludrocortisone was added. Three months prior to the current presentation, hydrocortisone was discontinued in favor of fludrocortisone monotherapy for unclear reasons. Subsequently, she struggled with symptomatic hypotension, with her peak systolic blood pressure rarely exceeding 100 mm Hg; this persisted despite doubling of the fludrocortisone dose from 0.1 to 0.2 mg/day.

Upon initial evaluation, the patient’s blood pressure was 80/50 mm Hg and her heart rate was 60 beats/min. Initial laboratory studies were significant for a serum potassium level of 2.3 mmol/L (normal range, 3.5–5.1 mmol/L) and magnesium of 1.3 mg/dL (normal range, 1.8–2.4 mg/dL); her serum sodium, chloride, and bicarbonate levels were within normal limits. Serum cortisol drawn at 4:00 AM was 3.4 μg/dL (normal range, 3.7–19.4 μg/dL). Computed tomography of the abdomen revealed atrophied adrenal glands but no other explanation for her gastrointestinal symptoms (Figure 1).

The patient was given 3 L of normal saline and 100 mg of hydrocortisone intravenously, started on a norepinephrine infusion, and admitted to the intensive care unit. Subsequent management included continuation of hydrocortisone at a dose of 100 mg every 8 hours, resumption of thyroid hormone replacement, aggressive potassium repletion, and rapid weaning of norepinephrine. Her diarrhea resolved and no source of infection was identified. Hydrocortisone was tapered to an oral maintenance dose of 20 mg every morning and 10 mg every afternoon. Upon discharge, an endocrinology referral was made due to suspicion for autoimmune polyglandular syndrome-2 (APS-2).

DISCUSSION
Adrenal crisis (AC) is defined as an acute deterioration in a patient with AI associated with absolute or relative hypotension that improves following parenteral glucocorticoid administration (1). Other manifestations include fatigue, weakness, fever, altered sensorium, anorexia, nausea, vomiting, secretory diarrhea, abdominal pain, hyponatremia, hyperkalemia, metabolic acidosis, and rarely hypoglycemia (2). The combination of abdominal pain and fever may lead to an incorrect diagnosis of acute abdomen and potentially catastrophic surgical exploration (3).
Hypotension results not only from hypovolemia but also from deficiency of cortisol itself, which exhibits a variety of genomic and nongenomic effects on vascular tone (4). Hypernatremia results from renal salt wasting, volume depletion, and resultant hypersecretion of antidiuretic hormone (ADH) caused by aldosterone insufficiency. Additionally, cortisol exerts direct and indirect negative feedback on ADH secretion; thus, its deficiency also leads to elevated ADH levels (5). Hyperkalemia is attributable to the loss of aldosterone, which normally promotes the urinary excretion of dietary potassium. In our patient, these classic abnormalities were not observed. Her normal serum sodium and low serum potassium levels may be explained by zealous mineralocorticoid replacement in combination with chronic gastrointestinal potassium and magnesium losses.

Common precipitants of AC include infection, surgical procedures, trauma, and abrupt withdrawal of glucocorticoid therapy (2). AC occurs more frequently in patients with primary compared to secondary AI, likely reflecting residual glucocorticoid secretion in the latter (1, 6). In a large German retrospective cohort study, the incidence of AC was higher in patients with APS-2 and highest in those with APS-2 and type 1 DM (6).

It is crucial that diagnostic testing not cause a delay in treatment. When AC is suspected, intravenous fluids (1 L normal saline in the first hour followed by continuous administration) and glucocorticoids (100 mg of hydrocortisone followed by 200 mg over 24 hours as a continuous infusion or in divided doses every 6 hours) should be administered promptly with concurrent testing of serum chemistries, cortisol, and adrenocorticotropic hormone (7). Long-term maintenance therapy usually consists of oral hydrocortisone (15 to 25 mg/day) or cortisone acetate (20 to 35 mg/day) in two or three divided doses. Most patients also require fludrocortisone at a dose of 0.05 to 0.2 mg/day (7). It cannot be overemphasized that patients with primary AI must never discontinue glucocorticoid replacement for any reason. As the present case illustrates, discontinuation of glucocorticoid therapy can have disastrous consequences despite adequate mineralocorticoid replacement.

The autoimmune polyglandular syndromes are a group of disorders characterized by endocrine and nonendocrine immune-mediated dysfunction. Three main syndromes have been described. Autoimmune polyglandular syndrome-1 (APS-1) is an autosomal recessive disorder caused by mutations in the autoimmune regulator (AIRE) gene, which results in a loss of central tolerance, the process by which self-reactive T cells are eliminated in the thymus during early differentiation. It usually manifests during infancy with mucocutaneous candidiasis; primary AI and hypoparathyroidism occur later. APS-1 is associated with other autoimmune diseases including type 1 DM, vitiligo, alopecia, hepatitis, pernicious anemia, and primary hypothyroidism. The diagnosis is made by genetic testing. Hormone replacement and aggressive treatment of mucocutaneous candidiasis are the mainstays of treatment (8). APS-2, also known as Schmidt syndrome, is the most common autoimmune polyglandular syndrome. In contrast to APS-1, APS-2 is a polygenic disorder associated with particular HLA class II haplotypes in addition to mutations in several non-HLA genes. Onset is during adulthood, and the individual endocrine and nonendocrine components may develop years or decades apart. Primary AI plus either autoimmune thyroid disease or type 1 DM are the principal manifestations; associated diseases include celiac disease, pernicious anemia, myasthenia gravis, vitiligo, and alopecia. Treatment focuses on the identification and management of the component autoimmune conditions (8).

The third form, immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare disorder caused by mutations in the forkhead box P3 (FOXP3) gene resulting in functional or quantitative deficiency of regulatory T cells. The disease manifests in the first days to months of life with severe autoimmune enteropathy, dermatitis, and type 1 DM and may be rapidly fatal if untreated. Immunosuppressive drugs can be effective in ameliorating autoimmune and allergic disease but are associated with significant toxicity. Restoration of regulatory T-cell function via hematopoietic stem cell transplantation offers the potential for cure (8).

Whipple's disease is an infection caused by the Gram-positive bacillus *Tropheryma whippelii*. Invasion or uptake of the bacteria can occur in various parts of the body. The differential diagnoses are broad due to the wide spectrum of infection, and the disease is diagnosed based on biopsy of suspected lesions, usually in the small intestine. We present the case of a 56-year-old man with no significant prior medical history who presented with swelling and pain in the left eye. Review of systems revealed 6 months of persistent diarrhea, and intestinal biopsy revealed periodic acid-Schiff–positive macrophages.

**CASE REPORT**

A 56-year-old man with no significant prior medical history presented with swelling and pain in the left eye. He was found to have a complicated pseudomonal infection involving the periorbit and sinuses as well as bilateral pneumonia with cavitary disease. For 6 months, he had endured persistent diarrhea, night sweats, fatigue, a 60-pound weight loss, and hyperpigmentation of the skin. Upper endoscopy showed gastritis but no masses or bleeding ulcers. Small bowel biopsies were obtained, and histologic evaluation demonstrated small intestinal mucosa with villous blunting and expansion with periodic acid-Schiff–positive macrophages within the lamina propria (Figure 1). Whipple’s polymerase chain reaction (PCR) was obtained but returned negative results. Treatment for Whipple’s disease was initiated with doxycycline and hydroxychloroquine. The patient demonstrated complete remission of his symptoms.

**DISCUSSION**

The annual incidence of Whipple’s disease is approximately 1 per 1,000,000 people (3). In general, it is noted to have two distinct stages. The first stage is a prodromal stage consisting of nonspecific findings such as arthralgias, adenopathy, and fever. The second stage is the steady-state stage consisting of organ-specific findings such as diarrhea, weight loss, and neurological symptoms. The typical time course from onset of the prodromal stage to the steady-state stage is thought to be around 6 years, but it can be triggered much more quickly in certain situations such as an immunocompromised host (2).

The current methods for diagnosis are culture, serology, pathology (i.e., duodenal biopsy), and molecular testing. Data...
have shown that use of PCR techniques on intestinal biopsies is not necessary to confirm the diagnosis. Additionally, PCR tests risk contamination by environmental DNA, lack visual controls, and are difficult to perform on paraffin sections (4). In this case, the diagnosis was confirmed with periodic acid-Schiff staining of duodenal biopsies as well as villous atrophy. Though the Whipple's PCR test was negative, small bowel histology was determined to be pathognomonic for Whipple's disease. A dramatic response to targeted therapy further confirmed the diagnosis.

Without treatment, Whipple's disease can be fatal and even with treatment relapse can occur. This case illustrates the importance of clinical suspicion driving a diagnosis and indicates that current diagnostic methods for Whipple's disease may be limited.


**Avocations**

Photo copyright © Jed Rosenthal, MD. Dr. Rosenthal is a cardiologist in Dallas, Texas (e-mail: jedr2@sbcglobal.net).
The occurrence of upper-extremity arterial disease is less common than that of the lower extremities. Nevertheless, exercise-induced symptoms, when present, can significantly affect functional capacity and limit quality of life. We report a case of exertional right upper-extremity pain and severe right axillary artery disease that was revascularized using an off-label drug-coated balloon technology with resolution of symptoms.

Clinical manifestations of upper-extremity arterial disease tend to be distinct from those of lower-extremity disease, given the abundance of collateral circulation (1, 2). The main focus in managing upper-extremity arterial disease is treatment of preexisting cardiovascular risk factors with aggressive medical therapy and lifestyle modification. When refractory symptoms ensue, surgical or percutaneous revascularization should be considered. Surgery with bypass grafts has been associated with improved patency compared to endovascular therapy, but with comparable complication rates (3). When endovascular therapy is considered, the preferred method remains controversial (4, 5). We present a patient with symptoms of right upper-extremity claudication and likely obstructive atherosclerotic disease of the axillary artery who underwent successful revascularization using drug-coated balloon angioplasty with subsequent resolution of symptoms.

CASE REPORT

A 66-year-old woman presented with right arm claudication. She had a prior history of hypertension, hyperlipidemia, pulmonary sarcoidosis, rheumatic heart disease, atrial fibrillation, and a permanent pacemaker for tachy-brady syndrome. She had extensive atherosclerotic disease with known nonobstructive coronary and carotid artery disease and previous percutaneous revascularization for peripheral arterial disease. The patient had been maintained on aspirin and clopidogrel.

She presented with progressive symptoms of right arm discomfort, aggravated by exercise and heavy-object lifting. Examination disclosed a 40 mm Hg systolic blood pressure differential between the upper extremities and a diminished right radial pulse. Ultrasound of the upper extremities demonstrated severe right and moderate left axillary artery disease. Computed tomographic (CT) angiography confirmed the ultrasound findings.

Figure 1. Digital subtraction angiography images (a) before intervention, showing diffuse, obstructive atherosclerotic disease in the right axillary artery, and (b) after treatment with drug-coated balloon angioplasty.
A 6Fr 90 cm Cook sheath was advanced via the left common femoral artery into the right brachiocephalic trunk for endovascular intervention using standard sheath delivery techniques. Unfractionated heparin with a goal partial thromboplastin time of 250 to 300 seconds was given. The lesions in the axillary artery were crossed using a 0.018˝ gold-tip Glidewire (Terumo Medical Corp., Somerset, NJ). The 0.018˝ glidewire was exchanged for a supportive 0.035˝ SupraCore wire (Abbott, and showed multifocal obstructive atherosclerotic lesions of the axillary arteries bilaterally. Serologic studies had been negative for an underlying inflammatory and/or autoimmune process with the exception of a mildly elevated erythrocyte sedimentation rate. The patient underwent upper-extremity angiography, confirming the sonographic and CT angiography findings (Figure 1a). Given optimal medical therapy and refractory right arm claudication, the patient opted for endovascular therapy.

### Table 1. Summary of published data on patency rates of upper-extremity revascularization

<table>
<thead>
<tr>
<th>First author (Ref)</th>
<th>Year</th>
<th>Number of patients/narrowings</th>
<th>Follow-up in months</th>
<th>Narrowest artery</th>
<th>Revascularization</th>
<th>Patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowman (11)</td>
<td>1983</td>
<td>10/10</td>
<td>13</td>
<td>Subclavian and innominate</td>
<td>PTA</td>
<td>90%</td>
</tr>
<tr>
<td>Wilms (12)</td>
<td>1987</td>
<td>22/23</td>
<td>25</td>
<td>Subclavian</td>
<td>PTA</td>
<td>82%</td>
</tr>
<tr>
<td>Burke (13)</td>
<td>1987</td>
<td>27/30</td>
<td>36</td>
<td>Subclavian, innominate, and vertebral</td>
<td>PTA</td>
<td>NA</td>
</tr>
<tr>
<td>Cook (14)</td>
<td>1989</td>
<td>6/6</td>
<td>18</td>
<td>Subclavian</td>
<td>PTA</td>
<td>83%</td>
</tr>
<tr>
<td>Jaschke (15)</td>
<td>1989</td>
<td>12/12</td>
<td>12</td>
<td>Subclavian, innominate, and axillary</td>
<td>PTA</td>
<td>91%</td>
</tr>
<tr>
<td>Qi (16)</td>
<td>1991</td>
<td>125/125</td>
<td>46</td>
<td>Subclavian and vertebral</td>
<td>PTA</td>
<td>99%</td>
</tr>
<tr>
<td>Hebrang (17)</td>
<td>1991</td>
<td>52/52</td>
<td>29</td>
<td>Subclavian</td>
<td>PTA</td>
<td>91%</td>
</tr>
<tr>
<td>Perrault (18)</td>
<td>1993</td>
<td>11/11</td>
<td>38</td>
<td>Subclavian</td>
<td>PTA</td>
<td>100%</td>
</tr>
<tr>
<td>Millaire (19)</td>
<td>1993</td>
<td>50/50</td>
<td>41</td>
<td>Subclavian</td>
<td>PTA</td>
<td>86%</td>
</tr>
<tr>
<td>Kumar (20)</td>
<td>1995</td>
<td>27/31</td>
<td>NA</td>
<td>Subclavian</td>
<td>Stent</td>
<td>NA</td>
</tr>
<tr>
<td>Motarjeme (21)</td>
<td>1996</td>
<td>112/151</td>
<td>60</td>
<td>Innominate, subclavian, carotid, and vertebral</td>
<td>PTA</td>
<td>97%</td>
</tr>
<tr>
<td>Martinez (22)</td>
<td>1997</td>
<td>17/17</td>
<td>19.4</td>
<td>Subclavian</td>
<td>Stent</td>
<td>81%</td>
</tr>
<tr>
<td>Rodríguez-Lopez (9)</td>
<td>1999</td>
<td>69/70</td>
<td>13</td>
<td>Subclavian</td>
<td>Stent</td>
<td>73%</td>
</tr>
<tr>
<td>Körner (23)</td>
<td>1999</td>
<td>37/43</td>
<td>15</td>
<td>Subclavian and innominate</td>
<td>PTA</td>
<td>72%</td>
</tr>
<tr>
<td>Schillinger (24)</td>
<td>2001</td>
<td>115/115</td>
<td>44</td>
<td>Subclavian</td>
<td>PTA ± stent</td>
<td>59%</td>
</tr>
<tr>
<td>González (25)</td>
<td>2002</td>
<td>9/9</td>
<td>37.4</td>
<td>Subclavian</td>
<td>PTA</td>
<td>89%</td>
</tr>
<tr>
<td>Angle (26)</td>
<td>2003</td>
<td>21/21</td>
<td>27</td>
<td>Subclavian</td>
<td>PTA ± stent</td>
<td>79%</td>
</tr>
<tr>
<td>Modarai (3)</td>
<td>2004</td>
<td>41/41</td>
<td>48</td>
<td>Subclavian and innominate</td>
<td>PTA ± stent</td>
<td>82%</td>
</tr>
<tr>
<td>Amor (27)</td>
<td>2004</td>
<td>86/89</td>
<td>42</td>
<td>Subclavian</td>
<td>Stent</td>
<td>81%</td>
</tr>
<tr>
<td>De Vries (5)</td>
<td>2005</td>
<td>110/110</td>
<td>34</td>
<td>Subclavian</td>
<td>PTA ± stent</td>
<td>88%</td>
</tr>
<tr>
<td>Filippo (28)</td>
<td>2006</td>
<td>42/42</td>
<td>60</td>
<td>Subclavian</td>
<td>Stent</td>
<td>71%</td>
</tr>
<tr>
<td>Przewlocki (29)</td>
<td>2006</td>
<td>75/76</td>
<td>24.4</td>
<td>Subclavian and innominate</td>
<td>PTA ± stent</td>
<td>77%</td>
</tr>
<tr>
<td>Sakai (30)</td>
<td>2007</td>
<td>26/28</td>
<td>6</td>
<td>Subclavian</td>
<td>Stent</td>
<td>100%</td>
</tr>
<tr>
<td>Abu Rahma (31)</td>
<td>2007</td>
<td>121/121</td>
<td>41</td>
<td>Subclavian</td>
<td>PTA ± stent</td>
<td>70%</td>
</tr>
<tr>
<td>Van Noord (32)</td>
<td>2007</td>
<td>43/43</td>
<td>12</td>
<td>Subclavian and brachiocephalic</td>
<td>PTA ± stent</td>
<td>76%</td>
</tr>
<tr>
<td>Linni (33)</td>
<td>2008</td>
<td>40/40</td>
<td>50.1</td>
<td>Subclavian</td>
<td>Stent</td>
<td>95%</td>
</tr>
<tr>
<td>Sixt (4)</td>
<td>2009</td>
<td>107/108</td>
<td>12</td>
<td>Subclavian and brachiocephalic</td>
<td>PTA ± stent</td>
<td>88%</td>
</tr>
<tr>
<td>Yu (34)</td>
<td>2010</td>
<td>14/14</td>
<td>12</td>
<td>Subclavian</td>
<td>Stent</td>
<td>93%</td>
</tr>
<tr>
<td>Wang (35)</td>
<td>2010</td>
<td>59/61</td>
<td>40.7</td>
<td>Subclavian</td>
<td>Stent</td>
<td>85%</td>
</tr>
<tr>
<td>Song (36)</td>
<td>2012</td>
<td>148/148</td>
<td>67</td>
<td>Subclavian</td>
<td>Stent</td>
<td>49%</td>
</tr>
<tr>
<td>Babic (37)</td>
<td>2012</td>
<td>56/56</td>
<td>40</td>
<td>Subclavian</td>
<td>Stent</td>
<td>83%</td>
</tr>
<tr>
<td>Li (38)</td>
<td>2013</td>
<td>71/71</td>
<td>27</td>
<td>Subclavian</td>
<td>Stent</td>
<td>85%</td>
</tr>
<tr>
<td>Higashimori (39)</td>
<td>2013</td>
<td>59/60</td>
<td>49</td>
<td>Subclavian</td>
<td>Stent</td>
<td>86%</td>
</tr>
<tr>
<td>Almeida (40)</td>
<td>2014</td>
<td>16/16</td>
<td>12</td>
<td>Subclavian</td>
<td>Stent</td>
<td>100%</td>
</tr>
<tr>
<td>Che (41)</td>
<td>2016</td>
<td>167/167</td>
<td>60.6</td>
<td>Subclavian</td>
<td>Stent</td>
<td>87%</td>
</tr>
</tbody>
</table>

*NA indicates not available; PTA, percutaneous transluminal angioplasty.*
Chicago, IL). The right axillary artery lesions were subsequently predilated with a 4.0 mm × 40 mm Armada balloon (Abbott, Chicago, IL), followed by drug-coated balloon angioplasty with an IN.PACT Admiral 4.0 mm × 120 mm balloon (Medtronic, Minneapolis, MN). Postintervention angiography revealed excellent luminal expansion without evidence of flow-limiting dissections (Figure 1b). Postprocedurally, the patient reported resolution of her right upper-extremity symptoms, and the blood pressure differential had resolved. At 6- and 12-month follow-up, she remained asymptomatic, with 2+ right brachial, radial, and ulnar pulses.

**DISCUSSION**

Given the rarity of atherosclerotic axillary artery disease, most data on short- and long-term outcomes following percutaneous transluminal angioplasty (PTA) and/or stenting of focal upper-extremity atherosclerotic disease are extrapolated from subclavian artery revascularization (6) (Table 1). In a retrospective study evaluating outcomes in 274 patients treated with either a conservative (n = 165) or invasive (n = 109) approach for subclavian artery atherosclerotic disease with a median follow-up of 42 months, patients treated with PTA had a 60% risk reduction for the development of a hemodynamically significant stenosis (P < 0.01), defined as an upper-extremity blood pressure differential of ≥20 mm Hg compared with conservative treatment (7).

Improvements in stent technology, coupled with widespread use, paved the way for studies evaluating the efficacy of stenting in upper-extremity vessels. An initial study by Sueoka et al (8) evaluated the efficacy of balloon-expandable stents in treating proximal subclavian artery stenosis causing subclavian steal syndrome after failure of an initial approach with PTA, with a procedural success rate of 100%. Subsequent studies by Rodríguez-Lopez et al (9) and Henry et al (10) demonstrated good short- and mid-term patency rates, with similar long-term patency rates compared with PTA. A recently published meta-analysis of 35 noncomparative studies with 1726 patients examining PTA and stenting in subclavian arterial occlusive disease found that technical success rates were higher in stented patients, without a statistical difference in rates of symptom resolution and long-term primary patency rates (6). We report the first case of symptomatic axillary artery disease successfully treated with off-label drug-coated balloon angioplasty and resolution of symptoms postprocedurally.

26. Angle JF, Matsumoto AH, McGraw JK, Spinosa DJ, Hagspiel KD, Leung DX, Tribble CG. Percutaneous angioplasty and stenting of left subclavian artery stenosis in patients with left internal mammary-coronary bypass...


Combined mitral and aortic valve stenosis caused by two different etiologies, rheumatic and congenital

William C. Roberts, MD, and Joshua K. Dodderer, BS

Table 1. Pertinent findings in the five patients with stenotic congenitally bicuspid aortic valves and stenotic rheumatic mitral valves

| Case number | Age at VR (years) | Sex | BMI (kg/m²) | PAW (mean) | RV (s/d) | RA (mean) | LV (s/d) | Ao (s/d) | LV-Ao (psg) | PAW-LV (mdg) | AV area (cm²) | MV area (cm²) | AV weight (g) | MV weight (g) |
|-------------|-----------------|-----|-------------|------------|--------|--------|--------|--------|---------|---------|------------|------------|-------------|-------------|-------------|
| 1           | 44              | M   | 26          | 21         | 86/19  | 16     | 126/14 | 108/66 | 18      | 16      | –          | 1.54       | 0.9         | 3.8         |
| 2           | 46              | M   | 26          | 26         | 48/18  | 13     | 139/17 | 133/88 | 28      | 15      | 0.46       | 0.95       | 1.37        | 3.44        |
| 3           | 50              | M   | 27          | 39         | 56/18  | 13     | 173/40 | 146/88 | 27      | 25      | 1.0        | 1.28       | –           | –           |
| 4           | 53              | F   | 34          | –          | –      | –      | –      | –      | –       | –       | –          | –          | –           | –           |
| 5           | 74              | F   | 21          | 33         | 79/17  | 54     | 226/19 | 195/85 | 31      | –       | 0.53       | 0.95       | –           | –           |

Ao indicates aorta; AV, aortic valve; BMI, body mass index; LV, left ventricular; mdg, mean diastolic gradient; MV, mitral valve; PAW, pulmonary artery wedge; psg, peak systolic gradient; RA, right atrium; RV, right ventricular; s/d, peak systole/end diastole; VR, valve replacement.

Described herein are five patients who had double left-sided cardiac valve replacement for mitral and aortic valve stenosis resulting from two different etiologies: rheumatic heart disease, the cause of the mitral stenosis, and congenital heart disease (bicuspid valve), the underlying cause of the aortic stenosis.

Combined mitral and aortic valve stenosis in the same patient today in the Western world is relatively uncommon. Worldwide, its most common cause is rheumatic heart disease. Today in native Europeans and in European Americans, the most common cause of this combination appears to be massive mitral annular calcification (probably the consequence of atherosclerosis) as the cause of the mitral stenosis and either congenital (unicuspid or bicuspid aortic valve) or nonrheumatic causes (tricuspid aortic valve) as the cause of the aortic stenosis (atherosclerotic etiology) (1). On very rare occasions, the mitral stenosis may be the result of rheumatic heart disease and the aortic stenosis, the result of an underlying congenital heart disease (unicuspid or bicuspid aortic valve). Such was the case in the five patients described herein.

