Baylor University Medical Center Proceedings

The peer-reviewed journal of Baylor Scott & White Health

Original Research

3 Repeat ablation and hospitalization following cryptobacterial ablation of atrial fibrillation at a single tertiary medical center by C. East et al

7 Results of repair of iliac artery aneurysms with the sandwich technique by R. A. Shute et al

11 Interpretation of positive troponin results among patients with and without myocardial infarction by Y. M. Tescion et al

16 Relation between proprotein convertase subtilisin/kexin type 9 and directly measured low-density lipoprotein cholesterol by K. M. Tescion et al

21 Factors associated with reduced radiation exposure, cost, and technical difficulty of inferior venacava filter placement and retrieval by M. Noll et al

26 Optimizing laboratory test utilization in long-term acute care hospitals by R. A. Mora et al

30 Inappropriate use of antibiotics in patients undergoing gynecologic surgery by J. Joyce et al

33 Concussion knowledge among rehabilitation staff by G. Saltbary et al

38 Factors associated with performance in an internal medicine clerkship by C. Colbert et al

Case Studies

41 Late presentation of fatal hyperammonemic encephalopathy after Roux-en-Y gastric bypass by A. Nagare and A. Z. Fenves

44 Recurrent epiploic appendagitis mimicking appendicitis and cholecystitis by C. Lorente et al

47 Endovascular therapy using flow diversion for giant internal carotid artery pseudoaneurysm arising in the setting of an insidious pulmonary macroadenoma by A. F. Saad et al

50 Pulmonary artery aneurysm by R. A. Shute et al

52 Understanding vascular-type Ehlers-Danlos syndrome and avoiding vascular complications by A. Carter and A. Z. Fenves

54 Right atrial thrombus and its causes, complications, and therapy by M. M. Benjamin et al

57 Intrauterine surgery by R. L. Rosenthal and J. O. Franklin

59 ST-elevation acute myocardial infarction due to arterial thrombosis in a 29-year-old woman with normal coronary arteries by E. Male et al

62 A variant of Brugada syndrome by M. P. Schweizer et al

64 Electrocardiogram after operation for a subarachnoid hemorrhage by D. L. Glancy

66 Primary spinal epidural B-lymphoblastic lymphoma by R. K. Nambiar et al

69 B-cell lymphoma, thiamine deficiency, and lactic acidosis by U. Macieron et al

71 Dasatinib-induced chylothorax in chronic myeloid leukemia by Z. O. Baloch et al

74 Blood group change in acute myocardial infarction by R. K. Nambiar et al

76 Subcutaneous panniculitis-like T-cell lymphoma by M. T. Sugeeth et al

80 Focal cutaneous sebaceous cell carcinoma following radium-223 extravasation by E. C. Benjardens et al

84 A nodular-ulcerative form of secondary syphilis in AIDS by G. O. Onogun et al

85 An approach for safe conversion of an oral endotracheal tube to a nasal endotracheal tube by M. Hofkamp and Z. Diao

86 Inception of computer circuit boards causing esophageal impaction and small bowel obstruction by R. K. Senan and H. Salem

88 Bullet fragment-induced lead arthropathy with subsequent fracture and elevated blood lead levels by S. A. McKunch et al

92 Identification of foci of H. influenzae with reversible herniation of temporomandibular joint soft tissue into the external auditory canal on multidetector computed tomography by S. Mittal et al

94 Anticonvulsant hypersensitivity syndrome secondary to carbamazepine by S. C. Brown and R. L. Dauterive

97 Ruptured ectopic pregnancy with a negative urine pregnancy test by M. Hughes et al

99 Electromyogram-evoked focal myositis by A. Smith et al

Historical Studies

101 Henry Burton Jacobs, William Osler’s intimate friend by C. S. Bryan

106 A 1911 postcard of the National Hospital for the Paralysed and Epileptic highlighting European medical specialty training by A. Zubar and C. J. Boes

Editors and Book Review

109 On becoming a physician by K. S. Swan

112 Improving health outcomes through patient education and partnerships by T. E. Patrick et al

114 Parliament of Whores, revisited by H. L. Fred and M. Scheid

116 Reflections on the retirement of John W. Hyland, MD, by R. M. Solis

117 Targeted on race to France and World War I: a father’s experience by D. G. Cantwell

121 Book review: Howard and Georganna: Sixty Years of Marriage and Medicine by S. P. Marynick

From the Editor

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

Miscellaneous

2 Clinical research studies enrolling patients

29 Acknowledgment of reviewers for volume 29

56 Associations: Photograph by J. L. Manning

65 Associations: Photograph by R. M. Solis

87 Associations: Photograph by J. D. Cantwell

96 Associations: Photograph by R. M. Solis

123 Baylor Scott & White Health news

128 Reader comments: Operative management of dermatofibrosarcoma protuberans of the breast by F. Saputo and P. Chassampion, author reply by M. Kinney and S. Knox

Indexed in PubMed, with full text available through PubMed Central

www.BaylorScottandWhite.com

Baylor Scott & White Medical Center

Baylor University Medical Center

Scott & White Medical Center

Tarrant Regional Medical Center

McLane Children’s Scott & White Clinic

Baylor Scott & White Health

www.BaylorScottandWhite.com

The largest not-for-profit health care system in Texas, and one of the largest in the United States, Baylor Scott & White Health was born from the 2013 combination of Baylor Health Care System and Scott & White Healthcare. For more information on our nearly 50 hospitals and more than 900 patient care sites, please visit www.BaylorHealth.com and www.sw.org.
Volume 30, Number 1 • January 2017

Editor in Chief
William C. Roberts, MD
William.Roberts1@BSWHealth.org

Associate Editor
Michael A. E. Ramsay, MD

Founding Editor
George J. Race, MD, PhD

Editorial Board
Jenny Adams, PhD
W. Mark Armstrong, MD
Alejandro C. Arroliga, MD, MS
Sharon G. Bakos, MD
David J. Ballard, MD, PhD
Madhava R. Beeram, MD, MBA
Raul Benavides Jr., MD
John D. Cantwell, MD
Mark A. Casanova, MD
James W. Choi, MD
Cristie Columbus, MD
Barry Cooper, MD
Gregory J. Dehmer, MD
Daniel C. DeMarco, MD
Gregory G. Dimijian, MD
Cara A. East, MD
John P. Erwin III, MD
Michael Emmett, MD
Andrew Z. Fenves, MD
Katherine H. Fiala, MD
Giovanni Filardo, PhD
James W. Fleshman, MD
Steven M. Frost, MD
W. Bruce Fye III, MD
Dennis R. Gable, MD
D. Luke Glancy, MD
Robert D. Greenberg, MD
Bradley R. Grimsley, MD
Joseph M. Guileyardo, MD
Carson Harrod, PhD
H. A. Tillmann Hein, MD
Daragh Heitzman, MD
Roger S. Khetan, MD
Göran B. Klintmalm, MD, PhD
John K. Krause, MD
Bradley T. Lembcke, MD
Jay D. Mabrey, MD
Michael J. Mack, MD

Editorial Staff
Managing Editor
Cynthia D. Orticio, MA, ELS
Cynthia.Orticio@BSWHealth.org

Administrative Liaison
Bradley T. Lembcke, MD

Design and Production
Aptara, Inc.

Baylor University Medical Center Proceedings is published quarterly (January, April, July, and October). Proceedings is indexed in PubMed and CINAHL; the full text of articles is available both at www.BaylorHealth.edu/Proceedings and www.pubmedcentral.nih.gov. The journal’s mission is to communicate new medical information, or previously described information presented in a more elegant or understandable manner, and to offer a mechanism to present patient, physician, and historic stories to enlighten and inspire readers.

Funding for the journal is provided by the Baylor Health Care System Foundation. Funding is also provided by donations made by the medical staff and subscribers. These donations are acknowledged each year in a journal issue. For more information on supporting Proceedings and Baylor Scott & White Health with charitable gifts and bequests, please call the Foundation at 214-820-3136. Donations can also be made online at http://give.baylorhealth.com.

Statements and opinions expressed in Proceedings are those of the authors and not necessarily those of Baylor Scott & White Health or its board of trustees.

Guidelines for authors are available at http://www.baylorhealth.edu/Research/Proceedings/SubmitaManuscript/Pages/default.aspx.

Subscriptions are offered free to libraries, physicians affiliated with Baylor Scott & White Health, and other interested physicians and health care professionals; donations are suggested for print subscriptions. To add or remove your name from the mailing list, call 214-820-9996 or e-mail Cynthia.Orticio@BSWHealth.org. POSTMASTER: Send address changes to Baylor Scientific Publications Office, 3500 Gaston Avenue, Dallas, Texas 75246.

Advertising is accepted. Acceptance of advertising does not imply endorsement by Baylor Scott & White Health. For information, contact Cindy Ortizio at Cynthia.Orticio@BSWHealth.org.

Permission is granted to students and teachers to copy material herein for educational purposes. Authors also have permission to reproduce their own articles. Written permission is required for other uses and can be obtained through Copyright.com.

Copyright © 2017, Baylor University Medical Center. All rights reserved. Printed in the United States of America on acid-free paper. Press date: December 8, 2016.

To access Baylor’s physicians, clinical services, or educational programs, contact the Baylor Physician ConsultLine: 1-800-9BAYLOR (1-800-922-9567).
Currently, Baylor Scott & White Research Institute is conducting more than 2,000 research projects. Studies open to enrollment are listed in the Table. To learn more about a study or to enroll patients, please call or e-mail the contact person listed.

<table>
<thead>
<tr>
<th>Research area</th>
<th>Specific disease/condition</th>
<th>Contact information (name, phone number, and e-mail address)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesiology</td>
<td>Various device trials, measuring oxygenation levels; EEG algorithms of sedation, SpO2 and fluid volume levels, delivery of various anesthesia medications</td>
<td>Zhang Zhang 214-865-3128 <a href="mailto:Zhang.Zhang@BSWHealth.org">Zhang.Zhang@BSWHealth.org</a></td>
</tr>
</tbody>
</table>
| Asthma and pulmonary disease | Chronic obstructive pulmonary disease, asthma (adult), lung transplant, pulmonary hypertension, diaphragm impairment, rebreather, inhalation | Franci Crockett, CRT 214-820-5828 Franci.Crockett@BSWHealth.org  
Coryn Kinney, BS 214-818-7999 Coryn.Kinney@BSWHealth.org |
| Cancer | Breast, ovarian, endometrial, prostate, brain, lung, bladder, colorectal, pancreatic, and head and neck cancer; hematological malignancies, leukemia, multiple myeloma, non-Hodgkin's lymphoma; melanoma vaccine; bone marrow transplant | Grace Townsend 214-818-8472 cancer.trials@baylorhealth.edu |
| Central Texas | Cancer, cardiology, family medicine, gastroenterology, infectious disease, kidney, neurology, ophthalmology, orthopedics, pathology, pediatrics, plastic surgery, pediatrics, psychiatry, pulmonary, radiology, rheumatology, surgery, transplant, urology | Vanessa Hoeschler 1-888-863-3675 vanessa.hoeschler@bwshealth.org  
Johnr Nichols 1-888-863-3675 janr.nichols@BSWHealth.org |
| Diabetes (Dallas) | Type 1 and type 2 diabetes, cardiovascular events | Lisa Mamo, RN 214-818-7974 Lisa.mamo@bwshealth.org |
| Diabetes (Dallas) | Pancreatic islet cell transplantation for type I diabetics, who either have or have not had a kidney transplant | Anne Marie Jones 214-818-7623 Anne.Jones@BSWHealth.org |
| Emergency Medicine | Traumatic brain injury | Jon Thammavong 214-818-9667 Jon.Thammavong@BSWHealth.org |
| Gastroenterology | Inflammatory bowel disease | Sandra Kirby, RN 214-818-9792 Sandra.Kirby@BSWHealth.org |
| Heart and vascular disease (Dallas) | Aortic aneurysm, coronary artery disease, hypertension, poor leg circulation, heart attack, heart disease, congestive heart failure, angina, cardiac artery disease, familial hypercholesterolemia, renal denervation for hypertension, diabetes in heart disease, cholesterol disorders, heart valves, thoracicotomy, sternum, stem cells, critical limb ischemia, cardiac surgery associated with kidney injury, pulmonary hypertension | Merienie Boatman 214-820-2273 Merienie.Boatman@BSWHealth.org |
| Heart and vascular disease (Fort Worth) | Heart and lung transplant, mechanical assist device such as LVAD | Jessica Propps 214-620-1821 jessica.propps@bwshealth.org |
| Heart and vascular disease (Legacy Heart) | Atrial fibrillation, atrial fibrillation post PCI | Ava Wallace 817-922-2586 ava.wallace@bwshealth.org |
| Heart and vascular disease (Plano) | At risk for heart attack/stroke; previous heart attack/stroke/PCI; diabetes; atrial fibrillation; obesity/weight loss/disease; other heart-related conditions | Angela Germany 469-800-6409 angela.germany@bwshealth.org |
| Hepatology | Liver disease | Niechele Loyd 214-820-1710 Niechele.Loyd@BaylorHealth.org  
Theresa Cheyne 817-922-2579 Theresa.Cheyne@bwshealth.org |
| Infectious disease | HIV/AIDS | Bryan King, LVN 214-823-2533 bryan.king@btsic.org |
| Infectious disease | Hepatitis B | Niechele Loyd 214-820-1710 Niechele.Loyd@bwshealth.org  
Theresa Cheyne 817-922-2579 Theresa.Cheyne@bwshealth.org |
| Nephrology | Type 2 diabetes with chronic kidney disease | Verlie Slisk 214-820-4628 Verlie.Slisk@BWSHealth.org |
| Neurology | Stroke, migrane | Quynh Lan Doan 214-818-2522 Quynh.Lan.Doan@BSWHealth.org |
| Neurology | Multiple sclerosis, stroke | Vicki Stiles, RN 214-818-7929 victoria.stokes@BSWHealth.org |
| Neurology | Fabry disease, Gaucher disease types 1 & 3, and mucolipidosis type IV (or ML IV) | Mary Wallace 214-820-4752 Mary.Wallace@BSWHealth.org |
| Neurosurgery | Cerebral aneurysms | Kenneth Layton, MD 214-827-1600 Kenneth.Layton@bwshealth.org |
| Neurosurgery | Interventional stroke therapy | Tomica Harrison 214-820-2615 tomica.harrison@BSWHealth.org |
| NICU | Heart attack, heart disease; heart valve repair and replacement; critical limb ischemia; repair of aortic dissections with endografts; surgical/repair; atrial fibrillation; heart rhythm disorders; cardiac artery disease; congestive heart failure; gene profiling | Tina Worley, RN, BSN 469-814-4712 Christina.Worley@BSWHealth.org |
| Rheumatology (900 N. Central Expressway) | Rheumatoid arthritis, psoriatic arthritis, lupus, gout, ankylosing spondylitis | Elizabeth Venincasa, RN, BSN 214-987-1253 Elizabeth.Venincasa@BSWHealth.org |
| Rheumatology (900 N. Central Expressway) | Rheumatoid arthritis, psoriatic arthritis, lupus, gout, ankylosing spondylitis | Michelle Richardson, BA, CCR 254-202-2645 mrichardson@bacteriologics.com |
| Surgery | Chronic limb ischemia, pain management with chest tubes, colon polyps, diaphragm stimulators, and surgery as it pertains to GERD, breast cancer, esophagus, colon cancer, pancreas, lung, hernias, dizziness access, per-endoscopy morphology (PEGM), thoracic outlet syndrome | Tammy Fisher, RN, MSN, MBA 214-820-7221 Tammy.Fisher@BSWHealth.org |
| Transplantation | Bone marrow, blood stem cells | Grace Townsend 214-818-6472 Grace.Townsend@BSWHealth.org |
| Transplantation | Abdominal, solid organs, liver/kidney | Niechele Loyd 214-820-1710 Niechele.Loyd@bwshealth.org  
Theresa Cheyne 817-922-2579 Theresa.Cheyne@bwshealth.org |
| Trauma and critical care | Transfusion, trauma activation, critical care, acute care surgery | Evan Elizabeth Rainey 214-865-2410 Evan.Elizabeth.Rainey@BSWHealth.org |
| Waco | Diabetes, chronic kidney disease, COPD, hypertension, prevention of second cardiac event, atopic dermatitis | Michele Richardson, BA, CCR 254-202-2645 mrichardson@bacteriologics.com |
| Weight management | Obesity | Lisa Mamo, RN 214-818-7974 Lisa.Mamo@BSWHealth.org |
| Women’s Health (Fort Worth) | Uterine fibroids | Mary Cao 817-922-2574 Mary.Cao@BSWHealth.org |

Baylor Scott & White Research Institute is dedicated to providing the support and tools needed for successful clinical research. For more information, please contact Kristine Hughes at 214-820-7556 or Kristine.Hughes@BSWHealth.org.
Repeat ablation and hospitalization following cryoballoon ablation of atrial fibrillation at a single tertiary medical center

Cara East, MD, Teresa Phan, MS, MS, Giovanni Filardo, PhD, MPH, Jay Franklin, MD, Alan Donsky, MD, Kevin R. Wheelan, MD, and Robert C. Kowal, MD, PhD

Cryoablation for atrial fibrillation (AF) has rapidly become a mainstream treatment for AF. In this report, 163 patients who had undergone a cryoablation procedure at one clinical center were contacted by telephone 33.1 ± 3.3 months after the procedure. All patients had received cryoablation of the pulmonary vein ostia, although concomitant procedures were performed at the same time in over 50% of the patients, including radiofrequency and/or cryoablation of other areas of the left atrium. Freedom from a repeat ablation procedure was 87%, while freedom from recurrent hospitalization for AF was 89%, as compared to previous reports of 65%. Of the 13 patients who had a repeat ablation procedure, only one was found to have a reconnection of pulmonary veins, while 4 were found to have atrial flutter. Cryoablation for AF produces a durable result in most patients out to 3 years with better outcomes than previously reported.

Pulmonary vein isolation (PVI) has emerged as the gold standard of ablative strategies to treat medically refractory paroxysmal and persistent atrial fibrillation (AF) (1). But despite the superiority of catheter ablation based on PVI over antiarrhythmic drug therapy (2–4), recurrence rates of AF remain higher than desired (5). Among large trials, freedom from recurrent AF is about 65% (range 48%–77%), with follow-up limited to 12 to 28 months (6–18). For the cryoablation procedure, the second-generation cryoballoon catheter provides a larger and more uniform cooling zone (8, 9). We sought to determine the overall need for recurrent ablation procedures and hospitalizations for atrial arrhythmias among a group of consecutive patients who underwent ablation with the second-generation cryoballoon catheter.

METHODS

This study was a retrospective assessment of consecutive subjects who underwent cryoballoon-based catheter ablation of AF by 8 electrophysiologists (with 4 physicians performing 95% of the procedures) at the Baylor Heart and Vascular Hospital from May 18, 2012, through June 6, 2013. Follow-up after ablation was performed according to American Heart Association/Heart Rhythm Society guidelines for the first year and was at the discretion of each physician subsequently.

Patients were brought to the electrophysiology lab in a fasted state off all antiarrhythmic drug therapy. Under general anesthesia, a decapolar diagnostic catheter was placed in the coronary sinus via the femoral approach. After a single transseptal puncture, the 28 mm cryoballoon (Artic Front or Artic Front Advance, Medtronic, Inc., Minneapolis, MN) was introduced into the left atrium via a 12F steerable sheath (FlexCath, Medtronic). Pulmonary vein mapping was performed using either a 20-pole circular mapping catheter or an 8-pole transluminal circular mapping guide (Achieve, Medtronic). Catheter positioning was assessed by transluminal contrast injection and/or intracardiac echocardiography with the goal of complete pulmonary vein occlusion prior to lesion delivery. Cryo energy was delivered for 180 to 240 seconds at operator discretion, with a bonus lesion following isolation. Lesion duration was impacted by assessment for phrenic nerve dysfunction, esophageal temperature, balloon nadir temperature, and time to isolation, when measured. Only the 28 mm cryo balloon was used. PVI was reassessed 30 minutes after the final application at each vein.

A total of 218 patients were identified, and 163 patients were successfully contacted and interviewed. Patients were queried about whether any symptoms of AF had recurred, how the recurrent AF was diagnosed, how they perceived symptom resolution, if they had another ablation procedure, and if they had any subsequent hospitalizations for AF (separate from any ablation admissions).

For all patients, a chart review of the ablation procedure was performed. Information collected included the type of AF that had been present (paroxysmal, persistent, or both); if cardioversions for AF had ever been done; the subjective frequency of the AF preablation; the presence of the risk factors of hypertension, coronary artery disease, and cardiomyopathy; the presence and names of anticoagulant and antiarrhythmic medications before or after the procedure; the exact procedure...
that was done (including information on concomitant ablation sites treated); the number of pulmonary veins present and ablated; and the presence of any complications of the procedure. This study was reviewed and approved by the Baylor Research Institute institutional review board. All patients provided verbal phone consent.

Means, standard deviations, medians, interquartile range, and percentages were calculated to describe the study cohort. Freedom from recurrent atrial ablation or hospitalization for AF was estimated with a Kaplan-Meier analysis. Estimates were used to generate freedom from recurrent atrial ablation and freedom from hospitalization for AF curves in this study cohort.

RESULTS

A total of 163 patients were interviewed by telephone a mean of 33 months after the cryoablation procedure. The mean age of the patients was 64 years, and the group was divided about equally between men and women (Table 1). Most patients were white. Prior to the ablation, patients had had AF for 4½ years, and two-thirds had paroxysmal AF. Interestingly, one-third had a concomitant diagnosis of atrial flutter by history. This index AF ablation procedure was the second procedure for 7% and the third procedure for 3%.

Many patients (68%) were on an anticoagulant prior to the procedure, including dabigatran (37.6%), warfarin (34.8%), rivaroxaban (27.0%), and apixaban (0.9%). Similarly, many (66%) were on an antiarrhythmic medication at the time of evaluation for the ablation procedure (although all antiarrhythmic medication was held prior to the procedure), which included flecainide (32.4%), sotalol (19.4%), amiodarone (16.7%), dronedarone (13.0%), propafenone (9.3%), dofetilide (6.5%), and diltiazem (2.8%).

All patients in this study underwent cryoballoon PVI (Table 2). In addition, 10% to 20% of patients had either radiofrequency or cryoablation in other parts of the left atrium, and 20% specifically had an atrial flutter ablation in addition to the AF ablation. There were 16 complications, all of which resolved within 30 days (Table 3).

Nineteen patients had another ablation procedure, and for 13 of these 19, the next procedure was performed at our institution. In one patient with a repeat ablation procedure, there was a reconnection of the pulmonary veins (19). Seven patients were

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>63.6 ± 12.0</td>
</tr>
<tr>
<td>Male</td>
<td>95 (58.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>68 (41.7%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>157 (96.3%)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>4 (2.5%)</td>
</tr>
<tr>
<td>Duration of atrial fibrillation, months (mean ± SD)</td>
<td>56.2 ± 63.9</td>
</tr>
<tr>
<td>Time between ablation and interview, months (mean ± SD)</td>
<td>34.0 ± 3.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of atrial fibrillation</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal</td>
<td>108 (66.3%)</td>
</tr>
<tr>
<td>Persistent</td>
<td>33 (20.3%)</td>
</tr>
<tr>
<td>Both</td>
<td>22 (13.1%)</td>
</tr>
<tr>
<td>Concomitant atrial flutter, by patient history</td>
<td>63 (38.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Index ablation procedure was the</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First ablation procedure</td>
<td>146 (90.0%)</td>
</tr>
<tr>
<td>Second ablation procedure</td>
<td>12 (7.4%)</td>
</tr>
<tr>
<td>Third ablation procedure</td>
<td>5 (3.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>93 (57.1%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>21 (12.9%)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>25 (15.3%)</td>
</tr>
</tbody>
</table>

Table 2. Procedures performed among 163 patients who underwent a cryoablation procedure

<table>
<thead>
<tr>
<th>Procedure</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoablation pulmonary vein isolation</td>
<td>163 (100.0%)</td>
</tr>
<tr>
<td>Cryoablation plus radiofrequency to complete the pulmonary vein isolation</td>
<td>18 (11.0%)</td>
</tr>
<tr>
<td>Cryoablation plus balloon lesions to nonpulmonary vein areas</td>
<td>20 (12.3%)</td>
</tr>
<tr>
<td>Cryoablation plus radiofrequency to nonpulmonary vein areas</td>
<td>17 (10.4%)</td>
</tr>
<tr>
<td>Cryoablation plus typical atrial flutter ablation</td>
<td>33 (20.3%)</td>
</tr>
<tr>
<td>Cryoablation plus ablation on nonpulmonary vein atrial tachycardia</td>
<td>1 (0.6%)</td>
</tr>
</tbody>
</table>

*Some patients had more than one concomitant site treated.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% fewer spells</td>
<td>20 (13.9%)</td>
</tr>
<tr>
<td>75% fewer spells</td>
<td>14 (9.7%)</td>
</tr>
<tr>
<td>90% fewer spells</td>
<td>23 (16.0%)</td>
</tr>
<tr>
<td>No further spells</td>
<td>86 (60.1%)</td>
</tr>
</tbody>
</table>
found to have residual potential in a pulmonary vein antrum. Four patients had atrial flutter, including atypical atrial flutter. Various other locations of an electrical focus were found on the left atrial roof, posterior wall, superior vena cava, left atrial appendage, and right atrial appendage.

DISCUSSION

The main findings of our study were that, with long-term follow-up of an ablation procedure using the second-generation cryoballoon, 1) freedom from recurrent ablation was observed in 87% of subjects (Figure 1a); 2) freedom from hospitalization for atrial arrhythmias was seen in 88% of subjects (Figure 1b); and 3) most were either free of AF symptoms or had a reduced burden after a follow-up of nearly 3 years. Complication rates were acceptably low, and no procedural-related issues emerged late in follow-up. When AF recurred, there was a finding in the pulmonary veins, consistent with either a reconnection or incomplete ablation at the index procedure. All patients with recurrence underwent a successful second ablation procedure.

The majority of publications on AF and cryoablation have focused on freedom from 30 seconds of AF during the time period of 3 to 12 months postablation. More recent reports have focused on cryoablation for somewhat longer times and have shown a 65% rate of freedom from AF for 12 to 28 months postablation (Table 4) (6–18). This study thus demonstrated a higher success rate over a longer time of observation.

While freedom from AF represents a standard and important endpoint, it does not directly reflect the need for recurrent, expensive resource utilization. The cost of a typical AF ablation has been estimated at $80,000 and a hospitalization related to AF at $35,000. Prevention of repeat ablation procedures can also mitigate the risk of additional complications.

This was a retrospective, observational study, and 55 patients in the consecutive series could not be reached. This was a single-center study involving multiple operators. In this study, the presence of recurrent AF was assessed historically, and a routine systematic approach to AF monitoring was not performed. We were not able to correlate symptoms of palpitations in these patients to the presence or absence of any specific arrhythmia. Finally, we did not have data on resource utilization prior to patients’ index ablation.

Table 4. Freedom from atrial fibrillation with radiofrequency ablation and cryoablation

<table>
<thead>
<tr>
<th>First author, year of publication</th>
<th>N</th>
<th>Radiofrequency ablation</th>
<th>Cryoablation</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knecht, 2014</td>
<td>208</td>
<td>56%</td>
<td>48%</td>
<td>28</td>
</tr>
<tr>
<td>Mugnai, 2014</td>
<td>396</td>
<td>73%</td>
<td>63%</td>
<td>23</td>
</tr>
<tr>
<td>Cheng, 2015</td>
<td>1216</td>
<td>65%</td>
<td>67%</td>
<td>16.5</td>
</tr>
<tr>
<td>Wasserlauf, 2015</td>
<td>201</td>
<td>61%</td>
<td>60%</td>
<td>12</td>
</tr>
<tr>
<td>Squara, 2015</td>
<td>376</td>
<td>76%</td>
<td>73%</td>
<td>18</td>
</tr>
<tr>
<td>Aryana, 2015</td>
<td>1196</td>
<td>60%</td>
<td>77%</td>
<td>12</td>
</tr>
<tr>
<td>Luik, 2015</td>
<td>315</td>
<td>63%</td>
<td>64%</td>
<td>6</td>
</tr>
<tr>
<td>Straube, 2016</td>
<td>373</td>
<td>60%</td>
<td>70%</td>
<td>17</td>
</tr>
</tbody>
</table>

*From references 11 to 18.


Results of repair of iliac artery aneurysms with the sandwich technique

Ryan A. Shutze, Wes Oglesby, Allen Lee, MD, and William P. Shutze, MD

Patients undergoing endovascular repair (EVAR) of aortoiliac or iliac artery aneurysms may require sacrifice of one or both internal iliac arteries (IIAs). Until Food and Drug Administration–approved commercial grafts became available, endovascular IIA preservation was accomplished using the “sandwich” technique, but limited information is available regarding the results of this method. After obtaining institutional review board approval, we identified patients undergoing IIA preservation with the sandwich technique during EVAR at our institution. The patients have been followed prospectively since being identified to record patency rates and vascular symptoms or events. Twenty-four procedures were performed from 2011 through 2015 to treat iliac artery aneurysms. Fourteen of these procedures were done with concomitant EVAR using different endografts (Gore Excluder 11, Endologix AFX 2, Cook Zenith 1). Five were done to extend a previous EVAR that had developed a type Ib endoleak, 2 for an isolated external iliac artery aneurysm, 3 for an anastomotic aneurysm from a previous aortobiiliac graft, and 2 for isolated iliac aneurysm repair. There were 25 sandwich grafts (unilateral in 19, bilateral in 6). Contralateral embolization was performed in 5 cases. Immediate success rates were high, and patency rates were excellent at intermediate follow-up. Intraoperative type 3 endoleaks were not uncommon but usually resolved postoperatively. Endovascular IIA preservation is feasible with currently available devices using this technique. This procedure is recommended for preservation of the IIA during endovascular treatment of aortoiliac and iliac artery aneurysms when anatomy requires IIA preservation.

Endovascular repair (EVAR) has become the main treatment modality for abdominal aortic aneurysm (AAA). Iliac aneurysms occur in about 20% of patients undergoing AAA repair; if iliac artery ectasia is included, this percentage increases to 40% (1–3). Isolated common iliac artery (CIA) aneurysms account for 2% of all intraabdominal aneurysms and may require repair to prevent rupture if they are symptomatic or $>$35 mm in diameter (4). Because of this, patients undergoing EVAR of an aortoiliac or iliac artery aneurysm may require sacrifice of one or both internal iliac arteries (IIAs). This sacrifice has been accomplished using the occlude (with coils or plugs) and extend method (2, 3), but this method has the unfortunate consequence of increasing the risk for adverse effects such as buttock claudication, ischemic colitis, erectile dysfunction, spinal cord injury, and peroneal necrosis in a significant number of patients (1, 5, 6). Because of this risk, attempts have been made at IIA preservation during EVAR. The first Food and Drug Administration–approved commercial grafts for this purpose only became available in 2016, so IIA preservation has been accomplished using surgical revascularization, the bell-bottom technique, or surgeon-modified grafts (1, 7–9). Each of these methods has its limitations, so the sandwich technique (10) was developed (Figure 1). Since limited information is available regarding its results, we reviewed our experience with the sandwich technique for IIA preservation to better determine its immediate success and complications, as well as the long-term durability and patency of the iliac grafts.

METHODS

After obtaining institutional review board approval, we identified patients undergoing IIA preservation with the sandwich technique during EVAR at our institution. The patients have been followed prospectively since being identified to record patency rates, vascular symptoms, and other events such as reintervention or endoleaks. Patients were selected for IIA preservation on an individual basis if they were deemed to be at increased risk for complications from IIA occlusion. Patients were included if they had a patent inferior mesenteric artery that would be sacrificed, planned occlusion of the contralateral IIA, or an occluded contralateral IIA. Other patients selected for IIA preservation included very active patients who did not want to risk developing buttock claudication. Patients with IIA aneurysms were also treated with the sandwich technique since exclusion of the IIA aneurysm would require occlusion of the branches of the IIA, which is known to increase the risk of ischemic complications.

EVAR using the sandwich technique consists of eight steps: 1) bilateral femoral artery access (either percutaneous or open)
DISCUSSION

The presence of a dilated or aneurysmal CIA complicates the treatment of AAA, whether the treatment is with open surgical repair (12) or EVAR (13). As AAA treatment shifted from open repair to EVAR, the management of the IIA initially involved sacrifice. This meant occluding the ipsilateral IIA (with a plug or coils) and extending the end of the endograft into the EIA (5). This type of approach has been referred to as occlude and extend (14). Unfortunately, this leaves a significant number of patients with limiting buttock claudication. The risk of this is 16% to 50% if unilateral closure is performed but rises to 80% if bilateral IIA occlusion is done (15). There are other significant complications related to IIA sacrifice. These include spinal cord ischemic colitis (6), and erectile dysfunction (19).

After these hazardous sequelae became recognized, the importance of IIA preservation became more apparent. Initial attempts at preservation employed surgical revascularization of the IIA through a retroperitoneal exposure at the time of the endovascular aneurysm repair. However, an analysis of retroperitoneal (versus transabdominal) IIA revascularization showed an increase in surgical time, blood loss, complications, and length of stay (20), suggesting that EVAR plus retroperitoneal IIA

RESULTS

Twenty-four procedures were performed from 2011 through 2015 to treat iliac artery aneurysms. There were 22 men and 2 women with a mean age of 74 years (range, 63–87). Aneurysms were present in the CIA in 20 and in the IIA in 10, with a mean diameter of 4 cm (range, 2.6–9). Fourteen of these procedures were done with concomitant EVAR using different endografts (Gore Excluder 11, Endologix AFX 2, Cook Zenith 1). Five were done to extend a previous EVAR that had developed a type Ib endoleak, 2 for an isolated EIA aneurysm, 3 for an anastomotic aneurysm from a previous aortobiiliac graft, and 2 for isolated iliac aneurysm repair. There were 25 sandwich grafts (unilateral 19, bilateral 6) in the EIA (Viabahn 20, Excluder 2, Endologix 1, iCast 1) and in the IIA (Viabahn 24, iCast 1). Contralateral embolization was performed in 5 cases. Percutaneous femoral access was possible in 19 cases, contralateral embolization was necessary in 5, and brachial delivery was needed in 18. The immediate technical success rate was 100%, and average values were as follows: operative time, 210 minutes; estimated blood loss, 381 cc; fluoroscopy time, 45 minutes; contrast volume, 145 cc; and length of stay, 2.2 days. The only endoleaks present at the completion of the operation were type 3 (9).

Mean follow-up time was 19 months (range, 1–47). Of the 9 type III endoleaks observed on completion angiography, 8 resolved on follow-up computed tomography angiography and one required endoprosthetic extension. Six patients have stable aneurysms with small type II endoleaks. Two patients were lost to follow-up, but of the remaining 22 patients (25 sandwich grafts), 24 (96%) of the external iliac limbs were patent and 24 of the internal iliac limbs were patent. No patient had buttock claudication, bowel ischemia, or other pelvic arterial complication postoperatively, and 4 patients died during the follow-up period.

**Figure 1.** Internal iliac artery preservation techniques. (a) Occlude and extend: Red arrow demonstrates coil in internal iliac artery, and white arrow points to extension graft in external iliac artery. (b) Bell-bottom: Arrow points to large-diameter extender. (c) Sandwich graft: Arrows point to bilateral internal arteries. (d) Iliac branch graft: The white arrow points to the left iliac artery branch graft, the orange arrow points to the right external iliac artery branch graft, and the yellow arrow points to the right internal iliac artery branch graft.

and possibly left brachial artery access; 2) bifurcated stent-graft main body insertion through an ipsilateral femoral approach, positioned such that the distal end of the iliac limb is 1 cm above the IIA origin; 3) catheterization of the ipsilateral IIA through the EVAR main body via left brachial (or contralateral femoral) access with a long 5F catheter and a 0.035-inch extra-stiff guidewire; 4) sheath placement into the CIA limb; 5) placement of a covered stent (Viabahn, Gore, Flagstaff, AZ; or iCast, Atrium Medical, Austin, TX) inside the IIA main trunk (or the posterior division of the IIA in the case of IIA aneurysm) with a 5 cm overlap into the iliac limb; 6) positioning of an ipsilateral external iliac artery (EIA) limb extension parallel to the IIA stent; 7) simultaneous deployment of the iliac limb stent-grafts and postdilation only of the covered stent portions within the EIA and IIA; and 8) for bilateral IIA aneurysms extending into both IIAs, repetition of steps 3 to 7. Device diameters for the iliac grafts were selected according to the technique of Matteo and Cunningham (11).
revascularization was not advantageous over a straightforward open repair. Another study compared surgical IIA bypass to standard EVAR and found that the incidence of postoperative complications doubled with either bypass or embolization of the IIA (21).

The bell-bottom technique was developed for iliac arteries that are not excessively aneurysmal to exclude the dilated CIA and preserve flow into the IIA and successfully achieve an endovascular seal in the iliac system. With this technique, the surgeon places a short but larger-diameter endograft (designed for the abdominal aortic neck) into the iliac end of the main endograft and out into the iliac artery (22). The lower end flares out similar to a pair of bell-bottom pants. The limitations of this technique are that the iliac artery cannot be larger than 32 mm and that an adequate length of CIA must be available to accommodate the devices needed and allow for seal. The advantage of the bell-bottom technique versus exclude and extend is a lower complication rate of 6% vs 38% (14). However, the bell-bottom technique has also been shown to lead to a higher incidence of reintervention in the follow-up period (14% vs 2%) (13).

The sandwich technique was initially developed to address these concerns (10). With this technique, the aortoiliac graft terminates in the CIA just above the bifurcation. Two parallel grafts are placed into the lower portion of the iliac limb of the main endograft. One extends into the EIA and the other extends into the iliac artery. This creates a bifurcation, but both grafts are compressed inside the iliac limb. The smaller channel into both grafts has led to the concern that a significant number of these grafts will subsequently occlude. Our series is the largest single-center series reported in the United States and demonstrates excellent patency of these grafts at mid-term follow-up.

A combined series of 23 sandwich technique procedures in 22 patients at 2 institutions has been reported (23). The mean operative time, fluoroscopy time, estimated blood loss, contrast use, length of stay, and patency rates of 95% for the EIA limb and 88% for the IIA limb were similar to our findings. Another corroborating finding in this series was that all intraoperative type 3 endoleaks resolved on follow-up. The study also noted a low incidence of postoperative endoleaks: one type 1b (treated with an extension device) and 3 benign type 2 endoleaks. None of the patients treated with the sandwich technique had ipsilateral buttock claudication, but 4 patients who had contralateral embolization of the IIA suffered from buttock claudication on the side of the IIA sacrifice postoperatively.

Recently, commercially made iliac artery branch devices have become available. However, these devices have certain limitations based on anatomic requirements. For one device to be used, the CIA must be at least 50 mm in length and have a minimum diameter of 18 mm (24). It has been demonstrated that this device would be appropriate for only 20% to 25% of potential candidates. For the other device to be used, a minimum CIA diameter of 17 mm is mandatory and a minimum distance from the lowermost renal artery to the IIA ostium of 165 mm, 175 mm, or 185 mm is needed depending on the size of the aortic main body endograft being used. As a study site for this device, we screened 10 patients with CIA aneurysms, and all failed enrollment based on anatomic criteria. The limitations of the iliac artery branch devices mean that a significant number of patients will require a different approach to their iliac artery anatomy. Until these devices improve to be more universally applicable, the sandwich technique for IIA preservation will be necessary.

There are multiple limitations to the study. This project was retrospective, there was no control group, and the patients were selected for acceptable anatomy. Nonetheless, this technique deserves appropriate consideration for patients at increased risk for complications during EVAR with IIA sacrifice.


Interpretation of positive troponin results among patients with and without myocardial infarction

Kristen M. Tecson, PhD, William Arnold, PhD, Tyler Barrett, MD, Robert Birkhahn, MD, Lori B. Daniels, MD, Christopher DeFilippi, MD, Gary Headden, MD, W. Frank Peacock, MD, Michael Reed, MD, Adam J. Singer, MD, Jeffrey M. Schussler, MD, Stephen Smith, MD, Martin P. Than, MD, and Peter A. McCullough, MD, MPH

Measuring cardiac troponins is integral to diagnosing acute myocardial infarction (AMI); however, troponins may be elevated without AMI, and the use of multiple different assays confounds comparisons. We considered characteristics and serial troponin values in emergency department chest pain patients with and without AMI to interpret troponin excursions. We compared serial troponin in 124 AMI and non-AMI patients from the observational Performance of Triage Cardiac Markers in the Clinical Setting (PEARL) study who presented with chest pain and had at least one troponin value exceeding the 99th percentile of normal. Because 8 assays were used during data collection, we employed a method of scaling the troponin value to the corresponding assay’s 99th percentile upper reference limit to standardize the results. In 81 AMI patients, 96% had elevated troponin at the first test following initial elevation, compared to 73% of the 43 non-AMI patients ($P < 0.001$). Scaling troponin to the 99th percentile of normal yielded a median value that was 4.8 [2.2, 14.1] times higher than the 99th percentile cutpoint among AMI patients, compared to 2.3 [1.5, 6.5] times higher among non-AMI patients ($P = 0.04$). The rise in serial scaled troponin values distinguished the AMI patients. Scaling to the 99th percentile was useful for comparing troponin when different assays were utilized.

High-sensitivity troponin I testing has been shown to improve the early diagnosis of acute myocardial infarction (AMI) and aid with risk stratification (1–3). Investigators using a registry in Australia and New Zealand determined that high-sensitivity troponin I testing was associated with fewer in-hospital adverse events for patients hospitalized with possible acute coronary syndrome (4). There are multiple non-AMI clinical scenarios, however, where troponin may exceed the 99th percentile, including renal failure, stroke, heart failure, pulmonary embolism, sepsis, and hypertension (5). We capitalized on a data set of chest pain patients who had serial troponin assays performed, had at least one positive value, and had central adjudication of the outcome of AMI. We compared the characteristics, as well as the dynamic rise and fall of troponin, in this group of patients to better understand how to quantitatively evaluate the excursion of troponin and relate it to the confirmed diagnosis of AMI.

METHODS

We performed retrospective analyses on data collected from a prospective, multicenter, observational study (Performance of Triage Cardiac Markers in the Clinical Setting [PEARL]) that examined the use of troponin for the diagnosis of AMI in patients ≥21 years of age who presented to the emergency department with symptoms of possible AMI from August 2014 through February 2015. Patients with symptoms including sharp or dull chest pain, tightness, sensations of heavy weight on the chest, pain in the jaw or neck, pain radiating down the arms, and dyspnea were monitored for approximately 24 hours. A team of 3 experienced adjudicators (1 emergency physician and 2 cardiologists) independently reviewed case report forms and the 12-lead electrocardiogram recorded during initial evaluation plus at least one additional electrocardiogram if obtained in the subject evaluation period to form a diagnosis of AMI or non-AMI using contemporary guideline definitions (6). Discrepancies were discussed until consensus was reached. All institutions received institutional review board approval and patients’ informed consent prior to conducting this study.

Troponin was evaluated using one of the following tests: Abbott ARCHITECT STAT TnI (7), Abbott i-STAT® POC

From Baylor Heart and Vascular Institute, Dallas, Texas (Tecson, McCullough); Baylor Scott & White Research Institute, Dallas, Texas (Tecson); Texas A&M Health Science Center College of Medicine, Dallas, Texas (Tecson, Schussler, McCullough); Department of Clinical Affairs, Alere Inc., San Diego, California (Arnold); Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, Tennessee (Barrett); New York Methodist Hospital, Brooklyn, New York (Birkhahn); Division of Cardiovascular Medicine, University of California San Diego Health, La Jolla, California (Daniels); Inova Heart and Vascular Institute, Falls Church, Virginia (DeFilippi); Medical University of South Carolina, Charleston, South Carolina (Headden); Baylor University Ben Taub Hospital, Houston, Texas (Peacock); International Heart Institute of Montana, Missoula, Montana (Reed); Department of Emergency Medicine, Stony Brook University Hospital, Stony Brook, New York (Singer); Division of Cardiology, Baylor University Medical Center, Dallas, Texas (Schussler, McCullough); Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, Texas (Schussler, McCullough); Hennepin County Medical Center Emergency Department, Minneapolis, Minnesota (Smith); Emergency Department, Christchurch Hospital, and University of Otago, Christchurch, New Zealand (Than); and The Heart Hospital Baylor Plano, Plano, Texas (McCullough).

Corresponding author: Peter A. McCullough, MD, MPH, Baylor Heart and Vascular Institute, 621 N. Hall Street, Suite H030, Dallas, TX 75226 (e-mail: peteramccullough@gmail.com).
cTnI (8), Alere Triage® POC cTnI (9), Beckman Coulter Access® AccuTnI®+3 (10), Ortho VITROS® TnI ES (11), Roche Cobas® TnT (12), Siemens ADVIA Centaur® TnI-Ultra (13), or Siemens Dimension Vista® TnI (14). These tests yielded results in different measurable ranges with unique 99th percentile cutpoints. For that reason, we treated the data in two ways. First, we dichotomized the results as being either elevated or not elevated based on the 99th percentile cutoff rules for each assay. Second, to standardize the many troponin assays, we scaled the results using the ratio of the observed troponin value divided by the 99th percentile upper reference limit (“normal” value) (15). For example, a patient with a troponin value of 0.1 ng/mL using the Roche Cobas® TnT, which has a 99th percentile upper reference limit of 0.01 ng/mL, would have a scaled result of $0.1/0.01 = 10$. We interpret this as a troponin value that is 10 times that of the 99th percentile of normal. We considered results from both methods across the sequence of troponin tests following the initial elevated result.

Continuous variables are reported as medians [quartile 1, quartile 3], and categorical variables are reported as frequencies (percent). Differences between diagnosis groups were tested using Fisher’s exact test, 2-sample t test, or Wilcoxon rank sum test, as appropriate. All analyses were conducted using SAS 9.4, Cary, NC.

RESULTS

A total of 458 patients enrolled in the PEARL study from 8 facilities. Of the 458 patients, 20 withdrew during the observation period, leaving a total of 438 patients who received an adjudicated diagnosis. There were 1179 total troponin values, 391 (33%) of which were greater than the corresponding 99th percentile upper reference limit. A total of 124 (28%) of the 438 patients had at least one elevated troponin level and are the focus of this article. Eighty-one (65%) of the 124 patients were adjudicated as AMI and the remaining 43 (35%) as non-AMI. Among these 124 patients, the AMI group was more likely to have previously known coronary artery disease than the non-AMI group (57% and 31%, respectively; $P = 0.008$). Conversely, the AMI group was less likely to have renal failure compared to the non-AMI group (5% and 35%, respectively; $P < 0.001$). Sample characteristics for the 124 patients with elevated troponin appear in Table 1.

The median time from arrival to first elevated troponin was 1.17 [0.70, 3.25] hours for AMI patients and 0.97 [0.60, 4.13] hours for non-AMI patients ($P = 0.08$) (Figure 1). Additionally, the median time between the first elevated troponin and subsequent test was 3.79 [2.25, 6.77] hours for AMI patients and 3.80 [2.25, 5.70] hours for non-AMI patients ($P = 0.81$). Similarly, the median times between the first and second test following the initial elevation, as well as the second and third test following the initial elevation, did not differ ($P = 0.95$ and 0.37, respectively). The median number of troponin tests performed per patient until the first elevation occurred was 1 for both AMI and non-AMI patients; however, the median total number of tests performed for AMI patients was 4 [3, 5], compared to 3 [2, 4] for non-AMI patients ($P = 0.01$).

### Table 1. Study sample characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes (n = 81)</th>
<th>No (n = 43)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.6 ± 11.1</td>
<td>57 ± 16.7</td>
<td>0.58</td>
</tr>
<tr>
<td>Men</td>
<td>56 (69%)</td>
<td>28 (65%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Black</td>
<td>18 (22%)</td>
<td>17 (40%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0 (1%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56 (69%)</td>
<td>21 (51%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (9%)</td>
<td>4 (9%)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10 (12%)</td>
<td>6 (14%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Alcohol</td>
<td>15 (19%)</td>
<td>5 (12%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Arthritis</td>
<td>7 (9%)</td>
<td>4 (9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Asthma</td>
<td>6 (7%)</td>
<td>8 (19%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>46 (57%)</td>
<td>13 (31%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cancer</td>
<td>13 (16%)</td>
<td>6 (14%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>10 (12%)</td>
<td>4 (10%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21 (26%)</td>
<td>18 (42%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Emphysema</td>
<td>2 (3%)</td>
<td>1 (2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Gallstone</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>2 (3%)</td>
<td>3 (7%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Migraine</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>4 (5%)</td>
<td>3 (7%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4 (5%)</td>
<td>15 (35%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Seizure</td>
<td>1 (1%)</td>
<td>3 (7%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Smoke</td>
<td>43 (53%)</td>
<td>17 (41%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (1%)</td>
<td>3 (7%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2 (3%)</td>
<td>3 (7%)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

![Figure 1. Hours from arrival at the emergency department to the first elevated troponin result by myocardial infarction diagnosis.](image-url)
Of the 124 patients who had at least one elevated troponin, 114 (91.9%) had at least one subsequent test performed. Among the 77 retested AMI patients, 74 (96.1%) were confirmed to have elevated troponin on the following lab draw. In contrast, only 27 (73.0%) of the 37 retested non-AMI patients had an elevated result at the following test ($P < 0.001$) (Figure 2). After the first elevated troponin, a difference in the rate of elevation was not observed between AMI and non-AMI patients on the second or third subsequent lab draws ($P = 0.60$ and 0.31, respectively).

When considered as a continuous variable scaled to the 99th percentile upper reference limit, we observed a median troponin that was 4.8 [2.2, 14.1] times higher than the upper limit of normal among AMI patients, compared to a median 2.3 [1.5, 6.5] times higher than the upper limit of normal among non-AMI patients ($P = 0.04$). The AMI group’s median troponin during the first test following the initial elevation was 10.2 [3.4, 73.3] times that of normal compared to 2.0 [0.9, 5.5] times that of normal for the non-AMI group ($P < 0.001$). Further, the median paired difference between patients’ initial elevated troponin and subsequent test was 4.1 [0.1, 39.7] for AMI patients and –0.2 [–1.6, 0.5] for non-AMI patients ($P < 0.001$). Additionally, the median scaled troponin was 16.7 [4.3, 95.3] for AMI patients on the second lab draw following the initial elevated result, compared to 3.3 [2.0, 16.7] for non-AMI patients ($P = 0.002$). Finally, the median scaled troponin was 18.8 [4.0, 49.6] for AMI patients on the third lab draw following the initial elevation compared to 4.6 [2.1, 18.6] for non-AMI patients ($P = 0.03$). To verify that these findings were not driven by an uneven utilization of assays between AMI and non-AMI patients, we conducted chi-square tests and confirmed that there were no significant differences between the groups’ assays at any of the four lab draws analyzed ($P$ values = 0.30, 0.31, 0.44, 0.07). The differences and rates of change in median scaled troponin for AMI and non-AMI patients are shown in Figure 3 and Figure 4, respectively.

**Figure 2.** Rates of troponin elevation by diagnosis group and lab draw sequence.

**DISCUSSION**

Among 124 emergency department patients who presented with chest discomfort and at least one positive troponin value using contemporary sensitivity assays, 65.3% were confirmed to have AMI by an independent adjudication panel. Ninety-six percent of the AMI patients had confirmatory elevated troponins upon serial testing in the emergency department. Use of the 99th percentile cutpoint of normal and scaling of the elevation to that anchor provided clear differences in the excursions of troponin between those with and without AMI.

Our analyses provide a response to the criticisms regarding the high rate of false-positive cases generated as a result of considering the 99th percentile cutoff as positive or negative on single tests (16, 17). Considering the change in serial values of troponin concentration scaled to the 99th percentile has previously been shown as superior to the 99th percentile cutoff alone (18). After performing these analyses, we also considered the differences in raw troponin values between AMI and non-AMI patients at the 4 timepoints and found that they were in agreement with the scaled results ($P = 0.006$, $< 0.001$, $< 0.0001$, 0.04). Although using the raw and scaled values yielded similar statistical results, the conclusions drawn with the raw values were far more confounded due to the use of several assays,
whereas the scaled values offered a standardized interpretation, regardless of assay.

We found that the first troponin test alone was not sufficiently informative, nor was it elevated at an earlier time in those diagnosed as AMI or non-AMI. There was a quantitative difference in the rate of troponin elevation at the first test following initial elevation; however, a significant difference in the rates of troponin elevation was not observed in the second and third subsequent draws following the initial elevation among AMI and non-AMI patients. This was likely attributed to the differing rates of clinically driven retesting within each group over time. For example, only 23 (53.5%) patients without an AMI were tested ≥2 times after the initial elevation, compared to 67 (82.7%) of those retested with an AMI. This was not surprising because AMI patients were more likely to have a history of coronary artery disease pointing to a higher clinical suspicion and a more assiduous approach to the diagnosis of AMI.

Although we did not observe significant differences in dichotomized rates of troponin elevation at every lab draw, we did observe higher median scaled troponin values in AMI patients compared to non-AMI patients. As shown in Figure 3, the gradient of the troponin line sharply increased for those with AMI, while the line for those without AMI was relatively flat. This indicated that those with AMI had true ischemic rises, while those without AMI had slight elevations in troponin attributed to other causes. These results confirmed the findings of a previous study, which suggested that the method of scaling troponin in terms of the 99th percentile is viable (19). In another study, patients with asymptomatic AMI (as diagnosed via electrocardiogram) were shown to have higher median high-sensitivity troponin I values than patients who did not have an AMI (20). Our results and those of others suggest that the interpretation of the excursion of serial troponin rather than single troponin values is critical in the diagnosis of AMI.

This work was a retrospective secondary analysis of an observational data cohort and is therefore subject to the inherent limitations of such studies. The study enrolled via convenience sample, so there is the potential for selection bias. We conducted analyses based on many different contemporary troponin assays, including troponin I and troponin T across a variety of laboratory platforms. The multiplicity of testing was clinically determined and was clearly biased by the physician’s suspicion of AMI. Troponin testing provides no information to distinguish between type 1 or type 2 myocardial infarction. Because this analysis considered only those patients with elevated troponin, our sample size was small, which limited the power and generalizability of the results. Finally, we recognize that our study results may not generalize to populations with greater comorbidities, including renal failure, sepsis, heart failure, and other illnesses, where there may be greater proportions of troponin elevation or greater difficulty in determining AMI (21–23).

ACKNOWLEDGMENTS

The PEARL study was sponsored by Alere. The analysis and manuscript writing were funded in part by the Baylor Health Care System Foundation.

AUTHOR DISCLOSURES

William D. Arnold, PhD, is the director of clinical affairs at Alere San Diego, Inc., and is a full-time employee of that organization. Dr. Barrett is a consultant for Red Bull GmbH, Fuschl am See, Salzburg, and Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, and provides research support as site principal investigator for Janssen Pharmaceuticals, Inc., New Jersey, and Alere, San Diego, California. Dr. Peacock has research grants with Abbott, Alere, Banyan, Cardiorentis, Janssen, Portola, Pfizer, Roche, and ZS Pharma; is a consultant for Alere, Beckman, Boehringer-Ingelheim, Cardiorentis, Instrument Labs, Janssen, Phillips, Portola, Prevencion, Singulex, The Medicine’s Company, and ZS Pharma; and has ownership interests with Comprehensive Research Associates LLC and Emergencies in Medicine LLC. Dr. Smith is a consultant for Alere, Siemens, and Roche. Dr. Than has received institutional funding for clinical trials, as well as personal funding for education from Abbott, Alere, and Beckman. He has also received funding for speaking from Abbott, Alere, and Roche. The remaining authors have nothing to disclose.


Relation between proprotein convertase subtilisin/kexin type 9 and directly measured low-density lipoprotein cholesterol

Kristen M. Tecson, PhD, Katherine S. Panettiere-Kennedy, BS, Jane I. Won, BS, Puja Garg, PhD, Oluseun Olugbode, MS, and Peter A. McCullough, MD, MPH

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a regulator of low-density lipoprotein cholesterol (LDL-C) receptor (LDL-R) recycling and, thus, is a determinant of plasma LDL-C concentration. We sought to determine the relation between serum concentrations of PCSK9 and LDL-C while considering a variety of influential variables, including treatment for dyslipidemia. Using a prospective lipid clinic registry, we evaluated clinical variables, the results of advanced lipid testing, and PCSK9 concentrations determined by immunoassay. We evaluated the relationship between directly measured LDL-C and PCSK9 in serum by performing a simple linear regression. Correlation analyses were performed to examine the relationships of PCSK9 to other clinical and laboratory values and to test for differences in median PCSK9 across patient groups. Factors identified as potential predictors were considered jointly in a multivariate model. For the 26 patients in the analyses, a relationship was not detected between LDL-C and PCSK9 ($r = 0.009, P = 0.97$); however, PCSK9 was correlated with C-peptide ($r = 0.48; P = 0.01$) and heart rate ($r = 0.52; P = 0.006$). Median PCSK9 values differed between statin users (284.0 ng/mL [quartile 1 = 241.0, quartile 3 = 468.0]) and nonusers (219.0 ng/mL [quartile 1 = 151.0, quartile 3 = 228.0]; $P = 0.02$). More investigation is needed to evaluate the relationship between LDL and PCSK9, as well as the determinants of PCSK9, a major factor regulating cholesterol concentrations.

About 73.5 million (31.7%) adults in America have high levels ($\geq 130$ mg/dL) of low-density lipoprotein cholesterol (LDL-C), which is a causative factor for myocardial infarction, ischemic stroke, and cardiovascular death (1). LDL-C receptors (LDL-R) are found in high density on the surface of hepatocytes and work to remove cholesterol from the blood; however, the proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme binds to LDL-R, targets the LDL-R complex for lysosomal destruction, and prevents recycling of the LDL-R to the surface (Figure 1). When PCSK9 is removed, it cannot bind with LDL-R, which in turn allows the LDL-R to remove larger quantities of cholesterol from the blood than would otherwise be possible. Inhibiting the PCSK9 enzyme has been shown to lower cholesterol an average of 45% to 60% from baseline, irrespective of starting LDL-C and background treatment. The US Food and Drug Administration approved the first two PCSK9 inhibitors, alirocumab and evolocumab, in 2015 (2, 3). Genetic and metabolic factors contributing to LDL-C have been studied; however, less is known about the associations between plasma PCSK9 and clinical variables.

The Baylor Preventive Cardiology and Advanced Lipidology Program was conceived to evaluate and manage patients...
with family histories of premature cardiovascular death, healed myocardial infarction, and acute coronary syndrome events despite optimal medical therapy. A registry was created using patients referred to the program at the Baylor Heart and Vascular Hospital, Dallas, Texas, and the Baylor Heart Hospital, Plano, Texas. This paper describes these patients with respect to serum PCSK9 concentrations, catabolic determinants including apolipoprotein and lipid fractions, resultant LDL-C, other atherogenic lipid particles, the effect of PCSK9 on LDL, and factors contributing to PCSK9.