METHODS

Shown in Table 1 are pertinent findings in the five patients with combined rheumatic mitral stenosis and aortic stenosis superimposed on a congenitally bicuspid aortic valve. Photographs of the operatively excised valves are shown in Figures 1 and 2. Only Case 1 is still alive. Cases 2 to 5 survived from 6.9 to 14.4 years (mean 11.2) after the double valve replacement.

DISCUSSION

The patients described here had two different causes for the two stenotic valves on the left side of the heart: rheumatic heart disease for the mitral stenosis and congenital heart disease (bicuspid aortic valve) for the aortic stenosis. Relatively few such combinations have been reported previously. McReynolds and associates (2) in 1976 described an 18-year-old man with a purely regurgitant congenitally bicuspid aortic valve (without commissural fusion) and a diffusely fibrotic nonstenotic mitral valve proven to be of rheumatic etiology by the presence of Aschoff nodules in the left atrial wall. Tejada and associates (3) in 2001 described a 60-year-old woman who had a noncalcified congenitally bicuspid aortic valve and percutaneous valvuloplasty for a typical rheumatic stenotic mitral valve. Muthiah (4) in India in 2016 described by echocardiogram a...
41-year-old man with a “congenitally malformed” stenotic aortic valve and a stenotic mitral valve that appeared to be of rheumatic origin.

On occasion, in patients with rheumatic mitral stenosis, the aortic valve may have fusion of one of its three commissures, simulating a congenitally bicuspid aortic valve. In these circumstances, however, the ventricular aspect of the fusion appears as a V-shaped indentation, producing some space below the fusion. In contrast, with a congenitally bicuspid aortic valve, the ventricular aspect of the raphe area, which some may interpret as fusion of the two cusps, is flat, such that there is no space beneath the fusion. Such was the case in each of the five patients described herein, indicating that the aortic valve in each was congenitally malformed and not the result of rheumatic heart disease.


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**Figure 1.** Case 1. Mitral valve as viewed from the (a) ventricular aspect and (b) atrial aspect. Aortic valve as viewed from the (c) aortic aspect and (d) ventricular aspect.

**Figure 2.** Case 2. (a) Thickened mitral valve and (b) bicuspid aortic valve.
Described herein is the heart of a 2-day-old newborn, the product of a 25-week gestation, with atresia of two cardiac valves, one on the right side and one on the left side, apparently a previously undescribed entity.

The worst heart disease—the one allowing the shortest survival—is aortic valve atresia, the most common cause of death in the first month of life (1, 2). About 25% of these newborns with aortic valve atresia also have mitral valve atresia. The second most common condition associated with an atretic cardiac valve is pulmonic valve atresia. The occurrence of one right-sided atretic valve and one left-sided atretic valve in the same heart must be incredibly rare, but such was the case in the newborn described herein.

CASE DESCRIPTION

A 2-day-old female newborn after a 25-week gestation weighed 550 g. An electrocardiogram shortly after birth disclosed a prolonged P-R interval and sinus bradycardia. A technically difficult echocardiogram disclosed a dilated right ventricle, a normal-sized left ventricle, a large atrial septal defect with bidirectional flow, a large ventricular septal defect with bidirectional flow, a small (1 mm) patent ductus arteriosus with left-to-right flow, severe “pulmonic stenosis,” and an unobstructed aortic valve and aortic arch. The echocardiographic findings were interpreted as being consistent with tetralogy of Fallot.

The newborn died in the intensive care unit on the second day of life. At necropsy, the heart weighed 4.15 g. The cardiac findings are illustrated in the Figure. Both the mitral and pulmonic valves were atretic, the atrial septum was absent, and a ventricular septal defect was located caudal to the aortic valve, which arose from the dilated right ventricle. A narrowed patent ductus was present, and it was the only source of blood to the lungs.

In addition to the cardiac anomalies, a cleft lip was present, and it extended to involve the entire hard and soft palate. Cytogenetic SNP microarray analysis performed on an antemortem blood sample disclosed a normal female chromosome pattern with no deletions or duplications of known or potential clinical significance. Postmortem chromosome analysis also showed a normal female 46 XX karyotype. No numerical or structural anomalies were observed.

From the Baylor Heart and Vascular Institute (Roberts) and the Departments of Pathology (Roberts, Guileyardo) and Internal Medicine (Division of Cardiology) (Roberts), Baylor University Medical Center at Dallas; and the Department of Pediatric Cardiology, Texas Health Presbyterian Hospital, Dallas, Texas (Sing).

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structural aberrations were seen at the 500 G-band resolution. Examination of the placenta disclosed a three-vessel cord, premature villous architecture, severe acute chorioamnionitis, and mild acute funisitis.

**DISCUSSION**

Our patient had combined pulmonic and mitral valve atresia. Such a combination, to our knowledge, has not been reported previously. Death was probably the consequence of progressive narrowing of the ductus arteriosus.

A 44-year-old male cigarette smoker with an elevated serum cholesterol level and a family history of coronary artery disease experienced nocturnal chest pain. The following day he went to see a cardiologist. Five years earlier, this cardiologist had evaluated the patient for chest pain with an electrocardiogram (ECG) and blood tests and told him he was okay. The cardiologist scheduled the patient for a future stress test, but this time did not do an ECG, even at the patient’s request.

The patient had more chest pain that night and the following day went to a chiropractor who gave him an “adjustment” and recorded an ECG (Figure 1), which the chiropractor interpreted as normal. The next day the patient had worse and more prolonged chest pain and went to the hospital, where an ECG showed an acute anterolateral myocardial infarct (Figure 2). The serum creatine kinase peaked at 3148 U/L (reference, 24–200) with an MB fraction of 130.4 (reference, 0–44). The serum troponin I peaked at 41.50 ng/mL (reference, 0–0.60).

Cardiac angiography revealed marked hypokinesis of the distal one-half of the anterolateral wall of the left ventricle with an akinetic apex and a left ventricular ejection fraction of 45% (reference, ≥55%). Coronary arteriography showed a normal left main artery; subtotal occlusion of the left anterior descending artery distal to the first septal perforating branch with TIMI grade 1 flow and distal disease; 80% narrowing of the proximal portion of the right artery with a 50% narrowing in its middle portion; and only minimal irregularities in the left circumflex artery. Three days after angiography, the patient underwent a coronary arterial bypass operation with the left internal mammary artery anastomosed to the proximal portion of the left anterior descending artery, and reversed saphenous vein grafts anastomosed to the distal left anterior descending and the distal right arteries.

As described by Wellens and his associates, terminal T-wave inversion in the anterior precordial leads, as seen in Figure 1, predicts critical narrowing high in the left anterior descending coronary artery, the so-called Wellens warning.

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Figure 2. Electrocardiogram recorded a day later on admission to the hospital showed changes of acute anterolateral myocardial infarction.

typical preinfarction angina was not recognized as such by the cardiologist or the chiropractor. The typical Wellens warning on the ECG was not recognized because the cardiologist did not record an ECG despite the patient’s urging, and the chiropractor did not understand the pattern. Not surprisingly, both were subsequently sued.

Anaplastic large cell lymphoma is a rare disease associated with breast implants. We present the case of a woman who had had breast augmentation and multiple revisions over a period of 13 years and presented with recurrent fluid collections. The cause was determined to be anaplastic large cell lymphoma, which required removal of the implants, capsulectomy, and evaluation by a medical oncologist. The patient was not found to have metastatic disease on imaging studies. Breast implant–associated anaplastic large cell lymphoma is a poorly understood disease entity, and optimal treatment is unclear.

Breast implant–associated anaplastic lymphoma kinase (ALK)-negative large cell lymphoma (BIA-ALCL) is a rare clinical entity, with fewer than 400 reported cases in the literature, most of which are case reports. It was first described in 1997 (1) and has a suspected incidence of 0.3% per 100,000 women per year (2). This may be a gross underestimation, given the number of breast augmentation and reconstructive procedures performed worldwide, and could reflect the difficulty in establishing a diagnosis. This case report describes a 60-year-old woman with BIA-ALCL.

CASE STUDY

A 60-year-old white woman with no significant past medical history presented to her plastic surgeon with a grossly distorted, swollen, and enlarged left breast without evidence of a mass (Figure 1). There was no history of trauma or systemic symptoms. She previously had breast augmentation with multiple revisions; the first procedure took place when she was 43 years old. The procedure used polyurethane implants in the subglandular location. The patient subsequently had three further revisions of her augmentation secondary to recurrent fluid accumulation on the left breast.

At age 59, the patient began to have increasing firmness and tenderness of the left breast, which was associated with yet another fluid collection requiring implant exchange. The plastic surgeon performed further workup for this fluid accumulation prior to performing another revision of her augmentation. A diagnostic mammogram and ultrasound revealed only a small amount of fluid around the left implant in the 12 o’clock position. A computed tomography scan of the chest without contrast revealed an asymmetric undulating contour of the left breast prosthesis with mass effect from fluid of variable densities, with no evidence of implant rupture, but an inflammatory, infectious, or lymphoma etiology could not be ruled out. A discussion ensued with the patient concerning these findings; ultimately, she elected to have her implants removed without replacement until the etiology could be identified. The patient underwent bilateral implant removal with capsulectomies, which was uneventful on the right side. Fluid was evacuated on the left side and revealed a capsule that was thickened with a plaque-like mass and mucoid material associated with capsule posteriorly. This could not be entirely resected, as it adhered to the underlying chest wall beneath the pectoralis major muscle. The remaining mass was debrided with a scratch pad, drains were placed, and the wounds were closed. The patient healed well postoperatively.

Final pathology of the capsules revealed atypical infiltrate consistent with ALK-negative ALCI associated with a breast implant. Hematoxylin and eosin studies (Figure 2a) were...
and has an excellent prognosis in comparison to mass-forming disease or systemic ALK-negative ALCL, which may have more aggressive courses and worse prognoses (5).

To date, there is no consensus on the implant substance contributing to disease, but more cases have been reported with textured versus smooth implants. This may indicate that the inflammatory response is causative in disease formation, but that hypothesis has not been proven.

The differential diagnosis for BIA-ALCL is broad and includes dissemination from systemic ALCL, classical Hodgkin lymphoma, other primary breast lymphoma, misinterpretation of triple-negative breast carcinoma, seroma formation from trauma, and double capsule formation (2, 4, 5). Treatment options to date consist of surgical therapy including implant removal and capsulectomy versus surgical and systemic therapy with or without radiation, typically indicated if the patient has classic B symptoms (2, 4, 6). The FDA recommends reporting all confirmed cases to improve the understanding of this rare disease.


DISCUSSION
In 2016, about 290,000 women in the United States had breast augmentation using implants; 109,000 of these women received them for reconstruction after breast cancer (3). The Food and Drug Administration (FDA) released a statement in early 2017 concerning a rare cancer, ALCL, that has been linked to breast implants and is associated with nine deaths. The FDA has received 359 reports of BIA-ALCL and only recently released its statement because of advancements in the description of the disease and treatment recommendations as a result of numerous case reports in the literature.

A systematic review and structured expert panel was organized by Kim et al to advise clinicians when BIA-ALCL may be suspected. The panel agreed that there was an association between implants and ALK-negative ALCL and that a delayed or recurrent seroma beyond 6 months should be investigated with aspiration and cytologic analysis or flow cytometry to rule out infection and lymphoma (4).

In general, BIA-ALCL typically manifests as a seroma or fluid collection but may present with a discrete mass originating from the fibrous capsule around the implant as opposed to the breast parenchyma. Microscopically, the tumor cells are present in the seroma fluid or on the inner surface of the fibrous capsule and may form sheets along the capsule in mass-forming disease (5). Seroma-forming disease usually follows an indolent clinical course and has an excellent prognosis in comparison to mass-forming disease or systemic ALK-negative ALCL, which may have more aggressive courses and worse prognoses (5).

To date, there is no consensus on the implant substance contributing to disease, but more cases have been reported with textured versus smooth implants. This may indicate that the inflammatory response is causative in disease formation, but that hypothesis has not been proven.

The differential diagnosis for BIA-ALCL is broad and includes dissemination from systemic ALCL, classical Hodgkin lymphoma, other primary breast lymphoma, misinterpretation of triple-negative breast carcinoma, seroma formation from trauma, and double capsule formation (2, 4, 5). Treatment options to date consist of surgical therapy including implant removal and capsulectomy versus surgical and systemic therapy with or without radiation, typically indicated if the patient has classic B symptoms (2, 4, 6). The FDA recommends reporting all confirmed cases to improve the understanding of this rare disease.

Epstein-Barr virus–positive diffuse large B-cell lymphoma

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While the World Health Organization included Epstein-Barr virus (EBV)–positive diffuse large B-cell lymphoma (DLBCL) as a provisional entity of a lymphoma occurring in older individuals without any known immunodeficiency in 2008, it has since been recognized that this entity may occur in younger individuals. As a result, the 2016 revision has substituted the modifier “elderly” with “not otherwise specified” (NOS). The NOS highlights that there are more specific entities with neoplastic EBV-positive large B cells such as lymphomatoid granulomatosis. Diagnosis requires that there be no other cause of immunodeficiency and that other more specific entities with neoplastic EBV plus large B cells be excluded. We present the case of an 81-year-old woman hospitalized for generalized weakness, increasing confusion, unexplained weight loss, and intermittent fevers. Examination showed lymphadenopathy, lesions in the liver and small intestine, and a very high EBV viral load. She experienced a rapid demise and at autopsy was found to have EBV+DLBCL, NOS.

CASE PRESENTATION

An 81-year-old white woman presented to the emergency department after increased confusion and generalized weakness followed by an unwitnessed fall at home. She had a 20-pound weight loss over 2 months and intermittent fevers during the same time. Her past medical history was notable for a cerebrovascular accident 4 years prior, vascular dementia, diabetes mellitus type 2, paroxysmal atrial fibrillation, hyperlipidemia, gastroesophageal reflux disease, and hypothyroidism. On admission, she had a temperature of 97.7°, blood pressure of 118/58 mm Hg, and heart rate of 100 beats/min. Her blood work showed a white blood cell count of 3.2 K/μL and a platelet count of 94 K/μL. Cultures and testing for HIV, hepatitis B, hepatitis C, cytomegalovirus, and parvovirus B19 were all negative. Her Epstein-Barr virus (EBV) viral load was >1,100,000 IU/mL by polymerase chain reaction. A computed tomography (CT) scan of the chest, abdomen, and pelvis found multiple prominent lymph nodes. The abdominal ultrasound showed thickening of the gallbladder, but no overt cholecystitis. A CT of the head was negative. The patient was started on broad-spectrum antibiotics for continued fever and leukopenia, but treatment was discontinued because no source of infection was identified. The patient continued to decline and did not desire invasive life-sustaining measures; thus, comfort measures were started on hospital day 13, and she died shortly thereafter.

An autopsy was performed and revealed diffuse lymphadenopathy, especially in the paratracheal, periaortic, and peripancreatic areas. Microscopically, the lymph nodes showed massive effacement with infiltrates of large lymphoid cells (Figure 1a). These cells had scant to moderate amounts of basophilic cytoplasm, large irregular nuclei, and prominent nucleoli, and they focally extended through the capsules into the surrounding adipose tissue and into lymphatic vessels. Similar collections of atypical lymphoid cells were found in the lung interstitium, liver portal tracts and sinusoids, splenic white and red pulp, gastric submucosal vessels, epicardium, left atrium, and bone marrow. Immunohistochemistry testing showed that the tumor was positive for CD20 (Figure 1b), MUM1, and BCL2, had a proliferative index (Ki-67) of 60%, and was negative for BCL6, CD3, cMYC, and CD10. In situ hybridization for EBV (EBER-ISH) was positive (Figure 1c). The morphologic and immunophenotypic results represent a diffuse large B-cell lymphoma (DLBCL), post–germinal center type, consistent with EBV-positive DLBCL, not otherwise specified (NOS).

DISCUSSION

EBV is a double-stranded, enveloped virus that belongs to the Herpesviridae family. EBV shows tropism for epithelial cells as well as B-cell lymphocytes (1, 2). Almost all humans are exposed to EBV at some point in their life, and after exposure EBV confers a lifelong latency. This can cause problems in the aging population. With age, the immune system enters a state of immunosenescence characterized by a decrease in the diversity of B cells, causing an in vivo clonal expansion. At the same time, T-cell lymphocytes are decreasing in number with a decline in naïve T cells and T-cell receptor diversity (3). These changes result in more circulating cells with EBV-specific receptors. Cells with latent EBV infection express EBER protein and may express other proteins such as EBNA and LMP proteins (3). EBV also induces the NFκB pathway, which may be required for survival of the cells in DLBCL (2).
According to the 2016 World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, EBV+ DLBCL, NOS is diagnosed in apparent immunocompetent patients, usually over 50 years of age (4). This lymphoma was a provisional entity in the 2008 World Health Organization classification, entitled EBV+ DLBCL of the elderly, but the “elderly” designation was substituted with “not otherwise specified” with the recognition that this entity occurs in younger patients (4, 5). The NOS designation highlights that the lymphoma must be excluded from more specific entities with neoplastic EBV-positive large B cells, such as lymphomatoid granulomatosis, DLBCL associated with chronic inflammation, and the newly designated entity EBV-positive mucocutaneous ulcer (4).

EBV-positive DLBCL accounts for 8% to 15% of DLBCL in the Asian population (2–4). Within Western populations, the percentage is lower (<5%) (2, 3). Some studies found a median age of 71 and a slight male predominance. Lymph node involvement is seen in about 70% of cases. Microscopically, the lymph node architecture is effaced and consists of a uniform population of large cells with extensive necrosis, mitoses, and apoptoses. If minimal to no reactive component (small lymphocytes, plasma cells, or histiocytes) is seen, the disease is subclassified as monomorphic. The disease is classified as polymorphic if a reactive component is present (2, 3). This morphologic subclassification has not been shown to have prognostic implications (3).

The immunohistochemical profile is generally positive for B-cell markers CD20, CD19, CD79a, and PAX-5. CD10 and BCL6 are usually negative, while MUM1 is commonly positive. Cases with immunoblastic or plasmablastic features may lack CD20 expression (5). In situ hybridization for EBER is positive and is considered the most important test in diagnosis, with the highest diagnostic sensitivity (2).

EBV+ DLBCL has a poor response to treatment, so rapid detection is a necessity. Detection relies on clinical suspicion and looking for EBV in every case of DLBCL. The prognosis of EBV+ DLBCL is worse than that of EBV-negative tumors, with a median survival of 2 years (5, 6). Prognosis is worse in patients 70 years or older and in those with B symptoms. Currently, there is no uniformly accepted treatment for EBV+ DLBCL beyond the current standard therapy for DLBCL (2, 6).

The standard treatment for DLBCL is the combination of rituximab, a chimeric anti-CD20 monoclonal antibody, with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (2). Some studies suggest improved prognosis with more intensive regimens, such as combination rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) (7).

Lymphoblastic lymphoma is a rare aggressive neoplasm of T-cell or B-cell precursors resembling acute lymphoblastic leukemia, with no or limited bone marrow involvement, that develops more frequently in children and young adults. Lymphoblastic lymphoma of the B-cell type is uncommon, and extranodal presentation is even rarer. We report what is, to the best of our knowledge, the first reported case of B-lymphoblastic lymphoma (B-LBL) of the hard palate.

CASE REPORT

A 49-year-old man presented with pain and swelling in the hard palate for 3 months. Examination of the oral cavity showed diffuse, soft, nontender swelling in the hard palate (Figure 1a). There was no pallor, lymphadenopathy, or organomegaly. Computed tomography scan of the head revealed irregular rarefaction of the anterior aspect of the hard palate. An incisional biopsy of the lesion disclosed subepithelium diffusely infiltrated with a monotonous population of medium to large cells with vesicular nuclei, prominent nucleoli, and scanty cytoplasm (Figure 2). On immunohistochemistry, the cells were positive for CD20, CD34, Bcl2, and Tdt with an MIB labeling index of about 90%. The picture was diagnostic of B-LBL. His hemoglobin was 15 g/dL; platelets, 3.5 lakhs/mm³; and total leucocyte count, 7300/mm³. Lactate dehydrogenase was 540 U/L. His cerebrospinal fluid and bone marrow studies were normal. Computed tomography scans of the neck, thorax, abdomen, and pelvis were normal, and he was staged as stage 1. The patient was started on rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R-Hyper CVAD protocol). After completion of treatment, the lesion regressed (Figure 1b). The patient is on maintenance chemotherapy.

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Figure 1. (a) Diffuse swelling in the hard palate. (b) Regression of the lesion after one cycle of chemotherapy.

Figure 2. Monotonous population of medium to large cells with vesicular nuclei and scanty cytoplasm (hematoxylin and eosin, 100x).
of the first cycle of chemotherapy, his symptoms subsided and the lesions showed significant clinical and radiological regression (Figure 1b). At present, he is on maintenance chemotherapy.

DISCUSSION

LBL is a highly aggressive neoplasm of lymphoblasts that may be of either T-cell origin (T-LBL) or B-cell origin. Lymphoblastic lymphoma accounts for approximately 2% of all non-Hodgkin lymphomas, out of which T-LBL constitutes around 90% of cases (1). LBLs are grouped together with acute lymphoblastic leukemia in the 2008 World Health Organization classification of hematopoietic malignancies (2). These two entities are biologically very close but not identical; in LBL, the bone marrow is not involved or is only partially involved, with less than 20% infiltrating blast cells. LBL occurs commonly in children, mostly males. T-LBL usually presents with a mediastinal mass, central nervous system involvement, and pleural and pericardial effusion, whereas B-LBL presentation is more limited than that of T-LBL and the localized disease usually involves single nodal or extranodal sites such as skin, bone, and soft tissue (3, 4).

Lymphoid lesions of the palate can be either lymphomatous or benign lymphoid hyperplasia. Oral lymphomas are relatively rare and constitute about 4% of all oral malignancies (5). The oral cavity is the primary site of approximately 2% of all extranodal lymphomas (6). Lymphomas can affect both bony and soft tissue of the oral cavity, with the most frequent localization being the tonsil. The most common type is diffuse large B-cell lymphoma, mantle cell lymphoma, marginal zone B-cell lymphoma, Burkitt’s lymphoma, lymphomablastic lymphoma, peripheral T-cell lymphoma, and anaplastic large cell lymphoma have also been reported in the oral cavity (7). However, B-LBL arising from the hard palate has not been reported previously.

Clinical manifestations depend on the location of the lesion. The most common clinical appearance of non-Hodgkin lymphoma in the mouth is a nonhealing, painless ulceration (8). Patients may complain of localized or diffuse soft tissue swelling, pain, mucosal discoloration, paresthesias, anesthesias, and loosening of teeth (9).

Lymphoblastic lymphomas are treated similar to acute lymphoblastic leukemia with combination chemotherapy protocols consisting of intensive remission-induction chemotherapy, central nervous system prophylaxis, a consolidation chemotherapy, and subsequent maintenance therapy. Treatment of LBL with protocols derived from acute lymphoblastic leukemia therapy are effective, with an 82% event-free survival and an 85% overall survival at 5 years (10).

Natural killer/T-cell lymphoma invading the orbit and globe

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Natural killer/T-cell lymphomas are extremely rare and carry high mortality rates. Epidemiologically, these cancers tend to affect mainly Asian and South American patients and are associated with Epstein-Barr virus seropositivity. This report details a 78-year-old Vietnamese woman who presented initially with vitritis of unknown cause, but later developed proptosis and conjunctival involvement as her disease spread. Biopsies of the orbit, ethmoid sinus, and conjunctiva were found to be significant for natural killer/T-cell lymphoma. The case highlights the diagnostic difficulty of this tumor given its rarity and ability to mimic other disorders.

Most lymphomas involving the orbit and globe are non-Hodgkin’s B-cell lymphomas (1). Only about 2% of intraocular lymphomas are non-B-cell tumors, and those expressing natural killer (NK) cell markers are typically highly aggressive and carry a poor prognosis (2). Since they arise primarily from the nasal mucosa, NK/T-cell lymphomas have the ability to invade the orbit and globe (2). Herein we present a case of NK/T-cell lymphoma in a 78-year-old Vietnamese woman who initially presented with vision problems and was successfully treated with chemotherapy.

CASE REPORT

A 78-year-old Vietnamese woman with a past medical history of coronary artery disease, hyperlipidemia, and hypothyroidism presented with a 6-month history of blurred vision in the left eye associated with sporadic pressure-like pain in that eye. On exam, vision in the left eye was 20/50, and there was no improvement with pinhole testing. Her intraocular pressure in the left eye was 10 mm Hg. The patient demonstrated mild vitritis and periphlebitis with vascular sheathing in the temporal periphery on the left. She also manifested a pigmented chorioretinal scar in the superonasal periphery of the same eye. The remainder of the exam, including pupils and extraocular movements, was normal.