METHODS
Patients who were referred to the Baylor Preventive Cardiology and Advanced Lipidology Program were added to the preventive cardiology registry beginning in 2015 after informed consent was obtained. This study was approved by Baylor’s institutional review board. Laboratory values were provided via Atherotech, Inc. (Birmingham, AL). PCSK9 concentrations were measured in serum via a commercial quantitative sandwich enzyme immunoassay that utilized an anti-PCSK9 polyclonal antibody as the capture antibody.

We examined patients in this registry with available laboratory results as of April 7, 2016. We imputed values for LDL particle concentration, heart rate (HR), systolic blood pressure, and diastolic blood pressure, which were missing at <8%. We first studied the distributions of directly measured LDL-C and total secreted PCSK9 and then analyzed the strength of their linear relationship by performing a simple linear regression. We performed correlation (r) analyses using Pearson’s correlation and Spearman’s rank correlation, as appropriate, to examine the relationship of PCSK9 and other clinical and laboratory values. We tested for differences in median PCSK9 across patient characteristic groups using the Wilcoxon rank sum test (for groups with >5 patients). Those identified as potential predictors were considered jointly in a multivariate model using a stepwise selection method. Categorical variables are reported as frequencies and percents. Continuous variables are reported as means ± standard deviations or medians [25%, 75%], if skewed.

RESULTS
There were 26 patients in the preventive cardiology registry with available laboratory results as of April 7, 2016. The characteristics of these patients are presented in Table 1. Patients were primarily Caucasian (24; 92.3%) males (15; 57.7%), with an average age (± standard deviation) of 50.1 ± 13.7 years. Half (13) of the patients had hypertension, and over one-third (9; 34.6%) had a recent percutaneous coronary intervention. Although there were 2 (7.7%) subjects with diabetes, 3 subjects were taking diabetes medication (the subject without diabetes was taking metformin). The average patient was overweight, with a body mass index of 28.4 ± 6.4 kg/m².

The smoothed kernel densities of total secreted PCSK9 and LDL-C are shown in Figure 2. PCSK9 was heavily skewed to the right, with a median of 253 [219, 336] ng/mL. LDL-C was mostly symmetrical with a mean of 107.7 ± 43.1 mg/dL. Only 0.01% of the variability in LDL-C was explained by the linear regression of PCSK9 on LDL-C; a statistically significant linear relationship was not detected (r = 0.009; P = 0.97). The regression of PCSK9 on LDL-C along with the 95% confidence interval for mean predicted values is presented in Figure 3.

A moderate positive linear correlation was detected between PCSK9 and C-peptide (r = 0.48; P = 0.01). A similar moderate positive linear relationship was detected between PCSK9 and HR (r = 0.52; P = 0.006). The following variables did not have a significant correlation with PCSK9: total cholesterol, LDL

Table 1. Characteristics of the 26 patients in the preventive cardiology registry

<table>
<thead>
<tr>
<th>Variable</th>
<th>Count (%)</th>
<th>mean ± SD; median [25%, 75%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>15 (58%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.1 ± 13.7</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>24 (92%)</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>12 (71%)*</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (50%)</td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5 (20%)†</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>Recent percutaneous intervention</td>
<td>9 (35%)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>3 (12%)</td>
<td></td>
</tr>
<tr>
<td>Low-density lipoprotein (mg/dL)</td>
<td>121 [96, 174]</td>
<td></td>
</tr>
<tr>
<td>Proprotein convertase subtilisin/kexin type 9 (ng/mL)</td>
<td>253 [219, 336]</td>
<td></td>
</tr>
<tr>
<td>High-density lipoprotein (mg/dL)</td>
<td>56.6 ± 20.3</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>114.5 [90, 232]</td>
<td></td>
</tr>
<tr>
<td>Fasting at time of lab</td>
<td>16 (73%)‡</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>72.0 ± 13.9</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>127.9 ± 16.0</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78.7 ± 9.1</td>
<td></td>
</tr>
<tr>
<td>Height (inches)</td>
<td>68.3 ± 4.3</td>
<td></td>
</tr>
<tr>
<td>Weight (pounds)</td>
<td>189.5 ± 50.0</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.4 ± 6.4</td>
<td></td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>14 (54%)</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>17 (65%)</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>9 (35%)</td>
<td></td>
</tr>
</tbody>
</table>

*Out of 17 patients.
†Out of 25 patients.
‡Out of 22 patients.
particle concentration, high-density lipoprotein (HDL), HDL2, HDL3, HDL2A, HDL2B, HDL2C, HDL3A, HDL3B, pro-B-type natriuretic peptide, 1,5-anhydroglucitol (GlycoMark), apolipoprotein B, triglycerides, systolic blood pressure, diastolic blood pressure, height, weight, and body mass index. The correlation matrix for select variables is provided in Table 2.

Patients taking statins had a median PCSK9 value of 284.0 ng/mL [241.0, 468.0], while patients not taking a statin had a median PCSK9 of 219.0 ng/mL [151.0, 228.0]; a significant difference in median PCSK9 was detected between these two groups ($P = 0.02$). In contrast, median PCSK9 did not differ significantly by gender ($P = 0.83$), presence of hypertension ($P = 0.66$), or use of anticoagulation medication ($P = 0.63$). The mean PCSK9 did not differ for those who had a recent percutaneous intervention ($P = 0.07$) or for those taking a beta-blocker ($P = 0.19$).

Based on the correlation analyses and hypothesis tests, C-peptide, HR, and statin use were identified as variables to be considered for a multivariate model of PCSK9. A stepwise selection method identified the optimal model of PCSK9 to have only one predictor, C-peptide (overall $P = 0.01$), which had a moderate positive correlation of $r = 0.48$. We confirmed this result by building a multivariate model utilizing all three predictors, which resulted in an overall $P$ value of 0.08.

**DISCUSSION**

We found that in a small sample with detailed clinical and laboratory measures, there was no significant linear relation between directly measured LDL-C and PCSK9. In contrast, factors such as C-peptide and HR, which may reflect neurohormonal activation, appeared to have relationships to PCSK9 concentration (4). A relationship was also detected between statin use and PCSK9 concentration.

A larger study ($n = 3138$) conducted in Dallas in the early 2000s created a sample representative of the population characteristics from that geographical area. For subjects not on statins, the study reported a median PCSK9 serum level of 487 (range 22–2988 ng/mL) and observed significantly higher levels for women than men. There was also a weak correlation between PCSK9 and LDL-C ($r = 0.24$), as well as with triglycerides, insulin, and glucose (5). Similarly, a literature review by Lambert et al stated that studies consistently report positive correlations ($r = 0.15–0.58$) between circulating PCSK9 and LDL-C despite the fact that PCSK9 concentrations are not ideal surrogates for PCSK9 function (6–9). For these reasons, we anticipated finding a relationship between LDL-C and PCSK9 in our sample. Interestingly, 65.4% of the patients in our study were taking a statin, a higher proportion than typically observed in population-based studies (10). We observed a 30% higher concentration of PCSK9 in statin users, which may account for the reduced observed association between LDL-C and PCSK9, as statin use has been shown to increase the variability in this relationship (11). The observed treatment effect of statins on PCSK9 was in line with previous estimates of 14% to 47% (9). Our study adds to previous reports from larger populations in that we used directly measured LDL-C instead of a calculated value, thus enhancing precision of this measure and reducing the influence of triglycerides on the computation of LDL-C (12, 13).

We found a moderate correlation ($r = 0.48$) between PCSK9 and C-peptide. This may support previous reports of PCSK9’s relationships with insulin and glucose, as C-peptide is the stable insulin fragment and is a correlate of both plasma glucose and insulin resistance (9). Higher PCSK9 concentrations in those with hyperinsulinemia or insulin resistance may explain the modestly higher LDL-C values described in this population. Consistent with these observations, insulin resistance and the metabolic syndrome are associated with activation of the sympathetic nervous system, and this may have been reflected in the increased HR values we observed. We also detected a moderate correlation ($r = 0.58; P = 0.002$) between C-peptide and age, which was consistent with previous reports.
for older patients, but did not detect a relationship between PCSK9 and age.

The patient with the highest value of PCSK9 (>1000 ng/mL) was the oldest patient in the sample (78.6 years) and had a phenotype of heterozygous familial hypercholesterolemia with a treated LDL-C of 79 mg/dL; he was overweight (body mass index = 28.2 kg/m²), hypertensive, had extensive coronary artery disease with a prior bypass surgery, and was taking a statin. The patient had been taking alirocumab biweekly since October 2015. His lab draw included in this analysis occurred 10 days after the second administration of the drug. He was suspected of having a gain-of-function mutation of PCSK9, which results in high levels of LDL-C (14).

This study had all of the limitations of a small, cross-sectional pilot. The generalizability of these results is limited due to the small sample size and lack of racial diversity (>90% Caucasian). Differences in fasting times and other clinical factors could have played a role in preanalytic variability of PCSK9 concentrations. It is possible that the use of a polyclonal antibody as the capture antibody to measure PCSK9 in the assay created another level of analytic variability. The assay used to yield PCSK9 results had an upper limit of detection of 1000 ng/mL; however, only one patient had a value exceeding the upper limit, so it is unlikely that the quality of the analyses suffered due to the upper detection limit. Because proinsulin was not measured, we were unable to assess its relationship with PCSK9 or C-peptide. Laboratory values were drawn only one time per patient; hence the data presented in this manuscript were not robust to fluctuations, and we cannot make inferences on serial changes over time.

In conclusion, when using directly measured LDL-C in a mixed population of statin-treated and nontreated patients, we did not find an association between PCSK9 and LDL-C. PCSK9 had a significant linear relation with C-peptide and HR individually; however, the variables were only moderately associated, with correlations of approximately 0.5. This work also confirmed the influence of statins, which were associated with a 30% increase in PCSK9 levels. More work is needed to evaluate the relationship between LDL and PCSK9, as well as the determinants of PCSK9, a major factor regulating cholesterol concentrations.


Table 2. Pearson’s correlation matrix for select variables among 26 patients in the preventive cardiology registry

<table>
<thead>
<tr>
<th></th>
<th>APOB</th>
<th>CRP</th>
<th>HDL</th>
<th>LDL (calculated)</th>
<th>LDL (direct)</th>
<th>LDL PC</th>
<th>LPA</th>
<th>LP-PLA2</th>
<th>PCSK9</th>
<th>TC</th>
<th>TRIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOB</td>
<td>1</td>
<td></td>
<td></td>
<td>-0.14</td>
<td>-0.26</td>
<td>0.82</td>
<td></td>
<td>-0.26</td>
<td>0.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>0.48</td>
<td></td>
<td></td>
<td>-0.12</td>
<td>-0.16</td>
<td>-0.16</td>
<td>-0.12</td>
<td>0.48</td>
<td>-0.70</td>
<td>-0.28</td>
<td>0.19</td>
</tr>
<tr>
<td>HDL</td>
<td>0.57</td>
<td></td>
<td></td>
<td>0.09</td>
<td>0.67</td>
<td>0.67</td>
<td>0.57</td>
<td>0.45</td>
<td>0.45</td>
<td>0.54</td>
<td>-0.56</td>
</tr>
<tr>
<td>LDL (calculated)</td>
<td>1</td>
<td></td>
<td></td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>0.67</td>
<td>0.67</td>
<td>0.98</td>
<td>0.90</td>
</tr>
<tr>
<td>LDL (direct)</td>
<td></td>
<td></td>
<td></td>
<td>0.09</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>0.79</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL PC</td>
<td></td>
<td></td>
<td></td>
<td>0.67</td>
<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
<td>0.98</td>
<td>0.98</td>
<td>0.98</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LPA</td>
<td>1</td>
<td></td>
<td></td>
<td>0.17</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LP-PLA2</td>
<td></td>
<td></td>
<td></td>
<td>0.12</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>PCSK9</td>
<td></td>
<td></td>
<td></td>
<td>0.12</td>
<td>0.38</td>
<td>0.38</td>
<td>0.38</td>
<td>0.38</td>
<td>0.38</td>
<td>0.38</td>
<td>0.38</td>
</tr>
<tr>
<td>TC</td>
<td></td>
<td></td>
<td></td>
<td>0.09</td>
<td>0.49</td>
<td>0.49</td>
<td>0.49</td>
<td>0.49</td>
<td>0.49</td>
<td>0.49</td>
<td>0.49</td>
</tr>
<tr>
<td>TRIG</td>
<td></td>
<td></td>
<td></td>
<td>0.56</td>
<td>0.59</td>
<td>0.59</td>
<td>0.59</td>
<td>0.59</td>
<td>0.59</td>
<td>0.59</td>
<td>0.59</td>
</tr>
</tbody>
</table>

APOB indicates apolipoprotein B; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PC, particle concentration; LPA, lipoprotein(a); LP-PLA2, lipoprotein-associated phospholipase A2; PCSK9, proprotein convertase subtilisin/kexin type 9; TC, total cholesterol; TRIG, triglycerides.


Factors associated with reduced radiation exposure, cost, and technical difficulty of inferior vena cava filter placement and retrieval

Matthew Neill, MD, Hearns W. Charles, MD, Daniel Pflager, and Amy R. Deipolyi, MD, PhD

We sought to delineate factors of inferior vena cava filter placement associated with increased radiation and cost and difficult subsequent retrieval. In total, 299 procedures from August 2013 to December 2014, 252 in a fluoroscopy suite (FS) and 47 in the operating room (OR), were reviewed for radiation exposure, fluoroscopy time, filter type, and angulation. The number of retrieval devices and fluoroscopy time needed for retrieval were assessed. Multiple linear regression assessed the impact of filter type, procedure location, and patient and procedural variables on radiation dose, fluoroscopy time, and filter angulation. Logistic regression assessed the impact of filter angulation, type, and filtration duration on retrieval difficulty. Access site and filter type had no impact on radiation exposure. However, placement in the OR, compared to the FS, entailed more radiation (156.3 vs 71.4 mGy; \( P = 0.001 \)), fluoroscopy time (6.1 vs 2.8 min; \( P < 0.001 \)), and filter angulation (4.8° vs 2.6°; \( P < 0.001 \)). Angulation was primarily dependent on filter type (\( P = 0.02 \)), with VenaTech and Denali filters associated with decreased angulation (2.2°, 2.4°) and Option filters associated with greater angulation (4.2°). Filter angulation, but not filter type or filtration duration, predicted cases requiring >1 retrieval device (\( P < 0.001 \)) and >30 min fluoroscopy time (\( P = 0.02 \)). Cost savings for placement in the FS vs OR were estimated at $444.50 per case. In conclusion, increased radiation and cost were associated with placement in the OR. Filter angulation independently predicted difficult filter retrieval; angulation was determined by filter type. Performing filter placement in the FS using specific filters may reduce radiation and cost while enabling future retrieval.

 Inferior vena cava filter (IVCF) placement is performed to prevent pulmonary embolism in patients with or at risk of deep venous thrombosis in the abdomen, pelvis, and lower extremities and in those who have a contraindication to or have failed anticoagulation. The number of IVCF placements has increased in the United States over time (1). There is a national initiative to remove optional filters as soon as they are achievable, not only to protect patients but also to protect staff from scattered radiation (4, 5). Understanding variables that lead to higher procedural radiation doses can suggest strategies to reduce dose. Furthermore, with current nationwide focus on reducing health care costs as health care moves away from fee-for-service models toward bundled payment systems, delineating strategies to reduce procedure costs is essential (6). The purpose of the study was to delineate sources of increased radiation and cost in IVCF placement and aspects of placement predicting difficulty in filter retrieval.

METHODS

This single-center retrospective review included all patients who underwent IVCF placement from August 2013 to December 2014, identified by searching the picture archiving and communication system. Demographic and procedural data were obtained from the electronic medical record. A total of 299 IVCFs were placed; 252 cases were performed in the fluoroscopy suite (FS) and 47 in the operating room (OR). Nine operators placed filters in the FS with an average of 10.3 (range 1–27) years of experience; 6 operators placed filters in the OR with an average of 12.3 (range 2–34) years of experience (\( P = 0.72 \)). No operator placed filters in both locations. Preferred FS filters were Denali, VenaTech, ALN, and Option/Option Elite; preferred OR filters were the Option/Option Elite, Celect, Eclipse, and Meridian. FS procedures were performed using an AXIOM Artis digital system (Siemens Medical Solutions USA, Inc, Malvern, PA) or a Polystar TOP system (Siemens Medical Solutions USA, Inc, Malvern, PA). OR procedures were performed using an Artis Zeego system (Siemens Medical Solutions USA, Inc, Malvern, PA). We recorded the type of anesthesia used, radiation dose, fluoroscopy time, venous access site (femoral vs jugular), filter type, filter tilt (the angle between the long axis of the cava and the long axis of the filter), and distance of the filter tip from...
the most inferior renal vein (distance from the superior tip of the filter to the most inferior aspect of the most inferior renal vein). If the filter was positioned with the tip above the lowest renal vein, the distance was documented as a negative value, measured from the bottom of the vein. Suprarenal IVCs were excluded from analysis of distance from the renal vein. In assessing radiation exposure, patients without documented radiation dose and those undergoing multiple fluoroscopic procedures were excluded. Patients with inadequate images were excluded from analysis of filter position.

The difference in cost between FS and OR procedures was estimated by assessing data available in the hospital cost allocation system. Direct costs of each procedure were not available, such that only comparative savings could be estimated. Cost estimates included procedure time in hours multiplied by per hour salary dollars of attending physician proceduralist; the cost of 1 hour of recovery time in the postanesthesia care unit after OR cases vs the cost of 1 hour of recovery on a standard hospital floor under routine nursing care following procedure room cases; and the difference in cost of intraprocedural medications in each setting. Medication use was determined by examining procedure records; the most commonly used medications were lidocaine for FS cases and lidocaine and propofol for OR cases.

We documented the number of retrievable filters that were retrieved, the time from placement to retrieval, fluoroscopy time, number of retrieval instruments (e.g., snare), and complications. Retrievals were categorized as difficult if the procedure required more than one instrument (e.g., additional snare or forceps) or >30 minutes of fluoroscopy time.

Statistical analysis was performed using GraphPad Prism 6 (Graphpad Software, La Jolla, CA). Multiple linear regression assessed the impact of patient and procedural variables on the fluoroscopy time, radiation dose, filter angulation, and distance from the most inferior renal vein. Multiple logistic regression assessed the impact of filtration duration, filter type, and filter angulation on the difficulty of retrieval. Institutional review board approval was obtained; the need for consent was waived given the retrospective nature of the study.

RESULTS

A total of 299 IVCs were placed (Table 1), most commonly in inpatients (87%) in the FS (84%) with local anesthesia only (84%), via jugular access (70%), using contrast venography (94%). Denali, Venatech, and Option filters were most commonly used. To assess for variables contributing to radiation exposure and accuracy of placement, several multiple regression analyses were performed, with age, gender, use of carbon dioxide, inpatient vs outpatient status, indication for placement, jugular vs femoral access, filter type, type of anesthesia, and location of placement (FS vs OR) as the independent variables (Table 2). Ten cases performed in the OR and 68 cases in the FS were excluded from the analysis of radiation dose and fluoroscopy, either because these data were not reported or available in the stored images or because other fluoroscopic procedures were also performed.

### Table 1. Demographic and procedural data for 299 patients receiving inferior vena cava filter placement

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 ± 1</td>
</tr>
<tr>
<td>Men</td>
<td>155 (52%)</td>
</tr>
<tr>
<td>Inpatients</td>
<td>260 (87%)</td>
</tr>
<tr>
<td>Indication for filter placement</td>
<td></td>
</tr>
<tr>
<td>VTE with contraindication to anticoagulation</td>
<td>170 (57%)</td>
</tr>
<tr>
<td>VTE progression on anticoagulation</td>
<td>24 (8%)</td>
</tr>
<tr>
<td>Prophylactic (high risk with contraindication to anticoagulation)</td>
<td>81 (27%)</td>
</tr>
<tr>
<td>Caval thrombus</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Extensive VTE with limited cardiopulmonary reserve</td>
<td>16 (5%)</td>
</tr>
<tr>
<td>Location of procedure</td>
<td></td>
</tr>
<tr>
<td>Fluoroscopy suite</td>
<td>252 (84%)</td>
</tr>
<tr>
<td>Operating room</td>
<td>47 (16%)</td>
</tr>
<tr>
<td>Anesthesia</td>
<td></td>
</tr>
<tr>
<td>Local only</td>
<td>252 (84%)</td>
</tr>
<tr>
<td>Nursing sedation</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Monitored care</td>
<td>26 (9%)</td>
</tr>
<tr>
<td>General</td>
<td>9 (3%)</td>
</tr>
<tr>
<td>Venous access site</td>
<td></td>
</tr>
<tr>
<td>Femoral</td>
<td>90 (30%)</td>
</tr>
<tr>
<td>Jugular</td>
<td>209 (70%)</td>
</tr>
<tr>
<td>Carbon dioxide venography performed</td>
<td>19 (6%)</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>3.2 ± 0.2</td>
</tr>
<tr>
<td>Radiation dose (mGy)</td>
<td>78.7 ± 6</td>
</tr>
<tr>
<td>Angulation (degree)</td>
<td>3.0 ± 0.1</td>
</tr>
<tr>
<td>Distance from most inferior renal vein (cm)</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>Filter</td>
<td></td>
</tr>
<tr>
<td>VenaTech</td>
<td>86 (29%)</td>
</tr>
<tr>
<td>Denali</td>
<td>106 (35%)</td>
</tr>
<tr>
<td>Option/Option Elite</td>
<td>70 (24%)</td>
</tr>
<tr>
<td>ALN</td>
<td>15 (5%)</td>
</tr>
<tr>
<td>Celect</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>Eclipse</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Meridian</td>
<td>6 (2%)</td>
</tr>
</tbody>
</table>

VTE indicates venous thromboembolism, including pulmonary embolism and deep vein thrombosis.

A total of 213 retrievable filters were placed; attempts were made to retrieve 68 of them (32%). On average, retrieval required 12.9 minutes (range 1.2–167.1) of fluoroscopy time; 9 procedures (13%) required more than one retrieval device (e.g., additional snares or forceps). To assess the impact of filter type, angulation, and duration from placement to retrieval on the difficulty of retrieval, these were used as independent variables in multiple logistic regressions for procedures requiring more than one retrieval device and procedures requiring >30 minutes...
Table 2. Multiple linear regression models for radiation dose, fluoroscopy time, and filter angulation

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Independent predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation dose</td>
<td>Location of placement ($P = 0.03$)</td>
</tr>
<tr>
<td>($P = 0.003$)</td>
<td>FS: 71.4 mGy</td>
</tr>
<tr>
<td></td>
<td>OR: 156.3 mGy</td>
</tr>
<tr>
<td>Indication ($P = 0.0008$)</td>
<td>VTE with contraindication to anticoagulation: 72.6 mGy</td>
</tr>
<tr>
<td></td>
<td>Progression of VTE on anticoagulation: 71.2 mGy</td>
</tr>
<tr>
<td></td>
<td>Prophylactic in patients with high risk of VTE: 66.3 mGy</td>
</tr>
<tr>
<td></td>
<td>Caval thrombus: 140.6 mGy</td>
</tr>
<tr>
<td></td>
<td>VTE with low cardiopulmonary reserve: 178.9 mGy</td>
</tr>
<tr>
<td>Fluoroscopy time ($P &lt; 0.0001$)</td>
<td>Location of placement ($P = 0.0001$)</td>
</tr>
<tr>
<td></td>
<td>FS: 2.8 min</td>
</tr>
<tr>
<td></td>
<td>OR: 6.1 min</td>
</tr>
<tr>
<td></td>
<td>Venous access site ($P = 0.02$)</td>
</tr>
<tr>
<td></td>
<td>Femoral: 3.4 min</td>
</tr>
<tr>
<td></td>
<td>Jugular: 3.2 min</td>
</tr>
<tr>
<td>Filter angulation ($P &lt; 0.0001$)</td>
<td>Location of placement ($P = 0.03$)</td>
</tr>
<tr>
<td></td>
<td>FS: 2.6°</td>
</tr>
<tr>
<td></td>
<td>OR: 4.8°</td>
</tr>
<tr>
<td>Filter type ($P = 0.02$)</td>
<td>VenaTech: 2.2°</td>
</tr>
<tr>
<td></td>
<td>Denali: 2.4°</td>
</tr>
<tr>
<td></td>
<td>Option: 4.2°</td>
</tr>
<tr>
<td></td>
<td>Celect: 4.6°</td>
</tr>
<tr>
<td></td>
<td>Meridian: 4.7°</td>
</tr>
<tr>
<td>Gender of patient ($P = 0.03$)</td>
<td>Male: 2.8°</td>
</tr>
<tr>
<td></td>
<td>Female: 3.3°</td>
</tr>
<tr>
<td>Distance from the most inferior renal vein ($P = 0.03$)</td>
<td>Anesthesia type ($P = 0.03$)</td>
</tr>
<tr>
<td></td>
<td>Monitored anesthesia care: &lt;1 cm</td>
</tr>
<tr>
<td></td>
<td>Conscious sedation: &lt;1 cm</td>
</tr>
<tr>
<td></td>
<td>Local anesthesia: &lt;1 cm</td>
</tr>
<tr>
<td></td>
<td>Venous access site ($P = 0.0001$)</td>
</tr>
<tr>
<td></td>
<td>Femoral: 0.3 cm</td>
</tr>
<tr>
<td></td>
<td>Jugular: 1.0 cm</td>
</tr>
</tbody>
</table>

FS indicates fluoroscopy suite; OR, operating room; VTE, venous thromboembolism.

Table 3. Estimated cost savings for procedures performed in the fluoroscopy suite compared with the operating room

<table>
<thead>
<tr>
<th>Line item</th>
<th>Estimated savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staffing$^a$</td>
<td>$112.50</td>
</tr>
<tr>
<td>Recovery$^b$</td>
<td>$106.57</td>
</tr>
<tr>
<td>Medication$^c$</td>
<td>$225.43</td>
</tr>
<tr>
<td>Total</td>
<td>$444.50</td>
</tr>
</tbody>
</table>

$^a$ Calculated from average reported procedure times multiplied by attending proceduralist salary, estimated from the hospital cost allocation system.

$^b$ Calculated as cost savings for 1 hour of monitoring on standard hospital floors after fluoroscopy compared with 1 hour in the postanesthesia care unit after operating room cases; estimated from the hospital cost allocation system.

$^c$ Cost difference of most commonly used medications for monitored anesthesia care or general anesthesia compared with local anesthesia, estimated from the hospital cost allocation system.

of fluoroscopy time. The regression analysis predicting the need for more than one retrieval device was significant ($P = 0.0002$), with filter angulation being the only independent predictor ($P = 0.0008$), but not filter type ($P = 0.50$) or filtration duration ($P = 0.99$). On average, filters requiring more than one retrieval device were angulated by 5.3° (SE 0.8; range 3–15), whereas filters requiring only one device were angulated by 3.0° (SE 0.2; range 0–12) ($P = 0.02$). The regression predicting fluoroscopy time exceeding 30 minutes was also significant ($P = 0.01$), with filter angulation as the only independent predictor ($P = 0.02$), but not filter type ($P = 0.15$) or filtration duration ($P = 1.00$). On average, filters requiring more than 30 minutes of fluoroscopy time for removal were angulated by 4.0° (SE 0.2; range 3–15), whereas those requiring less than 30 minutes of fluoroscopy time were angulated by 2.7° (SE 0.3; range 0–12; $P = 0.10$).

We estimated cost savings for performing IVCF placement in the FS compared with in the OR. All OR cases entailed some form of anesthesia, including general anesthesia or monitored anesthesia care, whereas an anesthesiologist was involved in only 5% of FS cases. Most FS cases involved only a local anesthetic (92%). Cost savings were estimated to be $444.50 per case, favoring FS procedures (Table 3). The anesthesiology physician salary was not available in the hospital cost allocation system. The cost of preferred filters in each area was excluded, although on average, those in the OR were $50 more expensive than those in the FS.

There were 6 (2%) adverse events during IVCF placement: 1 contrast reaction, 1 filter malposition, and 4 access site hematomas. Only 1 (0.4%) of these events required further management (neck exploration for hematoma after jugular venous access). There were 22 deaths (8%) within 1 month, all unrelated to filter placement. Among 213 retrievals, there was 1 (0.5%) incision site bleeding, and 1 filter (0.5%) that could not be retrieved, became mangled, and was left in place, with a suprarenal filter placed instead. This latter case involved an Option filter.

DISCUSSION

This study demonstrates that IVCF placement is accurate, safe, and can involve radiation exposure similar to or lower than previously reported values. An accepted fluoroscopy time of 2.8 minutes and cumulative dose of 166 mGy have been published, compared with the 3.2 minutes and 79 mGy reported here. The adverse event rate (2%, or 6 of 299 procedures) reported herein is significantly lower than that in older studies (20%–80%), likely due to equipment and procedural advancements.
Technical and contextual variables can lower radiation dose and procedure cost. In this study, the type of venography and the venous access site did not impact the radiation dose.

The only variable that was noted to increase dose and fluoroscopy time was placement in the OR, as opposed to the FS. The cause for this difference is likely multifactorial. FS procedures were performed by interventional radiology physicians, whereas OR cases were performed by vascular surgeons. Radiologists receive extensive training in radiation safety and protection and are tested on these principles as part of American Board of Radiology certification (http://www.theabr.org/ic-dr-core-exam#CoreExamStudyGuides). Nonradiologists are relatively uninformed about basic radiation principles (9). Invasive cardiologists, for example, demonstrate poor adherence to radiation protection (10), and not all fellows receive formal radiation education (11). Similarly, nearly half of vascular surgery fellows do not receive formal radiation training (12, 13). The lack of emphasis on dose reduction among non–radiology-trained operators and radiation doses and fluoroscopy times found in OR cases, as there was no difference in the quality of the fluoroscopic equipment or average years of operator experience. Our findings here complement a recent report that interventional radiologists use less radiation during dialysis access interventions than vascular surgeons (14).