The patient was initially diagnosed with uveitis and treated with a dexamethasone intravitreal implant; however, she developed recurrence of symptoms after implant dissolution. Serologic workup was performed that included tests for antineutrophil cytoplasmic antibody, toxoplasma IgM and IgG, rapid plasma reagin, QuantiFERON tuberculosis, and Lyme antibodies, all of which were negative. The patient also demonstrated a normal erythrocyte sedimentation rate, C-reactive protein level, and angiotensin-converting enzyme level. Magnetic resonance imaging with contrast demonstrated a metallic foreign body in the preseptal upper lid but was otherwise unremarkable and notably negative for any mass lesions, including central nervous system lymphoma, and an anterior chamber paracentesis failed to yield diagnostic results.

Two months later, the patient returned with an inflamed salmon-colored lesion within the medial conjunctiva of the left eye and markedly decreased visual acuity on the left to 20/200. Examination demonstrated supra-, infra-, and abduction deficits on the left with mechanical ptosis, as well as 5 mm of proptosis and mild resistance to retropulsion.

Due to the presence of a metallic foreign body, a contrast-enhanced computed tomography (CT) scan of the head was substituted for magnetic resonance imaging. This scan demonstrated extensive opacification of the left maxillary and ethmoid sinuses, as well as an invasive pattern of hyperdense material filling the majority of the left intraconal space, which extended anteriorly, causing protrusion of the subcutaneous tissue of the inferior eyelid (Figure 1).

The patient underwent orbitotomy with biopsy of the abnormal tissue in the left orbit and ethmoid sinus as well as a conjunctival biopsy. Pathology results revealed intermediate- to large-sized neoplastic CD2+, CD56+, CD57+ lymphoid cells, highlighting an atypical prominent population of true NK cells (Figure 2). In situ hybridization for Epstein-Barr virus was strongly and diffusely positive in neoplastic cells. The diagnosis of extranodal NK/T-cell lymphoma nasal type was made, and the patient underwent tumor staging. A positron emission tomography (PET) scan demonstrated extensive metabolically active disease, indicating a stage IVA diagnosis. The patient received three of six planned cycles of gemcitabine, oxaliplatin,
NK/T-cell lymphoma does occasionally invade the globe or ocular adnexa and represents approximately 1% to 3% of all lymphoproliferative lesions in these locations (4). Over 70% of these cancers localize to the nasopharynx with inflammation and local tissue destruction (5); however, angioinvasion allows widespread dissemination to the gastrointestinal tract (6), skin (7), and central nervous system (8). A recent review that included 24 patients with primary nasal or nasopharyngeal NK/T-cell lymphoma identified six patients (25% of the study population) who suffered vision-threatening complications that stemmed from uveitis/vitritis and/or orbital inflammation (5). Intraocular and orbital presentations of the malignancy have been confused with a range of diagnoses, including orbital cellulitis (9, 10), nonspecific orbital inflammation (6), conjunctivitis, anterior uveitis, and optic neuritis (11).

The prognosis of extranodal NK/T-cell lymphomas is worse than that of their B-cell counterparts (12). While early stage, localized disease is highly curable, metastatic disease and refractory cases carry a 5-year survival rate of <10% (13). Treatment for localized disease (stage I/II) includes chemotherapy and radiotherapy; however, disseminated disease is treated with

**DISCUSSION**

NK/T-cell lymphoma is a rare and aggressive subtype most common in Asian and South American populations and associated with EBV (3). While most ocular and orbital lymphomas are of the non-Hodgkin’s B-cell variety, the nasal type and L-asparaginase (GELOX) chemotherapy. Her therapy was suspended due to severe treatment-induced debilitation; however, she remains in complete remission by both CT and PET scan as of her most recent follow-up 10 months following her initial oncologic consultation.

**Figure 1.** A CT scan taken after the development of left-sided proptosis shows (a) hyperdense material filling the left intraconal space and protruding into the inferior eyelid and (b) prominent maxillary and ethmoid sinus opacification.

**Figure 2.** Pathology results confirming the diagnosis of natural killer/T-cell lymphoma: (a) in situ hybridization for Epstein Barr virus on orbital tissue showing intermediate- to large-sized neoplastic cells with nuclear irregularities that stain strongly positive (1000×); (b) CD3 immunohistochemical stain of orbital tissue (1000×); (c) CD5 immunohistochemical stain of orbital tissue (1000×); (d) CD56 immunohistochemical stain of orbital tissue (1000×); (e) sinonasal mucosa with an abnormal lymphoid infiltrate displaying some nuclear irregularity underlying normal respiratory epithelium (200×).
combination chemotherapy (14). Furthermore, expression of P-glycoprotein (an active drug-export mechanism) on NK/T-cell lymphoma cells confers multidrug resistance (15), so regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisolone have largely been replaced with methotrexate- and ifosfamide-containing regimens (16). L-asparaginase is another crucial component of the chemotherapeutic regimen, and phase II studies of dexamethasone, methotrexate, ifosfamide, etoposide, and L-asparaginase (SMILE) therapy have shown 1-year overall survival and progression-free survival rates of 45% and 45%, respectively (17). This patient was treated with GELOX, which in one prospective study showed a 2-year overall survival rate of 86% and a progression-free survival rate of 86%, with a local relapse rate of 15% and systemic relapse rate of 11% (18).

It is important to consider the diagnosis of NK/T-cell lymphoma in patients complaining of orbital swelling, especially those with concomitant findings of ocular inflammation or other systemic complaints. Orbital biopsy should be considered in cases of chronic uveitis with nondiagnostic vitreous biopsy and orbital imaging findings. When diagnosed early, treatment with radio- and chemotherapy can be effective for regional sino-orbital NK/T-cell lymphoma.

Blastic plasmacytoid dendritic cell neoplasm following acquired erythropoietic protoporphyria

John R. Krause, MD, Laura Baugh, MD, Alicia Swink, MD, and Micah Burch, MD

A 56-year-old Texas rancher with a prior diagnosis of acquired erythropoietic protoporphyria secondary to an underlying myelodysplastic disorder developed an uncommon tumor, blastic plasmacytoid dendritic cell neoplasm (BPDCN). During his initial disease, analysis revealed a TET2 mutation, which is the most common mutation associated with BPDCN. This article discusses this unusual hematopoietic neoplasm, the possible evolution from erythropoietic protoporphyria, and the underlying myelodysplastic process.

CASE REPORT

A 56-year-old Texas rancher was diagnosed with erythropoietic protoporphyria secondary to an underlying myelodysplastic disorder, refractory anemia with ring sideroblasts, in 2014 (1). His chromosome analysis revealed no abnormalities, but a mutational analysis revealed a TET2 mutation. His skin disease was well controlled with the high-dose beta-carotene supplement Lumitene and sun avoidance. The patient’s blood counts were monitored regularly and remained within normal parameters.

In January 2017, he presented to the emergency room with severe abdominal pain. He stated that he had also noted slowly enlarging lymph nodes in the prior 2 weeks. Physical exam revealed a diffuse violaceous rash across his trunk and upper extremities with diffuse adenopathy in his neck, axillae, and groin. Blood work revealed an elevated white blood cell count of 250 × 10⁹/L with 70% blasts, a hemoglobin of 8.5 g/dL, a hematocrit of 24.7%, and a platelet count of 134 × 10⁹/L. Flow cytometry revealed a population of cells positive for CD4, CD56, and CD123 consistent with a blastic plasmacytoid dendritic cell neoplasm (BPDCN). The diagnosis was confirmed by bone marrow aspirate and biopsy with appropriate immunostains (Figure 1).

The patient’s karyotype was diploid, and an acute myeloid leukemia fluorescent in situ hybridization panel was normal. CKit was negative. A TET2 mutation was detected on sequencing. The patient was initiated on a Hyper CVAD regimen (cyclophosphamide, vincristine, doxorubicin, and dexamethasone). He developed severe disseminated intravascular coagulation, respiratory distress, and renal insufficiency but slowly recovered without serious morbidity. The plans are to continue his chemotherapy regimen with an eventual allogeneic bone marrow transplant.

DISCUSSION

BPDCN is a rare malignant hematological neoplasm characterized by the clonal population of immature plasmacytoid...
dendritic cells (2–4). This entity has been known under various names including agranular CD4+ natural killer (NK) cell leukemia, blastic NK-cell lymphoma, blastic NK leukemia, and agranular CD4+, CD56+ hematodermic neoplasm. In the 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, this entity is classified under the acute myeloid leukemias (5). This is a clinically aggressive tumor derived from precursors of plasmacytoid dendritic cells, also known as professional type I interferon-producing cells or plasmacytoid monocytes (3).

The clinical features of BPDCN consist of two main patterns (6). One is characterized by an indolent onset (70%–90% of cases) dominated by skin lesions followed by tumor dissemination. The other (10%–30% of cases) has features of acute leukemia and systemic involvement from the beginning. BPDCN is characterized by a diffuse monomorphic blastic infiltrate of cells that can resemble lymphoblasts or myeloblasts. The diagnosis is based on immunophenotyping and relies on expression of CD4 and CD56 along with antigens more specific for plasma dendritic cells, including CD123, TCL1, CD303, CD2AP, BCL11a, and SPIB. Currently there is no consensus as to the minimal phenotype necessary to establish the diagnosis, but it is proposed that a confident diagnosis may be established when four of the five principal markers (CD4, CD56, CD123, TCL1, and CD303) are expressed (7, 8).

T-cell and B-cell receptor genes are usually germline with clonal bystander T cells responsible for the rare cases of reported T-cell receptor gene rearrangements. There are no specific karyotypic abnormalities, but complex aberrations may be present with six major recurrent targets, namely 5q (72%), 12p (64%), 13q (64%), q1 (50%), 15q (43%), and loss of chromosome 9 (28%) (9). Next-generation sequencing shows that TET2 is the most common mutated gene (8). Gene expression profiling studies have shown a signature distinct from myeloid and lymphoid acute leukemia (10). The presence of TET2 in the patients’ original diagnosis along with the presence of TET2 in BPDCN raises the possibility that this current lesion may have arisen from his prior underlying myelodysplastic lesion. BPDCN appears to be commonly associated with myelodysplastic features (8).

Despite the deceptively indolent clinical presentation with initial response in most cases to a variety of intensive chemotherapy regimens, the course is most always invariably aggressive, with median survival times from 10 to 16.4 months (7, 11). Occasional reports have noted longer survival/remission times following allogeneic hematopoietic stem cell transplantation (12, 13).

Sinonasal and laryngeal sarcoidosis

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Sarcoidosis is a chronic granulomatous inflammation of uncertain etiology that can involve any organ system in the body. Sinonasal and laryngeal involvement is rare, poorly understood, and difficult to diagnose. Additionally, the extent of the disease is variable, and the response to systemic corticosteroids is often poor. We report a case of a 55-year-old woman with prior cutaneous sarcoidosis who presented with chronic nasal congestion, difficulty breathing, dysphonia, and stridor, and biopsy of the nasal vestibule revealed non-caseating granulomatous inflammation.

CASE DESCRIPTION

A 55-year-old black woman with a history of obstructive sleep apnea and cutaneous sarcoidosis on oral corticosteroids presented with nasal stuffiness and obstruction, nasal discomfort, hoarseness, and difficult breathing made worse by lying down and alleviated by sitting up. Her symptoms started several months earlier and increased in severity several weeks prior to presentation. She had no fever, chills, cough, or weight loss. Physical examination revealed audible stridor and dark-colored skin plaques involving the nose in a butterfly distribution, the nasolabial folds, cheeks, forehead, and right arm. Her oral cavity examination revealed tender swollen gums and loose premolar teeth. Her vital signs and laboratory results were essentially normal except for an elevated erythrocyte sedimentation rate of 55 mm/hr (reference range, <30 mm/hr) and C-reactive protein of 1.4 mg/dL (reference range, <0.5 mg/dL). Her serum calcium level was normal at 9.3 mg/dL. Computed tomography (CT) of the neck revealed complete opacification of the left maxillary antrum with outward expansion of the sinus walls, an 8 mm mucous retention cyst in the right maxillary sinus, bilateral maxillary erosions, and destruction of the premaxilla, palate, and floor of the nose suspicious for malignancy. CT of the chest revealed bilateral hilar lymphadenopathy and four pulmonary nodules <2 cm in size. The patient underwent a bronchoscopic examination, which revealed an edematous and pink epiglottis and aryepiglottic and ventricular folds and a subglottic nodular lesion. CT of the chest revealed bilateral hilar lymphadenopathy and four pulmonary nodules <2 cm in size. The patient underwent a bronchoscopic examination, which revealed an edematous and pink epiglottis and aryepiglottic and ventricular folds and a subglottic nodular lesion. Diffuse yellowish endobronchial nodular lesions with underlying mucosal hyperemia involving the entire airway were present (cobblestone respiratory mucosa).

The patient was started on a high-dose systemic corticosteroid, oral methotrexate 12.5 mg once weekly, and azelastine-fluticasone 137 mcg–50 mcg nasal spray twice daily. However, she had multiple emergency department visits and readmissions for respiratory symptoms.

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The mortality rate is 1% to 5% and is mostly related to cardiac, pulmonary, and neurological complications (2).

Upper airway disease in sarcoidosis is uncommon and occurs in <2% of patients with sarcoidosis. Multiorgan involvement is uncommon in these patients. Benjamin et al reported that out of 5 patients with laryngeal involvement, only one had generalized disease (3). Neel et al found that only 7 of 13 patients with laryngeal sarcoidosis had other organ involvement (4). The clinical presentation of upper airway sarcoidosis varies from asymptomatic to severe. The main symptoms of sinonasal disease include nasal obstruction, crusting, and epistaxis (5). Laryngeal disease presents with hoarseness, dyspnea, dysphagia, chronic cough, obstructive sleep apnea, and airway obstruction, which could progress to upper airway obstruction and emergency cricothyrotomy (6). Fiberoptic nasolaryngoscopic examination of the nasal mucosa of patients with sinonasal sarcoidosis typically reveals pale, yellow nodular lesions and inflammation with mucus crusting (7). Our patient had these findings.

In laryngeal disease, the supraglottis region, mostly the epiglottis, is typically involved, followed by the arytenoids, aryepiglottic folds, and false vocal folds (8). The subglottis can be involved in 24% of the cases of laryngeal sarcoidosis. However, the glottis is very rarely affected (9). Flexible fiberoptic laryngoscopy often shows pale pink, edematous, and nodular thickening of the epiglottis, arytenoids, and aryepiglottic folds, a classic pattern of supraglottic involvement. Vocal cord involvement can lead to dyspnea, hoarseness, stridor, and immobility (9). Fiberoptic examination in our patient revealed edematous and pink aryepiglottic and vestibular folds with a subglottic nodular lesion; no epiglottic lesion was noted. Imaging with CT scans in sinonasal sarcoidosis reveals turbinate or septal nodularity/thickening (21%), osteoneogenesis, and bony erosions (15%–20%) (10). It is important to exclude other granulomatous diseases, such as fungal infections and polyangitis with granulomatosis. Direct bone involvement in sarcoidosis is relatively uncommon and occurs in <15% of patients; rarely the disease can extend from sinuses into intracranial structures (11).

Sarcoidosis of the upper respiratory tract is associated with lower rates of spontaneous remission and often requires systemic for worsening shortness of breath, nasal obstruction, and stridor. Oral prednisone was difficult to reduce due to rebounds in her respiratory symptoms. A rheumatologist then started her on a weekly subcutaneous injection of methotrexate 25 mg and oral hydroxychloroquine 400 mg daily. She reported improvement of nasal obstruction and stuffiness. Two months later, subcutaneous injections of 250 mg (2 mg/kg) of golimumab (Simponi®; Janssen Biotech, Horsham, PA) were started. She reported more improvement in her nasal symptoms and shortness of breath but no change in her hoarseness. The prednisone dose was decreased to 10 mg daily, and she has not recently required hospitalization.

**DISCUSSION**

Sarcoidosis is a chronic multisystemic disease of unclear etiology; it has a prevalence of 10 to 20 per 100,000 persons in the United States and is more common in women (1). Sarcoidosis typically affects patients under 40 years, with a peak among those in their 20s. The clinical course of sarcoidosis is variable; 60% to 70% of patients have a spontaneous remission, and 30% of patients have prolonged courses of more than 5 years.
treatment (8, 12). Spontaneous remission occurs only in about 10% of cases of laryngeal sarcoidosis (13). The role of corticosteroids in the clinical management of sarcoidosis is well established through its effects on lymphocyte-macrophage function. The lack of a response after 3 months of corticosteroid treatment suggests irreversible fibrotic disease, nonadherence to therapy, or an inadequate dose of prednisone. Inhaled corticosteroid therapy provides simple and safe drug delivery to sites of inflammation. Some studies have demonstrated that nasal steroids have a benefit similar to oral steroids in sinonasal sarcoidosis (14). However, data are limited on the effectiveness of inhaled corticosteroids in laryngeal sarcoidosis (15). Current treatment regimens often include hydroxychloroquine and methotrexate or azathioprine in cases with glucocorticoid resistance or corticosteroids in laryngeal sarcoidosis (14). Current treatment regimens often include hydroxychloroquine and methotrexate or azathioprine in cases with glucocorticoid resistance or severe side effects. Hassid et al. reported a good response to hydroxychloroquine in a patient with extensive sarcoidosis of the paranasal sinuses (16).

Recent studies have demonstrated that sarcoidosis patients with high levels of spontaneously released tumor necrosis factor–alpha (TNF-α) in bronchoalveolar lavage had a significantly greater risk of disease progression and corticosteroid resistance than those with a normal TNF-α level (43.8% vs 8.3%, respectively) (17). Randomized controlled trials have shown favorable results with TNF-α antagonists for the treatment of chronic active sarcoidosis (18). Judson and Baughman studied the effectiveness of infliximab therapy in chronic sarcoidosis. No cases of laryngeal sarcoidosis were included in the study, but a few cases of nasal sarcoidosis were included. At 24 weeks, the total score of extrapulmonary sarcoidosis severity was decreased by >40% in the infliximab group compared to the placebo group (19). Clinicians should consider alternative therapies, such as anti–TNF-α inhibitors, early in the course when the response to usual therapy is poor.

Minimally invasive endoscopic surgery with intranasal corticosteroid injection improves symptoms with minimal morbidity and reduces the need for systemic corticosteroids in most patients. Surgical excision using cold instruments, CO2 lasers, or microdebriders has been reported with good results (20). In sinonasal sarcoidosis, minimally invasive surgeries, including endoscopic sinus surgery, can significantly improve the quality of life, especially in those with severe nasal obstruction. Frequent saline nasal irrigation is recommended in all patients with sinonasal disease to eliminate nasal crusting.

Cavernous sinus syndrome

Rakul Nambiar, MD, and Sreejith G. Nair, DM

Cavernous sinus syndrome (CSS) is a condition characterized by multiple cranial nerve palsies manifesting with ophthalmoplegia, ptosis, and facial sensory loss due to involvement of adjacent cranial nerves. Tumors, trauma, and vascular, infectious, and noninfectious inflammatory disorders have all been described as causes. Lymphomas have been reported to involve the cavernous sinus, both as primary cavernous sinus lymphomas or as secondary lesions. Here, we describe the case of a 63-year-old man with untreated chronic lymphocytic leukemia (CLL), diagnosed 4 years earlier, who presented with CSS. Our patient underwent standard chemotherapy, but he succumbed to infection during the neutropenic period.

Neoplastic B-cell infiltration in chronic lymphocytic leukemia (CLL) has been described in skin, lung, pleura, kidney, and gastrointestinal tract tissues. However, involvement of the central nervous system (CNS) is very rare (1), and symptomatic CNS involvement in CLL is known to be rarer (1). Reported cases of CNS involvement in CLL have demonstrated a diverse and nonspecific spectrum of symptoms: headaches, mental status changes, cerebellar signs, cranial nerve abnormalities, and weakness of extremities (1). Here we report an unusual case of a patient with untreated CLL who presented with cavernous sinus syndrome (CSS). To the best of our knowledge, CLL causing CSS has not been reported previously.

CASE REPORT

A 63-year-old man presented with double vision. He first noticed diplopia 2 months prior to evaluation, stating it waxed and waned in intensity. One month later, he had recurrent severe diplopia, most prominent on leftward gaze, accompanied by nausea, headache, and photophobia. His symptoms persisted and progressed to include left-sided eyelid heaviness 1 month after presentation. He had a 4-year history of asymptomatic Rai stage I CLL (lymphocytosis with lymphadenopathy, without organomegaly or cytopenia). He was on regular follow-up during the 4 years with blood counts, along with clinical examination at 3-month intervals.

On examination, his Eastern Cooperative Oncology Group performance score was 2. Neurological exam revealed left ptosis, sluggish pupillary reflex, lateral gaze palsy, diminished medial gaze, and limited intorsion of the left eye. Visual acuities were 6/6 in the right eye and 6/9 in the left eye. Dilated fundus examination was normal. The left corneal reflex was absent, and he also had hypoaesthesia in the territory of the first and second divisions of the right trigeminal nerve. In addition, multiple cervical lymph and axillary nodes were palpable, and the spleen was palpated 2 cm below the left costal margin. The rest of the neurological and physical examination was unremarkable.

The white blood cell count was 108,000/μL, and a peripheral blood smear revealed 60% atypical lymphocytes. His hemoglobin level was 11.5 g/dL and platelet count, 163,000/μL. His lactate dehydrogenase level was 736 IU/L (normal range, 313–618 IU/L). Peripheral blood flow cytometric analysis was diagnostic of CLL. Bone marrow aspiration revealed 60% small atypical lymphoid cells, and bone marrow biopsy showed interstitial and nodular infiltration by atypical lymphoid cells, having clumped chromatin among normal hematopoietic elements. Fluorescence in situ hybridization (deletion 11q, deletion 13q, and deletion 17p) and conventional cytogenetic analysis of the peripheral blood did not reveal any abnormalities. Magnetic resonance imaging (MRI) of the patient’s brain revealed an asymmetric enhancing lesion in the left cavernous sinus, encasing the carotid artery and extending to the trigeminal cave (Meckel’s cave) (Figure). These findings were suggestive of neoplastic infiltration of the left cavernous sinus.

A diagnostic lumbar puncture was performed, and cerebrospinal fluid (CSF) revealed a white blood cell count of 20 leukocytes/mm³ (lymphocytes, 80%; neutrophils, 20%), glucose of 80 mg/dL, and total protein of 54 mg/dL. Cytological examination demonstrated the presence of small monomorphic lymphocytes in the CSF suggestive of CLL cells. The patient received high-dose methylprednisolone and was started on fludarabine (25 mg/m²/day intravenously for the first 3 days), cyclophosphamide (250 mg/m²/day intravenously for the first 3 days), and rituximab (375 mg/m²/day intravenously on day 1) (FCR regimen). He improved symptomatically after steroids; however, his status worsened after chemotherapy and he

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developed sepsis during the neutropenic period. He died on postchemotherapy day 12.

**DISCUSSION**

Cavernous sinus syndrome is characterized by ophthalmoplegia and sensory deficits over the head due to combined deficits of the three cranial nerves (third, fourth, and sixth) responsible for eye movements and pupil function, and at least one branch of the trigeminal nerve. The wide-ranging types of pathologies that involve the cavernous sinus can be classified as tumoral, congenital, infectious, inflammatory, granulomatous, and vascular.

Among the tumors involving the cavernous sinus, head and neck tumors are the most likely to metastasize to the cavernous sinus. The other common primary sites in patients with cavernous sinus metastases are breast, lung, and prostate. Lymphomas have been reported to involve the cavernous sinus, as primary lymphomas (2–4) or as secondary lesions, and may occur as unilateral or bilateral lesions (5, 6). Lymphomas may involve the cavernous sinus as a result of invasion or metastasis originating in the head and neck region, or metastasis of systemic origin. Burkitt lymphoma (6), diffuse large B-cell lymphoma (7), T-cell lymphoblastic lymphoma (4), and diffuse small B-cell lymphoma (8) have all been reported as primary lymphoma and as metastases in the cavernous sinus, but to our knowledge CLL involvement has never been reported in the literature. Infectious causes such as fungus and tuberculosis were considered because of the immunocompromised status of our patient. However, an infectious cause was less likely in our patient, in view of the presence of CLL cells in the CSF. Moreover, the CSF culture was negative.