In addition to radiation exposure, IVCF placement in the FS was associated with a >$400 estimated cost reduction compared with placement in the OR. This study calculated the estimated cost to the hospital, rather than billable services to the patient, and excluded the cost of the anesthesiologist who is required for all OR cases, as this information was not available in the cost allocation system. Most cases (92%) performed in the FS entailed local anesthesia alone, and only 5% involved the services of an anesthesiologist. Findings are in line with a prior study reporting that IVCF placement was roughly $1000 more expensive per procedure for placement in the OR compared to placement in the FS, with most of the cost due to the presence of an anesthesiologist (15). Intravenous sedation is considerably less expensive than general anesthesia for many procedures (16–19). Similarly, a recent report documented significantly decreased cost but similar lower complication rates for chest Mediport placement by interventional radiology compared with surgery (20). Our findings suggest significant reduction in cost to the hospital when IVCF placement is performed in the FS compared to the OR.

The efficacy of an IVCF depends on accuracy of placement and caval course and configuration (21–24). This study showed significant differences between filters regarding the final angulation of the filter relative to the central caval axis. Interestingly, Denali filters had significantly less angulation (2.4°) than Option/Option Elite (4.2°), Celect (4.6°), and Meridian filters (4.7°). The reduced tilt of Denali filters could lead to better function of the filter and may reduce difficulty in future retrieval. Prior studies conflict as to whether filter angulation contributes to difficulty in retrieval, with some indicating that tilt does not play a role (25, 26), and others suggesting tilt does impact ease of retrieval (24, 27, 28). In this study, angulation of the filter was the only independent predictor of difficult filter retrieval, as indicated by prolonged fluoroscopy time and use of additional retrieval devices. These data may explain the observation that Option filters are more challenging to retrieve, with longer retrieval procedure times and more equipment (29). Such data could impact decisions regarding filter placement.

We report here a 32% retrieval rate, in line with prior studies demonstrating 10% to 30% rates prior to instituting a robust filter follow-up program (30, 31). With dedicated attention to tracking filters placed and recalling patients, retrieval rates may increase to 50% to 60%. Given the recommendation of the US Food and Drug Administration to remove filters as soon as they are no longer needed, more work is needed to delineate which follow-up programs are most effective and least costly to ensure retrieval (2, 3).

The primary limitation of this study was its retrospective design, which allowed for bias in patient selection and referral patterns. The large discrepancy in the number of procedures performed in the OR vs the FS limits the conclusions that can be made regarding the impact on radiation exposure. Bias in patient selection, referral patterns, and differences in fluoroscopy equipment cannot be removed from the retrospective study design. While there was no difference in the years of experience between the operators in the FS and those in the OR, there may be interindividual differences in technique that impacted the amount of radiation used. Because of the retrospective, nonrandomized nature of the study, it is impossible to make firm conclusions as to the source of the increased radiation dose observed for OR cases; prospective studies assessing interventions such as radiation education would be necessary to ascertain whether discrepancies in training could account for the observed differences in technique. Also, because certain filters were preferentially used in the OR as opposed to the FS, there may be bias in regard to the precision of placement. The lack of access to anesthesiology costs limited the optimal estimate of cost savings. Furthermore, lack of access to actual procedural costs made calculating direct costs impossible and prohibited the ability to assess the statistical significance of cost differences.


24 Baylor University Medical Center Proceedings Volume 30, Number 1


17. Covins S, Sridhar D, Charles HW. Denali, ALN, and Option/Option Elite


Laboratory tests can be considered inappropriate if overused or when repeated, unnecessary “routine” testing occurs. For chronically critically ill patients treated in long-term acute care hospitals (LTACHs), inappropriate testing may result in unnecessary blood draws that could potentially harm patients or increase infections. A quality improvement initiative was designed to increase physician awareness of their patterns of lab utilization in the LTACH environment. Within a large network of LTACHs, 9 hospitals were identified as having higher patterns of lab utilization than other LTACHs. Meetings were held with administrative staff and physicians, who designed and implemented hospital-specific strategies to address lab utilization. Lab utilization was measured in units of lab tests ordered per inpatient day (lab UPPD) for 8 months prior to the initial meeting and 7 months after the meeting. A repeated measures mixed model determined that postintervention lab utilization improved, on average and adjusted by case mix index, by 0.37 lab UPPD (t = −3.61, 95% CI 0.17 to 0.58) compared to the preintervention period. Overall, the case mix index 8 months prior to the intervention was no different than it was 7 months after the initial meeting (t[8] = −0.96, P = 0.37).

Patient safety and outcome measures, including percentage of patients weaned from a ventilator, readmission rates, central catheter utilization rates, and the incidence of methicillin-resistant Staphylococcus aureus and other multidrug resistant organisms, showed no significant change. Hospital staff meetings focused on lab utilization and the development and deployment of tailored lab utilization strategies were associated with LTACHs achieving significantly lower lab utilization without negatively impacting quality outcomes.

Laboratory tests are crucial in clinical decision making; however, tests can be considered inappropriate if overused, i.e., when tests are ordered but are not directly indicated, when initial testing is inappropriate based on patient evaluation, or when repeated “routine” testing is not necessary (1). For chronically critically ill patients treated in long-term acute care hospitals (LTACHs), inappropriate testing can result in unnecessary blood draws that may result in potential harm to patients (2). Lab test overutilization can also lead to an increase in false-positive results (3). Strategies for optimizing lab test utilization include physician education, improved test requisition processes through an enhanced electronic medical record (4), standardized clinical assessment (5), improved communication between clinicians and lab professionals (6, 7), and elimination of standing orders (8, 9). A quality initiative, the Clinical Variability Project (CVP), was designed to reduce clinical variability in lab test utilization in LTACHs. The CVP had three directives: 1) examine the variability of laboratory test utilization in multiple LTACHs; 2) present lab test utilization data to hospital administration and physicians; and 3) support process changes and measure the impact of these changes on patterns of lab test utilization.

METHODS

A total of 9 LTACHs (4 freestanding and 5 hospital-within-hospital, with an average of 46 beds per hospital) were selected for the CVP based on the presence of a relatively high average number of lab units per patient day (UPPD) compared to over 100 LTACHs within the same health care organization. The LTACHs studied were located in Pennsylvania, Florida, New Jersey, South Carolina, and Ohio.

In the first phase of the CVP, the volume of lab UPPD was examined for each LTACH. Lab UPPD was defined as the total volume of lab tests for each LTACH divided by the total number of patient days. A lab UPPD correlates with any study or panel that is ordered (complete blood count, basic metabolic panel, albumin, magnesium, etc.); no data were available for the amount of blood (number of tubes) drawn. The most frequent lab tests included basic and comprehensive metabolic panels and complete blood count. Information on lab test frequency, the percentage of patients, and the number of patient days that had lab tests done was also collected but was not included in the analysis.

For the second phase of the CVP, overall patterns of lab utilization were presented to hospital administrators and physicians who treated patients in the LTACH. Monthly lab UPPD data from the previous 8 months, specific to each LTACH, were
presented to the group, together with comparative data from 92 other LTACHs. In most of the participating LTACHs, the overall lab UPPD data had not been presented in aggregate prior to the meeting. During the presentation, care was taken to make sure the purpose of the meeting was positive and not punitive; physicians were never told that they were ordering too much or that they were doing something clinically incorrect.

In the third phase of the CVP, processes were developed by each hospital administrative and clinical staff, at each LTACH, to optimize lab utilization; no predesigned bundle was provided to the hospital administrators. Approximately 1 month after the initial meeting, conference calls were conducted with each participating LTACH during which evidence-based best practices for chronically critically ill patients were reviewed, including studies that examined the potential clinical implications from patterns of lab ordering (2, 3). It was left up to each LTACH administration and the clinical team to determine the best way to implement processes for lab test optimization.

Following the third phase, the impact of the CVP on subsequent lab utilization was determined for all LTACHs; lab UPPD was measured monthly 8 months prior to the initial meeting (beginning January 2015) and 7 months after the meeting (ending April 2016). Independent variables included an indicator for the intervention occurring at the end of the 8th month, time points (in months) at which the respective lab UPPD measurements were obtained, and the average monthly LTACH case mix index (CMI). CMI was used in the model because different levels of patient acuity could have contributed to different rates of lab utilization. Results were analyzed using a linear mixed-effect model with restricted maximum likelihood estimation to investigate the association between the intervention and the direction of lab UPPD trends over time and also to investigate the assumption that CMI is associated with the baseline and trend of lab UPPD. Rather than using the mean response for the pre- and postintervention periods, the variation in monthly lab UPPD was determined by modeling the variance-covariance matrix of the residuals for lab UPPD for each hospital. This method takes into account variability within and between hospitals.

**RESULTS**

The CVP intervention had a significant main effect [\( F(1, 34.33) = 13.04, P = 0.001 \)]. The overall mean lab UPPD 8 months prior to intervention was 3.25 (SD = 1.14); the CMI was 1.24 (SD = 0.13). The linear mixed model that included CMI as a random covariate (AIC = 152.12) outperformed the model that omitted it (AIC = 156.02). On average, lab utilization decreased by 0.09 UPPD each month per hospital following the intervention. The average unadjusted decrease in lab utilization by the end of the postintervention period was 0.49 UPPD (Figure 1).

Patient safety and outcome measures were examined in a series of paired \( t \) tests pre- and postintervention to determine whether reduction in lab UPPD had unintended consequences. As displayed in Table 1, there were statistically significant differences (at a .05 significance level) in pretest to posttest scores for lab UPPD, but not for any of the patient safety and outcome measures. Overall, CMI 8 months prior to the intervention was no different than CMI 7 months after the initial meeting (\( t[8] = -0.96, P = 0.37 \)). Similarly, the percentage of patients weaned from the ventilator, readmission rates, and central catheter utilization rates were not significantly different after the intervention (Table 1). In addition, the incidence of central line–associated bloodstream infection, methicillin-resistant *Staphylococcus aureus* infection, and other multidrug resistant organism infection remained unchanged after the intervention (Table 1).

All the LTACHs studied had a decrease in lab UPPD over the 15-month period. The effect of the intervention had a magnitude (\( \beta \)) of 0.37 (\( t = -3.61, 95\% \text{ CI} 0.17 \) to 0.58) when

---

**Table 1. Descriptive statistics and \( t \) test results for lab units per patient day, case mix index, safety measures, and outcome measures for the preintervention and postintervention periods**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Pre – post mean difference</th>
<th>95% CI</th>
<th>R</th>
<th>t</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPPD</td>
<td>0.48</td>
<td>0.46</td>
<td>0.13</td>
<td>0.83</td>
<td>0.93*</td>
</tr>
<tr>
<td>CMI</td>
<td>-0.03</td>
<td>0.09</td>
<td>-0.09</td>
<td>0.04</td>
<td>0.75*</td>
</tr>
<tr>
<td>Vent wean</td>
<td>0.06</td>
<td>0.12</td>
<td>-0.04</td>
<td>0.15</td>
<td>0.65</td>
</tr>
<tr>
<td>Readmissions</td>
<td>-0.01</td>
<td>0.03</td>
<td>-0.03</td>
<td>0.02</td>
<td>0.86*</td>
</tr>
<tr>
<td>Central lines</td>
<td>0.02</td>
<td>0.12</td>
<td>-0.07</td>
<td>0.11</td>
<td>-0.13</td>
</tr>
<tr>
<td>CLABSI</td>
<td>0.40</td>
<td>0.60</td>
<td>-0.06</td>
<td>0.08</td>
<td>-0.11</td>
</tr>
<tr>
<td>MRSA</td>
<td>-0.14</td>
<td>0.27</td>
<td>-0.34</td>
<td>0.07</td>
<td>0.55</td>
</tr>
<tr>
<td>Other MDRO</td>
<td>-0.09</td>
<td>0.40</td>
<td>-0.40</td>
<td>0.22</td>
<td>0.90*</td>
</tr>
</tbody>
</table>

* \( P < 0.05 \).

UPPD indicates units per patient day; CMI, case mix index; CLABSI, central line–associated bloodstream infection; MRSA, methicillin-resistant *Staphylococcus aureus*; MDRO, multidrug-resistant organisms.
adjusted by CMI. Successive measurements of lab UPPD within a given hospital resulted in an estimated variance of 0.19 and an estimated correlation of 0.54, both of which were significant at the \( P < 0.001 \) level, verifying the appropriateness of the repeated measures design.

Each hospital administration and clinical staff developed a set of policies, processes, and procedures to improve patterns of lab utilization in their LTACH. Because these processes were not standardized, changes in levels of lab test utilization could not be associated with specific action plans that were implemented in the LTACHs included in the CVP. However, several processes were used at more than one LTACH; the 10 most frequent processes used to optimize lab test utilization are summarized in Table 2.

### DISCUSSION

Successful laboratory utilization management typically involves several interventions that include ordering, monitoring, follow-up (10), and formulary restriction combined with restrictive reporting (11). The current study demonstrated that, in LTACHs with relatively high rates of lab test utilization, physician education and hospital staff awareness of patterns of laboratory utilization can effectively support lab test optimization. Despite lab UPPD significantly decreasing from pretest to posttest, CMI remained unchanged after the intervention, indicating that lab utilization was not correlated with patient acuity. Patient safety and outcome measures, including percentage of patients weaned from a ventilator, readmission rates, central

<table>
<thead>
<tr>
<th>Table 2. List of processes implemented to improve patterns of laboratory test utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Determine the clinical reasoning behind the most frequently ordered lab tests.</td>
</tr>
<tr>
<td>2. Present comprehensive aggregate data to physicians: case mix index, lab test costs, budgeted goals, outcomes, quality metrics, trends, and individual physician ordering practices.</td>
</tr>
<tr>
<td>3. Provide information from peer-reviewed publications that include evidence-based lab utilization practices for the patient populations being treated.</td>
</tr>
<tr>
<td>4. Provide information on the potential clinical implications of lab ordering patterns.</td>
</tr>
<tr>
<td>5. Provide comparative data from other units or hospitals that have different patterns of lab test utilization but have similar types of patients or similar case mix index values.</td>
</tr>
<tr>
<td>6. Select a physician champion who will organize educational sessions and provide the information required for improving lab test utilization.</td>
</tr>
<tr>
<td>7. Develop goals and a method for measuring and communicating successful lab test utilization management through frequent meetings that will sustain practice changes.</td>
</tr>
<tr>
<td>8. Reduce or eliminate standing orders for lab tests.</td>
</tr>
<tr>
<td>9. Determine whether specific directives are necessary, e.g., having blood drawn on specific days unless there is a specific medical necessity.</td>
</tr>
<tr>
<td>10. Engage all executive administrative staff and provide effective and non-judgmental communication to all physicians involved in patient care.</td>
</tr>
</tbody>
</table>

There are no generally accepted targets for over- or under-utilization of lab tests. Initiatives to reduce the number of lab tests often have short-term success based on the type of changes implemented in the hospital; effective processes for lab test utilization reduction typically involve changes to data collection, patient evaluation, and education (4). Results of the CVP initiative have determined the importance of education in LTACHs that have relatively high lab utilization rates. Reduction in lab test utilization can have substantial cost savings; for the majority of tests ordered in the 9 LTACHs, the average 2016 Medicare fee schedule payment is $15. Based on the average amount and an unadjusted reduction of 0.49 lab UPPD, the 9 LTACHs studied realized a potential savings of approximately $1,000,000 for the 7 months after the intervention.

Limitations of the CVP include a lack of standardization of the education component; the material presented at each initial meeting was amended following input and requirements from each LTACH. Also, no standard set of policies and procedures was used to optimize patterns of lab utilization in each LTACH. Each hospital administration and clinical staff developed their own set of processes and procedures that they thought would improve patterns of lab utilization in their facility. Specific action plans developed at each LTACH were not examined separately or analyzed for their ability to impact levels of lab test utilization; therefore, it is not possible to infer which processes were most effective in optimizing lab test utilization.

Implementation of the CVP has resulted in reduction of variability in lab test utilization through different combinations of policies and procedures, in multiple LTACHs. The process of establishing an initial hospital administrative and clinical staff meeting focused solely on lab test utilization, together with recent lab test utilization data and the development and deployment of tailored lab utilization strategies, can result in reduced lab utilization variability in LTACHs with relatively high utilization rates. Reduced lab test utilization variability can result in a significantly lower overall utilization rate without negatively impacting quality outcomes.


Acknowledgment of reviewers for BUMC Proceedings, volume 29

Our thanks to those who reviewed and critiqued manuscripts submitted to Baylor University Medical Center Proceedings for publication in volume 29. Reviewing scientific papers is an often unrecognized, arduous, and time-consuming task. We are grateful to our 75 editorial board members and to the following additional reviewers for contributing their valuable comments and suggestions.

Traci N. Adams, MD
Robert D. Anderson, MD
Manish D. Assar, MD
Malay Y. Bhatt, MD
Robert D. Black, MD
James Broadway, PhD
Christopher J. Burnett, MD
Jennifer C. Cather, MD
Ari M. Cedars, MD
Scott A. Celinski, MD
Jomuna T. Chaiban, MD
C. C. Chang, MD
Arpitha Chiruvolu, MD
Carl E. Couch, MD
Marco Cura, MD
John J. Cush, MD
Tuoc N. Dao, MD
Graca M. Dores, MD
Robert L. Fine, MD
Karen L. Fink, MD, PhD
Gerald Fletcher, MD
Barry A. Franklin, PhD
Herbert L. Fred, MD
Frederick G. Freitag, DO
Vincent E. Friedewald Jr., MD
John Garrett, MD
Karina de Souza Giassi, MD
Robert M. Goldstein, MD
Stevan A. Gonzalez, MD
Vinayak Govande, MBBS
Paul A. Grayburn, MD
John Griffin, MD
Kenneth Gross, MD
Stanley J. Grossman, MD
Scott Grundy, MD, PhD
Robert Haley, MD
Shelley A. Hall, MD
J. Kent Hamilton, MD
Tamara Hew-Butler, DPM, PhD
Houston E. Holmes III, MD
Allan S. Jaffe, MD
Ronald C. Jones, MD
Robert C. Kowal, MD, PhD
Kennith F. Layton, MD
Brian Lima, MD
Isaac Melguizo-Gavilanes, MD
M. Alan Menter, MD
Katherine Meredith, PsyD
Christopher B. Michael, MD
Osman Mir, MD
Kimberly Monden, PhD
Rosemary Nustas, MD
J. Theodore Phillips, MD, PhD
Claus Pierach, MD
Linda Plank, PhD
Nicholas J. Procaccini, MD
Fayez Raza, MD
Samuel Refetoff, MD
Habib ur Rehman, MBBS
Caitriona Ryan, MD
Susan Seago, MD
Paula Shiroma-Bender, JD
Matthew D. Shuford, MD
William P. Shutze, MD
Athanasios D. Soulas, MD, PhD
Louis M. Sloan, MD
Jeffrey S. Stroup, PharmD
Manish Thapar, MD
Richard L. Vera, MD
Adriana M. Villa, MD
Ivan Vrcek, MD
Matthew V. Westmoreland, MD
Jonathan Whitfield, MD
Jackie R. York, MD
Inappropriate use of antibiotics in patients undergoing gynecologic surgery

John Joyce, MD, Jessica Langsjoen, MD, Cynthia Sharadin, BA, Thomas J. Kuehl, PhD, and Wilma I. Larsen, MD

We retrospectively examined prophylactic antibiotic use and documentation of wound classification in patients having gynecologic surgery at a tertiary hospital. Of the 326 cases reviewed, 175 (54%) received prophylactic antibiotics when not indicated according to guidelines of the American College of Obstetricians and Gynecologists. Antibiotic administration varied significantly \( (P < 0.02) \) among the different types of surgery, being given in 82% of laparoscopic cases, 35% of nonobstetrical dilation and curettage and operative hysteroscopy procedures, and 51% of open abdominal procedures. There were no recorded episodes of anaphylaxis or pseudomembranous colitis. In conclusion, antibiotic use is high among gynecologic surgeons at a tertiary hospital, but this use was unnecessary.

To improve compliance with publicly reported metrics, our institution developed a preoperative order set that included the Surgical Care Improvement Project (SCIP) guidelines for hysterectomies. Although SCIP recommends prophylactic antibiotics for hysterectomy, the preoperative order sets did not designate gynecologic procedures for which antibiotic prophylaxis use was not recommended. The objective of this study was to examine the use of prophylactic antibiotics in patients undergoing gynecologic surgery at Scott and White Memorial Hospital when antibiotics were not recommended per the American College of Obstetricians and Gynecologists (ACOG) guidelines \( (1) \). Our secondary objective was to determine if the surgeries were appropriately classified as to wound type, as this could affect a surgeon’s decision on whether or not to give antibiotics.

METHODS

This retrospective study was performed at Scott & White Memorial Hospital in Temple, Texas. The study was approved by the Scott & White institutional review board prior to data collection as an exempt project not requiring patient consent. All gynecologic surgical procedures performed between January 1, 2012, and December 31, 2013, for which antibiotics were not recommended per ACOG were identified through current procedural terminology codes. Patients were excluded if they were younger than 18 years old, had an infection at the time of surgery that required use of antibiotics, or had concomitant procedures (including nongynecologic surgery) for which antibiotics were indicated per SCIP guidelines. All data were obtained from the electronic medical record system.

Patients were included only once, even if they underwent multiple procedures. Data were recorded for patient age, body mass index \( (\text{kg/m}^2) \), presence or absence of diabetes mellitus, and whether or not the patient was taking steroids or other immunosuppressants. The documented primary wound class \( (2) \) was recorded from the operative log. The primary surgeon for each case was recorded and kept confidential. Prophylactic antibiotics were recorded as antibiotics administered up to 1 hour prior to incision on the day of surgery. The charts were reviewed for adverse events (vaginal candidiasis, anaphylactic reactions, hives, rash, diarrhea, \textit{Clostridium difficile} colitis) associated with antibiotic use occurring within 6 weeks postoperatively.

The primary objective was to determine the percentage of cases in which prophylactic antibiotics were administered when not indicated according to ACOG guidelines. An a priori sample of 180 surgeries was calculated to detect a 10% difference of antibiotic administration among three groups: 1) laparoscopy, 2) laparotomy, and 3) transcervical procedures \( (\text{Table 1}) \). The three groups were divided into subgroups of procedures for further analysis. A total sample size of 320 cases was then calculated to detect a 10% difference in antibiotic administration among the seven subgroups. Cases were selected in a haphazard fashion to represent all surgical subgroups and surgeons. Secondary objectives included determining the accuracy of preoperative wound classification in the operative log compared to the findings documented in the operative report, the number of adverse events in cases where antibiotics were administered, and the variation of antibiotic use among the gynecologic specialties.

Analysis of prophylactic antibiotic administration among groups, subgroups, and gynecologic specialties was performed using the chi-square test. Univariate comparison for associating patient characteristics prior to surgery and prophylactic antibiotic use was analyzed using the Mann-Whitney U test for patient age in years, Student’s \( t \) test for patient body mass index.

Table 1

From the Department of Obstetrics and Gynecology, Baylor Scott & White Healthcare, and the Texas A&M School of Medicine and Health Sciences, Temple, Texas. Corresponding author: Wilma Larsen, MD, Department of Obstetrics and Gynecology, Baylor Scott & White Health, 2401 South 31st Street, Temple, TX 76508 (e-mail: Wilma.Larsen@BSWHealth.org).
Inappropriate use of antibiotics in patients undergoing gynecologic surgery

January 2017

RESULTS

Among 326 surgical cases reviewed, surgeons ordered prophylactic antibiotics in 175 (54%, confidence interval [CI] 48.1–59.2). The percentage of prophylactic antibiotic administration varied significantly ($P < 0.02$) between each of the major types of surgeries: laparoscopic surgery (82%), nonobstetrical dilation and curettage or operative hysteroscopy (35%), and open abdominal procedures (51%). Antibiotic use did not differ ($P = 0.82$) between laparoscopic adnexal surgery (78%) and open adnexal surgery for benign conditions (76%). Antibiotic use varied among the four gynecologic specialties ($P < 0.001$). The gynecologic oncology surgeons administered prophylactic antibiotics in 61 out of 65 cases (94%, CI 85%–98%), and the reproductive endocrinology surgeons administered prophylactic antibiotics in 37 out of 39 cases (95%, CI 83%–99%). This pattern was significantly higher than that seen with the urogynecologists and general gynecologists who administered prophylactic antibiotics in 23 out of 43 cases (53%, CI 38%–69%) and in 53 out of 168 cases (32%, CI 25%–40%), respectively. No significant difference was found between the use of antibiotics by the gynecologic oncologists and reproductive endocrinologists ($P > 0.05$). The general gynecologists were the most compliant with recommended guidelines ($P < 0.05$).

Patients who received inappropriate prophylactic antibiotics were significantly older ($P < 0.001$), but did not differ in body mass index ($P = 0.06$), diabetes ($P = 0.80$), or steroid use ($P = 0.08$). Among those who received inappropriate prophylactic antibiotics, there were 11 (3%) adverse events, but no anaphylaxis or pseudomembranous colitis. Furthermore, 79% of laparoscopic and 89% of open procedures were misclassified as clean-contaminated by the operating room staff (Table 2).

DISCUSSION

Prophylactic antibiotic use in gynecologic surgeries when not indicated is exceedingly high at this tertiary hospital, with significant variation among major types of surgeries. Fortunately, adverse events remained low, without one recorded episode of *Clostridium difficile* colitis or anaphylaxis. In gynecologic surgery, prophylactic antibiotics are intended to prevent surgical site infection in procedures that expose the abdominal cavity

### Table 1. Reviewed procedures by group and subgroup where antibiotic prophylaxis is not indicated

<table>
<thead>
<tr>
<th>Group</th>
<th>Procedure</th>
<th>Current procedural terminology codes</th>
<th>Number, % (N = 326)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic procedures</td>
<td>Laparoscopic myomectomy</td>
<td>58545, 58546</td>
<td>16 (5%)</td>
</tr>
<tr>
<td></td>
<td>Operative laparoscopic procedures involving fallopian tubes and/or ovaries, ectopic pregnancy</td>
<td>58660, 58661, 58662, 58670, 58671, 58672, 58673, 58679, 59150</td>
<td>78 (24%)</td>
</tr>
<tr>
<td>Transcervical procedures</td>
<td>Dilation and curettage, diagnostic and/or therapeutic (nonobstetrical)</td>
<td>58120</td>
<td>48 (15%)</td>
</tr>
<tr>
<td></td>
<td>Hysteroscopy, endometrial ablation with/without hysteroscopy, and Essure tubal ligation</td>
<td>58555, 58558, 58559, 58560, 58561, 58562, 58535, 58563, 58565</td>
<td>73 (22%)</td>
</tr>
<tr>
<td>Open procedures</td>
<td>Open myomectomy</td>
<td>58140, 58146</td>
<td>6 (2%)</td>
</tr>
<tr>
<td></td>
<td>Open tubal ligation</td>
<td>58600, 58605, 58615</td>
<td>49 (15%)</td>
</tr>
<tr>
<td></td>
<td>Open procedures involving the fallopian tubes with/without the ovaries, with/without malignancy</td>
<td>58700, 58720, 58740, 58750, 58752, 58760, 58770, 58805, 58825, 58900, 58920, 58925, 58940, 58943, 58950, 58952, 58953, 58954, 58957, 58958, 58960</td>
<td>56 (17%)</td>
</tr>
</tbody>
</table>

### Table 2. Recorded wound classifications in operative log

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Clean (N = 36)</th>
<th>Clean-contaminated (N = 232)</th>
<th>Contaminated (N = 4)</th>
<th>Dirty (N = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic myomectomy</td>
<td>1 (7%)</td>
<td>14 (93%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Laparoscopy adnexa</td>
<td>18 (24%)</td>
<td>57 (76%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nonobstetrical dilation and curettage</td>
<td>1 (2%)</td>
<td>46 (96%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hysteroscopy, ablation, Essure</td>
<td>0 (0%)</td>
<td>70 (96%)</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Open myomectomy</td>
<td>1 (20%)</td>
<td>4 (80%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Open tubal ligation</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Open adnexal procedures (benign and malignant)</td>
<td>14 (26%)</td>
<td>40 (73%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
to the polymicrobial flora of the vagina (1). This also includes procedures where instrumentation breaches the endocervix in patients with a history of pelvic inflammatory disease or surgical findings suggestive thereof (e.g., hydrosalpinges).

Although both the reproductive endocrinologists and oncologists had high rates of unindicated prophylactic antibiotics, the postoperative infection rate has historically been much higher with oncology patients in our institution. Theoretically, the scrutiny that the oncologists receive when an infection occurs may have influenced them to order antibiotics for most patients. Although this finding most likely reflects individual practice patterns of a small number of surgeons, it nonetheless emphasizes the need for direct individual outreach and education to challenge dogma and change entrenched practice patterns.

The overuse of prophylactic antibiotics and misclassification of surgical wounds by operating room staff is not unique to our institution. Wright et al (3) identified an overuse rate of 40% and discovered that low-volume surgeons were more likely to order prophylactic antibiotics when not indicated. Low-volume surgeons may not be as familiar with the indications for prophylactic antibiotics. Another explanation is that universal administration of prophylactic antibiotics may be an unintended consequence of systems designed to track and promote adherence to quality metrics; physicians may prescribe the antibiotics to prevent scrutiny.

Our high rates of surgical wound misclassification are reflective of previously reported discrepancies between diagnosis-based and circulating nurse-based surgical wound classification (4). As performance on risk-stratified quality measures becomes increasingly influential in determining reimbursement rates for inpatient care (5), institutions have significant interest in reviewing their ability to accurately record their quality metrics. Failure to do so will not only decrease revenue, but also misdirect future quality improvement efforts and skew public perception of quality of care (4).

This study was limited by its retrospective design and the inability to account for adverse events that were not documented in the patient’s record. A notable strength of this study is its reproducibility for other institutions to perform their own internal audit of their quality metric reporting.

Concussion knowledge among rehabilitation staff

David Salisbury, PsyD, Michael Kolessar, PsyD, Librada Callender, BA, and Monica Bennett, PhD

A concussion knowledge survey was completed by 561 rehabilitation professionals across a wide range of disciplines in a nationwide rehabilitation hospital system. Item questions were structured to reflect key areas of concussion knowledge targeted in a prior consensus statement. The vast majority of staff provided responses consistent with the current concussion literature regarding concussion diagnosis and symptom presentation immediately after concussion. Greater variability was seen for items assessing beliefs about the typical recovery from concussion, best care practices, and long-term effects from concussion. Factors such as profession, years of experience, and work with concussion or traumatic brain injury were not consistently related to better performance on the survey. Prior concussion-focused education/training was related to better survey performance. This survey highlights the pressing need to educate frontline health providers regarding concussion recovery and best care practices.

Rehabilitation clinicians have experienced the challenges of treating complicated concussion cases where recovery was altered by noninjury factors, including initial mismanagement of symptoms, excessive activity restrictions, polypharmacy, secondary gain factors, exacerbation of premorbid pain, and psychiatric disorders. Survey-based studies have shown utility in the assessment of concussion knowledge with specific subgroups of health care providers (1–8), but a survey solely targeting multidisciplinary rehabilitation settings has, to our knowledge, not been conducted. Such a survey could facilitate understanding of how factors such as medical/rehabilitation specialty, years of experience, level of experience with concussion patients, and other provider-specific variables impact concussion knowledge and care, with the ultimate goal of guiding future training. Therefore, the objective of this study was to develop, administer, and analyze results of a survey targeting knowledge about concussion diagnosis, treatment, and expected recovery among rehabilitation staff across inpatient and outpatient rehabilitation settings along with sports care clinics.

METHODS

The survey was based upon key concepts in the consensus questions from the 4th International Conference on Concussion in Sport, including clarifying a definition of concussion, concussion recovery, and potential long-term consequences (9). The questions were developed by six neuropsychologists in lead roles in concussion clinics, and response choices were guided by an extensive literature review. The survey was then piloted with 10 rehabilitation staff in the fields of physical therapy, occupational therapy, speech therapy, athletic training, and psychology. The novel survey was intended to briefly and broadly assess concussion knowledge in our health care organization but not replace more comprehensive concussion surveys.

The survey contained two sections. The first portion included 10 questions clarifying professional practice, years of experience, and experience with head injury and other neurological populations. The second portion of the survey included 10 questions focused upon three primary components of concussion knowledge: concussion diagnosis, treatment, and recovery (Table 1). Seven of the questions could be answered in a yes/no format, while the remaining three questions were answered in a multiple choice format.

The survey was approved via expedited review by our institutional review board. It was preceded with an electronic survey cover letter that explained the objectives to participants. The survey was disseminated via provider e-mail lists or routed through directors to inpatient and outpatient providers affiliated with many of our rehabilitation centers throughout the country (17 inpatient rehabilitation hospitals and related outpatient centers).

A total of 561 participants responded to the survey. All responses were anonymous, and the survey was hosted by a

From the Baylor Institute for Rehabilitation (Salisbury, Kolessar, Callender) and Baylor Scott & White Health (Bennett), Dallas, Texas.

The authors disclose receipt of support for the research: DS and MK acknowledge support from the Ginger Murchison Foundation Traumatic Brain Injury Research Fund; LC and MB acknowledge support from The National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR grant number 90DP0045-01-0). NIDILRR is a center within the Administration for Community Living (ACL), Department of Health and Human Services (HHS). The contents of this manuscript do not necessarily represent the policy of the Ginger Murchison Foundation Traumatic Brain Injury Research Fund, NIDILRR, ACL, or HHS, and readers should not assume endorsement by the federal government.

Corresponding author: David B. Salisbury, PsyD, ABPP, Department of Neuropsychology, Director of Clinical Training, Baylor Institute for Rehabilitation, 411 N. Washington Avenue, Dallas, TX 75246 (e-mail: dsalisbury@bir-rehab.com).
Health Insurance Portability and Accountability Act–compliant version of SurveyMonkey.

Survey results were summarized with SAS 9.3 software (Cary, NC) using appropriate descriptive statistics including means and standard deviations or medians and ranges for quantitative variables, and counts and percentages for categorical variables. Comparisons of scores across groups were performed using analysis of variance (ANOVA). Significant ANOVA tests were followed by pairwise comparisons to determine which groups were different. Tukey’s adjustment for multiple comparisons was used.

RESULTS

A large portion of the respondents were physical therapists and athletic trainers, but a wide range of disciplines were captured (Table 2). Among respondents, the majority worked in outpatient (47%) or inpatient settings (27%). The participants were also predominantly quite experienced in their discipline and had worked for years in the rehabilitation setting. A slight majority (60%) had received some form of formal concussion education/training, including continuing education, although only 9% were part of a concussion or sports health clinic.

Encouragingly, common misperceptions about concussion requiring loss of consciousness, contact to the head, and symptom onset immediately after concussion were not endorsed by the preponderance of participants (Figure 1). As expected, there was less consistency in responses about the typical recovery from concussion, with most participants choosing the 1 day to 3 months (63%) or 3 to 6 months (22%) options. Given variable scientific data, both answers could be supported by the literature, yet the briefer recovery time is more consistent with the metaanalytic studies (10–13).

In the second portion of the survey that contained questions related to best care practices, concussion recovery, and long-term effects, the discrepancy in beliefs greatly increased. Many (41%) indicated that some initial activity restriction after a concussion represented best practice. Still, a sizeable portion of respondents advocated for removal of all cognitive and physical activity for a week (27%) or even no activity until all symptoms had resolved (31%). Such activity restriction has not been supported by studies and may even increase the risk for prolonged recovery and symptom exacerbation (14, 15). Furthermore, many respondents endorsed the benefit of multidisciplinary care in the initial days after a concussion (35%). Given the rapid natural resolution of symptoms expected with uncomplicated concussions, there is currently limited support for immediate engagement in multiple therapies (14, 15). For more prolonged symptoms, multidisciplinary therapies targeting linger symptoms may be of benefit (16). A majority (58%) also endorsed the notion that increased patient complaints months after a concussion were related to a “more severe” concussion. Prolonged and more severe concussion complaints have alternatively been strongly linked to secondary factors such as litigation status, premorbid physical status, and psychiatric history (11, 17–21). Finally, questions related to chronic traumatic encephalopathy (CTE) were included given the extensive recent media coverage and increased frequency of patient/family concerns about this potential syndrome. The misperception that a single concussion increases one’s risk for CTE was believed by a surprisingly large portion of the participants (64%). While CTE remains a widely debated phenomenon, most proponents suggest that repetitive head trauma is a necessity as compared to an isolated concussion (22, 23).

<table>
<thead>
<tr>
<th>Item</th>
<th>Responses (correct response in italic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A concussion requires loss of consciousness.</td>
<td>• Yes</td>
</tr>
<tr>
<td></td>
<td>• No</td>
</tr>
<tr>
<td>2. A concussion requires contact to the head.</td>
<td>• Yes</td>
</tr>
<tr>
<td></td>
<td>• No</td>
</tr>
<tr>
<td>3. After a recent concussion, a person has a greater risk for another concussion.</td>
<td>• Yes</td>
</tr>
<tr>
<td></td>
<td>• No</td>
</tr>
<tr>
<td>4. Problems related to a concussion always begin immediately after the concussion.</td>
<td>• Yes</td>
</tr>
<tr>
<td></td>
<td>• No</td>
</tr>
<tr>
<td>5. Most people recover from a concussion in 1 day to 3 months</td>
<td>• 1 day to 3 months</td>
</tr>
<tr>
<td></td>
<td>• 3 to 6 months</td>
</tr>
<tr>
<td></td>
<td>• 6 to 12 months</td>
</tr>
<tr>
<td></td>
<td>• 12 to 24 months</td>
</tr>
<tr>
<td></td>
<td>• 24 or more months</td>
</tr>
<tr>
<td>6. The current evidence best supports which of the following recommendations related to a return to activity following concussion:</td>
<td>• A reduction in activities following a concussion is not necessary.</td>
</tr>
<tr>
<td></td>
<td>• Patients can return to activities within 2 to 5 days as symptoms improve, decreasing mental or physical activity if any symptom recurrence happens.</td>
</tr>
<tr>
<td></td>
<td>• There should be a removal from mental and physical exertion for a period of at least 7 days after a concussion.</td>
</tr>
<tr>
<td></td>
<td>• Patients should continue a practice of total brain rest (physical and mental) until they are symptom free.</td>
</tr>
<tr>
<td>7. During the first few days after a concussion, best practices of care include outpatient therapies (e.g., speech therapy, vestibular therapy, physical therapy, occupational therapy).</td>
<td>• Yes</td>
</tr>
<tr>
<td></td>
<td>• No</td>
</tr>
<tr>
<td>8. Patients who have concussion-related complaints months later usually experienced a more severe injury.</td>
<td>• Yes</td>
</tr>
<tr>
<td></td>
<td>• No</td>
</tr>
<tr>
<td>9. A single concussion increases your risk for chronic traumatic encephalopathy (CTE).</td>
<td>• Yes</td>
</tr>
<tr>
<td></td>
<td>• No</td>
</tr>
<tr>
<td>10. Is CTE an established medical condition that can be diagnosed?</td>
<td>• Yes</td>
</tr>
<tr>
<td></td>
<td>• No</td>
</tr>
<tr>
<td></td>
<td>• Unknown</td>
</tr>
</tbody>
</table>

Table 1. Knowledge questions on the concussion survey
Further analysis of responses was conducted based upon professional background, prior concussion training, and experience with various patient populations (Table 2). Respondents in job roles that often involve initial contact and follow-up after concussion within our health care system (e.g., psychologists, athletic trainers, and physicians) had a higher percentage of correct scores. Respondents who had received formal training targeting concussion care \((P < 0.001)\) or were part of a concussion/sports health clinic \((P < 0.001)\) also performed better on the survey. Surprisingly, the small portion of the group \((n = 16)\) who reported the largest percentage of work with concussion cases \((>50\%)\) had lower scores than the rest of the sample. In general, years of experience in one’s professional field and experience in the rehabilitation setting were not significantly related to performance on the concussion survey. Furthermore, experience with moderate to severe traumatic brain injury and other non–traumatic brain injury–related neurological disorders was not predictive of greater item accuracy on the survey.

**DISCUSSION**

This survey further illuminates gaps in the knowledge base regarding concussion diagnosis, recovery, and long-term prognosis. Despite the overwhelming percentage of rehabilitation professionals who demonstrated an accurate understanding of basic issues surrounding concussion diagnosis, the range of responses for later questions dealing with expected recovery and outcome is consistent with prior studies showing concerning variability in concussion knowledge among health providers \((2, 4, 5)\). The breadth of disciplines captured within our rehabilitation setting and the large number of respondents help clarify that continuing education and training are needed across providers. It is erroneous to assume that professional background, years of experience, or experience within a particular setting consistently translate into a stronger understanding of concussion-related care issues.

<table>
<thead>
<tr>
<th>Job role</th>
<th>N (%)</th>
<th>Percent correct (mean ± SD)</th>
<th>(P) value</th>
<th>Significantly different groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy technician (1)</td>
<td>20 (4%)</td>
<td>55.0 ± 16.4</td>
<td>5, 6, 7</td>
<td></td>
</tr>
<tr>
<td>Occupational therapist (2)</td>
<td>47 (8%)</td>
<td>57.4 ± 10.9</td>
<td>5, 6, 7</td>
<td></td>
</tr>
<tr>
<td>Physical therapist (3)</td>
<td>252 (45%)</td>
<td>63.8 ± 15.0</td>
<td>5, 6, 8, 10</td>
<td></td>
</tr>
<tr>
<td>Speech therapist (4)</td>
<td>27 (5%)</td>
<td>60.0 ± 13.0</td>
<td>5, 6</td>
<td></td>
</tr>
<tr>
<td>Psychologist (5)</td>
<td>16 (3%)</td>
<td>82.5 ± 12.4</td>
<td>1, 2, 3, 4, 8, 9, 10</td>
<td></td>
</tr>
<tr>
<td>Athletic trainer (6)</td>
<td>112 (20%)</td>
<td>72.1 ± 11.9</td>
<td>1, 2, 3, 4, 8, 9, 10</td>
<td></td>
</tr>
<tr>
<td>Physician (7)</td>
<td>16 (3%)</td>
<td>71.3 ± 17.5</td>
<td>1, 2, 8, 9, 10</td>
<td></td>
</tr>
<tr>
<td>Registered nurse (8)</td>
<td>34 (6%)</td>
<td>54.7 ± 17.8</td>
<td>3, 5, 6, 7</td>
<td></td>
</tr>
<tr>
<td>Administrative (9)</td>
<td>10 (2%)</td>
<td>50.0 ± 18.3</td>
<td>5, 6, 7</td>
<td></td>
</tr>
<tr>
<td>Other (10)</td>
<td>27 (5%)</td>
<td>53.0 ± 19.0</td>
<td>3, 5, 6, 7</td>
<td></td>
</tr>
<tr>
<td>Formal training in concussion care</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (1)</td>
<td>322 (60%)</td>
<td>68.1 ± 15.1</td>
<td>2, 3</td>
<td></td>
</tr>
<tr>
<td>No (2)</td>
<td>228 (41%)</td>
<td>58.6 ± 15.0</td>
<td>1, 3</td>
<td></td>
</tr>
<tr>
<td>Unknown (3)</td>
<td>6 (1%)</td>
<td>40.0 ± 16.7</td>
<td>2, 3</td>
<td></td>
</tr>
<tr>
<td>Part of a specialized concussion or sports health clinic</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (1)</td>
<td>48 (9%)</td>
<td>72.3 ± 16.7</td>
<td>2, 3</td>
<td></td>
</tr>
<tr>
<td>No (2)</td>
<td>494 (88%)</td>
<td>63.3 ± 15.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unknown (3)</td>
<td>19 (3%)</td>
<td>58.4 ± 19.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Percentage of work with concussion cases</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25% (1)</td>
<td>505 (90%)</td>
<td>64.3 ± 15.4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>25% to &lt;50% (2)</td>
<td>40 (7%)</td>
<td>63.0 ± 17.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥50% (3)</td>
<td>16 (3%)</td>
<td>53.8 ± 25.3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Years of experience in current role</td>
<td>0.49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>90 (16%)</td>
<td>62.0 ± 16.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–5</td>
<td>130 (23%)</td>
<td>64.7 ± 15.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–9</td>
<td>111 (20%)</td>
<td>63.0 ± 16.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>230 (41%)</td>
<td>64.6 ± 16.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of experience in rehabilitation setting</td>
<td>0.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>81 (14%)</td>
<td>59.6 ± 14.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–5</td>
<td>122 (22%)</td>
<td>64.3 ± 16.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–9</td>
<td>112 (20%)</td>
<td>64.3 ± 14.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>209 (37%)</td>
<td>64.4 ± 16.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not applicable, no rehab experience</td>
<td>32 (6%)</td>
<td>66.9 ± 19.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (1%)</td>
<td>72.0 ± 13.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of work with moderate to severe traumatic brain injury</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25% (1)</td>
<td>445 (79%)</td>
<td>64.7 ± 15.3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>25% to &lt;50% (2)</td>
<td>53 (10%)</td>
<td>64.5 ± 16.7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>50% to &lt;75% (3)</td>
<td>44 (8%)</td>
<td>57.7 ± 19.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥75% (4)</td>
<td>19 (3%)</td>
<td>57.4 ± 17.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Instead, the survey results show that concussion education and training are related to a better knowledge base.

Specifically, more advanced education focused on the nuances of concussion recovery, risks for complicated recovery, and noninjury factors that can impact recovery is warranted for rehabilitation professionals. A demarcation between the more common uncomplicated recoveries as compared to high-risk cases with exacerbating factors may be an ideal target for rehabilitation staff education. In our experience, the cases of prolonged recovery can be overly represented in rehabilitation caseloads, which can result in a skewed perspective of concussion sequelae.

The frequency of exacerbating iatrogenic effects after concussion from misinformation cannot be overemphasized (24, 25). For concussion patients identified as having premorbid or injury-related risk factors for a complicated recovery, an appropriate understanding of recovery can facilitate needed multidisciplinary referrals. More importantly, minimizing unneeded services and unnecessary restrictions can limit potential symptom misattribution and avoid the potential for secondary symptoms due to excessive restriction from exercise, school/work, and social activities (14).

A few limitations in this study are worthy of mention. Similar to most survey studies, it is possible that the characteristics of those who responded to the survey differed from those of nonrespondents. There was no systematic way to determine characteristics of those who took the survey compared with those who declined, and a response rate could not be obtained. The respondents were primarily from a few disciplines, which is largely a result of their high representation in the health care organization targeted. The data for less represented groups must be interpreted with caution. The wide variety of settings across numerous states and lack of defined concussion training within our system would make it unlikely that the majority of respondents had a similar background in concussion training. Still, the concussion knowledge base and experience of rehabilitation staff may not mirror those of other professionals in different settings.

Hence, this study should not be interpreted to suggest that specific disciplines are better qualified to provide concussion care.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the expertise of Mark Barisa, PhD, Jessica Clark, PhD, Sidney Dickson, PhD, and William Garmoe, PhD, who assisted with the development of the survey.

Factors associated with performance in an internal medicine clerkship

Colleen Colbert, PhD, Tresa McNeal, MD, Maybelline Lezama, MD, Martha Chandler, ACUME, Lisa Forrester, MD, Austin Metting, MD, Curtis Mirkes, DO, Holly Van Cleave, MD, Sonny Win, MD, and John D. Myers, MD

The purpose of this retrospective study was to examine the relationship between demographic and educational variables and student performance on an internal medicine (IM) clerkship in order to target areas for educational intervention and potential early remediation. This study examined data associated with third-year medical student performance (N = 505) during the IM clerkship at Baylor Scott & White, Temple/Texas A&M Health Science Center College of Medicine from 2005 to 2011. Multiple regression analysis (N = 341) showed that a model containing the following variables was significantly associated with scores on the National Board of Medical Examiners (NBME) subject exam, accounting for 46.5% of the variance: Objective Structured Clinical Exam (OSCE), Medical College Admissions Test (MCAT), US Medical Licensing Exam (USMLE) Step 1, second-year grade point average (GPA), and clinical evaluation. A model containing USMLE Step 1, clinical evaluation, and NBME was significantly associated with OSCE score, accounting for 30% of the variance. Additionally, a model containing age, MCAT score, undergraduate GPA, NBME subject exam score, and OSCE was significantly associated with clinical evaluation score, accounting for 22% of score variance. Age accounted for the most unique variance in clinical evaluation score. Gender and IM interest group were not significantly associated with any outcome variable. In conclusion, in contrast to previous studies in the field, we did not find a significant association between undergraduate GPA and NBME score. Our findings supply further evidence that the OSCE, typically believed to be a clinical performance exam, actually assesses a broader set of domains. Interest group membership did not confer any academic benefit to medical students in IM clerkships in our study.

The association between medical student academic variables and academic performance on clerkships has been examined in previous studies (1–4). Studies have also examined nonacademic variables, including demographic and internal variables (e.g., intrinsic motivation), as contributors to clerkship performance (5–10). The purpose of this study was to examine both types of variables in relation to internal medicine (IM) clerkship performance, with a goal of continuous program improvement. This appears to be the first time interest group membership was examined in a study of academic performance on the IM clerkship.

METHODS

This single-site, retrospective study examined academic and nonacademic data associated with student performance on the IM clerkship at Baylor Scott & White, Temple/Texas A&M Health Science Center College of Medicine (BSW-Temple/A&M) from 2005 to 2011. As the IM clerkship was not offered at all campuses during the study’s time frame, we utilized data from the Temple campus only to ensure an adequate sample size and identical educational experiences. At the time of the study, the 12-week IM clerkship at BSW-Temple/A&M included 8 weeks of inpatient and 4 weeks of outpatient experiences. The IM clerkship grade on all campus sites comprises the following: Objective Structured Clinical Exam (OSCE) score (20%), National Board of Medical Examiners (NBME) subject exam score (30%), and clinical evaluation score (50%).

The IM interest group at BSW-Temple/A&M is open to students interested in IM. The group, with approximately 20 members per year, provides peer support and access to physician mentors and sponsors activities focused on careers in IM. Meeting topics include academic expectations during the third year, preparation for residency, career options, work-life balance issues, selection of faculty advisors, and residency interviews. Most members enter careers in IM.

The study was approved by the institutional review board (IRB) at Texas A&M University. Scott & White Healthcare’s IRB granted oversight to the Texas A&M IRB.

Data were collected from educational records of 505 third-year medical students who participated in the IM clerkship at BSW-Temple/A&M between June 2005 and June 2011. Data sources included academic and demographic data from the IM

From Baylor Scott & White Health (Colbert, McNeal, Lezama, Chandler, Forrester, Metting, Mirkes, Van Cleave, Win, Myers) and Texas A&M Health Science Center College of Medicine (Colbert, McNeal, Lezama, Forrester, Metting, Mirkes, Van Cleave, Win, Myers), Temple, Texas. Dr. Colbert is now with Cleveland Clinic Lerner College of Medicine of Case Western Reserve University.

A poster reporting the results of this study was presented at the Association of American Medical Colleges Southern Group on Educational Affairs meeting, April 18–20, 2013, in Savannah, Georgia.

Corresponding author: Colleen Y. Colbert, PhD, Cleveland Clinic Education Institute, 9500 Euclid, NA25, Cleveland, OH 44195 (e-mail: colberc2@ccf.org).
Clerkship Office in Temple, Texas, and Student Affairs Office and Registrar’s Office from Texas A&M. Formal data collection did not end until summer 2012.

The following data were collected for each subject: name, age (in years), gender, undergraduate major, IM interest group membership, undergraduate GPA, overall IM clerkship grade, OSCE scores, clinical evaluation scores from attendings, NBME subject exam scores (raw and converted), MCAT score, USMLE Step 1 and 2 scores, and GPA for the first, second, and third years of medical school. Names were initially linked to demographic and academic data, but all data utilized for analysis and reporting were deidentified. Data diagnostics were run to ensure that normality assumptions were met. NBME converted scores (grades) were utilized, as both raw and converted scores had similar ranges and standard deviations and met normality assumptions. Descriptive statistics (SPSS Version 16.0) were used to characterize the sample. Pearson product-moment correlation coefficients were generated to examine relationships among variables. Multiple regression analyses were run to address research questions. Squared partial correlations allowed us to examine the unique variance contributed by predictor variables once shared variance was removed (11). The significance threshold was set at $P < 0.05$. Missing values were not replaced prior to analyses.

## RESULTS

Student ages ranged from 24 to 57 ($M = 29.75; SD = 4.09$), and females ($N = 251$) comprised 49.7% of the sample. Of the 505 students, 108 (21.4%) were members of the IM interest group. Most students in the sample (387, 76.6%) were science majors as undergraduates. Means and ranges for the academic variables are listed in the Table.

A multiple regression analysis ($N = 341$) was run to determine the strength of relationships between predictor variables and NBME as the outcome variable. As first- and third-year GPA were found to be highly correlated with second-year GPA, they could not be entered into the regression model as predictor variables due to multicollinearity issues (12). A model containing the following predictors was significantly associated with NBME subject exam scores: OSCE score, MCAT, USMLE Step 1, second-year GPA, and clinical evaluation score. The model provided a good fit to the data—$F$ ($9, 331$) = 17.183, $P < 0.001$, $R^2 = 0.318$, adjusted $R^2 = 0.300$—accounting for 30% of the variance in OSCE score. Gender, age, IM interest group membership, MCAT score, second-year GPA, and undergraduate GPA were not significantly associated with OSCE score. NBME score accounted for the most unique variance based upon squared partial correlations.

A multiple regression analysis ($N = 341$) was run to determine the strength of relationships between predictor variables and OSCE score as the outcome variable. A model containing the following predictors was significantly associated with OSCE score: USMLE Step 1, clinical evaluation, and NBME score. The model was found to provide a good fit to the data—$F$ ($9, 331$) = 11.647, $P < 0.001$, $R^2 = 0.241$, adjusted $R^2 = 0.220$—accounting for 22% of the variance in clinical evaluation score. Gender, IM interest group, USMLE Step 1, and second-year GPA were not significantly associated with clinical evaluation score in this model. Age accounted for more unique variance in clinical evaluation score than other predictors based upon squared partial correlations. A low to moderate positive correlation between age and clinical evaluation score was found ($r = 0.203; P < 0.001$).

## DISCUSSION

This study found that clinical evaluation and OSCE scores were significantly and positively associated with NBME subject exam scores, supplying further evidence that the OSCE, considered to be a clinical exam, assesses a broader range of clinical performance domains, including some that underlie performance on the NBME exam (12). USMLE Step 1, MCAT, and second-year GPA were also significantly associated with NBME subject exam scores (1, 2, 13). In contrast to previous research, we did not find a significant association between USMLE Step 1 and clinical evaluation score (14) or between undergraduate GPA and NBME score. Additionally, as USMLE Step 1 was significantly associated with NBME score in the regression analysis, an association between USMLE Step 1 and clinical evaluation score may have been expected, but was not found. In examining variables associated with OSCE performance, we found that NBME score accounted for more unique variance than other variables. The OSCE in the IM clerkship utilizes standardized patients for a majority of the stations. We assumed that the clinical evaluation score would therefore account for more unique variance than the NBME score.

### Table. Academic variable means and ranges

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCAT score</td>
<td>432</td>
<td>28.08 ± 3.44</td>
<td>15–39</td>
</tr>
<tr>
<td>USMLE Step 1</td>
<td>420</td>
<td>217.96 ± 19.10</td>
<td>101–262</td>
</tr>
<tr>
<td>NBME IMED</td>
<td>504</td>
<td>85.64 ± 6.73</td>
<td>61–100</td>
</tr>
<tr>
<td>Undergraduate GPA</td>
<td>502</td>
<td>3.68 ± 0.26</td>
<td>2.35–4.00</td>
</tr>
<tr>
<td>Second-year GPA</td>
<td>486</td>
<td>3.12 ± 0.59</td>
<td>1.21–4.00</td>
</tr>
</tbody>
</table>

GPA indicates grade-point average; IMED, internal medicine subject exam; MCAT, Medical College Admissions Test; NBME, National Board of Medical Examiners; USMLE, US Medical Licensing Exam.
Our study showed that age was significantly and positively associated with clinical evaluation score. This finding contrasts with other studies, wherein older age was associated with lower clerkship grades and risk for academic difficulties (5, 7). Gender was not significantly associated with academic variables in this study, which also contrasts with prior research (4, 5, 10, 15, 16). No association was found between interest group membership and academic performance, which is a new finding. We hypothesized there would be a positive association between interest in IM, a proxy for intrinsic motivation, and clerkship academic performance, based upon other findings in the literature (4, 17–19).

This was a single-site study, and findings may not generalize to other academic settings. As with other retrospective studies, the findings can speak to associations among variables, but not causality. We were limited to the data already existing within students’ academic records. The retrospective nature of this study prevented us from determining whether age represented a set of attributes not measured, such as better study skills among older students. Strengths of the study included adequate sample size, variables examined, and analysis methods. It was beyond the scope of this study to examine the influence of clerkship curricular requirements, such as patient loads, on academic performance.

ACKNOWLEDGMENTS

We would like to thank Glen Cryer, former publications manager for Baylor Scott & White Healthcare, Temple, for his assistance with this paper.

Late presentation of fatal hyperammonemic encephalopathy after Roux-en-Y gastric bypass

Amulya Nagarur, MD, and Andrew Z. Fenves, MD

Worldwide, there have been <25 reported cases of hyperammonemic encephalopathy associated with Roux-en-Y gastric bypass surgery in the absence of cirrhosis. We describe a 42-year-old woman who presented with subacute but progressive neurological decline late in her postoperative course, which deteriorated despite multiple conservative and aggressive measures, including hemodialysis, in an attempt to reduce measured plasma ammonia levels. This syndrome of hyperammonemic encephalopathy represents a serious, underrecognized, and potentially treatable complication after Roux-en-Y gastric bypass.

Roux-en-Y gastric bypass (RYGB) surgery results in clinically important and durable cardiometabolic effects and has become an adjunctive measure in ameliorating adverse health outcomes in obese patients (1). RYGB has become the most widely employed weight loss operative procedure in the US (2). There are now numerous patients who have developed severe and symptomatic hyperammonemia at variable intervals after RYGB (3). We describe yet another patient with this relatively rare but neurologically devastating complication after successful RYGB.

CASE DESCRIPTION

A 42-year-old woman who had RYGB 11 years earlier presented with severe protein malnutrition and altered mental status. The patient had a longstanding history of elevated serum ammonia levels (of unclear etiology) being managed with lactulose and rifaximin. Several days prior to hospitalization, she developed worsening confusion and vomiting. She had a 50-pound unintentional weight loss over the preceding 6 months despite adequate oral intake. She was evaluated at an outside hospital where a plasma ammonia level was 498 μmol/L (reference, 12 to 48 μmol/L). Given declining mental status and refractory hyperammonemic encephalopathy, she was intubated and transferred to our intensive care unit.