CNS involvement of CLL remains a poorly studied phenomenon. The clinical manifestations of CNS involvement in CLL are heterogeneous and include headache, cranial nerve palsies, cerebellar signs, visual problems, and motor and/or sensory deficits. Imaging studies are neither specific nor sensitive in the detection of CNS involvement; the diagnosis is usually confirmed by lumbar puncture. At present, there are no established guidelines for treatment of CLL patients with CNS involvement. Most patients have been treated with intrathecal chemotherapy with or without radiation therapy or systemic chemotherapy (1). Intrathecal rituximab has been found to be effective in aggressive B-cell lymphomas; however, its efficacy in CLL has not been assessed (9). For CLL patients with leptomeningeal disease, fludarabine-based therapy has been found to be effective and may be a favorable therapeutic option (10). In our patient, a combination of fludarabine, cyclophosphamide, and rituximab (FCR regimen) was very toxic, and he succumbed to sepsis during the neutropenic period.

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**Figure.** MRI of the brain with contrast, (a) axial view and (b) coronal view, showing asymmetric enhancing thickening in the left cavernous sinus (arrow).
Inverted papilloma of the nasal cavity is a benign neoplasm, although it can be locally invasive and has the potential for malignant degeneration. Inverted papilloma of the temporal bone is extremely rare. We describe a case of a 44-year-old woman who was treated for nasal inverted papilloma and was later found to have inverted papilloma of her temporal bone. The patient required several procedures to remove the inverted papilloma from the nasal cavity and temporal bone, and she is currently free of recurrence.

Inverted papilloma (IP) is the second most common benign neoplasm of the nasal cavity, though it is relatively rare with a reported frequency of 0.6 to 1.5 per 100,000 per year. It is more common in men than women, and it usually occurs in the fifth to sixth decades of life (1). Nasal IP originates from the Schneiderian mucosa of the sinonasal tract and is most commonly attached on the lateral nasal wall (2). At the temporal bone, IP is exceedingly rare and much less is known about this entity than nasal IP. Only 32 cases of IP involvement of the temporal bone have been reported in the literature (3–6).

CASE DESCRIPTION

A 44-year-old woman presented with nasal obstruction, and a right nasal mass consistent with IP was found on exam. The patient underwent endoscopic resection of this lesion in 2009 and was found to have multifocal IP located on the right middle turbinate, the right posterior nasal septum, and the left torus tubarius. The patient was reported to have persistent disease on the left torus tubarius; she was subsequently lost to follow-up. She presented 21 months later with new right-sided conductive hearing loss and underwent myringotomy with tympanostomy tube placement. At the time of surgery, a fleshy mass was biopsied from the middle ear that was consistent with IP with severe dysplasia. Nasal endoscopy at that time indicated recurrent disease on the right side, without involvement of the eustachian tube orifice intranasally.

The patient underwent right middle ear exploration and was found to have tumor encroaching into the eustachian tube orifice. She also underwent directed biopsies endoscopically of suspicious nasal lesions. Specimens from the middle ear and nasal cavity revealed IP and no malignancy. Definitive endoscopic resection was performed on the patient’s nasal lesions, at which point the margins were clear of papilloma by final pathology. Four months after this resection, additional middle ear exploration was performed, and disease extending into the eustachian tube orifice with focal high-grade dysplasia was found (Figures 1 and 2). The IP in the middle ear was completely grossly removed with forceps and potassium titanyl phosphate laser. The patient had a 30 pack-year history of smoking, and at this time, she stopped smoking and switched to electronic cigarettes. She currently has an anterior tympanic membrane perforation allowing for office surveillance. Genotyping for human papillomavirus (HPV) was negative in the nasal tissue but positive for HPV 11 in the middle ear space.
At 3-year follow-up from her last procedure, the patient showed no evidence of tumor persistence or recurrence in the nose or the ear. Follow-up magnetic resonance imaging (MRI) at that time was also negative for disease. The current plan of treatment involves close observation with serial MRI and endoscopic surveillance of the nasal cavity and middle ear. The patient has been discussed at the multispecialty tumor board for possible radiation in the future should her disease develop malignant transformation.

**DISCUSSION**

Middle ear involvement with IP is an unusual finding that is rarely reported in the literature. There are three theories for the development of temporal bone IP: direct spread of tumor through the eustachian tube, conversion of ectopic rests of Schneiderian membrane in the temporal bone, and embolic seeding of tumor cells outside the sinonasal tract (3). The most common presenting symptoms of temporal bone IP are hearing loss and otorrhea (5). Middle ear IP is associated with an increased risk of malignancy, particularly if the lesions are recurrent (3). A recent series of 32 patients with temporal bone IP reported invasive carcinoma in 28% of patients and carcinoma in situ in 16% (5).

The middle ear lesion in this case demonstrated HPV 11 positivity. Nasal IPs have been associated with this and other HPV isotypes (7). However, HPV 16 and 18 have been more classically associated with malignancy. A recent meta-analysis of 31 case-controlled studies showed statistically significant association of high-risk HPV subtypes 16 and 18 with malignant sinonasal IP—with type 18 having a stronger association with malignancy than type 16 (8). The role of HPV in the development of IP has yet to be elucidated. Additionally, the clinical significance of isolating HPV in the middle ear specimen but not in the nasal specimen is unclear. Roh et al performed a retrospective review of 54 patients and found no significant difference in HPV status and rate of recurrence; in the same review, there was an association between smoking and IP recurrence, although this finding was not statistically significant (9). Since our patient has stopped smoking, she has experienced no additional recurrence of her IP.

The primary treatment modality for this benign disease is surgical. Mitchell et al reported a combined lateral and anterior skull base approach for extirpation of the eustachian tube in order to definitively manage malignant transformation of IP in this area (6). Complete excision of the tumor is important to reduce the risk of recurrence. Recurrence rates with mucosal stripping have been measured at 52.2%, whereas drilling the tumor base, cauterizing the tumor base, and complete excision have recurrence rates of 4.9%, 4.7%, and 0%, respectively. Recurrence at the tumor base is thought to be caused by rests of abnormal epithelium or tumor within the bone (10). Radiation, though not used routinely in most cases of IP, has been used as adjuvant therapy in certain cases. To date, there are no definitive recommendations regarding the role of radiation in treating this rare entity.

In this case, the authors will continue close observation and serial imaging. They have had thorough discussions with the patient regarding adjuvant radiation due to the recurrent nature of her tumor with severely dysplastic features. This case underscores the need for further data on this topic.

Congenital midline nasal anomalies are rare, with a prevalence of 1 in 20,000 to 40,000 births and with 5% to 7% of them being nasal glioma. Differential diagnoses of nasal anomalies include nasal dermoid cysts, gliomas, encephaloceles, nasal polyps, and some other rare anomalies. Due to current medical technological advancements, most of these anomalies are easily correctable, though delaying management may lead to fatal effects. This report describes two cases—one of nasal glioma and one of nevus lipomatosus cutaneous superficialis—that presented as respiratory distress in a newborn. Approximately 10 to 20 cases of these two conditions have been described; notably, this is the second documented case of nevus lipomatosus cutaneous superficialis with nasal presentation.

Two cases involving congenital midline anomalies in neonates manifesting as respiratory distress in newborns are discussed here, one with a diagnosis of nasal glioma and one with a diagnosis of nevus lipomatosus cutaneous superficialis (NLCS) in the nasal cavity. Approximately 20 cases of nasal glioma have been reported in English publications; less than 10 cases of NLCS, with only one other case involving the nasal cavity, have been reported (1–6).

CASE 1

A 40-week and 1-day-old gestational age female infant born in a tertiary center to a 27-year-old mother with good prenatal care and an uncomplicated pregnancy was initially transferred to the newborn nursery for routine care after receiving Apgar scores of 9 and 9 at 1 and 5 minutes of life. Subsequently the infant developed worsening respiratory distress along with increased difficulty breathing and intercostal retractions at 8 hours of life. A nurse reported three consequent desaturations in the newborn nursery; the attending neonatologist was consulted, and the infant was transferred to a tertiary neonatal intensive care unit (NICU) for further management. The infant was placed on nasal bubble continuous positive airway pressure at 4 cm of water for respiratory support with a fraction of inspired oxygen of 21%. A chest x-ray obtained in the NICU showed no obvious abnormalities. A complete blood count with differentials obtained at the time of NICU admission was within normal limits as well. The pediatric otolaryngology department was consulted for evaluation of respiratory obstruction. The infant was found to have a “fleshy mass” in the right anterior nasal cavity via nasal endoscopy (Figure 1a). The patient underwent computed tomography of the face, which showed a 1.2 × 1.1 × 0.7 cm anterior nasal mass with possible tiny central calcification. Magnetic resonance imaging of the

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face was also performed. The patient was temporarily treated with phenylephrine for significant nasal congestion and was weaned off oxygen by the third day of life. At the time, she was tolerating appropriate feedings and gaining weight. The patient underwent endoscopic surgical excision of the nasal mass by pediatric otolaryngology without complication. Surgical pathology examination confirmed heterotopic glial tissue (nasal glioma). The patient recovered well with no postoperative feeding or breathing problems.

**CASE 2**

A 39-week-old gestational age infant was admitted to the NICU immediately after delivery for respiratory distress on continuous airway pressure at 5 cm of water. The NICU team was called to delivery for variable and late decelerations secondary to meconium-stained amniotic fluid. The pregnancy was complicated by maternal obesity, rubella nonimmune status, and oligohydramnios. Physical examination was pertinent for a right upper lid coloboma, preauricular appendage, and large nasal appendage from medial right nares. The infant was gradually weaned off oxygen support and transitioned to all oral feeds. Magnetic resonance imaging of the face demonstrated a 0.9 × 0.7 × 0.8 cm exophytic mass arising from the right nasal fossa along with fat signal. The infant was discharged from the NICU due to stable breathing and feeding and was closely followed as an outpatient by the pediatric otolaryngology department. At 4 months of age, the patient underwent endoscopic surgical excision (*Figure 1b*) by pediatric otolaryngology without complication. Surgical pathology examination confirmed NLCS. The patient recovered well, with no further breathing or feeding issues.

**DISCUSSION**

Nasal gliomas account for approximately 5% of all congenital nasal anomalies. The differential diagnoses of midline nasal anomalies that result from atypical embryologic development include nasal gliomas, dermoid cysts, and encephaloceles (7). The word “nasal glioma” is something of a misnomer, as it implies a neoplastic condition (7, 8). In fact, approximately 60% of these nasal gliomas are extranasal; 30% of them are intranasal lying within the nasal cavity, mouth, or pterygopalatine fossa; and 10% are mixed (1, 2). In 20% of cases, gliomas connect to the intracranial space via fibrous stalk (8). Histologically, these tumors are a product of astrocytic neuroglial cells intertwined with fibrous and vascular connective tissue explicitly enclosed with skin or nasal respiratory mucosa.

Midline nasal anomalies should be considered when assessing infants with respiratory distress. Intranasal lesions often present with nasal obstruction, which can sometimes cause life-threatening airway obstruction in infants due to their obligate nasal breathing. When significant nasal obstruction occurs in infants, feeding is also affected; some infants may even require temporary feeding tube support until treatment can take place. A comprehensive physical examination is crucial for diagnosis, and pediatric otolaryngology consultation and appropriate neuroimaging studies should be promptly considered when suspicion exists in order to diagnose and treat the condition effectively. Prompt intervention may be required due to obstructive symptoms.

The treatment of choice is surgical excision, which has a 4% to 10% recurrence rate. A detailed preoperative assessment is essential to demarcate the precise position and extension of the tumor, rule out cranial involvement, and plan an appropriate surgical approach. The traditional approach for an intracranial connection is a frontal craniotomy; other potential approaches may include a transfacial lateral rhinotomy (7). Intranasal endoscopic approaches are increasingly utilized and may be considered alone for intranasal lesions and in combination with other approaches for more complex lesions.

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A deep neck abscess is uncommon in the newborn period. In this case, we noted a clindamycin-sensitive methicillin-resistant *Staphylococcus aureus* infection characterized as a deep neck abscess in an 8-day-old boy. He was admitted to the pediatric intensive care unit with a progressively enlarging indurated mass below the mandible. Imaging confirmed the mass as a submandibular abscess. The patient received antibiotics in addition to incision and drainage, with resolution of the abscess.

**CASE DESCRIPTION**

A healthy male newborn was born at 37 weeks’ gestation to a 22-year-old gradaiva 2 para 1 mother who was induced due to preeclampsia. The birth had no noted complications, including trauma or procedures. The mother was negative for group B *Streptococcus*. The infant spent 6 days in the nursery due to physiologic jaundice, received phototherapy, and was transitioned to home without difficulty. He presented 1 day after discharge on the 8th day of life for newborn follow-up and was noted to have left lateral neck swelling under the angle of the mandible, which had started the previous night. The patient did not have fever, vomiting, or diarrhea. The mass measured 4 to 6 cm and was noted to be indurated and tender to palpation with erythema and ill-defined borders. There was no sign of trauma or fistula in the skin. No stridor, respiratory distress, or retropharyngeal or parapharyngeal fullness was noted on exam. Hematologic workup showed a white blood cell count of 27.6 cells/μL (normal range 5–21) and a C-reactive protein of 22.6 mg/L (normal range <10). Blood and cerebrospinal fluid cultures were negative for organisms. An ultrasound demonstrated a heterogeneous mass measuring 2.0 cm with prominent lymph nodes along the left cervical chain. The patient was given broad-spectrum intravenous antibiotics. Repeat imaging with computed tomography showed a multiloculated abscess below the left mandibular angle (Figure). Incision and drainage of the abscess demonstrated purulence, and cultures were positive for clindamycin-sensitive MRSA. The patient was managed postoperatively for 8 days with culture-directed therapy and was discharged home. An immunologic workup was negative for any deficiencies.

**DISCUSSION**

Infection is the most common cause of neck swelling in the pediatric population, with lymphadenitis being the predominant etiology. Other potential causes of neck swelling include a variety of congenital, inflammatory, benign, and malignant lesions. In the neonatal period, the most common pediatric neck lesions are thyroglossal duct remnant and branchial cleft anomalies (3). However, in our patient, the abrupt onset, associated induration and erythema, and posterolateral location at the angle of the mandible suggested an inflammatory process, which was confirmed upon imaging to be suppurative lymphadenitis.

In a study of 445 neck masses in children, 2% were diagnosed with suppurative lymphadenitis, with MRSA being the most common pathogen. The average age for this cause was 7.3 years, with a range from 4 months to 15 years (4). A review of the literature revealed a paucity of data regarding neonatal neck infections. One study from Texas Children’s Hospital looking at children up to 60 days old from whom *S. aureus* was isolated demonstrated that two-thirds (67%) of abscesses isolated MRSA (5).

A highly prevalent location of suppurative lymphadenitis is along the anterior jugular chain, which is consistent with the location of our patient’s abscess. The lymph node involvement is usually unilateral and is a result of a pyogenic infection of...
male infants at 7 to 12 days of age are most at risk for neonatal MRSA infections (10). This infection could have been introduced from the mother handling the patient, which could produce subclinical breaks in the patient’s skin, allowing bacteria to colonize the wound.

Fetal ventriculomegaly and herpes encephalitis following primary maternal herpes simplex infection

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Uteroplacental transmission of a primary herpes simplex virus (HSV) infection in pregnancy has been reported; however, HSV ventriculomegaly of the neonate has not been well documented in utero. We present a case of a 19-year-old woman who developed a primary HSV outbreak at 17 weeks of gestation and was treated with acyclovir. A congenital malformation scan at 18 weeks of gestation demonstrated no fetal abnormalities; however, an ultrasound at 33 weeks showed a new finding of ventriculomegaly. Additionally, hydrocephalus was confirmed with magnetic resonance imaging. New-onset ventriculomegaly in the setting of primary HSV infection in pregnancy should be considered as an in utero diagnostic indicator of antenatal herpes simplex infection and herpes encephalitis.

CASE DESCRIPTION

A 19-year-old G3P1102 woman presented for prenatal care at 17 weeks and 5 days of gestation. Her past medical history was significant for methamphetamine abuse, tobacco abuse, and negative maternal Rhesus factor (1). Obstetric history included an uncomplicated spontaneous term vaginal delivery and an additional preterm delivery at 35 weeks, secondary to placental abruption with a positive urine drug screen for methamphetamine. The patient complained of painful lesions on her vulva during the initial prenatal visit and was subsequently diagnosed with a primary HSV infection. The patient was then started on acyclovir (200 mg taken by mouth 5 times daily for 10 days). Viral cultures were obtained and found to be positive for HSV-2. A subchorionic hemorrhage had been noted during a routine anatomy scan at 17 weeks of gestation.

Prior to the HSV outbreak, the patient had a normally appearing and normally growing male fetus at 17 weeks and 5 days and again upon follow-up at 25 weeks of gestation (Figure 1). A repeat ultrasound around 33 weeks of gestation revealed severe lateral ventricle dilation (Figure 2). She declined amniocentesis.

The patient presented with contractions and signs of active labor 2 days after the fetal abnormality was noted on the ultrasound, at 34 weeks and 1 day of gestation. As no herpetic lesions were present on a bright light exam, the infant was delivered vaginally at the request of the patient. Upon delivery, the infant had no respiratory effort and the Apgar score was 1 and 7 at 1 and 5 minutes, respectively. The infant was intubated and noted to have multiple skin lesions, which also cultured positive for HSV-2. Shortly after admission to the neonatal intensive care unit, the infant began to have seizures. Ultrasound and magnetic resonance imaging findings (Figure 3) of the neonate confirmed hydrocephalus with severe lateral ventricle dilation. The infant died on the fifth day of life within 6 hours of being withdrawn from respiratory support. The placenta was culture positive for HSV-2 and showed signs of acute chorioamnionitis.

DISCUSSION

As HSV infection becomes increasingly common in people of reproductive age, the rate of neonatal HSV exposure is likely...
to increase. In an effort to prevent HSV transmission during delivery, patients have been widely counseled to consider a cesarean section instead of vaginal delivery. Prevention of intrauterine transmission of HSV to the fetus is not well understood. Alternatively, it is known that a primary HSV outbreak during pregnancy increases the transmission rate to the neonate and that a primary outbreak is linked to increased risk of perinatal morbidity (2). In this case, the standard of care regarding HSV in pregnancy was followed: the patient was given a course of acyclovir at the time of her primary HSV outbreak with plans to start suppression at 36 weeks (3). Sadly, in this case, the fetus developed multiple terminal complications from the in utero herpes infection, which included the discovery of fetal ventriculomegaly.

Complications related to HSV in pregnancy are both rare and serious. Rates of neonatal HSV from maternal-fetal transmission are approximately 31:100,000 births—a rate that includes the risk of herpetic meningitis contracted by infants exposed to HSV during vaginal delivery (4). Intrauterine or transplacental transmission of HSV to the fetus is even rarer, and what is known largely comes to us through case reports. Known complications of intrauterine HSV infection include seizures, lethargy, irritability, tremors, poor feeding, temperature instability, bulging fontanelle, chorioretinitis, microcephaly, microphthalmia, and hydranencephaly (5–7). Hydranencephaly is defined as the “absence of cerebral hemispheres, which have been replaced by fluid-filled sacs” (8). In this case, the infant was found to have hydrocephalus, “a condition marked by an exces-
Usefulness of nuclear whole-body bone scanning for diagnosis of leprosy

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Leprosy, or Hansen’s disease, is rare in the United States. Given its rarity, as well as the pathognomonic dermatologic findings, there are few cases in which nuclear medicine imaging plays a role in the diagnostic workup. We present a 39-year-old man who presented with chronic abdominal pain, skin ulcers, and hypercalcemia who underwent computed tomography of the chest and a whole-body bone scan to evaluate for possible underlying neoplasm due to his profound hypercalcemia. Although the diagnosis of leprosy had been established by lower-extremity skin biopsy upon admission, workup for other potential concurrent etiologies of hypercalcemia was performed before initiating therapy. We present the computed tomography scans, nuclear medicine images, and corresponding skin findings of this case.

CASE DESCRIPTION

A 39-year-old man presented to the emergency department with several months of chronic abdominal pain and profoundly elevated serum calcium (>14 mg/dL), along with nonhealing ulcers (Figure 1b, 1c) and numbness in his legs. Chest computed tomography was performed for evaluation of any possible underlying malignancy, which identified multiple lung opacities, including a small cluster of nodules in the right upper lobe.

Figure 1. (a) The patient’s face and (b, c) lower-extremity nodules and ulcerations. (d, e) Transaxial images of diagnostic chest computed tomography demonstrating pulmonary opacities (arrow).

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measuring up to 1.5 × 3.0 cm (Figure 1d, 1e). A biopsy of the lower extremity yielded the diagnosis of leprosy. A 99m Tc-methylene diphosphonate whole-body bone scan was performed 4 weeks after initial presentation to assess the causes of the osseous disease—whether infectious, metabolic, or metastatic—based on the combination of hypercalcemia with lung nodules and biopsy-proven leprosy. This scan demonstrated a classic pattern and distribution of uptake related to leprosy (6), including diffuse uptake in the face and distal upper and lower extremities consistent with periostitis (Figure 2).

**DISCUSSION**

A prior study of two patients with leprosy and bone scintigraphy was published in 1976, which showed findings similar to our case (7). Leprous periostitis is an infrequent manifestation of leprosy, found in 3% to 45% of leprosy patients with deformities (8), and is often associated with atrophic neuropathic osteoarthropathy, which represents a spectrum of bone and joint destructive processes associated with neurosensory deficits (9). Periostitis and osteitis in patients with leprosy have usually been described as confined to the small bones of the face, hands, and feet (9). Multiple prior discussions by clinicians as well as paleopathologists examining remnants from medieval times, when leprosy was more prevalent, argue that the tibia and fibula are among the most common sites of periostal disease manifestation (10). Although leprosy is an uncommon disease, the use of bone scintigraphy can help determine if there is periostitis and the extent of involvement.

Baylor Scott & White Health

News

**U.S. News & World Report recognizes 11 Baylor Scott & White Health hospitals**

Baylor Scott & White Health has the most nationally ranked medical centers of any health care system in Texas in this year’s *U.S. News & World Report* Best Hospitals list:

- The Heart Hospital Baylor Plano is ranked #16 nationally for cardiology & heart surgery.
- Baylor University Medical Center at Dallas is ranked #29 nationally for gastroenterology & GI surgery and #41 for ear, nose, & throat. High-performing medical specialties recognized as being in the top 10% of the nation include cancer, diabetes & endocrinology, geriatrics, nephrology, neurology & neurosurgery, orthopedics, and pulmonology. This is the 25th year that the medical center has been on the list.
- Scott & White Medical Center – Temple is ranked #44 in the nation for ear, nose, & throat. High-performing medical specialties recognized as being in the top 10% of the nation are gastroenterology & GI surgery and pulmonology.
- Baylor Scott & White All Saints Medical Center – Fort Worth is ranked #47 nationally for cardiology & heart surgery. The hospital is rated high performing in congestive heart failure, colon cancer surgery, COPD, and knee replacement.
- Baylor Scott & White Medical Center – Round Rock is tied for #9 in the Dallas metro area and tied for #23 in the state of Texas. The hospital is rated high performing in congestive heart failure, colon cancer surgery, COPD, and knee replacement.

Eleven Baylor Scott & White Health medical centers were recognized in *U.S. News*’ Best Regional Hospitals category, either by being ranked or by being rated “high performing” in common procedures and conditions:

- Baylor University Medical Center at Dallas is ranked #2 in the Dallas metropolitan area and #3 in Texas. The hospital is rated high performing in aortic valve surgery, heart bypass surgery, congestive heart failure, colon cancer surgery, COPD, hip replacement, knee replacement, and lung cancer surgery.
- Scott & White Medical Center – Temple is ranked #7 in the state of Texas. The hospital is rated high performing in congestive heart failure, colon cancer surgery, COPD, and knee replacement.
- The Heart Hospital Baylor Plano is rated high performing in abdominal aortic aneurysm repair, aortic valve surgery, heart bypass surgery, congestive heart failure, and lung cancer surgery.
- Baylor Scott & White Medical Center – Plano is tied for #9 in the Dallas metro area and tied for #23 in the state of Texas. The hospital is rated high performing in colon cancer surgery and COPD.
- Baylor Scott & White Medical Center – Grapevine is tied for #9 in the Dallas metro area and tied for #23 in the state of Texas. The hospital is rated high performing in heart bypass surgery, colon cancer surgery, and COPD.
- Baylor Scott & White Medical Center – Irving is tied for #9 in the Dallas metro area and tied for #23 in the state of Texas. The hospital is rated high performing in congestive heart failure, COPD, and knee replacement.

- Baylor Scott & White All Saints Medical Center – Fort Worth is ranked #15 in the Dallas metro area and #34 in the state of Texas.
- Baylor Jack and Jane Hamilton Heart and Vascular Hospital is rated high performing in abdominal aortic aneurysm repair and congestive heart failure.
- Baylor Scott & White Medical Center – Frisco is rated high performing in hip replacement.
- Baylor Scott & White Medical Center – Round Rock is rated high performing in hip replacement.
- Baylor Medical Center at Uptown is rated high performing in hip replacement.

“I am proud of the exceptional care teams at Baylor Scott & White that deserve this recognition for the outstanding care they provide millions of Texans each year,” said Jim Hinton, president and CEO, Baylor Scott & White Health. “These rankings and ratings underscore the trust patients place in Baylor Scott & White medical centers, whether they are seeking care for common conditions or highly specialized treatments.”

**Baylor Scott & White Health and United Surgical Partners International join in ownership of Texas Spine & Joint Hospital**

Baylor Scott & White Health and United Surgical Partners International (USPI) announced a new partnership with Texas Spine & Joint Hospital in Tyler, Texas. As of August 1, 2017, Texas Spine & Joint is officially part of the Baylor Scott & White statewide network.

“We are excited by the opportunity to partner with USPI and this great group of physicians to serve the people of Tyler, Smith County, and all of East Texas,” said Jim Hinton, president and CEO, Baylor Scott & White Health. “We believe this is an excellent way to expand our high-value integrated delivery network into new communities throughout the state.”

As the integration process continues, bringing the hospital into the Baylor Scott & White system will further enable physicians and other caregivers to provide increasingly coordinated care to patients. Providers will be able to more easily access quality clinical resources, including a large network of specialty medical expertise.

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**UPCOMING CME PROGRAMS**

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

- **2nd Annual Dr. Matthew L. Davis Trauma Symposium**, October 27, 2017, at the Frank W. Mayborn Civic and Convention Center, Temple, Texas
- **Cardiology Update for Primary Care**, December 1–2, 2017, at the Westin at the Domain in Austin, Texas
- **44th Annual Williamsburg Conference on Heart Disease**, December 3–5, 2017, at Williamsburg Conference Center, Williamsburg, Virginia

For more information, visit [http://cmebaylor.org/conferences](http://cmebaylor.org/conferences).
White Health Home Care agencies have joined Waco. Staff and care team members from the locations: Brenham, College Station, Huntsville, home health services to 57 counties from eight Texas. The newly formed joint venture delivers Fort Worth area and much of North and Central Scott & White’s footprint including the Dallas-Health Group, effective August 1, 2017.

### RECENT GRANTS

- **Mandatory estimates of vaccine effectiveness against medically attended, PCR-confirmed influenza in West South Central US**
  - Principal investigator: Manjusha Gaglani, MD
  - Sponsor: Centers for Disease Control and Prevention
  - Funding: $800,000
  - Award period: 8/1/2017–7/31/2018
- **Core_apt measure of PCR-based influenza vaccine effectiveness in inpatient adults**
  - Principal investigator: Manjusha Gaglani, MD
  - Sponsor: Centers for Disease Control and Prevention
  - Funding: $450,000
  - Award period: 8/1/2017–7/31/2018
- **Familial and early onset colorectal cancer**
  - Principal investigator: Ajay Goel, PhD
  - Sponsor: National Institutes of Health
  - Funding: $372,400
  - Award period: 8/1/2017–7/31/2018
- **Development of microRNA biomarkers for noninvasive detection of colorectal cancer**
  - Principal investigator: Ajay Goel, PhD
  - Sponsor: National Institutes of Health
  - Funding: $349,917
  - Award period: 7/1/2017–6/30/2018
- **Role of acid in the development of Barrett’s esophagus**
  - Principal investigator: Rhonda Souza, MD
  - Sponsor: National Institutes of Health
  - Funding: $265,574
  - Award period: 5/23/2017–7/31/2018
- **Reflux-induced epithelial-mesenchymal transition in benign Barrett’s esophagus**
  - Principal investigator: Rhonda Souza, MD
  - Sponsor: National Institutes of Health
  - Funding: $254,143
  - Award period: 5/26/2017–8/31/2017
- **Endoscopic, histologic, and molecular characterization of esophageal wound healing after radiofrequency ablation of Barrett’s esophagus**
  - Principal investigator: Rhonda Souza, MD
  - Sponsor: National Institutes of Health
  - Funding: $251,545
  - Award period: 5/2/2017–4/30/2018
- **Pharmacometric optimization of second-line drugs for MDR tuberculosis treatment**
  - Principal investigator: Tawanda Gumbo, MD
  - Sponsor: University of Cape Town/National Institutes of Health
  - Funding: $149,104
  - Award period: 2/15/2017–1/31/2018
- **Quantifying infectiousness of undiagnosed tuberculosis cases and impact of enhanced community-based active case finding strategy using novel diagnostic tools: a randomized controlled trial**
  - Principal investigator: Tawanda Gumbo, MD
  - Sponsor: Civilian Research & Development Foundation
  - Funding: $72,065
  - Award period: 4/22/2016–4/19/2018
- **SUSTAIN for better health and health care for older adults**
  - Principal investigator: Alan Stevens, PhD
  - Sponsor: Texas A&M University Health Science Center/Department of Health and Human Services
  - Funding: $50,000
  - Award period: 8/1/2016–7/31/2018
- **Physically realistic virtual surgery**
  - Principal investigator: Ganesh Sankaranarayanan, PhD
  - Sponsor: Rensselaer Polytechnic Institute/National Institutes of Health
  - Funding: $48,225
  - Award period: 7/1/2015–8/31/2017
- **Affect regulation training for alcohol use disorder: a stage II efficacy trial**
  - Principal investigator: Suzy Gulliver, PhD
  - Sponsor: Research Foundation for the State University of New York/National Institutes of Health
  - Funding: $13,343
  - Award period: 4/1/2017–3/31/2018

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**Baylor Scott & White Health, Texas Home Health form joint venture**

As health care continues to evolve, high-quality care is increasingly important in the home setting. With that in mind, Baylor Scott & White Health, the largest not-for-profit health care system in Texas, and Texas Home Health, an AccentCare, Inc. company and leader in post-acute health care, have formed a new home health joint venture company, Texas Home Health Group, effective August 1, 2017.

Texas Home Health Group operates in Baylor Scott & White’s footprint including the Dallas-Fort Worth area and much of North and Central Texas. The newly formed joint venture delivers home health services to 57 counties from eight locations: Brenham, College Station, Huntsville, Marble Falls, McKinney, Taylor, Temple, and Waco. Staff and care team members from the legacy Texas Home Health and Baylor Scott & White Health Home Care agencies have joined the new joint venture, with operations being managed by Texas Home Health.

**New centers seek early detection and prevention for esophageal cancer**

An innovative new program dedicated to treatment and prevention of esophageal diseases is allowing clinicians and researchers to collaborate directly on patient care.

Funded by the National Institutes of Health and Baylor Scott & White Research Institute, the Center for Esophageal Research and its associated Center for Esophageal Diseases at Baylor University Medical Center at Dallas offer a unique program that investigates the full spectrum of research on conditions such as gastroesophageal reflux disease and Barrett’s esophagus.

“What’s most exciting about the centers is the collaboration between a productive lab and a patient-oriented clinical care team to really explore how we can better the lives of patients living with esophageal diseases,” said Vani Konda, MD, director of clinical operations for the Center for Esophageal Diseases.

With both bench and bedside components, physicians are provided more opportunities for translational research, and researchers can gain a better understanding of disease states over time. Equipped with advanced clinical and laboratory equipment and a patient-oriented care team, the centers have the necessary resources to conduct comprehensive research designed to uncover early detection and prevention methods—a critical step in reducing the rising incidence of esophageal cancer.

“Baylor Scott & White Health offered an opportunity to really develop these clinical and research centers that go hand in hand. That’s what’s unique about this—the ability to really make inroads into these diseases,” said Stuart Spechler, MD, chief of gastroenterology at Baylor University Medical Center Proceedings Volume 30, Number 4
PHILANTHROPY NOTES

■ Pancreatic cancer patients seeing promising results in AGAP Trial at Baylor

For many patients with inoperable pancreatic cancer, hope is fleeting. The 5-year survival rate for pancreatic cancer hovers around 5%, the lowest of all cancers. But a new clinical trial at Baylor Charles A. Sammons Cancer Center in Dallas is giving hope to a group of pancreatic cancer patients. Thus far, all patients enrolled in the AGAP Trial at Baylor have seen their tumors shrink from an inoperable state to an operable one.

According to Carlos Becerra, MD, the principal investigator for the study, one of the most interesting findings is that all of these patients have had negative margins on pathology post-surgery. There’s been so much enthusiasm around the trial that, after launching in January 2016, researchers reached their enrollment goal of 16 patients by the year’s end. They also recently received approval to increase the number of participating patients to 20. The increase will enhance the study’s statistical power. “This trial has invigorated the pancreas team here at Baylor,” said Scott Celinski, MD, another principal investigator for this study.

The researchers are also collecting samples from patients in the trial to study biomarkers that can possibly be used to detect pancreatic cancer at an earlier stage. Currently, most patients are not diagnosed until the disease is advanced.

All of this work is funded entirely by philanthropy, specifically a grant from the Jeanne Shelby Fund for Cancer Research at Communities Foundation of Texas. When the donor who established this fund first met with Baylor Scott & White researchers 2 years ago, she said her desire was to fund a clinical trial that would “provide options for pancreatic cancer patients who had no other options left.” Now, preliminary data are showing that the clinical trial she funded may help her fulfill that goal.

■ Jamie Lee Curtis to speak at 18th annual Celebrating Women luncheon

Emmy and Golden Globe award-winning actress, New York Times best-selling author, and advocate in the fight against breast cancer Jamie Lee Curtis will be the featured speaker at the 18th annual Baylor Health Care System Foundation Celebrating Women luncheon on Thursday, October 26, at the Hilton Anatole Hotel in Dallas.

At age 40, Jamie Lee experienced the same terrifying fear that hundreds of thousands of women face each year: the fear that she may have breast cancer. Thankfully, she said, “everything turned out fine, but it brought me very close to understanding how lucky I am to have access to all these resources and great doctors.”

Jamie Lee has a history of involving herself in causes she cares about in an effort to give back. The fight against breast cancer is no different. “You get involved because of your heart,” she said. “For me, there is no more important work—besides being a good mom to my kids—than using my celebrity to get more exposure for a specific cause such as this.”

Each year, approximately 1,200 passionate men and women attend the Celebrating Women luncheon in a show of support for Baylor’s efforts to fight the disease in North Texas. Since the first Celebrating Women luncheon in 2000, more than $28 million has been raised to help Baylor Scott & White Health fight breast cancer in North Texas.

■ Hope is closer to having a home than ever before

The American Cancer Society selected Baylor University Medical Center at Dallas as the location of its newest Hope Lodge, a home-like facility that offers free accommodations for cancer patients who have to travel long distances for their care. Baylor Scott & White Health has donated the use of prime real estate, valued at $4 million, to the American Cancer Society for this initiative. This location will also serve as the regional headquarters for the American Cancer Society. Funding for Hope Lodge Dallas relies solely on philanthropic support, and approximately $25 million is needed for capital expenses, annual programming, and operations. To date, more than $14 million has been raised thanks to generous support from numerous donors. Dallas–Fort Worth is one of the largest metropolitan areas in the country without a Hope Lodge, and this facility fills a huge need.

■ Boone Powell Sr. Luncheon highlights Arts in Medicine program

Throughout history, pictures, stories, dances, music, and drama have been central to healing. Research indicates that music can decrease pain, nausea, and anxiety; lower blood pressure; and stabilize heart rates. According to JaeJeung So, art therapist at Baylor University Medical Center at Dallas, art therapy also has a healing effect: “With serious illnesses, patients feel they have little control over their diseases and/or their lives. Art therapy allows them to gain a degree of freedom by putting on canvas what words can’t explain, literally allowing them to see what they are feeling.”

Baylor University Medical Center at Dallas, with the assistance of several generous friends, is helping to connect patients with the healing power of arts. The Arts in Medicine program at Baylor Dallas is a philanthropically funded initiative created to integrate music, visual arts, performing arts, and research to promote healing and to enhance the lives of patients, families, visitors, clinicians, and employees.

The Arts in Medicine program was the featured topic at the eighth annual Boone Powell Sr. Society Luncheon in May. This society was created to honor those who have made commitments to Baylor Health Care System Foundation through a planned gift or in their estate plans, and more than 100 members and guests gathered at this year’s recognition luncheon. Special guests included Paula Walker, who donated $1 million in 2015 to fund the core patient components of the Arts in Medicine initiative, and Harriet Jeffers, who is leaving a $500,000 bequest for the program.

The program included a panel discussion led by Foundation President Rowland K. Robinson with James Fleshman, MD, chief of surgery at Baylor Dallas; Kelly Crayton, RN, nurse manager at Baylor T. Boone Pickens Cancer Hospital; Tony Arant, certified music practitioner; JaeJeung So, art therapist; and Sara Chigani, music therapist. The panelists shared personal stories of the changes they’ve seen in patients though the healing power of arts and music. From reduced anxiety following a double mastectomy, to advances in speech following traumatic brain injury, to enhanced memory recall for an Alzheimer’s patient, the Arts in Medicine program is touching lives across all areas of care.

For information on how you can support these or other initiatives at Baylor Scott & White Health – North Texas, please contact Baylor Health Care System Foundation at 214.820.3136.
University Medical Center. While esophagus problems are common, not many programs offer specialized training in this area, so it provides an educational opportunity for future gastroenterologists.

**Baylor Scott & White – Grapevine, Tarrant County EMS teams adopt Pulsara**

Patients experiencing a heart attack or stroke can benefit from a new communication technology, Pulsara, a smartphone app implemented by 11 northeast Tarrant emergency medical services (EMS) teams and Baylor Scott & White Medical Center – Grapevine.

The hospital is the first in the Baylor Scott & White Health system and the first in Tarrant County to implement smartphone technology to support care for these patients. The app allows EMTs in the field who recognize symptoms of a stroke or heart attack to simply tap a button on their smartphones. This tap notifies the hospital team that an ambulance is on its way with a critical patient. As the paramedic enters more information, such as the patient’s medical history and vital signs, every team member receives a secure update. To date, the hospital has used the technology for a possible 115 myocardial infarctions and 117 strokes.

**Brain and Spine Center at Baylor Scott & White Medical Center – Plano opens**

A new center dedicated to brain and spine services has opened at Baylor Scott & White Medical Center – Plano. The Brain and Spine Center offers comprehensive care within both medical and surgical specialties. Some of these services are brain tumor surgery, movement disorders and epilepsy treatment, neuromodulation, complex spine surgery, minimally invasive spine surgery, peripheral nerve disorders treatment, and headache and stroke care.

“Our community has indicated they want to have these highly specialized services available here in Plano,” said Jerri Garison, president, Baylor Scott & White – Plano. “We built a strong team of physicians and specialty certified nurses to care for patients with these complex neurological and neurosurgical diseases.”

The neurosurgeons and neurointerventional radiologists on the medical staff at Baylor Scott & White – Plano specialize in minimally invasive surgical techniques. The hospital uses the StealthStation surgical navigation system, which enables neurosurgeons to precisely track the location of surgical instruments throughout a procedure. The StealthStation system introduces an advanced version of Stealth technology—a combination of hardware, software, tracking algorithms, image data merging, and specialized instruments to help guide them during surgical procedures such as biopsy, tumor resection, and deep brain stimulation lead placement. A new epilepsy monitoring unit is part of the hospital’s expansion of its intensive care unit to 32 beds from 16 beds. Four beds in the new unit will be dedicated to epilepsy monitoring.

**Researchers show curcumin protects against chemoresistant pancreatic cancer**

Curcumin is known for its powerful anti-inflammatory and antioxidant benefits, but a new study by researchers at Baylor Scott & White Research Institute reveals an additional benefit: its potential to overcome chemoresistance in pancreatic ductal adenocarcinoma (PDAC), a common but aggressive form of cancer in the pancreas.

The study, “Curcumin sensitizes pancreatic cancer cells to gemcitabine by attenuating PRC2 subunit EZH2, and the lncRNA PVT1 expression,” was published in Carcinogenesis. Previous research demonstrated the advantages of taking curcumin preventatively, but this is the first study of its kind to demonstrate benefits of curcumin as an adjunct to chemotherapy.

Resistance to chemotherapeutic drugs is a major challenge in caring for patients with PDAC, the fourth leading cause of cancer-related deaths in the US. Patients may respond to chemotherapy initially, but as cancer stem cells form, the body can develop drug resistance. Now, researchers have developed an improved understanding of the molecular events underlying the development of pancreatic stem cells and the role that curcumin—the main component of turmeric—plays in overcoming resistance to vital chemotherapy drugs.

“By treating certain cells with small doses of curcumin, we were able to reverse the pathways that lead to chemoresistance,” said Ajay Goel, PhD, director of gastrointestinal research and translational genomics and oncology at Baylor Scott & White Research Institute and author of the study. “This is an important breakthrough that could lead to better prognosis and longer lives for patients with chemoresistant pancreatic cancer.”
Jesus on the night when he was betrayed took bread, and when he had given thanks, he broke it and said, “This is my body which is for you. Do this in remembrance of me.” —1 Corinthians 11:23–24

We never spoke and were never formally introduced. I didn’t even know her name. But when the CPR ended, I held her hand as she died.

The cardiovascular intensive care unit fellow had texted me 45 minutes earlier, making sure to leave out any personal identifiers including her name. We had to be careful not to violate the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Violations of HIPAA could mean fines of tens of thousands of dollars. Worst case, a doctor could do time in federal prison.

I knew she was more than 80 years old and had come in with an ST-elevation myocardial infarction (STEMI). I learned that she lived in hospice and carried a diagnosis of dementia.

“Medicine svc?” I texted the fellow.

“Medicine won’t take STEMI” was the reply. “ER called STEMI.”

Calling the interventional team in the middle of the night for this? What about her dementia? What about the hospice? What were we doing? Experience told me to get dressed and head to the hospital. I arrived in the emergency room in less than 10 minutes and met the nurse who had accompanied the patient from hospice.

“She is not DNR,” she told me. “The family had discussed it in the past but couldn’t reach an agreement.”

“She is in hospice?”

“Yes.”

“But she is not DNR.”

“Yes.”

I quickly moved to the nurses’ station and grabbed a phone. I dialed the family contact listed in her electronic health record, a daughter who lived in a town nearby.

“This is Dr. Michel calling from the hospital.”

“Yes. How is Mom doing?”

“Well, she is having a big heart attack, and I wanted to talk to you about that. I wanted to make sure that we are doing the right thing as we work to take care of her.”

“Thank you. Well, of course. Please do whatever you think you need to do.”

“Oh, okay, well, that would mean taking her down to the lab and putting tubes into her arteries and trying to open the blockage causing her heart attack.”

“Oh okay.”

“But I wanted to make sure that she and you, . . . that the family would want that.”

“Oh of course! We want you to do whatever you need to do to save her if you can.”

“But she has dementia? And is in hospice?”

“Yes. I saw her today. She seemed fine. She didn’t mention feeling at all sick. Of course, she doesn’t talk much. But she seemed happy.”

“And she would want to be treated aggressively?”

“Is there a less aggressive treatment that would work?”

“Well, no.”

“Okay then.”

“Okay.”

The mechanical drives clanged as heavy doors opened, revealing the large trauma bay. Small, thin, pale, and gray, my patient lay motionless in a heap on a gurney, the center of attention. A heavy-set nurse towered over her, arms extended, applying 100 compressions a minute to her chest in guideline-perfect order. I thought I heard an occasional crunch. Ribs breaking? A respiratory technician stood near her head using a black bag to force air into her lungs.

I felt some relief. Perhaps this would end here and now.

“I have a rhythm,” an excited ER resident exclaimed. “Stop CPR.”

“Let’s get her to the lab!”

I had to move quickly to avoid being run over as patient and gurney, propelled by a stampede of physicians, nurses, and technicians, erupted from the room.

Time is myocardium. Door-to-balloon time is a quality metric. Our exceptionally fast door-to-balloon time makes us

From the Office of Clinical Ethics and Palliative Care, Baylor Scott & White Health (Fine), and the Division of Cardiology, Scott & White Memorial Hospital, Temple, Texas (Michel).

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a top 50 hospital. We are number one in patient satisfaction. I remember seeing all this and more on a billboard once. Metrics and reputation on the line.

The interventional team awaited us. Three gowned figures stood like statues as we flooded the catheterization laboratory and adjacent control room.

“STEMI!” Their pagers had gone off 30 minutes earlier, calling them in to perform interventional last rites, a Viaticum, in honor of this woman whose life would end tonight.

In the Catholic faith, the dying are anointed with holy oil, given the Eucharist and offered absolution for their sins in the hope of a safe passage into heaven. But holy oil and Eucharist are not on our formulary. And priests? I am sure we have none.

“Do you want a balloon pump?”

I worked hard not to say something sarcastic—something smug, cutting, and disrespectful. Did our Viaticum require a balloon pump? I thought not.

“I say no to the balloon pump. Let’s get the artery open and see how she does.”

We had no power to anoint or absolve. There were no prayers. There was no moment of silence. No family member spoke.

Metrics would be obtained. Quality measures weighed. Had we protected her medical records? Would her satisfaction be high or merely average? Would she recommend us to family and friends?

Betadine swabbed her groin. A sterile drape was laid down, reducing her to a small circle of pink flesh. Our bearded interventional fellow plunged a large needle into that flesh and maneuvered until a small geyser of blood erupted from the hub. A wire was passed, then a catheter.

“What about an Impella? Her pressure sucks.”

We opened up her IV, and warm salt water ran into her veins as quickly as gravity would allow.

“Start dopamine.”

On the monitor, I watched the catheter climb her aorta like a snake. The interventional fellow deftly maneuvered the catheter around the arch of the aorta and into the ostium of the right coronary artery. Dye flowed and a whirring mechanical sound indicated that pictures were being recorded. Thrombus had obstructed the artery in its mid portion. A small wire was quickly inserted and soon emerged from the catheter tip, worming its way down the artery and across the blockage.

“We’ve lost her pressure. Start CPR!”

Our catheter registered reassuring pulsations. But her heart had stopped. Her sinus node screamed. Her ECG showed electrical gyration amped up by the dopamine and epinephrine we had given her. But after a lifetime of constant motion, her heart relaxed and would beat no more.

Death was with us and for the first time we fell silent.

I found her family huddled in the waiting room. They seemed like nice people. I recounted the timeline of her death. They cried and hugged each other. Then they hugged me and thanked me and my team. For what? We had not saved her.

And only then I heard her name.

“Joanne.”

Rest in peace, Joanne.

VIATICUM REDUX

Although the first story is how the scene played out, here is how it could have happened.

Be kind and compassionate to one another, forgiving each other, as in Christ God forgave you. —Ephesians 4:32

We never spoke and were never formally introduced, though I did know her name—Joanne. Lying peacefully, her daughter by her side, she held my hand as she died.

The cardiovascular intensive care unit fellow had texted me 45 minutes earlier, making sure to leave out any personal identifiers, including her name. I knew she was more than 80 years old and had come in with a STEMI. I learned that she lived in hospice and carried a diagnosis of dementia. I arrived in the emergency room in less than 10 minutes and met the nurse who had accompanied the patient from hospice.

“She is DNR,” she told me. “The family has discussed it and are all in agreement.”

“Okay, good.”

I quickly moved to the nurses’ station and grabbed a phone. I dialed the family contact listed in her electronic health record.

“This is Dr. Michel calling from the hospital.”

“Yes? How is Mom doing?”

“Well, she is having a big heart attack, and I wanted to talk to you about that. I wanted to make sure that we are doing the right thing as we work to take care of her.”

“Thank you. Well, of course. Please do whatever you think you need to do.”

“Okay, well, I think we need to take good care of your mom by controlling her pain, giving her oxygen, and working to make certain that if this is the day that God calls her home, as I believe that it is, that she has safe passage. You might want to come to the hospital to hold her hand.”

“Thank you. I am on my way.”

“4 mg of morphine” I called out as I held my arms high, waving away the swarm of physicians gathered around our patient.

“Comfort measures only! No cath. Tell the team to go home.”

We moved her out and away from the noise and confusion of the ER. Flowers and birds played across a wallpaper forest that decorated her room. Soft music played and she was surrounded by pillows. She was calm, breathing softly but evenly, bundled in soft sheets and warm blankets.

The chaplain joined me and we took advantage of the calm and quiet to review her chart. I learned her name, Joanne. She had been married but her husband, Thomas, had passed away last year. She had three children: Susan, Mary, and Elizabeth. Susan, the daughter I had spoken with by phone, soon joined us. Together we sat on either side, holding her hands in ours.

As the minutes passed, her breathing became weaker and more shallow. Her face showed neither pain nor fear. Her eyes opened slightly from time to time. At times she murmured. After 30 minutes or so she slipped away. I swear that I saw her smile at the end.