On arrival at our hospital, she was ill-appearing and intubated. Her Glasgow Coma Scale score was 3 out of 15. She was afebrile, with a heart rate of 97 beats per minute and blood pressure of 135/85 mm Hg. With 16 cm H2O of positive end-expiratory pressure and 30% fraction of inspired oxygen, her oxygen saturation was 95%. She was unresponsive to noxious stimuli and had intact brainstem reflexes, a non-distended abdomen with prior laparoscopy scars, and diffuse anasarca.

Her serum albumin level was 1.4 g/dL; aspartate transaminase, 47 U/L; alanine transaminase, 24 U/L; alkaline phosphatase, 222 U/L; total bilirubin, 1.0 mg/dL; and international normalized ratio, 1.4. Plasma amino acids showed a citrulline level of 12 nmol/mL (reference, 17–46 nmol/mL). Serum glutamine and glutamate, as well as urine orotic acid levels, were normal. Her plasma zinc level was 0.34 mcg/mL (reference, 0.66–1.1 mcg/mL).

Noncontrast computed tomography (CT) imaging of the head disclosed bilateral cerebral edema and loss of the gray-white matter differentiation. Magnetic resonance imaging of the brain revealed diffuse T2/FLAIR hyperintensity compatible with acute hyperammonemic encephalopathy. Electroencephalography was equivocal for epileptiform activity. Abdominal ultrasound showed a macronodular liver, small volume ascites, and patent vasculature. An abdominal CT scan revealed no focal hepatic lesions, enteric fistulas, or evidence of vascular shunting.

She underwent transjugular portal pressure measurement and liver biopsy. There was no portal hypertension, and core biopsies revealed marked cholestatic hepatitis but no cirrhosis. During her hospitalization, she was treated with lactulose and rifaximin. She also underwent one session of hemodialysis. Zinc repletion, intravenous thiamine, and dextrose-containing fluids resulted in normalization of serum ammonia levels. She nevertheless progressed to status epilepticus, sepsis, and multisystem organ failure and died after a prolonged hospital stay.

CASE DISCUSSION

Gastric bypass–related hyperammonemia (GaBHA) is becoming an increasingly recognized entity (3). Shared phenotypic characteristics have emerged upon review of the 21 previously reported cases of this postoperative entity (3, 4)
There is a predilection for women (age range, 34 to 69 years) without established liver disease. Hyperammonemic encephalopathy manifests at varying time intervals after RYGB, ranging from early (months) to late (latest known case, 28 years postoperatively). Given the initial nonspecific signs and symptoms, there may be significant delays in management. The syndrome is often met with high case fatality and poor prognosis.

There are numerous etiologies for nonhepatic hyperammonemia (Table 1). The specific mechanisms driving the hyperammonemic state after RYGB may be multifactorial. As it has been almost exclusively observed in women, X-linked partial ornithine transcarbamylase (OTC) deficiency has been implicated (Figure 2). Previously asymptomatic heterozygous OTC-deficient women can present when faced with catabolic stressors, and biochemical profiling is consistent with impaired urea cycle function. Zinc deficiency has also been proposed to interfere with OTC function (5). Nongenetic mechanisms of increased ammoniagenesis have been considered, including portosystemic shunting, severe hepatic dysfunction, and overgrowth of intestinal flora. A profound catabolic state may also play a role, driving protein breakdown and accumulation of nitrogenous waste products.

Conservative management approaches with lactulose and rifaximin have resulted in modest reductions in measured ammonia levels. Repletion of deficient amino acids, zinc, micro nutrients, and intravenous glucose infusion may attenuate the catabolic state. Surgical reversal of the RYGB anatomy in one patient, and occlusion of a splenorenal shunt in another patient, have improved clinical trajectories (6, 7). Although the measured plasma ammonia levels were lowered in our patient after hemodialysis, she had persistent encephalopathy. The lack of success of renal replacement therapy may be

---

**Figure 1.** Shared phenotypic characteristics of hyperammonemic encephalopathy after Roux-en-Y gastric bypass surgery. AA indicates amino acid; \( \text{NH}_3 \), ammonia.

**Figure 2.** Urea cycle and associated enzymes.

**Table 1. Causes of nonhepatic hyperammonemia**

- Urease-producing bacteria (*Proteus*, *Klebsiella*, *Escherichia*, and *Morganella* species, *Helicobacter pylori*)
- Drugs (valproic acid, 5-fluorouracil, carbamazepine)
- Surgery (bariatric surgery, ureterosigmoidostomy, lung and bone marrow transplants)
- Hyperalimentation (total parenteral nutrition)
- Anatomic (portosystemic shunts)
- Errors in metabolism (urea cycle disorder, fatty acid oxidation defect, organic acidemia, pyruvate metabolism disorder)
related to her late presentation, irreversible hyperammonemic effects on neurons, and brain parenchymal saturation (8).

Hyperammonemic encephalopathy represents an under-recognized complication after RYGB and carries serious consequences, with mortality approaching 50%. Rigorous screening for select metabolic derangements (e.g., plasma ammonia, zinc, and serum albumin) in high-risk patients may facilitate early detection of this clinical entity. Genetic screening for OTC deficiency may also be considered, although this approach has not been fruitful in reported patients (3). Evaluating for in vivo OTC enzymatic activity in fresh liver tissue is of particular interest, but this requires a liver biopsy. A global registry of identified and confirmed cases may assist in further elucidating potential screening measures and management strategies. We welcome our colleagues to contact us regarding similar patients as we try to build on our collective experience.

Epiploic appendagitis (EA) is a rare cause of acute abdominal pain caused by inflammation of an epiploic appendage. It has a nonspecific clinical presentation that may mimic other acute abdominal pathologies on physical exam, such as appendicitis, diverticulitis, or cholecystitis. However, EA is usually benign and self-limiting and can be treated conservatively. We present the case of a patient with two episodes of EA, the first mimicking acute appendicitis and the second mimicking acute cholecystitis. Although recurrence of EA is rare, it should be part of the differential diagnosis of acute, localized abdominal pain. A correct diagnosis of EA will prevent unnecessary hospitalization, antibiotic use, and surgical procedures.

CASE REPORT

A 66-year-old Caucasian woman presented with a 3-day history of progressively worsening right mid abdominal pain exacerbated by positional change. On a pain scale of 1 to 10, she rated the pain an 8. She had some degree of anorexia, but denied any associated chills, fever, nausea, vomiting, change in bowel habits, or skin rash. Her past medical history included hypertension, hyperlipidemia, hypothyroidism, and stress-induced cardiomyopathy. Her only abdominal surgeries consisted of C-sections. Two years prior, she had a colonoscopy showing no diverticulosis or significant polyps. Her family history was significant for gallbladder disease requiring cholecystectomies.

On physical examination, she was ambulatory and not in acute distress. She was afebrile, nonicteric, had normal vital signs, and her BMI was now 28 kg/m² after dieting. Key findings on physical exam were point tenderness in the right upper quadrant with a positive Murphy sign. A positive Murphy sign increases the likelihood of an inflamed gallbladder and occurs when the patient arrests inspiration as the examiner palpates the abdominal right upper quadrant while the patient is taking a deep breath. The differential diagnosis included acute cholecystitis and recurrent EA. Her complete blood count, comprehensive metabolic panel, and lipase levels were normal. Abdominal ultrasonography showed a normal gallbladder, liver, and pancreas. Once again, the CT scan was diagnostic, showing a mass of similar size and location as the previous EA lesion. The patient was treated with analgesics and antiinflammatory medication, and her symptoms resolved within 5 days.

DISCUSSION

Epiploic appendages are 50 to 100 pedunculated peritoneal fat pouches oriented in two rows parallel to the taenia coli of the colon, between the cecum and rectosigmoid junction, each usually 1 to 2 cm thick and 0.5 to 5 cm long (3). Each epiploic appendage is supplied by two endarteries, originating from the vasa recta, and one single tortuous vein that passes through a narrow stalk at its base (3). The peduncular shape and...
narrow vascular supply stalk makes epiploic appendages prone to torsion, leading to ischemic or hemorrhagic infarction, and susceptible to venous thrombosis (3).

Primary EA is a rare cause of acute abdominal pain thought to be caused by appendage torsion or venous thrombosis (3). In a case series of 58 patients with EA, 48% of cases occurred in the sigmoid colon, 28% in the descending colon, 7% in the transverse colon, and 17% in the ascending colon (6). Thus, EA often presents with lower abdominal pain mimicking diverticulitis and appendicitis, and there are few documented presentations that mimic cholecystitis (7, 8). Secondary EA results from inflammation of an adjacent organ, such as cholecystitis, pancreatitis, diverticulitis, or appendicitis (5, 9). These infarcted appendages undergo fat necrosis and calcify and may either stay attached to the colon or detach to become peritoneal loose bodies or “parasitized epiploic appendages” by reattaching to surfaces within the abdominal cavity, like the spleen (3).

Primary EA clinically presents as an abrupt onset of acute, well-localized, nonmigratory abdominal pain, often in the lower abdominal quadrants, that worsens with movement. The patient usually is afebrile without nausea, vomiting, anorexia, or change in bowel function (3, 6). On physical examination the patient presents with localized tenderness and possible guarding. Usually vital signs and laboratory values are within normal limits, but mild leukocytosis and slight elevation of C-reactive protein have been reported in some cases (1, 3, 4).

EA is diagnosed via CT scan (preferred) and ultrasonography (6, 9). In CT, the inflamed epiploic appendage usually appears as a 1.5-cm to 3.5-cm fat-attenuation lesion adjacent to the colon with a peripheral rim of hyperattenuation (representing inflamed peritoneum), usually with a central dot of high attenuation (representing the thrombosed vein), with surrounding fat stranding (representing increased edema), and with asymmetric wall thickening of the colon, due to the inflammation being...
greater in the area surrounding the colon than on the colon wall itself (6, 9). Omental infarctions and mesenteric panniculitis may have clinical presentations similar to that of EA, but can be distinguished from EA on CT because omental infarctions usually are larger than 5 cm and lack a hyperattenuating rim (9), and mesenteric panniculitis appears as a fat-attenuation lesion within the mesentery usually with a “fat-ring sign,” which represents preserved noninflamed fat around vessels (9). Ultrasonography identifies an inflamed epiploic appendage as a noncompressible hyperechoic mass adjacent to the colon wall at the site of pain usually with a hypoechoic rim, representing inflamed peritoneum, and absence of blood flow on Doppler due to torsion or thrombosis (9).

Before CT scans were established as standard diagnostic imaging tools, EA was a surgical diagnosis treated by laparoscopic surgical excision. However, EA is considered a benign, self-limiting lesion that usually resolves spontaneously within days to weeks and can be treated conservatively with over-the-counter analgesics and antiinflammatory medications (1, 2). Rarely, surgical interventions are needed due to complications, such as small bowel obstruction due to adhesions or external compression (6).

Recurrence of EA is rare, but has been documented in cases managed conservatively. In a case study of 10 patients with EA treated conservatively, Sand et al observed recurrence of EA in 4 out of the 10 patients (3). Recurrence was also observed in a case report of one patient on peritoneal dialysis (4). Authors of both articles suggest involvement of the same epiploic appendage in both presentations and recommend considering laparoscopic excision for these cases. Only one case report described recurrence of EA involving two distinct epiploic appendages, both with similar presentation and treated by laparoscopic excision due to severe symptoms (5). Even though surgical excision would remove the inflamed epiploic appendage that is causing irritation, the benefit of surgical excision should be weighed against its risks—mainly anesthesia complications, excessive bleeding, and infection—and cost (1–3).

The patient in this report had two occurrences of EA, each with similar clinical presentation but eliciting pain in different abdominal quadrants, first with right flank pain, mimicking retrocecal appendicitis, and later in the right upper quadrant, mimicking acute cholecystitis. Possible risk factors for developing EA are obesity and postprandial strenuous exercise, supported by some case reports (7, 10) but not by others (3). From the patient’s past medical history, only obesity (BMI >30 kg/m²) during the first episode of EA and being overweight (BMI 25–29.9 kg/m²) during the second episode could predispose her for developing EA. CT scans taken in each instance found an inflamed epiploic appendage of similar dimensions in the ascending colon adjacent to the hepatic flexure. The recurrent EA could be due to involvement of the same epiploic appendage in both presentations, causing pain in different quadrants because the colon has some range of mobility within the abdominal cavity, or it could be due to involvement of a neighboring epiploic appendage.

EA should be part of the differential diagnosis of acute abdominal pain because it is a benign, self-limiting lesion that can be diagnosed with CT and treated conservatively. Correct diagnosis avoids unnecessary hospitalizations, antibiotic treatment, and surgeries.

Endovascular therapy using flow diversion for giant internal carotid artery pseudoaneurysm arising in the setting of an invasive pituitary macroadenoma

Amin F. Saad, MD, Almas Syed, MD, Keyan B. Marashi, MD, Brian D. O’Rourke, MD, Joseph H. Hise, MD, Michael J. Opatowsky, MD, MBA, and Kenneth F. Layton, MD, MS

This report illustrates the unusual occurrence of a pseudoaneurysm arising in the setting of a skull base mass and describes the first reported use of endovascular flow diversion therapy in such a setting. A 63-year-old man with occasional headaches during the preceding month presented with the acute onset of severe left retroorbital headache and oculomotor nerve palsy. Computed tomography (CT) and CT angiogram revealed a destructive skull base mass with an associated giant probable pseudoaneurysm of the cavernous segment of the left internal carotid artery. The patient underwent endoscopic transsphenoidal biopsy with a subsequent diagnosis of prolactinoma. Endovascular therapy utilizing two Pipeline™ flow diversion embolization devices was performed with subsequent resolution of the patient’s headache and improvement in his cranial nerve deficits/cavernous sinus syndrome.

Aneurysms coincident with invasive skull base masses are unusual. An association between pituitary neoplasms and intracranial aneurysms has been documented. The acute development of a cavernous sinus syndrome with associated cranial nerve deficits in conjunction with an aneurysm entirely encased within a neoplastic lesion supports the diagnosis of an acutely enlarging pseudoaneurysm, and we describe the first reported use of endovascular flow diversion therapy in such a setting. This case illustrates a diagnostic pitfall with the potential for grave implications in patient outcome if an associated vascular lesion is not appreciated at the time an intracranial mass is diagnosed.

Case Presentation

A 63-year-old man with minor headaches in the preceding month presented to the emergency department following the acute onset of severe left retroorbital headache, proptosis, mydriasis, ophthalmoplegia, and diplopia. Noncontrast head computed tomography (CT) (Figure 1a) revealed a large destructive central skull base mass. Subsequently pre- and postgadolinium brain magnetic resonance imaging (MRI) (Figure 1b, 1c) delineated the margins and character of the skull base mass, which was centered in the clivus and extended to encase the left greater than right cavernous segments of the internal carotid arteries (ICAs) with partial destruction of the petrous carotid canals. A hypointense T2 signal was identified with heterogeneous enhancement following gadolinium administration. A suspicious large flow void within the region of the cavernous segment of the left ICA was confirmed to reflect a probable pseudoaneurysm on postgadolinium imaging and subsequent CT and catheter angiography (Figure 2), which revealed additional dysplastic irregular lobular projections arising from the pseudoaneurysm sac. The patient underwent an endoscopic transsphenoidal biopsy of the lesion. Histopathologic findings showed a pituitary adenoma, and subsequent laboratory testing showed serum prolactin levels to be 14191.5 ng/mL (normal range 2.1–17.7), compatible with the diagnosis of a prolactinoma.

The patient was loaded with aspirin and clopidogrel for 1 day and subsequently underwent endovascular therapy utilizing two overlapping Pipeline™ flow diversion embolization devices (Medtronic, Minneapolis, MN) measuring 4.25 × 30 mm and 4.5 × 16 mm (Figure 3), extending to the supraclinoid ICA. This resulted in an immediate and marked decrease in contrast flow within the pseudoaneurysm sac and contrast stasis. Cabergoline medical therapy was initiated to treat his prolactinoma.

The patient’s headache resolved, and he was discharged in good condition 5 days following endovascular therapy. The patient continued to experience proptosis, mydriasis, and mild diplopia at the time of discharge, although he did experience an improvement in his ophthalmoplegia. On follow-up catheter angiography, the pseudoaneurysm was markedly decreased in size with only trace filling of a subcentimeter residual pseudoaneurysm sac. The patient’s cranial nerve palsies also greatly improved during the 6 months following discharge, and he has continued to do well.

Discussion

The incidence of intracranial aneurysms arising in association with pituitary adenomas is greater than the incidence

From the Departments of Diagnostic and Neurointerventional Radiology, Baylor University Medical Center at Dallas. Dr. Saad is now with Stanford University, and Dr. Marashi is now with University of Utah, Salt Lake City.

Corresponding author: Amin F. Saad, MD, Department of Radiology, Neuroradiology Division, Stanford University, 300 Pasteur Drive, MC 5105, Stanford, CA 94305 (e-mail: aminsaaadm@gmail.com).
of aneurysms arising in the general population (0.5%–7.4%) (1), as well as the incidence of aneurysms coexistent with intracranial masses of nonpituitary origin. The pathogenesis of this increased incidence is uncertain. Proposed etiologies include increased blood flow through vessels supplying the tumor, hormonal effects, and direct neoplastic infiltration (1). The concept of increased tumoral blood flow via internal carotid branch vessels is supported by the fact that the greatest proportion of adenoma-associated aneurysms arise from the ICA (50%) (1). A hormonal influence on the incidence of aneurysm formation is supported by the fact that the greatest incidence of adenoma-associated aneurysms occurs in the context of acromegaly (50%) (1), with associated increased insulin-like growth factor–1 potentially playing a role in the formation of intracranial aneurysms, as well as the more diffuse vasculopathic changes that can be seen in these patients, to include widespread cerebrovascular dolichoectasia (2). The contribution of tumor infiltration is supported by the statistically significant increase in aneurysm incidence in the setting of cavernous sinus invasion.

Figure 1. (a) Axial noncontrast head CT in bone windows demonstrates extensive lytic destruction of the central skull base (arrow). (b) Axial T2-weighted image reveals hypointense signal within the mass (arrow) in addition to a large flow void in the region of the cavernous left internal carotid artery (arrowhead). (c) Axial T1-weighted postgadolinium image shows heterogeneous contrast enhancement of the mass with robust enhancement (arrowhead) of the flow void noted on the T2-weighted image.

Figure 2. (a) Axial source image, (b) sagittal, and (c) coronal reformatted images from a CT angiogram show a giant pseudoaneurysm of the cavernous segment of the left internal carotid artery (arrows) with a dysplastic cephalad projecting lobule (arrowheads). These findings are confirmed on a (d) lateral projection digital subtraction angiography image following a left internal carotid artery injection.
(3), as well as a case reported by Mangiardi et al that described a macroadenoma invading the walls of a giant cavernous carotid aneurysm on a postmortem examination (4). In our case, the fact that the entire pseudoaneurysm was encased within the mass that had invaded the cavernous sinus may provide additional support for the theory of direct neoplastic infiltration, particularly the clinical evidence of acute pseudoaneurysm enlargement supporting an underlying loss of integrity of the vessel wall.

The utility of flow diversion devices has been realized in treating giant aneurysms not amenable to traditional coiling, as well as in therapy of pseudoaneurysms arising secondary to trauma or iatrogenic causes. Vascular remodeling following flow diversion embolization is an established phenomenon that also occurs in pseudoaneurysms with an associated decrease in sac size and is particularly desirable in cases of symptomatic mass effect. Improvement in associated cranial nerve palsies is variable, although the degree of improvement likely relates to the duration and degree of compression.


Figure 3. Frontal (a) oblique and (b) lateral projection digital subtraction angiography images show placement of two overlapping Pipeline embolization devices (arrows) traversing the wide pseudoaneurysm neck with associated sluggish flow of contrast within the pseudoaneurysm sac.
Aneurysms of the hand are rarely encountered and more rarely reported. The least common locations of these aneurysms are the palmar and digital arteries. The etiologies of these entities are quite varied, although they usually present as a pulsatile mass. Following a thorough evaluation, including arterial anatomic imaging, they should be repaired. The reported results following repair have been good. Herein we report a girl with a spontaneous palmar artery aneurysm and its management.

Arterial aneurysms of the hand are rare and most commonly involve the ulnar artery (1). Palmar artery aneurysms (PAA) and digital artery aneurysms (DAA) are even more uncommon. We found published reports of only 105 PAA cases (2) and 23 DAA cases (3). These aneurysms are usually posttraumatic, but spontaneous aneurysms or pseudoaneurysms in the hand have rarely been reported. Here we describe such a case.

CASE REPORT
A 16-year-old girl was referred by her primary care physician for evaluation of possible PAA. She had a several-month history of a pulsating mass in her left palm and denied any trauma. A duplex ultrasound (Figure 1) and a computed tomographic angiogram showed a focal aneurysm appearing to involve the deep palmar arch. Thrombus was present within it. She was initially managed conservatively but the aneurysm enlarged and interfered with her clarinet playing, and she elected to have it treated. Her preoperative Allen’s test was negative.

While under general anesthesia, her arm was exsanguinated and a tourniquet was inflated. An incision was made in the mid-palmar crease just proximal to the aneurysm’s location to avoid contracture. The superficial palmar aponeurosis was divided and the decompressed aneurysm was identified. It was originating off of a digital artery immediately after its takeoff from the deep palmar arch. The tourniquet was deflated and the aneurysm filled with blood. The feeding artery was test clamped, and there was preservation of excellent biphasic Doppler flow in all five digits. The aneurysm was resected without repair of the artery (Figure 2). The wound was closed and the hand was placed in a bulky dressing and splinted. The patient had a normal recovery and returned to all activities, including playing her clarinet.

From Texas Vascular Associates, Dallas, Texas (R. A. Shutze, W. P. Shutze); Surgical Care Associates, Lexington, Kentucky (Leichty); The Heart Hospital Baylor Plano, Plano, Texas (W. P. Shutze).

Corresponding author: William P. Shutze, MD, 621 N. Hall Street, Suite 100, Dallas, TX 75226 (e-mail: William.Shutze@BSWHealth.org)
mycotic (7), occupational (5), or congenital (8). These aneurysms may occur in the superficial palmar arch (1), deep palmar arch (9), common digital artery (10), or proper digital artery (11). A PAA (12) has arisen from a primary vascular tumor and another after carpal tunnel surgery (6).

The usual presentation of PAA and DAA is a painless pulsatile mass in the palm or digit. Digital clubbing (13) and median nerve compression symptoms (1) have been reported.

The diagnosis has usually been made by arteriography, but more recently it has been established by ultrasound, CT angiography, and magnetic resonance (MR) angiography (4). The advances in ultrasound, CT, and MR have made arteriography no longer mandatory, and these noninvasive modalities can be used successfully for diagnosis and surgical planning. Prior to surgical treatment, the vascular anatomy must be well defined and an Allen’s test should be performed.

The recommended treatment for these aneurysms is resection and reconstruction unless the aneurysm is thrombosed and there is no distal ischemia. Also, if there is adequate collateral circulation, tedious microvascular repair with a vein graft may not be necessary, as in our case. Reported surgically repaired patients have generally done well without reports of long-term disability or recurrence. Despite the advances in endovascular technology, reports of endovascular treatment are lacking at this time. The dearth of reports in the literature may be related to the infrequent incidence of this condition and the perception that sacrifice rather than preservation of arterial flow would be required.


Figure 2. (a) The location of the palmar artery aneurysm marked with blue dots. (b) Operative exposure of the palmar artery aneurysm. (c) Resected palmar artery aneurysm.
Understanding vascular-type Ehlers-Danlos syndrome and avoiding vascular complications

Jocelyn Carter, MD, MPH, and Andrew Z. Fenves, MD

Vascular-type Ehlers-Danlos syndrome (EDS) is a rare inherited connective tissue disorder caused by a mutation in type III procollagen. It has the highest mortality rate among the six types of EDS. Patients with this syndrome often have typical medical histories and a characteristic physical examination. We present two patients with this rare disorder and highlight the diagnostic and treatment challenges.

Near the turn of the 20th century, Drs. Ehlers and Danlos described individuals with increased skin elasticity, hyperextensible joints, susceptibility to ecchymoses, and cutaneous lesions (1). This description, combined with the initial cases presented by Russian dermatologist Dr. Tschernogobow at the Moscow Venereology and Dermatology Society conference in 1892, added validity to the concept, and wide acceptance of Ehlers-Danlos syndrome (EDS) was garnered by 1936 (2). Six different subtypes of EDS have been described by the Villefranche classification schematic (3). Vascular-type EDS (EDS type 4), a rare inherited connective tissue disorder caused by a mutation in type III procollagen (Col3A1), has the highest mortality rate of the six types of EDS (3). It has an autosomal dominant transmission with 100% penetrance and comprises 5% to 10% of all cases of EDS. Vascular-type EDS is often characterized by major and minor criteria including vascular rupture or dissection, narrow facies, hyperpigmentation, pale skin with visible subcutaneous vessels, and easy bruisability. Fatal complications such as arterial dissections, digestive tract rupture, and other organ rupture can occur in up to 80% of affected individuals before the age of 40. The syndrome is linked with genetic abnormalities in types I, III, or V collagen critical to extracellular matrix formation. We present two cases of vascular-type EDS that highlight the diagnostic and treatment challenges encountered with these patients.

PATIENT 1

A 31-year-old man presented with sudden-onset, bilateral upper abdomen pain and several bouts of bilious emesis. His past medical history was notable for bilateral inguinal herniorrhaphies and bilateral shoulder dislocations in high school. His family history was negative. On admission, he had a fever of 101.5°F but was hemodynamically stable. His physical examination was remarkable for pale skin, periorbital hyperpigmentation, talipes equinovarus, and exaggerated joint laxity. His laboratory studies were notable only for a leukocytosis. A computed tomography (CT) scan of the abdomen and pelvis demonstrated a left common and external iliac dissection (with evidence of prior extravasation without active leak) as well as bilateral renal infarcts, a small left common iliac aneurysm (1.7 cm), and a question of bilateral renal artery aneurysms. A renal artery duplex study was inconclusive regarding the presence of renal artery aneurysms, and a renal angiogram was ordered. A CT scan of the head, neck, and chest showed no additional significant vascular changes. Concerns for a connective tissue disease or a genetic syndrome prompted rheumatology and genetics consults. The genetics team suggested vascular-type EDS as the most likely diagnosis. The renal angiogram was then cancelled due to the potential risk of renal dissection or obliteration. Rheumatological markers and hypercoagulability testing all returned negative. An angiotensin-converting enzyme inhibitor was started as standard therapy. Genetic testing later confirmed a diagnosis of vascular-type EDS with a Gly981Arg mutation.

PATIENT 2

A 69-year-old man presented to the hospital with urinary frequency. He developed pelvic discomfort, and a subsequent CT with intravenous contrast revealed a 6 × 6 mm renal stone at the right ureterovesicular junction with right-sided hydronephrosis. Important incidental findings on this scan were bilateral iliac aneurysms and focal dissections and pseudoaneurysms of the celiac, distal mesenteric, left gastric, superior mesenteric, and superior left renal arteries. The patient's past medical history included the presence of hypertension, previous kidney stones, and two previous cerebrovascular accidents. A recent admission for a transient ischemic attack prompted a cerebral contrast CT angiogram showing large aneurysms with a clot at the base of the right vertebral artery and an arteriovenous shunt in the distal right vertebral artery segment. The patient also had a history of inguinal and ventral hernia repairs. The patient's family history...
was notable for a brother who had an unexplained spontaneous bowel rupture requiring urgent surgical repair at age 60. His physical examination was notable for decreased strength in the right upper and lower extremities. A renal angiogram was scheduled to further evaluate the renal vasculature.

After an extensive negative rheumatologic evaluation, vascular surgery, rheumatology, and the genetics services suggested a diagnosis of vascular-type EDH, despite the lack of classical skin findings or facial appearance. Accordingly, vascular surgery cancelled the patient’s renal artery angiogram in fear of a high risk for potential arterial dissection. The patient subsequently had a genetic analysis in the 12 genes known to be associated with genetic forms of thoracic aortic aneurysms, including vascular-type EDS, Marfan syndrome, and related disorders. This panel was negative in this patient. However, given possible variations in disease-associated mutations, additional genetics testing was pursued. Deletion or duplication of one or more of the 12 exons in the thoracic aortic aneurysms and dissections panel was suspected, and the diagnosis of vascular-type EDS was maintained. Treatment with daily aspirin, losartan, simvastatin, and amlodipine was initiated.

**DISCUSSION**

In vascular-type EDS, vascular dissection or organ rupture may occur in the thorax and abdomen (50%), head and neck area (25%), or extremities (25%). This pathophysiology results from an identified collagen type III gene mutation (substitution of glycine) known as COL3A1 that results in decreased thermal stability and proteolytic processing in the proA1 chain of collagen type III (4). These defects lead to devastating complications, including vascular dissection (aneurysmal formation, arteriovenous fistulae, or dissection), gastrointestinal perforation, or uterine rupture (4). Common childhood occurrences in those affected by vascular-type EDS may include talipes equinovarus, inguinal hernia, pneumothorax, and recurrent joint subluxation or dislocation (4). Cerebrovascular complications may also occur, including intracranial hemorrhage due to carotid cavernous sinus fistulae or cervical arterial aneurysmal rupture (4). Historically, 25% of those with genetic testing confirming vascular-type EDS experience a significant medical problem requiring hospitalization by age 20 (~75% by age 40), and the median life expectancy for those with vascular-type EDS is 48 years (4).

Sequence analysis of COL3A1 confirms the clinical diagnosis of vascular-type EDS in over 95% of the cases. Most mutations are point (missense or skipping) mutations that lead to substitutions for glycine (substitution of glycine by glutamic acid driven by a mutation in exon 46 COL3A1) in the triple helical region of the collagen molecule. Other types of mutations have also been identified, such as splice site mutations, partial gene deletions, and rarely tested mutations resulting in COL3A1 haploinsufficiency (5). The types of mutations are thought to be relevant since missense and exon-skipping mutations of COL3A1 seem to be associated with a higher risk of vascular or organ rupture prior to the age of 23 years. Alternatively, individuals with haploinsufficiency mutations tend to have a lower risk of vascular or organ rupture, with major complications occurring before the age of 37 years (5). For these reasons, haploinsufficiency mutations have become of increasing interest, and some postulate that presentations of vascular-type EDS at older ages is a result of this type of mutation.

Characteristics associated with the two patients listed in the Table. While Patient 1 had confirmed genetic testing and fit a number of major/minor criteria, Patient 2 was older and had a number of vascular findings (aneurysms, pseudoaneurysms, hernias, cerebrovascular events) that are suggestive of EDS type 4. Although genetic testing could not be confirmed, patients presenting at older ages with milder forms of disease have been noted due to haploinsufficiency mutations that are not commonly tested for.

Despite these differences, recognizing basic variations in presentations will allow clinicians to consider a diagnosis of EDS type 4. Although it is a rare disease, the inability to recognize the pertinent medical history, key physical findings, and potential risks of elective procedures in this population may have devastating consequences. Being familiar with these domains is paramount to delivering optimal treatment and avoiding undesirable outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) on case presentation</td>
<td>31</td>
<td>69</td>
</tr>
<tr>
<td>Age (years) of symptom onset</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>Arterial, intestinal/uterine rupture or dissection</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Thin translucent skin</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Easy bruising</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Extensive scarring and hyperpigmentation</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Characteristic facies</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Small joint hypermobility</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Tendon/muscle rupture</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Joint subluxations or dislocations</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Talipes equinovarus</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>COL3A4 mutation</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Hernia/hernia repair</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Multiple aneurysms</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Family history of vascular rupture</td>
<td>Unknown</td>
<td>+</td>
</tr>
</tbody>
</table>

**Table. Certain clinical, morphological, and genetic characteristics in two patients with Ehlers-Danlos syndrome**

A 70-year-old man who presented with dyspnea and intermittent chest pain was found to have a large free-floating right atrial thrombus on two-dimensional echocardiogram. Atriotomy was performed, and an 18-cm-long thrombus was removed from the right atrium and inferior vena cava. Postoperatively, the patient developed cardiogenic shock treated by intravenous vasopressor agents and extracorporeal membrane oxygenation. The postoperative course was also complicated by bilateral pulmonary emboli requiring pulmonary artery thrombectomy. Right atrial thrombus is an underdiagnosed condition with a high mortality rate. The best management modality has not yet been established.

The incidence of thrombi of the right atrium (RA) is not well defined (1). Intracardiac thrombi are found in about 10% of cases of pulmonary thromboembolism (PTE). We herein present a case of a patient with a large RA thrombus, likely a thrombus in transit, with subsequent pulmonary emboli who died from cardiogenic shock following surgical intervention.

CASE DESCRIPTION

A 70-year-old black man with prior systemic hypertension, inferior wall myocardial infarction, compensated systolic heart failure, and stage III chronic kidney disease presented to the emergency department with complaints of worsening dyspnea and intermittent pleuritic chest pain. An electrocardiogram done in the emergency department showed sinus tachycardia with large S waves in lead I, large Q waves in lead III, and inverted T waves in lead III (S1Q3T3) and right bundle branch block. A two-dimensional echocardiogram (Figure 1) showed a large free-floating thrombus in the right atrium.

From Baylor University Medical Center at Dallas, Dallas, Texas.

Corresponding author: Mina M. Benjamin, MD, 2961 Index Rd., Apt. 115, Fitchburg, WI 53713 (e-mail: mehanni@wisc.edu).

Figure 1. Transthoracic echocardiography showing the right atrial thrombus (arrows) extending into the right ventricle: (a) parasternal long axis view; (b) apical four-chamber view; (c) five-chamber view; and (d) subcostal inferior vena cava view. AV indicates aortic valve; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.
atrium protruding into the right ventricle. The right and left ventricular functions were markedly depressed, with akinetic left ventricular inferior wall. The patient was started on a heparin drip and transferred to our institution. He was hemodynamically stable at presentation.

Based on the size of the free-floating RA thrombus, RA thrombectomy was done. An 18-cm-long thrombus was removed from the right atrium and inferior vena cava (Figure 2). The total time on cardiopulmonary bypass was around 39 minutes. Immediately after surgery, the patient became markedly hypotensive, requiring intravenous vasopressor agents, intraaortic balloon pump placement, and venoarterial extracorporeal membrane oxygenation. The patient also developed oliguric acute renal failure requiring continuous veno-venous hemodialysis. Seventy-two hours postoperatively, the pulmonary artery pressure was increased. Transesophageal echocardiogram showed a new nonobstructive echo density in the right main pulmonary artery. Computed tomography (CT) pulmonary angiography demonstrated large bilateral pulmonary emboli (Figure 3). The patient was taken again to the operative room and underwent successful bilateral thrombectomy with subsequent reduction of his pulmonary artery pressure. However, he remained in cardiogenic shock, requiring intense inotropic and vasopressor support and extracorporeal membrane oxygenation. In view of his poor clinical condition and prognosis, the family decided to withdraw organ support measures and the patient died. An autopsy was not performed.

DISCUSSION

The differential diagnosis of RA masses includes benign or malignant primary or metastatic tumors, tricuspid valve vegetations, and thrombi. Sometimes, RA thrombi are in transit, having migrated from the venous system to the heart; this is likely the case with the large tubular thrombus we describe in this case.

The actual incidence of RA masses is unknown and the condition is likely underdiagnosed, since only symptomatic patients are referred for workup (1). A review from Sweden reported a prevalence of RA thrombi of 7% in 23,796 autopsies, similar to the prevalence of left cardiac thrombi (2). The shallow anatomy of the RA appendage makes it a less likely site for thrombus formation in patients in atrial fibrillation; those with RA appendage thrombi tend to have a larger RA area and lower RA appendage emptying velocities than patients without thrombi (3, 4). Patients with mechanical valves, right-sided pacemaker leads, ventricular or atrial septal closure devices, and indwelling central venous lines are also at higher risk for RA thrombi (5, 6). RA thrombus has been described in about 10% of patients with PTE. Of patients with RA thrombi, 36% had pulmonary emboli and 6.5% of all patients with PTE confirmed at autopsy had RA thrombi (2).

RA thrombi are most commonly diagnosed with transthoracic echocardiography. However, in a study of 16 patients with RA thrombi, size, mobility, and site of attachment of thrombus were better defined by transesophageal echocardiography than by transthoracic echocardiography (7). Patients with proven or suspected RA thrombus are usually treated with anticoagulants, thrombolytic agents, or surgical thrombectomy, depending on thrombus morphology and risk of PTE (8–11).


Avocations

A photograph of the Horsehead Nebula, taken with an Orion 80 mm refractor telescope from Troy, Texas. This nebula is a collection of mostly hydrogen gas located next to the most rightward star in the belt of the constellation Orion. Photo by John L. Manning, MD (John.Manning@BSWHealth.org), program director of the Family Medicine Residency at Baylor Scott & White – Temple.
Inhaler syncope

Robert L. Rosenthal, MD, and Jay O. Franklin, MD

Syncope can result from certain activities that trigger an exaggerated physiological response in susceptible individuals; examples include cough, laugh, and micturition syncope. We report a novel cause for syncope, that due to reflex bradycardia and asystole produced by the use of asthma inhalers. We discuss the possible mechanisms for this effect and briefly review other breathing-related causes of bradycardia.

Syncope can result from certain activities that trigger an exaggerated physiological response in susceptible individuals such as cough, laugh, and micturition syncope. Vagally induced bradycardia mediates some of these responses. We report the case of a young man with repeated episodes of syncope while using his asthma inhaler. Inhaler syncope is a previously undescribed form of vagally induced bradycardia and asystole resulting in syncope.

CASE REPORT

A 22-year-old man sought evaluation following two episodes of syncope that occurred while using an asthma inhaler. He had had mild asthma since age 5 and used his inhalers infrequently. On the last two occasions, 4 months apart, using albuterol on one occasion and fluticasone on the other, he had syncope without premonitory symptoms, although he was nauseated on awakening. He had been otherwise healthy without a prior history of loss of consciousness. His cardiovascular exam, electrocardiogram, and echocardiogram disclosed no abnormalities. A simple prolonged breath-hold in the office did not provoke bradycardia. A standard tilt table test was performed, which was normal. At the termination of that study, the patient was instructed to use his fluticasone inhaler in his usual fashion, which entailed full expiration followed by a held inspiration of the drug without Valsalva maneuver. Following a breath-hold of less than 10 seconds and upon expiration, he developed a junctional rhythm followed by prolonged asystole of 11 seconds and loss of consciousness (Figure). His rhythm quickly recovered, although he remained nauseated, intensely diaphoretic, and hypotensive for several minutes afterward. Subsequent investigations with the patient only mimicking use of the inhaler resulted in a drop of heart rate from 115 during breath-hold to 55 beats per minute during expiration with no pauses. Inhalation of either albuterol or fluticasone by spraying in his mouth during normal breathing resulted in a drop of heart rate from 100 to 70 beats per minute without pauses, which was sustained through the respiratory cycle. A 30-day Holter monitor revealed an average heart rate of 76 with no pauses and no tachycardia independent of exercise.

Based upon these clinical observations, the mechanism of his syncope was believed to be vasovagal. He was instructed to increase his salt and fluid intake and, as his asthma was mild, to avoid using his inhalers. As there was also a hypotensive vasodepressor component to his events, pacemaker placement was reserved for failure of conservative management.

DISCUSSION

Other examples of breathing-related bradycardia and syncope have been described, but to our knowledge, this is the first reported case of syncope secondary to profound bradycardia related to use of an inhaler. The rapidity of onset of the bradycardia indicates a likely reflex mechanism not mediated by hypoxia or the Valsalva maneuver. The onset of asystole during expiration may be an extreme example of a normal respirophasic sinus arrhythmia in a vagotonic subject; however, that does not appear to be a sufficient explanation, as asystole could not be reproduced by breath-holding without concomitant use of the inhalers. Exposure to inhaler aerosol alone during normal breathing resulted in a heart rate decline in this individual. Exaggerated expiration followed by deep inspiration may be triggering pulmonary stretch receptors eliciting the classic Hering-Breuer reflex, a vagally mediated reflex that results in bradycardia and hypotension (1). In concert, stimulation of pulmonary C-fibers by the inhaled aerosols may also be triggering a vagal effect (2). Neither form of these vagal reflexes is felt to be powerful in adult humans, although it may be that by acting in conjunction they produced this response in a susceptible individual. His baseline tachycardia during these maneuvers was believed to be secondary to anxiety.

From the Division of Cardiology, Baylor Heart and Vascular Hospital, Dallas, Texas.

Corresponding author: Robert L. Rosenthal, MD, Division of Cardiology, Baylor Heart and Vascular Hospital, 621 North Hall Street, Dallas, TX 75226 (e-mail: Robert.Rosenthal@BSWHealth.org).
Among other examples, bradycardia, sometimes profound, is a frequent occurrence during the apneic phases of the condition sleep apnea. The degree of bradycardia produced is proportional to the length of the apnea and the degree of hypoxia produced. The bradycardia can be prevented by supplemental oxygen administration or atropine, indicating that there is a vagal component (3).

Pediatric breath-holding syncope is a condition in infants and young children with loss of consciousness associated with expiratory breath-hold (4). The onset of this syndrome, not familiar to many adult cardiologists, is usually by age 2 with resolution by age 4 to 5. There are two forms, pallid and cyanotic. The pallid form is usually in response to an unexpected sudden event such as a minor injury or a fright. The child gasps or cries briefly, followed by an expiratory breath-hold. This pallid variety is caused by a vagally mediated bradycardia, which can be prevented by atropine administration. The cyanotic variety of syncope has a more complex mechanism, usually following prolonged crying from emotional upset with a terminal expiratory breath-hold. Although a portion of these cyanotic infants also develop bradycardia, the mechanism of syncope is believed to be secondary to hypoxia. Permanent pacemaker placement has been employed in severe cases of both types of pediatric breath-holding syncope (5).

Finally, the diving reflex elicits a powerful bradycardic vagal response, which is employed therapeutically in the termination of supraventricular tachyarrhythmias. This reflex or response is shared in all air-breathing mammals and is a result of the combined and additive effect of breath-holding in association with facial immersion in cold water (6).

As contrasted with the above forms of breathing-related syncope, our case represents a unique variant. Dizziness and lightheadedness are listed as side effects of inhaler use on product labels, and a vagally mediated bradycardia should be considered as a possible explanation in those individuals.

Acute myocardial infarction (AMI) is rare in young adults. We present a case of a 29-year-old black woman who presented with an acute onset of chest pain while sleeping. Anterior wall ST-elevation AMI was diagnosed based on clinical presentation, electrocardiographic findings, and elevated cardiac biomarkers. Coronary angiography revealed a totally occluded proximal left anterior descending artery. The obstructing lesion, thrombus, was removed. There was no evidence of atherosclerotic disease or dissection. An evaluation for a hypercoagulable state was unrevealing. Echocardiography 1 year later revealed normal left ventricular wall motion and systolic function.

We report the case of acute coronary thrombosis in a 29-year-old woman without significant risk factors for coronary artery disease.

CASE REPORT

A healthy, 29-year-old black woman presented to the emergency department with substernal chest pain that awoke her from sleep approximately 30 minutes prior to arrival. The pain radiated to her left arm and was also associated with dyspnea. Ibuprofen did not alleviate her pain. She smoked 20 cigarettes a day for 5 years. She also used natural and synthetic marijuana, but not over the past 2 years. She had a body mass index of 28 kg/m², had no previous medical problems or prior surgery, and was not taking any medications. She had seven living children from six uncomplicated pregnancies, with the last being 1 year earlier. Her mother had antiphospholipid antibody syndrome. Chest radiograph was normal. Electrocardiogram revealed normal sinus rhythm with ST segment elevations in leads I, aVL, and V₄ to V₆ and ST segment depressions in leads III and V₁(Figure 1). A complete blood count and comprehensive metabolic panel were unremarkable. Her initial serum troponin level was 1.2 ng/mL, with a peak of 46.21 on serial measurement. Her total cholesterol was 122 mg/dL; low-density lipoprotein, 69 mg/dL; high-density lipoprotein, 34 mg/dL; and triglycerides, 60 mg/dL. A urine drug screen was negative for marijuana, cocaine, and amphetamines, and her pregnancy test was negative. The patient was given aspirin (325 mg), sublingual nitroglycerin (0.4 mg), and intravenous heparin (bolus 4000 units). Coronary angiography revealed an occlusion in the left anterior descending artery (Figure 2). She underwent thrombectomy using an AngioJet catheter system. Intracoronary optical coherence tomography and intravascular ultrasound revealed no plaque and no dissection. Percutaneous coronary intervention was not performed, and no stent was placed.

Transesophageal echocardiogram revealed a left ventricular ejection fraction of 30% with extensive anterior, anteroseptal, and apical wall motion abnormalities. Laboratory results (Table 1) were normal with the exception of an elevated C-reactive protein level. The patient was started on dual antiplatelet therapy with aspirin 81 mg daily and prasugrel 10 mg daily. In addition, a high-intensity statin, oral beta-blocker, and angiotensin-converting enzyme inhibitor were also initiated per the 2013 American College of Cardiology Foundation/American Heart Association guidelines for management of ST-elevation myocardial infarction. Due to the occurrence of acute coronary artery thrombosis of undetermined etiology, anticoagulation with warfarin was also initiated, with a goal international normalized ratio of 2 to 3. A temporary, wearable cardiac defibrillator was recommended at discharge due to her significantly reduced left ventricular ejection fraction; however, the patient declined the device. Additional recommendations included outpatient follow-up with the hematology/oncology clinic for continued evaluation of a possible coagulation disorder, given the presence of antiphospholipid antibody syndrome in a first-degree relative.

Our patient failed to take the prescribed medications and to follow up with hematology/oncology, and she did not undergo further testing. During a later hospitalization for pregnancy, she underwent echocardiography that demonstrated normal left ventricular systolic function and normal wall motion.

From the Cardiology Division, Baylor Scott and White Memorial Hospital, Temple, Texas (Male, Morton, Farber, Michel); and Texas A&M University Health Science Center College of Medicine, Temple, Texas (Michel).

Corresponding author: Jeffrey Michel, MD, FACC, Cardiology Division, Baylor Scott and White Memorial Hospital, 2401 South 31st Street, Temple, TX 76508 (e-mail: Jeffrey.Michel@BSWHealth.org).
DISCUSSION

While acute coronary syndrome is prevalent in individuals over 45 years of age, it is rare in those younger than 30 (1). AMI with angiographically normal coronary arteries is an important subgroup of AMI in young patients (1, 2). Some etiologies reported include coronary artery anomalies, cocaine-induced coronary artery vasospasm, a hypercoagulable state related to the use of oral contraceptive pills, and diseases such as systemic lupus erythematosus, antiphospholipid antibody syndrome, Factor V Leiden mutation, and nephrotic syndrome (3–5). The incidence of AMI in patients <45 years of age is estimated to be 2% to 10% of all AMIs (4–6). Although the incidence of AMI related to a hypercoagulable state is unclear, it may comprise approximately 5% of AMIs in young patients (4).

Figure 1. Initial electrocardiogram showing normal sinus rhythm, ST segment elevation in leads I, aVL, and V4 to V6, and ST segment depressions in leads III and V1.

Figure 2. Coronary angiograms showing (a) acute left anterior descending artery thrombosis and (b) left anterior descending artery after thrombectomy.
In our case, the only traditional coronary artery disease risk factor was prior tobacco use, with only a 5-pack-year history. Emergent coronary angiography revealed an acute left anterior descending artery thrombus, without evidence of atherosclerotic coronary disease, coronary artery dissection, or anomaly. Transthoracic echocardiogram showed no evidence of intracardiac thrombus, infective endocarditis, or valvular abnormality. Although the patient did report a remote history of substance abuse, her urine drug screen was negative for cocaine, amphetamines, and marijuana metabolites.

Table 1. Laboratory studies evaluating for a hypercoagulable state

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Result</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-nuclear antibody profile</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Anti-cardiolipin IgG (GPL)</td>
<td>&lt;9.4</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Anti-cardiolipin IgM (MPL)</td>
<td>&lt;9.4</td>
<td>&lt;12</td>
</tr>
<tr>
<td>Beta-2 glycoprotein IgG (SGU)</td>
<td>12</td>
<td>&lt;18</td>
</tr>
<tr>
<td>Beta-2 glycoprotein IgM (SMU)</td>
<td>&lt;9.4</td>
<td>&lt;18</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>7.3</td>
<td>0–3.2</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>16</td>
<td>0–20</td>
</tr>
<tr>
<td>Factor V Leiden mutation, C677T/A129BC</td>
<td>Not detected</td>
<td></td>
</tr>
<tr>
<td>Homocysteine, serum level (μmol/L)</td>
<td>4.7</td>
<td>5.0–15.0</td>
</tr>
<tr>
<td>Lupus anticoagulant panel</td>
<td>Not detected</td>
<td></td>
</tr>
<tr>
<td>MTHFR gene analysis</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Protein C, total antigen (%)</td>
<td>77</td>
<td>63–153</td>
</tr>
<tr>
<td>Protein C, functional (%)</td>
<td>97</td>
<td>83–168</td>
</tr>
<tr>
<td>Protein S, activity (%)</td>
<td>76</td>
<td>57–131</td>
</tr>
<tr>
<td>Protein S, free antigen (%)</td>
<td>61</td>
<td>55–123</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation</td>
<td>Not detected</td>
<td></td>
</tr>
</tbody>
</table>

GPL indicates IgG phospholipid unit; MPL, IgM phospholipid unit; SGU, standard IgG beta-2 glycoprotein unit; SMU, standard IgM beta-2 glycoprotein unit.

In our case, the only traditional coronary artery disease risk factor was prior tobacco use, with only a 5-pack-year history. Emergent coronary angiography revealed an acute left anterior descending artery thrombus, without evidence of atherosclerotic coronary disease, coronary artery dissection, or anomaly. Transthoracic echocardiogram showed no evidence of intracardiac thrombus, infective endocarditis, or valvular abnormality. Although the patient did report a remote history of substance abuse, her urine drug screen was negative for cocaine, amphetamines, and marijuana metabolites.

A variant of Brugada syndrome
Maryna Popp Switzer, DO, Mohamed Teleb, MD, Enoch Agunanne, MD, and Aamer Abbas, MD

Brugada syndrome is an inherited disorder that can present with syncope, cardiac arrest, or sudden cardiac death. Multiple genetic mutations have been described that cause this disease. We present a 56-year-old man who sustained an out-of-hospital cardiac arrest, was resuscitated, and was found to have typical features of the Brugada criteria on the electrocardiogram. Genetic testing was positive for a heterozygous mutation in the sodium voltage-gated channel alpha subunit 5 (SCN5A) gene with a p. Leu227Pro (L227P) variant located on exon 6. To our knowledge, this is the first described case with this variant causing malignant arrhythmia with a cardiac arrest.

Described initially in 1992, Brugada syndrome has an incidence of 0.05% to 0.60% (1, 2). Occurring most frequently in Asians, it is also observed in Caucasians, African Americans, and Hispanics. The syndrome is characterized by typical electrocardiogram characteristics consisting of right bundle branch block and ST segment elevations in leads V1 to V3. Brugada syndrome is inherited in an autosomal dominant pattern. Multiple genetic mutations have been described.

CASE PRESENTATION
A 56-year-old man sustained an out-of-hospital cardiac arrest. Shortly after he went to bed, his wife noticed he was having labored respirations. Since the family could not wake him, they initiated cardiopulmonary resuscitation and called emergency medical services. The patient was found to be in ventricular fibrillation; he was cardioverted and transferred to the University Medical Center with cardiopulmonary resuscitation in progress. On arrival, he was resuscitated, intubated, and mechanically ventilated. He was transferred to the medical intensive care unit, and a hypothermia protocol was initiated. Prior to this event, the patient did not have any syncpe or presyncopal episodes and was not taking any medications. He was adopted and did not know any medical history from his father’s side.

The first electrocardiogram (ECG) obtained following resuscitation demonstrated first-degree atrioventricular block with suspicious coving of the ST segment in lead V2 (Figure 1). Left heart catheterization revealed no evidence of coronary heart disease. Cardiac magnetic resonance imaging was negative for contractile abnormalities of the left ventricle, and there was no evidence of noncompacted myocardium or trabeculation. A repeat ECG was obtained during the hospitalization revealing coving of the ST segment in V1 and V2 consistent with the Brugada criteria (Figure 2). The patient made an excellent recovery with a return to normal neurological function. An implantable cardioverter defibrillator was placed prior to his discharge from the hospital. When genetic testing was obtained, a heterozygous mutation was found in the SCN5A gene with a L227P variant located on exon 6.

DISCUSSION
The Brugada syndrome is an inherited arrhythmogenic disorder. Individuals with Brugada syndrome are at a higher risk of arrhythmia, such as ventricular tachycardia or ventricular fibrillation, and of sudden cardiac death. The average age of presentation is 41 ± 15 years (3). Men are much more frequently affected than women, with a 9:1 ratio. Men are also more likely to be symptomatic, presenting with cardiac events such as syncope or cardiac arrest, and generally tend to have a worse prognosis (1, 4).
To diagnose Brugada syndrome, typical ECG findings need to be present, along with one of the following: a personal history of ventricular tachycardia or ventricular fibrillation, the presence of ventricular tachycardia or ventricular fibrillation during an electrophysiological study, a family history of sudden cardiac death or a coved-type ECG, or agonal breathing during sleep. Three types of ECG abnormalities have been described:

- Type 1 consists of coved-type ST segment elevation of ≥2 mm followed by a negative T wave.
- Type 2 is a saddle-back–type ST segment elevation of ≥2 mm that gradually decreases and is followed by a positive or biphasic T wave.
- Type 3 is an ST segment elevation <2 mm that does not meet criteria for type 1 or 2 (3).

Several genetic mutations are responsible for the regulation of different myocardium channels such as sodium, potassium, and calcium. These mutations include but are not limited to the SCN5A, GP1D-1, CACNA1C, CACNB2, SCN1B, KCNE3, SCN3B, and HCN4 genes (5). There are nearly 300 mutations associated with the gene SCN5A responsible for the sodium channel in the myocardium (6, 7). These mutations have been described in chromosome 3p21–24 (1). In a clinical analysis that evaluated 150 probands in patients with Brugada syndrome compared with ≥200 control subjects, wild-type (WT) SCN10A with WT-SCN5A in human embryonic kidney cells caused more arrhythmia effect, including PR interval prolongation (2). Since the discovery of Brugada syndrome, SCN5A has represented about 15% to 30% of all diagnosed cases, making it the most common genotype. A loss of function mutation of SCN5A leads to reduced sodium current available for exchange with the plasma membrane or actual alternation in channel properties. On the other hand, a gain of function leads to arrhythmia syndromes such as prolonged QT.

It is important to recognize that since 2004, more genetics analysis research has discovered the presence of rare nonsense SCN5A variants in 2% of healthy white subjects and 5% of healthy nonwhite subjects. This discovery is important for differentiating between the rare harmless mutations and the pathological ones. Multinational analysis evaluated 2111 patients referred for genetic testing for possible diagnosis of Brugada syndrome and involved 27 translated exons present in the SCN5A gene. The statistical analysis revealed four common mutations—E1784K, F861WfsX90, D356N, and G1408R—most of which were found to be missense mutations, with the rest involving radical mutations such as frame shift. Eighteen patients had mutations on exon 6, of which 13 were missense mutations, 4 nonsense, and 1 frame shift; none had the L227P variant (8). It is important to evaluate more variants to identify the pathological ones requiring early screening to prevent complications. As reported in our patient, the heterozygous mutation in the SCN5A gene with the L227P variant located on exon 6 seems to be the first reported in the literature causing arrhythmia and cardiac arrest.


January 2017 A variant of Brugada syndrome 63
While mopping the floor in her home, a 52-year-old woman experienced the worst headache of her life. The pain was frontal and midline and soon followed by dizziness, neck stiffness, nausea, vomiting, and tingling in the fingers of both hands. In the emergency department, a computed tomogram showed a subarachnoid hemorrhage that was probably due to a ruptured berry aneurysm. The following morning a cerebral arteriogram confirmed a berry aneurysm, which was located on the posterior communicating artery. She immediately went to the operating room where the aneurysm was clipped. She tolerated the procedure well.

On the first postoperative day, an electrocardiogram (ECG) was read by the computer as normal (Figure). However, inverted U waves, seen here in leads I and V₄ to V₆, have always been regarded as abnormal except when their occurrence is limited to lead aVR (1). In each of two large studies, 99% of patients with negative U waves had heart disease (2, 3). In another large study, 95% of patients with negative U waves also had other ECG abnormalities (4). Although the ECG in the figure showed no abnormality other than the inverted U waves, the patient’s admission ECG recorded 36 hours earlier had no U wave abnormality, but met the Lewis index (RI + SIII) – (RIII + SI) ≥ 1.7 mV, our oldest ECG criterion for left ventricular hypertrophy (5). Our patient’s index was 1.9 mV.

Systemic hypertension is the most common cause of inverted U waves in the left precordial leads, followed by coronary heart disease and left-sided valvular diseases (1, 4). In patients with right ventricular hypertrophy, inverted U waves may be seen in the right precordial leads (1).

From the Section of Cardiology, Department of Medicine, Louisiana State University Health Sciences Center, New Orleans, Louisiana.

Corresponding author: D. Luke Glancy, MD, 1203 West Cherry Hill Loop, Folsom, LA 70437 (e-mail: dglanc@lsuhsc.edu).

---

**Figure.** ECG in a 52-year-old woman recorded the day after her berry aneurysm was clipped and 1½ days after the aneurysm bled. See text for explication.
5. Lewis T. Observations upon ventricular hypertrophy with special reference to preponderance of one or another chamber. Heart 1914; 5: 367–403.

Avocations

Close-up of Colorado Columbine stamen. Photo © Rolando M. Solis (rmsolis@mac.com), an interventional cardiologist at Baylor Scott and White Health Garland and The Heart Hospital Baylor Plano.
Extranodal lymphomas constitute 20% to 30% of all non-Hodgkin’s lymphomas. The common sites involved are skin, stomach, brain, and small intestine. Epidural localization is a rare site for lymphomas, accounting for 10% of spinal epidural tumors. Lymphomas occurring primarily in the epidural space without other previously detected lymphomatous foci (i.e., primary spinal epidural lymphomas) represent an even rarer entity. We report a case of primary spinal epidural B-lymphoblastic lymphoma. The patient presented with paraparesis, and a spinal epidural lesion was diagnosed. Considering the rapidity of symptom onset, the possibility of epidural abscess was considered, and he underwent partial laminectomy with decompression of the lesion. Histopathology and immunohistochemistry were diagnostic of B-lymphoblastic lymphoma. The present case is the first report in the literature of B-lymphoblastic lymphoma presenting as a spinal epidural lesion.

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. Lymphoblastic lymphoma of the B-cell type is uncommon, and an extranodal presentation is even rarer. Lymphomas primarily occurring in the epidural space without other previously detected lymphomatous foci represent a very rare entity, and only a few cases have been documented. We report what is, to the best of our knowledge, the first reported case of primary spinal epidural B-lymphoblastic lymphoma.