“You will be with Papa soon,” Susan told her as she held her hand. “We love you.”

“Rest in peace, Joanne.”
Invited Commentary

Changing the conversation at the end of life: How the language we use impacts surrogates’ decision-making burden

Life is pleasant. Death is peaceful. It’s the transition that’s troublesome. —Isaac Asimov (1920–1992)

While death is an indisputable fact of life, we seem to have difficulty acknowledging this fact amid a rapidly evolving and cure-focused health care system. We hope each of us will experience a Lazarus-like raising from serious illness and return to a normal life. Likewise, physicians are raised in a culture of treatment, focused on cure at all cost, and consider death a failure to be avoided. Certainly, most of us want to be cured when it is possible, but how to care when cure is not possible and treatment becomes harmful is a neglected conversation.

Two similar but divergent scenes play out in “Viaticum,” by Dr. Fine and Dr. Michel (1). One tells the story of what often happens at the end of life; the other a story of what should happen at the end of life. While physicians are often aware of the nonbeneficence of certain treatments at the end of life, they may lack the training and skills needed to engage in difficult conversations. Several studies have shown people are aware of their own mortality and, when asked, can identify specific values they want honored at the end of life. They want to be at home, to be mentally aware, to be at peace with God, to be pain-free, and to avoid burdening their family. Interestingly, these preferences have remained stable in the published literature for about 20 years (2–4). Despite these expressed preferences, people also recognize they are unlikely to die at home and, when asked, cited an institution as the most likely place they expect to die (4). This discrepancy between what people hope for at the end of life and what usually happens is clearly illustrated in “Viaticum.”

In the first scene of “Viaticum,” Dr. Michel calls his patient’s family to confirm he is doing the “right thing” for their loved one. His hesitation to pursue aggressive medical intervention is challenged after he hears the daughter say, “Do whatever you need to do to save her,” even after he explains the invasive procedure and then confirms the patient has dementia and is on hospice care. This interaction is all too familiar to health care professionals: the provider knows the procedure may fix an immediate problem but won’t improve overall quality of life, yet the family wants the procedure, perhaps driven by the simple fact it was offered.

Contrast this scenario with scene 2, where Dr. Michel takes a step back before discussing what a procedure would entail and, instead, says, “Let me start by sharing my understanding of just how seriously ill your mother is and how near the end she is in her life’s journey.” This statement prepares the daughter for what will come next: breaking serious news and creating a plan of care that takes both her dementia and advanced cardiac disease into account. This second scenario includes more conversation about what care will be helpful in this situation and what treatment options would cause harm; it includes the words “may be dying,” and it places the physician in the position of making a recommendation rather than asking the family to make a choice.

The conversation illustrated in scene 2 in “Viaticum” represents the ideal for care at the end of life. In practice, this may not occur as frequently as it should, but it certainly is not due to a lack of evidence. Numerous studies in the past 20 years have focused on evaluating and improving care at the end of life. The lack of benefit of aggressive treatments in the final months of life has been well documented, and avoiding nonbeneficial interventions is supported by expert guidelines created decades ago. For example, the American Medical Association’s Council on Ethical and Judicial Affairs published guidelines in 1991 for the appropriate use of do-not-resuscitate orders, which remain a guiding statement more than 25 years later. The document describes nonbeneficial treatment as that which will not restore cardiorespiratory function or won’t achieve a patient’s goals (5). Read that last phrase again: won’t achieve a patient’s goals. Unfortunately, a patient’s goals and values are rarely elicited before treatment options are offered and, if they are, they are poorly documented. The lack of documentation also means this information is almost never available to guide care in an emergency.

The second key principle illustrated in “Viaticum” is the burden of decision-making that is placed on surrogates. In the first scene after Dr. Michel outlines what procedure is needed, he says, “I wanted to make sure that she and you, . . . the family would want that.” The family is now burdened with accepting or rejecting the proposed procedure based on their knowledge of medicine and their loved one who “seemed fine” earlier in the day.

There are two aspects of this situation worth exploring. The first is that physicians should use their expertise to make a recommendation. It is clear Dr. Michel is looking for any reason to avoid this procedure. If it was deemed nonbeneficial in his medical opinion, then the procedure should not be recommended (6). A 2012 study investigating patient preferences for medical decision-making reported that 97% of participants wanted their doctors to offer them choices and consider their opinions. But when it came time to decide, two-thirds of participants preferred that the doctor make the final decision (7). The second notable aspect is, without an expert recommendation,
the burden of decision-making falls entirely on the family. This burden is well known to cause harm: caregivers suffer negative emotions of stress, doubt, and guilt which can last for years, especially if an advance directive is not present (8). Caregivers can also be wrong about patient preferences (9) and often opt for more aggressive treatment (10)! While many caregivers may be involved in making medical decisions for their loved ones at the end of life, it should be noted that a living will is more beneficial than a medical power of attorney alone when it comes to making decisions about code status and limiting aggressive treatment interventions (11), and the presence of a living will reduces the emotional burden on caregivers (8).

Shared decision-making is a spectrum that ranges from patient choice to paternalism. “Viaticum” illustrates an attempt to honor patient autonomy for an acute problem in scene 1 and a clear medical recommendation that takes the whole person into account in scene 2. Hard paternalism would be decision-making without any input from patients or their loved ones and should be avoided, just as uninformed patient choice without any physician input should be avoided. Ideally, medical decisions should involve a collaboration between physician and patient: patients should share their understanding of their medical problems and what is most important to them given their situation (i.e., their goals and values), and physicians should offer treatment options aimed at accomplishing those goals (and avoid treatments that won’t accomplish the goal).

At first glance, this makes a lot of sense, but in practice it can be difficult to achieve without a framework to follow or additional training in communication skills. While palliative care as a medical specialty exists to support seriously ill patients and help with difficult conversations, the number of professionals practicing palliative care is small and growing slowly in comparison to the need. Truthfully, all healthcare professionals who will someday take care of patients with serious illness should achieve some measure of proficiency in serious illness conversation skills by the time they finish training.

Fortunately, changes within medical training and the health care system are supporting a greater focus on shared-decision making and communication skills. Structured programs like the Serious Illness Care Program (SICP) give health care providers a framework and the skills needed to engage in difficult conversations. SICP has grown out of a collaboration between a leading palliative care expert, Dr. Susan Block, and renowned surgeon Dr. Atul Gawande, as he wrote his bestselling book Being Mortal. The Serious Illness Guide, a set of eight questions used to guide conversations with seriously ill patients, aims to improve care by encouraging health care providers to have more, earlier, and better conversations. Baylor Scott and White is the first health care system in the US to partner with Ariadne Labs to fully implement the program across an organization of our size.

As a palliative care professional, I am frequently consulted when providers are struggling with how to care when cure is not possible. This is never an easy situation, but a few basic and universal principles can guide us through these conversations. First, we must understand both the biology and biography of our patient. Where is our patient in the trajectory of disease, but also who and where is our patient in the story of his or her life? Next, armed with that knowledge, we must utilize both the art and science of medicine to recommend interventions we believe are most appropriate—not for the disease, but for the patient who suffers with the disease. Finally, we must communicate our recommendation carefully, for language truly matters (12). Medicine well practiced is a team effort, and if we collectively continue to learn new skills (such as those embedded in the SICP), then we will truly provide our patients and their families with the most beneficial treatments and highest level of care that can be given.

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Fiftieth anniversary of the first heart transplant: The progress of American medical research, the ethical dilemmas, and Christiaan Barnard

Peter A. Alivizatos, MD

This year marks the 50th anniversary of the first heart transplant by South African heart surgeon Christiaan Barnard in Cape Town that caught the world completely unawares. Surprise was succeeded by admiration and idol-worshipping of the protagonist, who became famous overnight. Newspapers and television channels competed to interview him and reputable scientific associations to recruit him as the principal speaker at their conferences. The jet-set of the time embraced him and famous movie stars adored him. But was Barnard the one who was expected to do it, the “chosen” for this procedure?

Transplanting a heart had been the dream of surgeons from the beginning of the 20th century. In spite of Russian Vladimir Demikhov’s brilliant techniques in the experimental laboratory in the 1950s, the problem remained unsolved: the invention of a simple yet reliable and reproducible method of implantation so the heart would immediately take over the circulation. All this concerned the technical part, since the problem of rejecting the “foreign” organ still had to be addressed (1).

The first hurdle was cleared in the late 1950s at Stanford University by Professor Norman Shumway and his close associate Richard Lower (Figure 1), when they achieved the survival of dogs by combining an ingeniously simple surgical technique with local cooling to protect the transplanted heart. Lower came from Michigan; as a Midwesterner, he was a man of few words, with a strong accent and simple manners. After a brief period at Cornell University in New York, Dick, as he was known to his friends, moved to California and Stanford, where cardiac surgery under Norman Shumway was still in its infancy. Shumway came from the famous Minnesota School, which under Owen Wangensteen had made a name for pioneers in heart surgery, like John Lewis and C. W. Lillehei (2). Shumway, another Midwesterner, divided his time between surgery and a primitive experimental laboratory. Genius, however, does not require luxury; on the contrary, it performs its miracles with want and deprivation.

So in 1958 Lower was taken on as Shumway’s first trainee and together they began to experiment on dogs, looking for a way to operate with the heart stopped and dry, but also without compromising myocardial function, which would afterwards take over the circulation. Shumway created a bath in the pericardium in which a cold saline infusion continuously circulated as a preservative. They stopped the heart, therefore, clamping the aorta, and, after waiting an hour, released it to let the blood again circulate in the myocardium. While waiting, they would sit idly around the table until Shumway had the idea that perhaps they could cut into the heart at about the level of the ventricles and suture it together again before opening the

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aorta. They soon discovered that this procedure was extremely difficult, if not impossible, because there was no tissue left to stitch and furthermore it was so fragile that the animal died of hemorrhage. Then Lower had a brilliant idea: “Why don’t we use the heart of another dog so that there will be enough tissue for stitching?” (3). After the first failures, they started to have survivals. When the first dog had survived for a week, the press and television became involved, besieging the department chairman with questions. He was so annoyed that he demanded the dog be put down, causing the researchers dismay. Soon the chairman was dismissed for a different reason, yet Shumway wryly remarked: “Neither the dog nor the chairman lasted much longer, so perhaps some kind of poetic justice was achieved!” (1).

The following year they reported to the American College of Surgeons, before an empty auditorium, the stable survival from 1 to 3 weeks of eight dogs. It was obvious that their work was considered “utopian.” However, the publication that followed—concise and lucid like the one by Watson and Crick announcing in 1953 the discovery of the double helix of DNA, which won them a Nobel prize—is still today a landmark in the international bibliography (4).

During the next 7 years, the two researchers, Shumway at Stanford and Lower, now in Virginia, widened the field with innovative work and were considered by the experts to be the most likely to perform the first human heart transplant. However, in 1964 they were almost overshadowed, fleetingly as it turned out, by James Hardy of the University of Mississippi. He lost the race, though, when he implanted a chimpanzee’s heart into the chest of a dying man. The result was inevitable—hyperacute rejection—although Hardy and his associates attributed the failure to a size mismatch between donor and recipient resulting in low cardiac output (5). Hardy was expelled for quite a few years from the American College of Surgeons for unacceptable experimentation. When I was a fellow at Baylor University Medical Center in 1973, he came as a visiting professor and during a meeting with the housestaff expressed his bitterness over what, in his opinion, was an unjustly imposed penalty. However, there was no reaction 3 years later when Lower, in order to demonstrate the technical feasibility of a human transplant, grafted a human heart for which there was no suitable recipient into the chest of a chimpanzee, where it functioned for several hours. Well known for his cutting sense of humor, Lower named the procedure “a reverse Hardy”!

Unfortunately, the great opportunity for an ethical reward was lost to Lower in the fall of 1966, when there was the rare coincidence of a suitable donor and recipient. He did not proceed then for what proved later to be a secondary incompatibility of blood groups. Always conscientious and a perfectionist, he did not want to risk this historic operation with something that was a priori a negative factor on the scale of success, in spite of insistent urging to proceed by David Hume, chairman of the Department of Surgery at the Medical College of Virginia, who was legendary for his drive and aggressiveness (6).

There was also a third serious contender for the victor’s wreath for the first transplant: Adrian Kantrowitz, the charismatic, unbelievably industrious and persistent cardiac surgeon of Maimonides Hospital in New York, with 200 experiments under his belt. He had concentrated his efforts on a transplant in a baby on the assumption that its immature immune system was less likely to trigger rejection (7).

So these three, Shumway, Lower, and Kantrowitz, were the players in the arena, desperately trying to prepare a suitable candidate and to locate the necessary donor. Unfortunately, all three faced the same, seemingly insurmountable obstacle: the possible donor was considered dead only after all heart activity had ceased. The required wait until that happened usually meant that the graft was unsuitable for transplantation. Therefore, there was inactivity while the intensity of the rivalry reached its peak.

In 1966, the hitherto unknown Christiaan Barnard asked Dr. Hume if he could come to Virginia to observe his pioneering kidney transplants. He stayed for about 3 months and, encouraged by his fellow-countryman, the pump technician Carl Gosen, he took the opportunity to watch Lower in the animal laboratory. Impressed by the simplicity of the technique—great surgeons make any procedure look easy!—he came back a few weeks later to consolidate his knowledge. As he was leaving, he confided to Gosen that on his return to South Africa he would perform a human heart transplant. When Gosen questioned how he could do that without experimental work, he made the amazing statement: “Ja, I’ll do a couple of dogs!” He also added: “You here have too many prohibitions to negotiate before you can find a donor. We have no such obstacles in South Africa” (6).

His motive was his outsized ambition to make his mark and surpass his former colleagues at the University of Minnesota, among whom was Shumway. His excuse for doing an operation for which he was not prepared was the inability of his American colleagues to proceed because of the prohibitive legislation. With great perspicacity he had realized his advantage: in South Africa only the agreement of two doctors was required to declare death in a case of irreversible brain injury, even before the heart had stopped. It was the ace up his sleeve!

With this advantage, on December 3, 1967, Barnard transplanted the heart of 25-year-old Denise Darvall, victim of a road traffic accident, into the chest of 53-year-old Louis Washkansky (8) (Figure 2a). In spite of the legal protection and in order to forestall any possible graft deterioration while waiting for the heartbeat to stop, as the anesthesiologist was insisting, he speeded up harvesting with the intravenous administration of potassium (6). Thus, the transplant proceeded and history was made. Its success was not marred, even by Louis’s death 18 days later of pneumonia. Three days after Barnard, Kantrowitz performed the first transplant in America, but the baby lived for only a few hours. At the beginning of January 1968, Shumway carried out the first transplant in Stanford and this patient, also, lived for 18 days. In the interests of history, as Dr. Shumway stated, “No experimental orthotopic heart graft had survived more than a few hours in South Africa when Barnard’s initial clinical effort took the world by surprise” (9). As a matter of fact, by the time Christiaan Barnard had performed 48 transplants in the laboratory, that was 250 less than Norman Shumway and 210 less than Adrian Kantrowitz had performed (6).
Barnard’s boldness started a frenzy of heart transplants all over the world, even by surgeons who had criticized him at first for being “premature.” As Dr. Shumway put it in his inimitable, sarcastic way: “Suddenly heart transplants were being done in places where one would hesitate to have his atrial septal defect closed!” (9). In 1968, 104 such procedures were carried out, with only 10 survivors, and results for the next 3 years were similar (170 transplants with 24 survivors) (10). This made Life magazine in a 1971 issue withdraw its earlier enthusiastic report about transplants (Figure 2b). Even the demigod of American surgery, Denton Cooley, was forced to stop, saying, “The prescription for success in heart transplantation ‘cut well, tie well, get well’ is a naïveté. The problems come after surgery and they’re not surgical problems” (10). The epitaph of this period was pronounced succinctly by the pioneer of the 1948 mitral valvotomies, Charles Bailey, when he said that “cardiac transplantation is 10 years too early” (6). And so during the difficult decade of the 1970s, the torch of transplantation was kept alight by Stanford, inventing new techniques during the difficult decade of the 1970s, the torch of transplantation was kept alight by Stanford, inventing new techniques during the difficult decade of the 1970s, the torch of transplantation was kept alight by Stanford, inventing new techniques during the difficult decade of the 1970s, the torch of transplantation was kept alight by Stanford, inventing new techniques during the difficult decade of the 1970s, the torch of transplantation was kept alight by Stanford, inventing new techniques 

What was gained by Barnard’s audacity? Certainly not cyclosporine, as already mentioned. Some said that he speeded up the acceptance of brain death (15). But again, during that period, even without wanting to, it was Lower who was responsible. When he carried out his first transplant in May 1968, he was accused of taking the heart of a brain-dead donor, as it was still beating. He sat as a defendant along with 10 other physicians involved in the operation in the famous Tucker v. Lower case in Richmond in May 1972. The judge, A. Christian Compton, in his groundbreaking final jury instruction, allowed: “You shall determine the time of death . . . and in determining you may consider . . . the time of complete and irreversible loss of all function of the brain” (16). It opened the way for a change in legislation, which from that time has allowed us to do transplants.

Lower had been treated unfairly twice over. His labors were enjoyed by someone else while the system almost sent him to jail. I felt his bitterness one Saturday morning during grand rounds, in the spring of 1980, when I was the second-year resident in his program. Before all the stuff of the Medical College of Virginia, he gave the lecture on heart transplantation. His final comment has remained indelibly seared into my memory: “In 1966 I did not proceed with the heart transplant and God never forgave me for my hesitation. So glory and reputation went to Cape Town, South Africa, and not to Richmond, Virginia.”

Two conclusions: Firstly, we only repent of what we have not done. Secondly, the world respects thought, but worships audacity. Perhaps with some justification.
Allen and Shelly Dollar seemed like an ordinary couple. They had first met in high school, when Allen was a laboratory aide for Shelly’s 10th-grade biology class in a suburb of Washington, DC. They started dating and eventually married in 1980 and moved to Baltimore, where Shelly began nursing school at the University of Maryland and Allen enrolled in medical school at the same university. Their oldest daughter, Lauren, was born during Allen’s senior year. Shelly had to go on prolonged bedrest during the latter stages of pregnancy and never returned to nursing, focusing instead on becoming a full-time mother. They went on to have two more biological daughters. With occupations as a cardiologist and a nurse-art dealer, their financial future was secure. Yet their lives would change in 1993, when they were doing medical work in El Salvador with the nonprofit Children’s Cross Connection and encountered Gabriella (Gabby).

Gabby (Figure 1) was a 3-year-old orphan with severe cerebral palsy and bilateral congenital hip dislocations. They arranged for her to be transported to Atlanta to have her hips repaired, with the full intention of returning her to El Salvador. The Dollars grew so fond of her during her convalescence, however, that they decided to adopt her.

At the same time the Dollars were bringing Gabby home, they had initiated the adoption of a little boy, Jon (Figure 2a), from China, to go with their three biological daughters. (Shelly had been advised against further pregnancies.) Jon was also an orphan, from the Nanjing area, and had tetralogy of Fallot, which was becoming increasingly symptomatic. The adoption went through and Jon had successful surgical repair in Atlanta.

When Gabby and Jon were about 5 years old, Allen and Shelly decided that another boy in the family would be nice. They heard of two in an orphanage in Saltillo, Mexico, and decided to adopt both Hugo and Tony (Figure 2b) after a 2-year process and five trips to Mexico.

Allen has a close friend, Rick Hodes, MD (1), an internist who had trained at Johns Hopkins (Figure 3). For over 30 years, Dr. Hodes has cared for the poor in Ethiopia via the American Jewish Joint Distribution Committee and the Mother Teresa Home. He told Allen about a 15-year-old boy, Mesfin (Figure 4), who had postrheumatic mitral valve disease and pulmonary edema. Mesfin had left home to avoid being a burden on his coffee-farmer father, walking miles to the Mother Teresa Home. Allen arranged for him to come to Atlanta for mitral valve repair by Piedmont surgeon Jim Kauten. He returned home in good
condition, but later developed endocarditis and returned to Atlanta for a mechanical mitral valve procedure. Since follow-up care for this procedure, such as anticoagulant monitoring, was not available in his area, the Dollars took him in as a foster child.

While caring for Mesfin, friends at church told them about Todd, a 19-year-old boy with serious drug issues who needed a safe place to stay. He became another foster son and was able to quit the drug habit.

Tesh, one of Mesfin’s 13 siblings from Ethiopia, was living with Dr. Hodes and had expressed serious ambitions of becoming a filmmaker. The Dollars became his foster parents as well and enrolled him in the Savannah College of Art and Design. The 10 Dollar children continue to do well (Table 1, Figures 5 and 6).

Dr. Hodes had rented a home in Addis Ababa, where he looked after 10 children, aged 12 to 18, most of whom had serious medical issues that he was attending to. He was running out of funds to keep the house going, so Allen and Shelly founded a nonprofit organization to help care for the children (www.makingthegrade.info). The organization focuses on education and has evolved into the support of 60 children in seven homes (each with an adult home manager) in four cities throughout Ethiopia. The children and young adults, aged 5 to 25, are sponsored through grade school and college, and one has gone to graduate school. The Dollars provide all housing, food, tuition, books, and transportation, in addition to helping with job placement after completion of school. Shelly is in daily contact with the children and their house managers via e-mail and Skype. The estimated cost per year of supporting an Ethiopian child is $1200 to $3000.

<table>
<thead>
<tr>
<th>Child</th>
<th>Status</th>
<th>Current age</th>
<th>Present activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauren</td>
<td>Biological</td>
<td>32</td>
<td>Staff attorney, juvenile defense, Georgetown Law</td>
</tr>
<tr>
<td>Stephanie</td>
<td>Biological</td>
<td>30</td>
<td>Special education teacher and newlywed</td>
</tr>
<tr>
<td>Diane</td>
<td>Biological</td>
<td>27</td>
<td>Commercial helicopter pilot</td>
</tr>
<tr>
<td>Gabby</td>
<td>Adopted</td>
<td>27</td>
<td>Recently moved into her own home with assistants (due to her cerebral palsy)</td>
</tr>
<tr>
<td>Jon</td>
<td>Adopted</td>
<td>25</td>
<td>Administrator at George Washington Medical School</td>
</tr>
<tr>
<td>Hugo</td>
<td>Adopted</td>
<td>27</td>
<td>Cook in a fast food restaurant in San Antonio</td>
</tr>
<tr>
<td>Tony</td>
<td>Adopted</td>
<td>25</td>
<td>Truck driver; single, with a 3-year-old son, Allen</td>
</tr>
<tr>
<td>Mesfin</td>
<td>Foster</td>
<td>32</td>
<td>Perfusionist at the Texas Heart Institute</td>
</tr>
<tr>
<td>Todd</td>
<td>Foster</td>
<td>40</td>
<td>Vice president of a hospital in Colorado</td>
</tr>
<tr>
<td>Tesh</td>
<td>Foster</td>
<td>22</td>
<td>Senior film major at Savannah College of Art and Design</td>
</tr>
</tbody>
</table>

Table 1. The Dollar children

**Figure 3.** Rick Hodes, MD (right) with Allen Dollar.

**Figure 4.** Mesfin: (a) age 15 and (a) now, with Dr. Jim Kauten.

**Figure 5.** The Dollar family.

**Figure 6.** (a) Diane with her helicopter. (b) Todd Coe with baseball star son, Toby.
Allen continues as chief of cardiology at Grady Memorial Hospital (Figure 7). He recently gave up his hobby of motorcycle riding due to concerns that too many automobile drivers were inattentive, using their various devices while driving. Shelly continues with her interest in art but is busy running the non-profit organization.

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**Book Review**

*House Call: A Doctor’s Time in Medicine and Government* by J. Roy Rowland, MD, and Selby McCash


Reviewed by Thomas Gore, MD

Most of us physicians do good work on a daily basis. With a busy schedule every day that we are working—and we work a lot—most of us find it hard to get involved in community activities. We rarely get involved heavily in political campaigns. Most of us have not gone to the state house or to Congress to lobby our representatives on behalf of medicine. Yet we know of some physicians who are so inclined.

J. Roy Rowland, MD, is one such person. After many years of private practice in Dublin, Georgia, he got involved deeply in organized medicine. He got his feet wet with an organization called CONTROL, advocating a limit to government interference with medical care. He was a stalwart in the Medical Association of Georgia. He served in the Georgia Legislature for 6 years before retiring from practice and taking the incredible risk of running for Congress against an incumbent. He won and was reelected five times. He had a distinguished career for 12 years in the US House of Representatives from 1983 to 1995. In his autobiography, he outlines this exciting story of his life’s work in medicine and government service. This encompassed the time of Ronald Reagan’s presidency, the HIV/AIDS epidemic, the banning of Quaaludes, the Iran/Contra affair, and many other smaller issues. As one of the few physicians in Congress at the time, he became a respected leader when health care reform was front and center with the Clinton presidency.

This book is a captivating story of the times, the struggles, and the ultimate stalemate on health care reform. Just how close he came to forging a more moderate alternative to the Clinton plan becomes apparent to the reader. Spiced with humor and wise perspective, this book is a great guide for physicians. How to become more involved (the good, the bad, and the ugly) becomes clear through his life story. It is amazing how he kept his head on straight and maintained humility and a gentle persistence to act for the common good. I could not put the book down. I encourage physicians to read this newly published 300-pager. It tells a story for all time to remember about a great man who makes us proud to say we are his fellow physicians. We can learn much from his example.

The reviewer, Thomas B. Gore, MD, is a cardiologist in Lagrange, Georgia.
THE RADIUM GIRLS

The Radium Girls by Kate Moore is a shocking, heartbreaking, and tragic story involving a number of mainly teenage immigrant girls in Newark and Orange, New Jersey, and in Ottawa, Illinois, who painted watch dials containing radium (1). It describes the consequences of that radium poisoning. Kate Moore is a Sunday Times (London, UK) best-selling author, book editor, and ghostwriter. In 2015, she directed a production of These Shining Lights, a play about the radium girls, and found the dial painters’ stories so powerful that she was inspired to write the above-titled book. Her research took her to New York, Washington, DC, Newark and Orange, New Jersey, and Chicago and Ottawa, Illinois. She walked in the women’s footsteps, met their families, and visited their homes and graves and the sites of the dial-painting “studios.” The result is a magnificent but sad book. Although two previous books (2, 3) had been written on the radium girls’ stories, they focused entirely on the legal and scientific aspects. Kate Moore’s purpose was to put the radium girls center stage and tell the story from their perspective.

Marie and Pierre Curie, in 1898, discovered radium. It was so difficult to extract from its source that only a few grams were available anywhere in the world. In 1913, Sabin von Sochocky and George Willis, both physicians, founded in Newark, New Jersey, the Radium Luminous Materials Corporation (RLMC). Sochocky had invented the “paint” they used to paint watch dial numerals and hands with the luminous substance that made them visible in the dark. Sochocky had studied under the Curies and understood that radium carried great dangers. The time he studied with the Curies, Pierre was heard to remark that “he would not care to trust himself in a room with a kilo of pure radium, as it would burn all the skin off his body, destroy his eyesight and probably kill him.” By that time the Curies were intimately familiar with radium’s hazards, having suffered many burns themselves. Von Sochocky himself had experienced the wrath of radium that had infiltrated his left index finger, and he hacked it off.

Information on the side effects of radium, however, was unavailable to the public. Most people believed the effects of radium were all positive. That is what was reported in magazines and newspapers around the country. The watch dial painters at the RLMC plant were all women, mainly teenagers, who were recent immigrants to the USA. Most had minimal education. Some started working at the plant immediately after finishing grammar school. The women for the most part were very pleased to have the jobs. The girls sat in rows dressed in their ordinary clothes and painted dials at top speed because they were paid by the number of dials they painted. Each girl had a flat wooden tray of dials beside her. (At the time radium was the most valuable substance on Earth, selling for $120,000 for a single gram—$2.2 million at today’s value.) Each painter mixed her own paint, dabbling a little radium powder into a small white crucible, and added a dash of water and a gum arabic adhesive, a combination that created a greenish-white luminous paint, called “undark.” The fine yellow powder contained only a minuscule amount of radium mixed with zinc sulfide, with which the radium reacted to give a brilliant glow. The powder got everywhere. There was radium dust all over the studio. Little puffs of it hovered in the air before settling on the shoulders or hair of the dial painters. It made the girls themselves glow.

At the time, radium had been considered a magnificent cure-all, treating not just cancer but hay fever, gout, constipation, anything you could think of. Pharmacists sold radioactive dressings and pills. There were also radium clinics and spas for those who could afford them. It was believed that radium could restore vitality to the elderly. Wealthy customers drank it as a tonic. Radium water was drunk by the rich and famous, not by the working-class girls from Newark. It was a bit of a craze in American life. The element was dubbed “liquid sunshine,” and it lit up not just the hospitals and drawing rooms of America but its theaters, musical halls, grocery stores, and bookshelves. A song entitled “Radium Dance” became a huge hit after being in the Broadway musical Piff! Paff! Pouf! On sale were radium jock straps and lingerie, radium butter, radium milk, radium toothpaste (guaranteeing a brighter smile with...
although the company specialized in watch faces, it also had a lucrative government contract to supply luminous airplane instruments. The company also used its paint to make gun sights and ship compasses, so they could shine brightly in the dark.

The girls used slim camel hair brushes with narrow wooden handles. Each brush had approximately 30 hairs. Though the brushes were fine, the bristles had a tendency to spread, hampering the girls’ work. The smallest pocket watch they painted measured only 3.5 cm across its face, meaning the tiniest element for painting was a single millimeter in width. The girls could not go over the edges of these delicate parameters or they faced trouble. They had to make the brushes even finer, and there was only one way to do that: the girls put the brushes in their mouths. This technique, called “lip-pointing,” had come from China-painting factories. Unbeknownst to the girls, it wasn’t the way the dial painting was done in Europe where dial paint had been used for over a decade. Different countries had different techniques. But in none was lip-pointing used, probably because brushes weren’t used either: in Switzerland, there were solid glass rods; in France, small sticks with cotton wadding on the ends; and elsewhere in Europe, a sharpened wooden stylus or metal needles. Since radium was considered the wonder drug, the girls thought the lip-painting would benefit them. They got so used to the brushes in their mouth that they didn’t think about it.

The dial painters were paid well. Their pay was based on the number of dials they painted at an average rate of 1.5¢ a watch. The fastest workers could receive an astonishing paycheck. Some earned >3 times the salary of the average factory-floor worker. Some earned more than their fathers. They were ranked in the top 5% of female wage earners and on average took home $20 ($370) a week. Girls lucky enough to be employed felt blessed—they were one of the “shining girls.”

When the US entered World War I in 1917, the demand for luminous dial watches skyrocketed. The company built a plant down the road from Newark in Orange, New Jersey, closing the Newark plant. The company decided to do its own radium extraction, thus needing labs and processing plants. The RLMC expanded massively. The new site comprised several buildings, all located in the middle of a residential neighborhood. The new plant started operating 7 days a week, 24 hours a day. Perhaps 70 women had worked in the Newark studio; during the war that number tripled. Dial-painting girls rarely saw the men who worked in the laboratories or refining rooms except at the company picnics, which were fairly frequent. Just a few miles from the Orange plant site was Thomas Edison, who interestingly remarked, “There may be a condition into which radium has not entered that would produce dire results; everybody handling it should have a care.” Yet in the second-floor studio, the girls working there had not a care in the world. Here there were no lead aprons, no ivory-tipped forceps, no medical experts. The amount of radium in the paint was considered so small that such measures were not deemed necessary. In contrast, the lab workers in the Orange plant (all men) were provided protective equipment: lead-lined aprons and ivory forceps (for handling tubes of radium). In January 1921, von Sochocky, the company founder, would write that “one could handle radium only by taking the greatest precautions.”

At the height of operations in World War I, as many as 375 girls painted dials. In an attempt to save as much radium powder as possible, the girls were required before leaving for home to enter the darkroom to be brushed off; the “sparkling particles” were then swept from the floor into the dustpan to be used the next day. But no amount of brushing could get rid of all the dust. The girls were covered with it: their “hands, arms, necks, dresses, underclothes, even their corsets were luminous.” The clothing would shine in the dark as the girls went home glowing like ghosts.

The frequency of the lip-painting varied among the girls. Some would lip-paint on every numeral, sometimes even 2 or 3 times per number. Others did it only once for 2 or 3 numerals before the brush would dry. The girls weren’t entirely clear what was in the paint, although they did ask their managers. George Willis, cofounder, lectured the girls on radium and convinced them it was not dangerous; von Sochocky also told the girls that there was nothing hazardous in the paint. The radium was used in such a minuscule amount that it could not cause them harm.

In 1918, an estimated 95% of all the radium produced in the USA was given over to the manufacture of radium paint for use on military dials. At the end of that year, one in six American soldiers owned a luminous watch, and it was one of the Orange girls who painted it. The company executives rarely went into the studio where the girls painted the dials. On a rare visit, von Sochocky watched the girls dipping and brushing their brushes, he declared, “Do not do that!” He repeated to another girl: “Do not do that. You will get sick.” The girls soon went back to lip, dip, paint.

World War I ended on October 11, 1918. A total of 116,000 American soldiers had lost their lives, and the total death toll for all sides was about 17 million. Despite the ending of the war, the demand for luminous watches did not slow. In 1919, the company produced 2.2 million luminous watches. In 1920, the local residents around the Orange plant started to complain that factory fumes discolored their laundry and affected their health. One official took the unusual step of appealing to a resident: he gave a neighbor $5 ($68 today) compensation for her damaged washing. When all the other neighbors began requesting money, the company refused. A local newspaper article in 1920 stated that the company had offloaded some of its industrial waste by selling it to schools and playgrounds to use in their sandboxes; kids’ shoes turned white because of it. One child complained to his mother of a burning sensation in his hands. Yet, von Sochocky pronounced the sand “most hygienic” for children to play in.

In 1921, Sabin von Sochocky and George Willis were ousted in a corporate takeover. The new company was named United States Radium Corporation (USRC).
About 1921 the original dial painters from 1916 or so began having symptoms: toothaches, mouth sores, pain in the gums and jaws, aches and pains in their hips and feet. Teeth began falling out. One girl lost all of her teeth, and her jaw bone became so decayed that the dentist simply pulled it out of her mouth. The mouth sores made eating painful. One girl died when a mouth sore burrowed into the jugular vein, causing fatal hemorrhage. The dentists were baffled by these symptoms. Phosphorous poisoning was believed to be the problem, but phosphorous levels were not elevated. One dentist believed it was “an occupational condition” but wasn’t sure what occupation caused it.

One dentist, after examining one of the dial-painting girls whose teeth were falling out, notified the Industrial Hygiene Division of New Jersey to investigate. Within days an inspector toured the Orange plant, observed the dial-painting studio and especially the lip-pointing, and suggested that it was a “dangerous practice.” In January 1923, the deputy commissioner of the New Jersey Department of Labor also inspected the plant and commented: “It is my belief that the serious condition of the jaw [of one of the dial painters] has been caused by the influence of radium.” This was a radical idea at the time, although the USRC had files of reprints of radium studies suggesting the dangers of radium. The articles went as far back as 1906. Some months after his departure from the company, Dr. Willis became ill and in September 1922 he died. His right thumb had been amputated; tests revealed it was riddled with cancer. Willis published the findings of his illness in the February 1923 issue of the Journal of the American Medical Association, writing: “The reputation for harmlessness enjoyed by radium may, after all, depend on the fact that, so far, not very many persons have been exposed to large amounts of radium by daily handling over long periods. . . . There is good reason to fear that neglect of precautions may result in serious injury to the radium workers themselves.”

One by one, the radium dial painters, especially the original ones in Newark beginning in 1916 and 1917, developed multiple signs and symptoms. Because the girls kept in touch with one another, they learned that the illnesses among them had various commonalities. Eventually the company was sued. Although the girls won the verdict, they won very little money. The radium girls, however, did not die in vain. Although the women could not save themselves from the poison that riddled their bones, in countless ways their sacrifice saved many thousands of others.

In September 1922, 800 miles from Orange, New Jersey, a radium dial-painting plant was started in Ottawa, Illinois, a town of 10,816 people located 85 miles southwest of Chicago. They quickly hired local girls for the dial painting. When they stepped out at night, their dresses and hats and sometimes even their hands and face glowed from the phosphorescence of the luminous paint. The dial painting was an elite job for the poor working girls in the area.

World War II started in Europe in 1939, again producing an enormous demand for luminous dials to light the dashboards of military machines and the wristwatches of soldiers. Yet, thanks to the trials of the original watch dial painters and their colleagues due to their bravery in speaking out about what had happened to them, dial painting was now the most feared occupation among young women. No longer could the government sit idly by the radium girls’ demise. Safety standards were introduced that protected a whole new generation of dial painters based entirely on knowledge gained from the bodies of those women who had come before.

When the US entered the war in December 1941, the US radium dial-painting industry exploded, with USRC alone increasing its personnel by 1006%. Radium dials were even bigger business than the first time around: >190 g of radium was used by the US for luminous dials during World War II compared with <30 g used worldwide in World War I. In addition, chemist Glenn Seaborg, leader of the atomic bomb-making enterprise (the Manhattan Project), issued safety guidelines to the workers using radioactive plutonium based directly on the radium safety standards produced by the radium dial painters. An official of the US Atomic Energy Commission wrote: “If it hadn’t been for those dial painters, the [Manhattan] project management could have reasonably rejected the extreme precautions that were urged on it and thousands of workers might well have been, and might still be, in great danger.” The women had been, officials said, “invaluable.”

Even after World War II was over, the dial painters’ legacy continued to save lives as the world entered the age of atomic energy. Large-scale production of radioactive materials seemed inevitable. Five years after World War II ended, the nuclear arms race began; over the next decade hundreds of above-ground atomic tests were conducted across the globe. Just as radium had done to the dial painters, these isotopes, especially a particularly dangerous, newly created one called strontium-90, began to deposit in human bones. The Atomic Energy Commission dismissed the concerns. “The risks, it said, were very small when compared to the terrible future we might face if we fell behind in the nuclear defense effort.” The public, however, was troubled. After all, the radium dial painters’ agony had alerted the world to internal radiation. It was known that strontium-90 was chemically similar to radium. Medical studies began immediately, including in New Jersey and Illinois; later, the research would be amalgamated into the Center for Human Radiobiology, which was located in a multimillion dollar clinic called the Argonne National Laboratory, located 75 miles from Ottawa, Illinois. Special lead-lined rooms were constructed, buried under 3 feet of concrete and 10 feet of earth, in which the quantity of radium in the dial painters’ bodies was measured. The research was designed to help future generations. Some dial painters were still living. Radium was known to settle in the girls’ bones and known to cause late-onset sarcomas, but when such deadly tumors might begin to grow was unclear. Consequently, the living dial painters were sought in earnest. Employment records were procured and snapshots of those long-ago USRC picnics were unearthed. The girls were termed “a reservoir of scientific information.” Special investigators were hired to track them down. Those they found were usually willing to cooperate. A sister of one of the dial painters, who had never worked at the USRC plant, was found to be contaminated by radium. She had shared a bed with her sister.

In 1963, at least partly in response to the research on the dial painters, President John F. Kennedy signed the International Limited Test Ban Treaty that prohibited atomic tests above
ground, under water, and in outer space. Strontium-90 had been determined to be too dangerous for humanity. Today, 56 countries operate 240 nuclear reactors, and similar radioactive material powers nuclear ships and submarines. Yet, thanks to the radium girls whose experiences led directly to the regulation of radioactive industries, atomic power is able to be operated, on the whole, in safety.

Decade after decade, the dial-painting girls came to the Center for Human Radiobiology to be tested. They agreed to have bone marrow biopsies, blood tests, x-rays, and physical exams. They filled out questionnaires about their mental and physical health, took breathe tests, and had their body radium measured in the iron rooms beneath the earth. Autopsies were performed in some. Thousands of women helped with the study. Their contributions to medical science are incalculable.

The radium companies did not fare well. In 1979, the US Environmental Protection Agency (EPA) found that the former USRC site in Orange had levels of radioactivity 20 times higher than was safe. There was widespread contamination, both at the dial-painting site and at landfills where the company had dumped its radioactive waste. Almost 750 homes had been built on top of that waste. They too needed decontamination. More than 200 acres of land were affected in Orange, some to a depth of more than 15 feet. The EPA ordered the corporate successor of USRC to perform the cleanup work, but it declined. The courts were not forgiving. In 1991, the New Jersey Supreme Court found USRC “forever” liable for the contamination and declared the firm had had “constructive” knowledge about the dangers at the time it operated there. Residents sued the firm. Cases were eventually settled out of court. As for Radium Dial, despite the wartime boom, it went bust in 1943. The building it left behind in the center of Ottawa was found to be heavily contaminated. The building itself was destroyed in 1968.

The dial painters who had survived early did not escape unscathed. Some women were stricken early and then endured a half-life for decades. One girl was bedridden for 50 years. Many suffered significant bone changes and fractures; many lost their teeth. Many developed bone cancer, leukemia, and anemia. Some were given blood transfusions for years. Some developed severe osteoporosis with collapsed vertebrae requiring multiple operations. Many had amputations.

It was not until 1978 that the luminous processing plant in Ottawa, Illinois, was shut down. Inspectors found radiation levels there 1666 times higher than was safe. The abandoned building became something of a boogeyman for Ottawa residents, who became afraid to walk or even drive past it. The company, which was not apologetic, wiggled out of paying cleanup costs. It was not until 1978 that the luminous processing plant in Ottawa, Illinois, was shut down. Inspectors found radiation levels there 1666 times higher than was safe. The abandoned building became something of a boogeyman for Ottawa residents, who became afraid to walk or even drive past it. The company, which was not apologetic, wiggled out of paying cleanup costs. The companies obviously put profits before people.

THE MAYO CLINIC 2020 INITIATIVE

The Mayo Clinic is recognized worldwide as maybe the best patient-care institution in the world. Despite its 153-year success, Dr. John Noseworthy, Mayo’s chief executive officer, decided in 2009 that the institution needed to change because of declining revenue from government health programs, private insurers, and employers (4). When the head of cardiac surgery at Mayo asked him for two more operating rooms to meet the future demand for open-heart surgery, one of the clinic’s major revenue sources, Dr. Noseworthy not only said no, but insisted that they redesign all facets of heart surgery care and cut costs by 20%. That initial request sparked a year-long revamp—part of a wrenching Mayo Clinic overhaul involving nearly every aspect of the institution’s renowned system. “Overhaul,” the Mayo Clinic’s 2020 initiative, has involved >400 projects aimed at squeezing costs and improving quality and services. Dr. Noseworthy indicated that dozens of major reengineering projects have helped cut an accumulated $900 million in costs over the past 5 years.

The clinic also sought new areas for growth. Mayo took the lead—including committing $3 billion of its own capital—on a $5.6 billion urban development project now underway to transform its headquarters city of Rochester into a destination medical center.

The Mayo Clinic, with major facilities in Florida, Arizona, and a community-based health system of 19 hospitals and 44 clinics within 125 miles of Rochester, has 64,000 employees. It reported $11 billion in revenue in 2016, up 6% from 2015. The Mayo Clinic’s reputation for “patient-centered care” was embedded in its approach long before the term became a marketing buzzword. For Mayo, the concept includes bringing a team of specialists together to focus on the needs of patients with complex problems, typically providing a schedule of appointments within hours of patients’ arrival at the clinic. Patients do not have to make each appointment themselves or travel to specialists in different organizations. Mayo patients are welcomed by the volunteers who escort them to their appointments. A common medical record makes it gel. Instead of each physician keeping a private record for each patient, one record follows the patient.

Today at Mayo, nearly 1 in 5 operations involve multiple teams. The patient is nobody’s particular case; it’s Mayo’s case, said Dr. Noseworthy. That is hard to do at other places where people work in isolation. Mayo physicians are salaried, so there is no competition over fees or any incentives to order tests or procedures that a patient does not need in contrast to the much more common fee-for-service model in most medical centers.

Dr. Noseworthy, a Canadian-educated neurologist, started the inquiry into the institution’s readiness to face the future a year before he became CEO in 2009. Retooling projects included restructuring care for children with complex feeding, breathing, and swallowing disorders. The effort reduced average time to diagnosis to 4 days from 210 days and cut the use of anesthesia and imaging tests by nearly 50%.

Expanding the role of nurses in the care of epilepsy patients shaved an average of 17 minutes off the time doctors spent on a visit, increasing slots for new patients. Adding more clinicians to the emergency room during the afternoon reduced patient waiting times during high-demand evening hours. The initiative dubbed “eliminate white space,” intended to optimize physician calendars, allowed the scheduling of more time for new complicated patients while booking shorter (30-minute) times for follow-ups of “established” patients.

The heart surgery project began in 2009, the year that the surgeons asked for two more operating rooms. The surgeons,
of course, were initially disappointed in Noseworthy’s response, but ultimately everyone stepped up and did what was asked. Cardiac surgery was ripe for overhaul. An initial analysis showed as much as a twofold variation in surgeons’ average costs per case—from $55,000 to $110,000 in one procedure. The operating room teams competed to reduce the time from “wheels out,” when one operation was over, to when the room was set up for the next operation. Results for each surgeon’s room were posted, and staff met to discuss what worked and what did not. The exercise trimmed average turnover times about 50% to between 20 and 30 minutes.

The overhaul efforts revealed two main cost drivers: a patient’s length of stay and the surgeon’s use of mechanical heart valves. So many valve brands were on the shelf it was like going to a shoe store, the chief of heart surgery indicated. The Mayo Clinic, one of the US’s largest users of such valves, decided to use its purchasing power to negotiate lower prices and limit surgeons to models from two vendors. It took nearly 2 years for surgeons to agree on which ones. Everyone eventually came around. Physicians also began discharging out-of-town patients to a hotel a day or two before their flight home, and then seeing them for an outpatient visit. Previously many patients remained in the hospital until just before their flight. Surgeons accustomed to operating every other day began operating every day. New physician-developed protocols empowered nurses to streamline postoperative care, making it more efficient. Some shifts started later in the day to adjust to staggered operating room start times, to reduce overtime, and to avoid peaks and valleys in intensive care unit staffing. The results of these changes for cardiac surgery at the clinic reduced costs by millions of dollars and significantly narrowed the variation among surgeons in costs for heart procedures.

The heart surgery initiative and scores of projects like it are part of the organization’s continuing evolution. Outside analysts have provided the clinic with projections that over the next 5 years, its reimbursement could decline from 5% to 20%.

Other top hospitals are also facing cost pressures, including the Cleveland Clinic, which despite reducing $800 million of costs over the last 4 years, reported a 71% drop in operating income in 2016 to $139 million, citing reimbursement pressure, higher drug costs, and pension plan adjustments. Partners HealthCare, a Boston-based system founded by Harvard-affiliated Brigham and Women’s Hospital and Massachusetts General, said it planned to cut $600 million in costs over the next 3 years to better compete “in a challenging new regulatory, legislative, and consumer-driven environment.”

NEUROSURGERY AND PATIENT H. M.

On September 1, 1953, William Scoville, a neurosurgeon at the Hartford Hospital in Connecticut, operated on a 27-year-old man named Henry Molaison, who suffered from severe epilepsy (5). Scoville removed the left and right sides of the hippocampus from Molaison’s brain. The hippocampus, located near the center of the brain, forms a part of the limbic system that directs many bodily functions, and Scoville thought that epileptic seizures could be controlled by excising much of that portion of the brain. The result, however, was a total loss of both short-term and long-term memory. H. M., as he came to be known in medical writings (his real name was not disclosed until his death in 2008), could no longer remember anything he did. He could neither remember what he had eaten for the day (breakfast, lunch, or supper), nor could he find his way around the hospital. He failed to recognize hospital staff and physicians whom he had met only minutes earlier, remembering only Scoville, whom he had known since childhood. Every time he met a certain scientist from the Massachusetts Institute of Technology who was studying him regularly, she had to reintroduce herself again. He could not even recognize himself in recent photographs, thinking that the image in the pictures was some “old guy.” Yet he was able to carry on a conversation for as long as his attention was not diverted. H. M.’s condition suggested that the hippocampus was essential for the conversion of short-term memories to long-term memories.

Luke Dittrich, Scoville’s grandson, wrote Patient H. M.: A Story of Memory, Madness and Family Secrets. Much of the book describes with justified quiet indignation the failures of the neurological procedures that were widely practiced by Scoville and other neurosurgeons in the past century. Much of what we know about memory today comes from studying H. M. and the irreparable harm done to him.

BABE RUTH AND NASOPHARYNGEAL CANCER

Gabe Mirkin, who writes frequently on health, fitness, and nutrition, published a piece entitled “What killed Babe Ruth at age 53?” (6). Babe Ruth surely was our greatest baseball player. When he finished his baseball career, he held the record for most home runs (714), had a lifetime batting average of 0.342, batted in 2213 runs, had a slugging percentage of 690, got on base 47.4% of the time he batted, scored 2174 runs, hit for 5793 total bases, and was walked 2062 times. At age 19 (1914), Ruth signed to play professional baseball for the minor-league Baltimore Orioles and was soon pitching for the major-league Boston Red Sox. He quickly became the best pitcher in baseball, winning 24 games in 1917. In 1919, he was sold to the New York Yankees and was converted to a full-time right fielder because he was also the best hitter in baseball. His teams won 10 pennants and 7 World Series, 3 with Boston and 4 with New York. He retired at age 40 in 1935 and was one of the first five players to be elected to the National Baseball Hall of Fame.

In September 1946, Babe Ruth’s voice became raspy. He had headaches and constant severe pain in his left eye. The physicians told him that he had “sinusitis” caused by infected teeth, so three teeth were pulled. He then felt worse. His face swelled, his left eye swelled shut, and he was unable to swallow food. Radiographs showed a mass in the back of his neck, but all biopsies were negative for cancer. As the lymph nodes in his neck enlarged, he couldn’t eat, so he had to be fed through his veins. In November 1946, an operation on his neck allowed the diagnosis of cancer.

His hoarseness and many years of smoking cigars and drinking lots of alcohol led his physicians, and the rest of the world, to think that Babe Ruth had cancer of his larynx. He actually had nasopharyngeal carcinoma that starts in the back of the nose.
and mouth. His hoarseness and inability to swallow was caused by the cancer’s spread from his nose and throat to his neck to press on the nerves that control the muscles for swallowing.

More than 1000 cases of nasopharyngeal cancer are now diagnosed each year in the US. The most common known causes of nasopharyngeal cancer are the Epstein-Barr virus and the sexually transmitted human papillomavirus (HPV). HPV is spread commonly by sexual contact to cause cancers of the cervix, vagina, nose, throat, mouth, tonsils, and nasopharynx. Babe Ruth was a notorious womanizer. Every new sexual exposure is also a potential exposure to the >150 different HPV viruses.

In June 1946, Babe Ruth received radiation and 6 weeks of daily injections of teroteprin. Thus, he became one of the first humans to be treated with chemotherapy. Although Ruth did not know he had cancer, he agreed to take the experimental drug that helped him almost immediately. His neck lymph nodes shrank, his pain lessened, and he regained much of the recently lost 80 pounds. Unfortunately, the benefits of teroteprin were temporary, but nevertheless this was the start of chemotherapy. Methotrexate, a chemical similar to teroteprin, is of course still used today. Today most of the HPV-type cancers can be prevented by the HPV vaccination, but the latter must be given before any exposures have occurred.

WEST TEXAS OILFIELDS AND METHAMPHETAMINES (CRYSTAL METH)

Oilfield workers are well paid for their long hours, but one of the consequences of that often lonely existence is heavy drug use (7). Cocaine, marijuana, and opioids are very profitable to drug dealers in the remote locations where oil and gas drilling takes place. The favorite choice in West Texas is methamphetamine, a powerful stimulant. There is a powerful correlation between the rise of drilling activity and the number of crystal meth seizures in the area, a fivefold increase from 2009 to 2014 in the Permian Basin. Three times as many workers tested positive for methamphetamines in the first half of 2017 than in the first half of 2009. The increased drug abuse in West Texas has exacerbated the struggle of the oil industry to find workers as it rebuilds its labor forces after widespread layoffs during the recent downturn. It is the Mexican drug cartels that dominate the commerce of “meth” in West Texas. The meth is transported in liquid form across the US-Mexico border, stored in fake gasoline tanks, ice tea bottles, or windshield washer fluid reservoirs.

THE NEW HUMAN FOSSILS

The closest living relative to Homo sapiens are chimpanzees and bonobos, with whom we share an ancestor that lived over 6 million years ago. Until now, the oldest fossil that clearly belonged to Homo sapiens was discovered in Ethiopia in 2003; studies of the skull estimated it to be about 160,000 years old (8). Skulls discovered at another site were estimated to be around 195,000 years old. Discoveries such as these suggest that our species evolved in a small region of Africa, perhaps Ethiopia or in East Africa. Homo sapiens first spread out over the African continent. Much later, roughly 70,000 years ago, a small group of Africans made their way to other continents. Recently, at a site in Morocco, paleoanthropologist Jean-Jacques Hublin found fossils estimated to be 300,000 years old, thus providing evidence that Homo sapiens began much earlier than previously believed.

CREATIVITY BY AGE

Pagan Kennedy is the author of Inventology: How We Dream Up Things That Change the World (9). A 2016 Information Technology and Innovation Foundation Study found that inventors peak in their late 40s and tend to be highly productive in the last half of their careers. The study found that the average inventor sends in his or her application to the patent office at age 47 and that the highest-value patents often come from inventors >55 years of age. The study also found that among those granted international patents in information technology, materials science, and the life sciences, 29% were aged 26 to 45, 53% aged 46 to 60, and 19% aged 61 to 80. The study of Nobel physics laureates found that since the 1980s, they have made their discoveries on average at age 50. The study also found that the peak of creativity for Nobel winners is getting higher every year.

Kennedy described John Goodenough, who at age 57 co-invented the lithium-ion battery that shrank power into a tiny package. In the 1970s, the energy crisis inspired him to imagine how one could store power in tiny packages. Dr. Goodenough believes that the lithium-ion battery is liable to explode, is too expensive, and is too weak to compete effectively with petroleum. And now he and his team at the University of Texas at Austin filed a patent application on a new kind of battery. If it works as promised, it would be cheap, lightweight, and safe, and would revolutionize electric cars and kill off petroleum-fueled vehicles. His announcement at age 94 has caused a stir. It seems never to be too late.

CREATORS ON A COLOSSAL SCALE

My son Charles introduced me to Paul Johnson a few years ago, and subsequently he has become one of my favorite authors. Johnson, now 88 years old, has written nearly 20 books. He has done a trilogy of books: Creators: From Chaucer and Dürer to Picasso and Disney (10), Intellectuals: From Marx and Tolstoy to Sartre and Chomsky, and Heroes: From Alexander the Great and Julius Caesar to Churchill and de Gaulle. To me he is all three: a creator, an intellectual, and a hero. He puts his own thoughts into every facet of his writing. Although an Englishman, he authored A History of the American People (1997). The following comes from The Creators that describes rather briefly but beautifully the lives of 17 creators.

Geoffrey Chaucer (1342–1400): Chaucer may have been the most creative spirit ever to write in English. Indeed, according to Johnson, it could be argued that he created English as a medium of art. Before Chaucer, the ruling class spoke French and wrote in Latin. The rise of English as the language of law and government was formally recognized by the Statute of Pleading (1362) when Chaucer was a young man. It ordered that all court cases shall be pleaded, showed, answered, debated, and judged in English. The following year the Lord Chancellor for the first time opened Parliament with a speech in English. Chaucer, as Johnson writes, found a language and
left the literature. No man ever had so great an impact on the written tone. He had the creative gift of appealing strongly to a great number of people then and now. He is in a class by himself and a class joined by no one until Shakespeare. He was, and is, read for enjoyment. Over 80 complete manuscripts by Chaucer have survived out of many hundreds—perhaps over 1000—all published in the 15th century. When printing came to England, the Canterbury Tales was published, and it has been in print for 520 years. Even today it is one of the texts that teenagers begin in compulsion but finish in delight. And Chaucer has attracted a body of commentary and elucidation over the centuries, rivaled only by Shakespeare. His poems all together occupy many thousands of lines. Chaucer had a vocabulary of 8000 words, and he added over 1000 words to the English language.

**Albrecht Dürer (1471–1528):** Never a day passed without Dürer creating something, even when he was traveling. Dürer discovered that watercolors are perfect for a traveling artist, light to carry, easy to set up, and ideally suited for a quick landscape or town sketch while there was half an hour to spare. Dürer's initiative in adopting the new medium—watercolor—so he could record his travels and never waste a day was characteristic both of his intense unremitting industry and of his voracious appetite for new artistic experiences. His output included 346 woodcuts; 105 engravings; scores of portraits in various media; several massive altar pieces; etchings and drypoints; and 970 surviving drawings (of many thousands). Virtually all his work is of the highest possible quality, and he seemed to work at the limit of his capacities all his life. He pushed the frontiers of art forward. The number of firsts he scored in technical innovation is striking.

**William Shakespeare (1564–1616):** Johnson called Shakespeare the most creative personality in human history. Shakespeare was an inventor of English words on a scale without rivalry. Depending on the method of calculating, Shakespeare coined 2076 words by one method and about 6700 by another. There were 150,000 English words in his day, of which he used about 20,000, so his coinages were up to 10% of his vocabulary—amazing. He took some words out of the common stock of speech and baptized them in print, creating words by turning nouns into verbs and vice versa or by adding suffixes. There are 322 words that only Shakespeare ever used.

**Johann Sebastian Bach (1685–1750):** According to Johnson, Bach is the best example in our civilization of the importance of heredity or genes in the development of creativity. There were at least 85 members of the family, most of whom were musicians. Although Bach was in continuous musical practice, he was hardly what we would now call a "celebrity." He insisted on the highest standards for himself and others. He had strong religious beliefs and great moral probity and felt that music was one way of speaking to and serving God. Only nine of his significant works were published in his lifetime. Unlike any other composer in history, Bach wrote examples (often in formidable numbers) of every type of music then known, with the exception of opera, usually adding new dimensions by experimenting with fresh combinations of instruments or pushing the technical frontiers. He produced something new virtually every week of his life! Like Dürer, Bach composed even when traveling. He wrote music in his head, memorized it, and only afterward tried it out on the keyboard. He tended to write for an immediate performance, as did Shakespeare. Thus, most of Bach's organ work was written while he was principally an organist. At his death in 1750, the scores he wrote were divided among his surviving children and his widow, and it was then that the process of sale, dispersal, and loss began. The losses were enormous—over 100 church cantatas and more than half of his secular cantatas disappeared without a trace. Even so, what remains is astonishing. There are over 200 church cantatas, 34 secular cantatas, 5 masses, plus 2 settings for the Magnificat; 6 passions, 8 motets, 253 chorales and sacred songs; 260 organ works; about 200 works for other keyboard instruments; 7 works for lute; about 40 chamber works and 25 for orchestra; and a dozen studies in canonic music and counterpoint. There are probably about 1200 works total out of perhaps 1600 or 1700 composed. Considering the amount of time Bach had to spend playing, conducting, arguing with officials, teaching, and copying, this output is astonishing. It was an unceasing fountain of creativity.

**Joseph Mallord William Turner (1775–1851):** According to Johnson, Turner was a creative genius on the scale of Bach, in the sense that his painting was entirely original, unmistakably his own. It is impossible to confuse him with anyone else, and he painted on a prodigious scale. He was from first to last a painter of landscapes and buildings (exteriors and interiors), of seas and skies, mountains and lakes, rivers and forests, and nothing more. He never did portraits, still lifes, animals, or human figures (except for staffage). Within his chosen field, however, he was a master who has never been approached, let alone equaled. He never did anything in his life except draw and paint. He worked all day, every day. His family life was nothing, though he had two mistresses and fathered two daughters. Work occupied his entire life until a short time before his death at age 76. Unlike the works of Dürer and Bach, virtually all he did has come down, for he marketed it with great skill and energy or preserved it for the nation. Its extent is staggering: nearly 1000 oil paintings, some very large and elaborate, and about 20,000 drawings and watercolors. In addition, he left many sketchbooks, some still intact. He etched and engraved and supplied materials for publication in the commercial book market, imposing hard bargains on the men of business with whom he dealt. These activities were ancillary to his major trade: to sell large oil paintings to rich collectors at the highest possible prices. For this purpose he exhibited every year at the Royal Academy and also designed, built, and ran his own studio gallery.

**Katsushika Hokusai (1760–1849):** Hokusai created Japanese landscape painting from nothing and also portrayed Japanese life with dazzling graphic skill and an encyclopedic completeness that has never been equaled, throwing in Japan's flora and fauna for good measure. Hokusai did nothing else in life but paint. Like Dürer, Hokusai began with wood blocks but, unlike Dürer, he did not come from the wealthy bourgeois. He had no useful connections, no well-endowed wife; he worked fanatically hard all his life and made only a bare living. Whatever he did manage to save went to pay the gambling debts of a son and grandson.

**Jane Austen (1775–1817):** Her time as a female creator was always a source of embarrassment to her kin, even if they
had helped her on her way. She is one of the world's greatest novelists. She was never able to become a full-time writer, having domestic and social duties to perform, which took priority. She died at the age of 41 from Addison's disease, then, of course, incurable. Her output consists of six novels: Sense and Sensibility, Northanger Abbey, Pride and Prejudice, Mansfield Park, Emma, and Persuasion. Fame was beginning to come at the time of her death and it has continued to grow. Her novels have never been out of print for 2 centuries, and now more than 1 million copies a year are sold in paperback in the English-speaking world alone. (Another million copies are now produced in Hindustan.) Her letters were burned by her sister at her death. The family also altered and distorted the record to make Austen appear more genteel and socially law-abiding than she actually was.

**Augustus Welby Northmore Pugin** (1812–1852): Pugin was a creative artist of extraordinary sensibility and on an enormous scale. Pugin made gothic the dominant style for all religious and public buildings. He was one of the very few English architects and the only outstanding one with a firm and furious ideological posture. He not only despised but loathed the neoclassical architects of the previous generation. Pugin used the literary and illustrative skills he had inherited from his father to launch a series of propaganda work unique in art history of the Anglo-Saxon world. Pugin's output of aesthetic theory and practical guidance based on on-the-spot studies, massive reading and research, uncannily exact observation, and tens of thousands of drawings was without precedent in England and has had no successor. Most of Pugin's gothic designs for buildings, furniture, or anything else are entirely original.

**Eugène Viollet-le-Duc** (1814–1879): Essentially, this man was the French Pugin. He was hugely influenced by Pugin and made gothic respectable and even popular in France. His work was overwhelmingly in restoration. He protested at the way France's medieval heritage, the largest by far in the world, was being allowed to deteriorate. Viollet-le-Duc was the key figure in the national response. He is identified with three projects in particular: the restoration of Notre Dame in Paris, the rescue of the enormous and unique medieval town cathedral (palace and fortress) of Carcassonne, and the rebuilding of the magnificent castle at Pierrefonds. He was also involved in scores of other important restoration projects, churches, cathedrals, abbeys, and public buildings all over the country.

**Victor Marie Hugo** (1802–1885): Hugo was a creative artist on the grandest possible scale, according to Johnson, with the widest scope and the highest productivity. In all four great divisions of literature—poetry, drama, novel, and essay—he was equally productive and remarkable. At age 13, he was writing classical tragedies and stories, and at age 16 he was receiving public recognition. Thereafter, his output was incessant until he suffered a stroke at age 76. Even then he continued to write sporadically until his death at age 83. In all, he wrote 10 million words, of which 3 million were edited from his manuscripts and published posthumously. Hugo wrote every day of his life, be it only a love letter to his wife or to his principal mistress. Usually, it was one or more poems or several thousand words of prose—perhaps both. Poetry punctuated his life and seemed always to have been spontaneous, effortless, and fluent. He often wrote poetry first thing in the morning before breakfast. He was 20 when he published his first volume of verse. There are 24 books of poetry printed after the poems first appeared in newspapers. There are probably over 3000 poems by Hugo, a few very long, most short, some never published. He also wrote nine novels, the first in 1823 when he was 29. His plays began in 1827 with Cromwell. He dominated French literature in the 19th century, and he is the nearest equivalent to Shakespeare in France. He was immensely widely read both in France and abroad. Les Misérables was published simultaneously in eight major capital cities just before World War I. There are over 3 million copies of Hugo's novels in print today. At least 55 operas have been based on his works. That Hugo was phenomenally creative is unarguable based on sheer quality and quantity.

**Mark Twain** (1835–1910): Samuel Langhorne Clemens stands at the center of American literature. Indeed, he invented it. Mark Twain was not only a great creative artist but a quintessential American artist from first to last. His material was American even though he garnered or stole much of it from all over the world. His style was American, as was his vocabulary, verbal accent, ideological humor, comedy, indignation real or simulated, self-presentation, methods of literary commerce, and journalist flair. As Johnson put it, he was an American opportunist, an American plagiarist, an American braggart, egotist, and an American literary phenomenon. He liberated American letters. He taught American writers and public performers of all kinds a completely new set of tricks, which have been in use ever since. His creativity was often crude and nearly always shameless. But he was huge and genuine, overpowering, a kind of vulgar magic, making something out of nothing, then transforming that mere something into entire books that in turn hardened into traditions and cultured certitudes. He was the greatest of all literary con men. Twain took to public speaking, both for money and to publicize his books, early in his career as a writer, and his lectures quickly became a major source of income and fame. Indeed, it is hard to say if Twain in his lifetime was a better writer or speaker. His lectures were essentially humorous performances: they were dramatic and he was acting. He was essentially a standup comedian. Twain was an entertainer. He felt that getting people interested and making them laugh was what he was best at, the surest way to make money and his contribution to the health and wealth of mankind. He was not a novelist, poet, playwright, writer of philosophy or history, or travel writer, though he posed as such. His books are all entertainment. His two best books, The Adventures of Tom Sawyer and Adventures of Huckleberry Finn, his masterpiece, are also, when inspected closely, compilations of anecdotes.

**T. S. Elliott** (1888–1965): He launched modern poetry in the English-speaking world in 1922 with the publication of The Waste Land. He was a conservative by nature. Elliott was never once (except on holidays) photographed without a tie, wore a three-piece suit on all occasions, kept his hair trimmed, and was the last intellectual on either side of the Atlantic to wear spats. He was from an affluent family with strong concepts of duty and service, to God, country, community, and culture. If ever
there was a creative genius nourished by reading the classics of all nations, it was Elliott, the best educated and self-educated of English poets. He belonged to good clubs, associating superficially with the rich and well-born, but in essence he led a life of study, meditation, and sheer hard work on texts and languages. Though Elliott was a conservative by intellectual conviction and instinct, he had a passion for cultural innovation. He strongly approved of Cubism, for instance. He wished to bring about the same kind of revolution in poetry as had been achieved in painting, music, and the novel. The original of Elliott's masterpiece The Waste Land was given to Ezra Pound, who cut away the pretentious parodying and witty superstructure which Elliott had decorated the poems' hard despair. Pound dug out from the version Elliott gave him the fundamental bones of the poem of despair so that its music and rhythms can be heard and felt. The changes transformed the work into a masterpiece and one that was perceived as such the moment it was made public. The poem's success more or less instantly placed Elliott at the head of the profession of poetry, a position he occupied until his death 40 years later. Elliott was in his mid-30s when The Waste Land brought him fame. With Four Quartets, Elliott's active life as poet was essentially complete. He had created one of the most penetrating and memorable moves in the history of the art, and that was his contribution to Western culture. He wrote five plays. In 1948, Elliott received the Nobel Prize and shortly afterwards England's highest award, The Order of Merit. He also received 18 honorary degrees from universities throughout the world and was an honorary fellow of colleges in both Oxford and Cambridge.

**Louis Comfort Tiffany (1848–1933):** He was the greatest creator of glassware of modern times, perhaps of all times. Glassmaking is the least understood of the crafts. Making fine glass is an extraordinary mixture of creative skill, science, and accidents. Humans, according to Johnson, have been making glass for >500 years, but only quite recently did they discover the chemistry of what they were doing, and there is still a large element of unpredictability in some of the processes. Glass is made from sand. Unfortunately, it is likely that only about 10% of Tiffany's works have been preserved. His work was mainly art nouveau, the prevailing mode for most of Tiffany's career. Vast quantities of his work were destroyed deliberately. Both of his palatial homes containing the best of his art were sold off and demolished.

It is a matter of definition whether Tiffany was primarily an artist and creator himself or a “creator facilitator,” a man who made it possible by his vision and organizing ability for others to create and produce. He was certainly both, but which came first in his order of priorities is unclear. Although Tiffany understood glass technology thoroughly and was always introducing innovations in his work, he did not blow glass himself or cast it. Tiffany was a true innovator in that he was never content, was always experimenting, and delighted in setting himself and his assistants impossible tasks. By the turn of the 20th century he was employing 100 of the world's best glassworkers, paying them the highest wages, and encouraging them to produce any of their own ideas that he could research with his chemistry division. He also had an immense personal flair for marketing. After splendid but meretricious fame in his youth and neglect and contempt in his old age, followed by near oblivion, Tiffany stands in the top-rank of transatlantic craftsmen, a major creative artist.

**Cristobal Balenciaga (1895–1972) and Christian Dior (1905–1957):** Johnson indicated that of all the creative people he had come across, Balenciaga was easily the most dedicated to the business of making beautiful things. His work absorbed him totally, and there was no room in his life for anything or anyone else. When it became impossible (as he saw it) to produce work of the highest quality, he retired and quickly died. Making elegant clothes is one of the most ephemeral but oldest forms of art. Until the 16th century, complete outfits were the rarest of all artifacts to survive, and until quite modern times museums were lacking in even rudimentary collections of historic clothes. Until the 20th century, only the rich dressed well and fashionably. From earliest times there was an international trade in wool and other textiles, but made-up clothes rarely crossed frontiers until the 18th century. These two creators were designers and manufacturers of elegant female clothing. They produced women's clothes of the highest quality in material, design, cutting, sewing, fitting, and finish. Both worked in the 1950s and 1960s in Paris. Balenciaga, according to Johnson, was probably the most original and creative couturier in history. According to Johnson, Balenciaga had the superior skills of the two. Balenciaga dressed the very rich and Dior dressed the rich. Balenciaga's desire was to make women happy and to provide clothes that were comfortable despite their grandeur, their complexity, and the magnificence of their materials. He never used pins or extraneous stiffening of any kind. Balenciaga argued that if a woman was comfortable in her clothes she was confident, and if she was confident she was at her best and wore the clothes with style. Another of his principles was permanence. While Dior made changes twice a year (spring and fall), Balenciaga fundamentally produced permanent dresses. He believed that a woman could buy one of his dresses (his specialty was evening gowns) as an investment, and if properly looked after they would last forever. Not so, Dior. Another of Balenciaga's principles was the central importance of material in his designs. Textile and lace manufacturers, embroiderers, and specialists in gauze and dyes catered to him. The dresses from both of these creators were produced by human hands, bringing into existence the images created on paper from their powerful and inventive brains.

In contrast to Balenciaga, Dior could not actually make a dress. He was a designer. He also insisted on brilliant craftsmanship, and superlative materials were used in all of his dresses. The sewing was perfect, the cutting impeccable, and the fittings patient and exact. At the time of Dior's death his house employed 1000 of the finest experts ever gathered together under one roof. During the decade before his death (1957), Dior sold over 100,000 dresses made from 16,000 designed sketches using 1000 miles of fabric. He was an artist, stunningly quick with pen and brush. Except for Dior's superiority in draftsmanship, Balenciaga was in every other way immeasurably superior.

**Pablo Picasso (1881–1973):** According to Johnson, Picasso was perhaps the most restless, experimental, and productive
The first sound movie using the mouse was called Steamboat Willie and was shown in 1928. It was a huge success, not only because of Disney’s technical triumph of synchronized animation, but because of the ingenuity of what Disney got the mouse to do in producing noises. Therein lay his extraordinary gift, the imagination to enter into the head of a half-mouse, half-man and devise weird and hilarious things to do as the mouse steered a boat down the river. Thus, Disney invented the sound cartoon, a combination of imaginative drawing, scripting, and engineering science. It was, and remains, a wonderful example of creativity—the birth of a new art form. By the end of the 1920s, Mickey Mouse was the best known figure in movies. His voice was originally done by Disney himself.

Other characters devised by Disney soon appeared: Minnie Mouse, Figaro the Kitten, Chip the Chipmunk, Pluto, Goofy, and Donald Duck. Disney devised the infuriated animation of Donald to synchronize with irascible quacking noises. This was the first time in the history of art that drawings had not only been animated but vocalized. Disney spent money as fast as it came in. He insisted on reanimation, however time-consuming and expensive, until the results were right. Disney always put excellence before any other consideration.

The arrival of color, the improvement of background technique, the perfection of the soundtrack, the inclusion of high-quality orchestral music and singing, and financial factors persuaded Disney to break out of the funny cartoon and make feature-length fairy tales. The first one, Snow White and the Seven Dwarfs, was shown in cinemas all over the world in 1938. The success of Snow White financed a series of four big feature movies between 1938 and 1944: Pinocchio, Fantasia, Dumbo, and Bambi. All were successful. He eventually turned to filming nature itself, living but unanimated. His last years and after his death, the studio continued to make major all-animated movies, following his focus on nature. The influence of Disney on the presentation of visual images in the 20th century and beyond was immense.

There are no physicians or scientists among Johnson’s “creators.”

William Clifford Roberts, MD
August 10, 2017

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