**CASE PRESENTATION**

A 19-year-old man presented with a 1-month history of progressively worsening back pain and a weight loss of >5 kg over 3 months. Over the previous week, he had developed progressive asymmetric weakness of both lower limbs with decreased pain and temperature sensation without bowel or bladder involvement. On examination, there was tenderness in the thoracic region. Neurologic examination demonstrated bilateral lower limb spasticity with an asymmetric pyramidal pattern of weakness (right > left, Medical Research Council grade 3 and 2, respectively), with impaired sensation below the T4 level. Magnetic resonance imaging (MRI) of the spine demonstrated...
Primary spinal epidural B-lymphoblastic lymphoma

January 2017

Diffuse elongated epidural soft tissue in the posterior epidural space extending from D5 to the level of D10 with moderate to severe canal compromise (Figure 1a). The possibility of tuberculous spondylitis with epidural abscess was considered. Tests, including complete blood counts, erythrocyte sedimentation rate, renal function tests, liver function tests, and cerebrospinal fluid examination, were within normal range.

In view of the rapid onset of a neurological deficit, the patient underwent partial laminectomy with decompression of the lesion. Unhealthy brownish soft tissue was removed, but there was no pus. Histopathologic examination (Figure 2a) showed a monotonous population of medium to large cells with vesicular nuclei, prominent nucleoli, and scanty cytoplasm. On immunohistochemistry, the cells were positive for CD20, CD34, bcl2, PAX-5, and terminal deoxynucleotidyl transferase (Tdt) with an MIB labeling index around 90% (Figures 2b–2d). The picture was diagnostic of B lymphoblastic lymphoma. A computed tomography (CT) scan of the neck, thorax, abdomen, and pelvis did not reveal any lymph nodes. Marked pain relief was achieved postsurgery. The patient was started on combination chemotherapy with cyclophosphamide, vincristine, Adriamycin, and dexamethasone (hyper-CVAD protocol) with central nervous system prophylaxis (intrathecal methotrexate). After the patient completed the first cycle of chemotherapy, MRI showed complete radiological remission (Figure 1b). The patient received 8 cycles of chemotherapy and is currently receiving maintenance chemotherapy with methotrexate and 6-mercaptopurine.

DISCUSSION

Primary spinal epidural lymphoma (PSEL) is a subset of lymphomas in which there are no other sites of disease involvement at the time of diagnosis. Extranodal non-Hodgkin’s lymphoma (NHL) comprises 24% to 48% of all NHL (1), while PSEL accounts for 0.9% of all extranodal NHL (2, 3). The largest series to date was reported by Monnard et al (4), who studied 52 patients treated in nine institutions of the Rare Cancer Network between 1982 and 2002.

Epelbaum et al (5) described two phases of clinical presentation in PSEL. The first phase is the prodromal phase, during which localized back pain occurs. This phase may extend for months to a year. The second phase is characterized by a rapid neurological deterioration (over 2–8 weeks). The latter phase is due to spinal cord compression. Similar presentations have been described by others (6, 7).

The most common region involved is the thoracic spine, followed by the lumbar and cervical spine (4). The origin of PSEL remains unknown. Rubinstein (8) stated that PSEL arises from the lymphatic tissue present in the epidural space and proposed that mesodermal cells lining the epidural space may give rise to primary spinal lymphoma under appropriate conditions. Other authors support the hypothesis that PSEL originates from the vertebral body or from the paravertebral lymph nodes, which later extend onto the epidural space (9, 10).

Histologically, most tumors are B-cell lymphomas (intermediate and high grade), although low-grade B-cell neoplasms and...
T-cell lymphomas are occasionally observed (11–13). Seventy percent of the patients in a series were of intermediate grade, and the remaining 30% were high grade (5). Schwechheimer et al found an increased incidence of B-cell high-grade lymphomas in 11 of 19 cases, centroblastic lymphomas being the predominant type. Of significant note, no significant survival implications were based on histopathological classification (14).

Treatment of PSEL will almost always include emergency decompressive surgery, with or without resection, in the acute phase followed by radiotherapy and chemotherapy. Lymphoblastic lymphomas are treated similar to acute lymphoblastic leukemia with combination chemotherapy protocols consisting of intensive remission-induction chemotherapy, central nervous system prophylaxis, consolidation chemotherapy, and subsequent maintenance therapy for 18 months.

The initial manifestation of lymphoma presenting with a spinal lesion is rare; it is even rarer when encountered as an isolated disease focus. Hence, physicians should consider the possibility of a lymphoproliferative disorder in the differential diagnosis of compressive myelopathy. The clinical, radiological, and histological features of this disease can mimic other medical conditions causing compressive myelopathy, including pathological compression fractures, infectious lesions, or carcinomatous deposits. This makes the diagnosis difficult and often leads to significant delays in initiation of effective treatment.

B-cell lymphoma, thiamine deficiency, and lactic acidosis

Umair Masood, MD, Anuj Sharma, MD, Sonny Nijjar, MD, and Karthikeyan Sitaraman, MD

Type B lactic acidosis is found in the absence of tissue hypoperfusion, can be associated with malignancies, and can be caused by thiamine deficiency. We present a patient who presented with an abdominal mass that biopsy disclosed to be a diffuse large B-cell lymphoma. Because thiamine deficiency is a rare cause of lactic acidosis in cancer, the patient was treated with intravenous thiamine with rapid normalization of the lactic acid level. The level prior to treatment was low. The case emphasizes a rare cause of lactic acidosis.

Type A lactic acidosis is commonly due to marked tissue hypoperfusion, whereas type B lactic acidosis is found without tissue hypoperfusion (1). Rarely, lactic acidosis is associated with aggressive solid tumors such as lymphomas. It can be due to various causes including thiamine deficiency. We present a patient with type B lactic acidosis due to deficiency of thiamine in the setting of a B-cell lymphoma.

CASE DESCRIPTION

A healthy 72-year-old man presented to the emergency department with vague abdominal discomfort and swelling of his left lower extremity. He had a left lower quadrant palpable mass with mild diffuse tenderness and 2+ edema of the entire left leg. His bicarbonate level was 18 mmol/L (reference range, 24 mmol/L). Other laboratory findings revealed a lactic acid level of 6.7 mmol/L (reference range, 0.5–2 mmol/L) and hemoglobin of 10.2 g/dL (reference range, 13.5–17.5 g/dL). His anion gap was calculated to be 21 (reference range, 12–14). Liver function tests, including albumin and total protein levels, were normal (Table 1). A computed tomographic scan of the abdomen showed a 9.8 × 8.4 × 12.0 cm retroperitoneal mass that appeared contiguous with the left kidney, with moderate left-sided hydronephrosis (Figure 1). A left nephrostomy tube was placed. Biopsy of the retroperitoneal mass confirmed it to be a diffuse large B-cell lymphoma (Figure 2).

Despite adequate resuscitation and hydration, the patient’s lactic acid level remained elevated. At that point, his thiamine level was obtained, and the patient was treated with intravenous thiamine (500 mg every 8 hours). By the morning, the lactic acid level was 1.5 mmol/L. He was then started on chemotherapy for his malignancy. He had a prolonged hospital course with a chemotherapy-related complication of bone marrow suppression but eventually responded well and was transferred back to his hometown for physical rehabilitation and follow-up with oncology.

DISCUSSION

Type A lactic acidosis is commonly found in patients with marked tissue hypoperfusion that can be caused by sepsis.

Table 1. Laboratory findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/L)</td>
<td>136</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.3</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>97</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>18</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>18</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>135</td>
</tr>
<tr>
<td>Anion gap</td>
<td>21</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>45</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>38</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>98</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.6</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>6.5</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.5</td>
</tr>
<tr>
<td>Lactic acid (mmol/L)</td>
<td>6.7</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.2</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>30.5%</td>
</tr>
<tr>
<td>White blood cell count (cell/mcL)</td>
<td>7400</td>
</tr>
<tr>
<td>Platelets (/mcL)</td>
<td>210,000</td>
</tr>
</tbody>
</table>

From the Department of Internal Medicine, State University of New York Upstate Medical University, Syracuse, New York.

Corresponding author: Umair Masood, MD, Department of Internal Medicine, State University of New York Upstate Medical University, 750 East Adams Street, Syracuse, NY 13204 (e-mail: masoodu@upstate.edu).
cardiac failure, or hypovolemia. On the contrary, type B lactic acidosis is found in the absence of tissue hypoperfusion (1). It is a rare occurrence in patients with lymphomas, leukemias, and solid neoplasms. While the mechanism is not entirely understood, there are many proposed theories, which include intrinsic lactate production by the tumor cells, impaired clearance of lactate in kidney or liver dysfunction, and riboflavin or thiamine deficiency (2). Tumor cells have been found to have increased lactate production, as they primarily utilize aerobic glycolysis, which is also known as Warburg effect (3).

Thiamine acts as a cofactor for various enzymes involved in aerobic metabolism, such as pyruvate dehydrogenase. Therefore, its deficiency promotes anaerobic metabolism, which results in the production of lactate (3). Only a few reported cases illustrate this phenomenon in patients with lymphomas (4, 5). The cases have generally been reported in pediatric patients receiving parenteral nutrition without vitamin supplementation. Friedenberg et al examined this phenomenon in hematological malignancies and found type B lactic acidosis due to thiamine deficiency in patients with leukemia rather than lymphoma (6). Seligmann et al reported subclinical thiamine deficiency in 35% of 14 untreated CLL patients (7). Lactate levels were not reported in either of the studies.

Acknowledgments

The authors thank Dr. Daniel Zaccarini for providing the histological image.

Dasatinib-induced chylothorax in chronic myeloid leukemia

Zulfiqar Qtério Baloch, MD, Shabber Agha Abbas, MD, Hammad Bhatti, MD, Yvonne Braver, MD, and Sayed K. Ali, MD

Pulmonary adverse events are common abnormalities associated with the use of dasatinib in chronic myeloid leukemia. We present a case of a 69-year-old man who suddenly developed a rare chylothorax pulmonary adverse event following 10 months of dasatinib treatment.

Dasatinib is a second-generation potent and efficacious oral tyrosine kinase inhibitor, frequently used for imatinib-resistant or -intolerant BCR-ABL–positive chronic myeloid leukemia (CML) and for Philadelphia chromosome–positive acute lymphocytic leukemia (1). Pulmonary adverse events are reported in about 35% of patients. The most common pulmonary abnormalities associated with dasatinib include pleural effusion, pulmonary hypertension, and parenchymal opacities. Dasatinib-related chylothorax is an uncommon pulmonary adverse event.

CASE PRESENTATION
A 69-year-old man with CML for 5 years presented complaining of progressive dyspnea for about 5 days. He had previously been treated with imatinib and nilotinib. Imatinib was stopped due to treatment failure, while nilotinib was discontinued due to intolerable side effects despite dose reduction. He had been on dasatinib 100 mg once daily for about 10 months, which he seemed to tolerate well. On presentation, his vital signs were stable, but he remained dyspneic, worse on exertion. He had diminished breath sounds and increased egophony on his right side. A chest radiograph showed a pleural effusion, more prominent on his right side. His previous chest radiographs were normal. A subsequent chest computed tomography scan showed a moderate amount of fluid in his pleural space compromising the right lung without any adenopathy or lung masses (Figure 1). Thoracentesis revealed 1 L of thick milky-appearing fluid (Figure 2). Pleural fluid analysis showed a predominance of lymphocytes (90%) and a lactate dehydrogenase level of 120 U/L, glucose of 157 mg/dL, protein of 4.8 g/dL, amylase of 39 U/L, and triglycerides of 405 mg/dL. Adenosine deaminase was 15 U/L. Fungal, bacterial, and AFIB cultures were reported as negative.

Following thoracentesis, the patient’s dyspnea improved. A repeat chest radiograph showed no pneumothorax with improvement in his effusion. He was under observation for 24 hours prior to discharge and was advised to continue his dasatinib. He returned to our institution a few months later with similar symptoms requiring a therapeutic thoracentesis. His dasatinib dose was gradually decreased to 50 mg orally once daily, but continued to lead to symptomatic pleural effusions. He was switched to bosutinib and has been tolerating therapy well without any symptoms. He continues to follow up with our oncology and pulmonary services.

DISCUSSION
Here we present a rare case of dasatinib-induced chylothorax in a patient with CML. The patient’s history and thorough workup, including a CT scan of the chest, did not suggest any other possible etiology.
lymphatic flow, such as insult to the thoracic duct or its tributaries, causing leakage of lymphatic fluid into the thoracic cavity. Malignancy-induced thoracic duct obstruction is the leading cause of chylothorax, with most malignancies being lymphomas (70% of which are Hodgkin lymphomas) (2, 3). Generally, causes of chylothorax can be divided into traumatic or nontraumatic etiologies. Traumatic cases can then be further subdivided as iatrogenic or noniatrogenic (4). Iatrogenic traumatic causes include thoracic duct damage following subclavian vein catheterization and duct blockage due to central venous catheterization–related venous thrombosis (5). Noniatrogenic traumatic cases include thoracic duct damage following fracture, dislocation of the spine, childbirth, and penetrating trauma from knife or gunshot injuries (6, 7). Nontraumatic etiologies include malignancy, sarcoidosis, retrosternal goiter, amyloidosis, superior vena cava thrombosis, benign tumors, congenital duct abnormalities, and diseases of the lymph vessels such as yellow nail syndrome, lymphangioleiomyomatosis, and hemangiomatosis (4).

Dasatinib-induced chylothorax is a rare yet poorly understood phenomenon. Evidence suggests that microscopic disruptions in lymphatic channels lead to chylous effusions following dasatinib therapy rather than macro-level classical thoracic duct involvement. Despite the multiple heterogenous etiologies for the development of chylothorax, dasatinib is the only drug known to be associated with this adverse effect. The development of chylothorax during dasatinib therapy may not be drug related. A few metastatic prostate cancer patients receiving dasatinib therapy also developed chylothorax. Pleural fluid analysis demonstrated positive cytology. Therefore, the full course of chemotherapy was completed. In these patients, a significant clinical response was documented with complete resolution of chyle effusion despite no change in dasatinib therapy (8).

Dasatinib-related pleural exudative, transudative, and chylous effusions are all lymphocyte-predominant exudates (9). Possible mechanisms have been identified that may explain these effusions. The tyrosine kinase platelet-derived growth factor receptor beta (PDGFR-β) on pericytes regulates postnatal angiogenesis, lymphangiogenesis, mesangial and vascular smooth muscle cell proliferation, and pericyte recruitment to capillaries. Potent inhibition of PDGFR-β can result in significant fluid retention and microangiopathy and lead to defective vascular remodeling (10, 11). Similarly, inhibition of tyrosine kinases that are responsible for capillary integrity may be implicated, especially if they are overexpressed in the pulmonary vasculature and/or pleural epithelium. Src is a protooncogene encoding a nonreceptor tyrosine kinase, which belongs to a family of 11 nonreceptor tyrosine kinases collectively known as the Src family kinases. Yes and Src are members of this family and are widely expressed in hematopoietic cells in lung tissue (12, 13). Vascular permeability is mediated by vascular endothelial growth factor, which is directly dependent on Yes and on Cellular Src (c-Src), both of which are inhibited by dasatinib (14, 15). c-Src also independently regulates focal adhesions and adherens junctions, both of which are key in regulating cell adhesion (16, 17). It is interesting that dasatinib may target c-Src tyrosine kinases and is being used in clinical trials for non-Hodgkin lymphoma, metastatic breast carcinoma, and prostate carcinoma in addition to CML and Philadelphia chromosome–positive acute lymphocytic leukemia. Although the development of pleural effusions and chylous effusions present similarly with respiratory compromise and share possible biological mechanisms, they are considered separate distinct clinical adverse effects.

Chylothorax is defined according to Light's criteria as a turbid pleural effusion with triglycerides $>110$ mg/dL (18, 19). A visual inspection of the pleural fluid should be conducted, and milky pleural fluid should always be investigated for chylothorax. Not all chylothorax is exudative, with 20% of cases being transudative (20, 21). An important distinction should also be made between chylothorax and pseudochylothorax based on cholesterol and triglyceride concentrations (22). Pseudochylothorax consists primarily of cholesterol derived from longstanding pleural fluid cell debris. Pleural fluid cholesterol $>200$ mg/dL (5.18 mmol/L) with a pleural fluid triglyceride $<50$ mg/dL (0.56 mmol/L) is more likely pseudochylothorax. Chylothorax presents with concentrations of triglycerides in the pleural fluid $>110$ mg/dL (1.24 mmol/L) and with cholesterol concentrations $<200$ mg/dL (5.18 mmol/L). Pleural fluid findings should not be interpreted in isolation; rather, the clinical history and presentation should also be taken into account.

Although treatment discontinuation leads to symptom resolution, in certain cases dose reduction has produced the same effect (23). Given the therapeutic benefits of dasatinib therapy in the post-imatinib setting, initial efforts should be focused on treating the chylothorax by attempting dose reduction as opposed to discontinuing dasatinib altogether. Transiently discontinuing dasatinib until chest tube drainage and
supportive care measures achieve symptomatic improvement followed by dasatinib dose reduction has been suggested. In addition, the use of short-term steroids and diuretics has also been shown to be helpful (9). In our case, dose reduction alone was not sufficient, and switching from dasatinib to bosutinib was eventually required.


Blood group antigens are either sugars or proteins found attached to the red blood cell membrane. ABO blood group antigens are the most clinically important antigens because they are the most immunogenic. As red blood cell antigens are inherited traits, they are usually not altered throughout the life of an individual. There have been occasional case reports of ABO blood group antigen change in malignant conditions. We report two such cases of ABO antigen alteration associated with acute myeloid leukemia. These patients had suppression of their blood group antigens during their leukemic phase, and the antigens were reexpressed when the patients attained remission.

CASE DESCRIPTIONS

Two patients diagnosed with AML M5 (based on the French-American-British classification) had discrepancy in their detected blood group by forward cross-matching; their clinical and laboratory features are summarized in the Table. Reverse cross-matching was done in the first case, which failed to show the presence of anti-B antibodies. Reverse cross-matching revealed the presence of only anti-A antibodies. Elution and adsorption studies were performed. The patient’s red cells were incubated with anti-B sera, followed by elution of adsorbed anti-B on her cells. The elute was then tested with group B and group O red cells for the presence of anti-B antibodies. The elute showed positive results with B red cells but a negative reaction with group O red cells, thus confirming the presence of B antigen on the patient’s RBC. The patient was started on 7 + 3 induction with cytarabine and daunorubicin, followed by consolidation with high-dose cytarabine. The strength of reaction of the patient’s RBC with anti-B antibodies increased progressively with treatment. By the end of the second consolidation, there was strong reaction with anti-B antibodies, and she regained her original blood group (B group). Thus, the original blood group B antigen was suppressed during the leukemic phase, and upon remission B antigens were reexpressed. Similarly in the second case, the original blood group B antigen was suppressed during the leukemic phase, and B antigens were reexpressed upon remission.

DISCUSSION

Loss or diminished expression of RBC antigens has been reported in both solid and hematological malignancies. ABO blood group antigen is the most commonly altered blood group antigen (1–4). For hematopoietic diseases, the loss of expression

Table. Clinical and laboratory features of our cases

<table>
<thead>
<tr>
<th>Features</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>AML M5 (FAB)</td>
<td>AML M5 (FAB)</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>46 XX</td>
<td>50% 46 XY, 50% 45 XY</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>CD13, CD33, CD64, D117, anti-MPO, CD11c, CD34, HLA-DR positive</td>
<td>CD13, CD33, CD64, D117, anti-MPO, CD11c, CD34, HLA-DR positive</td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td>7 + 3</td>
<td>7 + 3</td>
</tr>
<tr>
<td>Consolidation</td>
<td>3 × high-dose cytarabine</td>
<td>3 × high-dose cytarabine</td>
</tr>
<tr>
<td>Original blood group</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Detected blood group</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Regained original blood group</td>
<td>After second consolidation</td>
<td>After second consolidation</td>
</tr>
</tbody>
</table>

AML indicates acute myeloid leukemia; FAB, French-American-British classification system; HLA-DR, human leukocyte antigen—antigen D related.
results predominantly from a mutation affecting antigen production in the stem cell. Complete or partial loss of antigen expression is seen among the progenitors of RBC arising from this affected stem cell, whereas the RBCs arising from unaffected stem cells usually express normal RBC antigens. Loss or weakening of ABO antigens is usually detected as a discrepancy in the forward and reverse typing of patients. ABO antigens are the most frequently reported blood group antigen alteration because they are routinely tested for all patients before transfusion.

A, B, and H antigens are formed from the same precursor substance. The production of ABO antigens depends on the functioning of two glycosyl transferases. The first enzyme, H transferase, adds L-fucose to the terminal galactose of the precursor substance. The H substance is then acted on by the A or B transferase, adds N-acetyl galactosamine or a galactose, respectively. There are two possible mechanisms for the weakening of ABO antigens in hematopoietic diseases. The first mechanism is the inactivation of A/B transferases, and the second is the inactivation of H transferase. In the first mechanism (5–8), there is decreased expression of the A and B antigens with a concurrent increase in H antigen. The H antigen is not converted to A and B antigen due to the inactivation of the A/B transferases. A and B transferase genes are encoded on chromosome 9, and they may be inactivated as a 9;22 chromosomal translocation. This is the plausible explanation for ABO alteration in CML. The second suggested mechanism for the loss of ABO antigens is inactivation of the H transferase encoded at 19q13 (9, 10). H transferase inactivation would result in decreased H substance and a resulting decrease in A and/or B substance.

ABO antigen alterations are more commonly seen in AML, although a translocation involving chromosome 9 is seldom seen in AML. In a study of 12 AML patients with weakening of the ABO antigens, it was noted that ABO gene inactivation was not random (11). In 4 of 12 patients studied, only the maternally derived A or B gene was noted to be affected, suggesting a possibility of genomic imprinting.

Loss and weakening of ABO antigens has also been reported prior to the diagnosis of an underlying hematopoietic malignancy. This is usually noted in the setting of myelodysplasia, where a patient with longstanding myelodysplasia has a blood group alteration and later manifests with AML (12, 13). Thus, any loss of ABO antigens should culminate in the search for an underlying hematopoietic malignancy. Variations in ABO antigens may also reflect the status of the malignancy. Upon remission, there is return of the original blood group, and with recurrence, there is suppression of blood group antigens (14).

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare form of skin lymphoma that is localized primarily to the subcutaneous adipose tissue without involvement of the lymph nodes. Clinically, the skin lesions mimic lipomas, while histologically they resemble panniculitis. We report a case of a young woman with SPTCL. She achieved complete remission after combination chemotherapy.

CASE DESCRIPTION

A 25-year-old woman presented with painless papulonodular skin lesions in the abdomen, chest, and limbs. The lesions had appeared 18 months earlier. She had a low-grade intermittent fever, had a poor appetite, and had lost 5 kg over the past 6 months. She had painless nodular subcutaneous skin lesions 1 to 2 cm in size involving all four limbs and the chest and abdomen (Figure 1a). The nodules were painless and erythematous. She had no other symptoms, organomegaly, or lymphadenopathy. A computed tomography scan showed subcutaneous soft tissue thickening with fat stranding in the upper chest, anterior abdominal wall, and upper arm bilaterally. T1- and T2-weighted magnetic resonance imaging of both arms showed intermediate-signal-intensity lesions in the skin and subcutaneous plane (Figure 1b). These lesions showed heterogeneous postcontrast enhancement, and underlying muscles showed normal signal intensities. Histopathological examination of a skin biopsy showed the subcutaneous tissue infiltrated by a neoplasm composed of atypical lymphoid cells with medium size scanty cytoplasm and a round nucleus with fine chromatin and small nucleoli. Angioinvasion was also present (Figure 2a). On immunohistochemistry, the tumor cells were positive for CD3, CD8, perforin, and granzyme and were negative for CD20, CD4, and CD56 (Figure 2b, 2c). The picture was diagnostic of SPTCL. Her hemoglobin was 8.8 g/dL; total leukocyte count, 5000/mm³; platelet count, 327,000/mm³; and erythrocyte sedimentation rate, 80 mm/1st hour. Her renal function, liver function, and serum electrolytes were normal. Her serum lactate dehydrogenase level was 1407 IU/L. A bone marrow study was normal. She was started on chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone. Her skin lesions resolved after two courses, and she completed six courses of chemotherapy. At present, she is alive and in complete remission 18 months after therapy.

DISCUSSION

SPTCL is a rare tumor of T-cell origin representing <1% of all non-Hodgkin’s lymphomas (2). It was first described...
in 1991 in an eight-case series, but was not recognized as a distinct entity by the World Health Organization until 2001 (2, 3). It affects young adults, with a median age at diagnosis of 39 years.

The disease typically follows a distinctive, indolent course of recurrent, self-healing subcutaneous nodules. Often it presents as multiple painless subcutaneous nodules on the extremities and trunk. In its early phase, the nodules may resolve without treatment and new nodules may develop on the same or different skin locations. Diagnosis of SPTCL is a challenge, especially in the early stages when the symptoms mimic other more common conditions such as benign panniculitis, eczema, dermatitis, cellulitis, and other skin and soft tissue infections. About three-fourths of patients with SPTCL have multifocal cutaneous involvement (4). More serious conditions associated with SPTCL include serosal effusions, hemophagocytosis syndrome, and pancytopenia.

Imaging is useful for diagnosis and for monitoring response to therapy. Diagnosis of SPTCL is based on pathological examination of skin and subcutaneous tissue, clinical characteristics, immunohistochemistry staining patterns, and molecular analysis. There are two distinct types of SPTCL based on the T-cell receptor phenotype and immunohistochemistry characteristics. The first, T-cell receptor αβ, is characterized by an indolent, protracted course and is usually CD4−, CD8+, and CD56−. The second, T-cell receptor γδ, is associated with rapid clinical deterioration and coexisting hemophagocytosis. It is usually CD4−, CD8+, and CD56+ (5). Currently, the T-cell receptor αβ subtype is designated as SPTCL, whereas the T-cell receptor γδ is designated as cutaneous gamma/delta positive T-cell lymphoma (6).

Chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone is the preferred regimen, with overall remission rates of 50% (7). In some cases, autologous bone marrow transplantation has been attempted. The overall 5-year survival rate for T-cell receptor αβ exceeds 80% (8). Our patient received six courses of combination chemotherapy and is alive with no evidence of disease 18 months after therapy.


Long-term sequelae due to extravasation of intravenous radioisotopes resulting in radiation injuries are rarely reported. As the use of radioactive isotopes for the treatment of osteoblastic metastases increases, information regarding the prevention, treatment, and long-term monitoring of suspected extravasation injury will become increasingly important. We present a patient with no previous history of skin cancer who developed an aggressive cutaneous squamous cell carcinoma at the site of prior radium-223 extravasation. We recommend that patients who experience extravasation of therapeutic radioisotopes be monitored by dermatologists for long-term sequelae. Cutaneous squamous cell carcinoma should be recognized as a rare but potential adverse event following cutaneous extravasation of radium-223 and is likely a side effect that is severely underreported.

Intravenous radium-223 improves survival and alleviates pain secondary to osteoblastic metastases in the setting of castration-resistant prostate cancer (1). Surprisingly, there are very few reports of local adverse effects related to extravasation of radiotherapies at the injection sites. Ionizing radiation is a well-established risk factor in the formation of cutaneous squamous cell carcinoma. Lichter et al discovered that the risk of cutaneous squamous cell carcinoma was increased by an odds ratio of 2.94 in patients with sun-sensitive phenotypes who received ionized radiotherapy (2). Although radium-223 has only been approved by the US Food and Drug Administration since 2013, we report a case of focal cutaneous squamous cell carcinoma that quickly developed after extravasation of radium-223. To our knowledge, this is the first published case of this possible side effect.

**CASE DESCRIPTION**

A 62-year-old man presented with a painful, hyperkeratotic papule on the left dorsal hand. He had no prior history of skin cancer but did have a history of metastatic prostate cancer with an extensive oncological therapy course, including treatment with intravenous radium-223 dichloride injections at an outside facility for painful osteoblastic metastases. During the first of three treatments (Figure 1), he noted extravasation of the radioisotope from the intravenous catheter in his left dorsal hand, which manifested as local pain, erythema, and edema. The patient denied any postincident correlate imaging procedures or survey meter assessment to verify the presence of radioactivity at the site. Four months later, he noted a rapidly growing, painful lesion at the exact injection site. Upon examination, there was a 1.2 cm hyperkeratotic plaque, which was not present at his last skin check 5 months earlier (Figure 2). There was no significant actinic damage or previous history of actinic keratosis in the area. A biopsy revealed an aggressive acantholytic squamous cell carcinoma. The patient then underwent Mohs micrographic surgery for definitive treatment.

**DISCUSSION**

Radium-223 dichloride is an alpha emitter that selectively targets and binds areas of increased metabolic activity and is approved for the treatment of pain secondary to osteoblastic metastases in the setting of castration-resistant prostate cancer. The ALSYMPCA (ALpharadin in SYMptomatic Prostate CANcer patients) trial was a phase 3 randomized double-blind trial that studied the effects and safety profile of radium-223. Common adverse events analyzed in the study included myelosuppression, gastrointestinal disturbance, fatigue, urinary tract infections, pathologic fracture, and progression of malignant neoplasms (1, 3). No cutaneous adverse effects were noted during the trial, and specifically there was no mention of local reactions at the injection site (3).

---

**From Texas A&M Health Science Center College of Medicine and the Department of Dermatology, Scott & White Medical Center – Temple, Temple, Texas.**

**Corresponding author:** Shannon C. Brown, MD, Department of Dermatology, Scott & White Medical Center – Temple, 409 W. Adams, Temple, TX 76501 (e-mail: Shannon.Brown@BSWHealth.org).
in surrounding tissue (9). Kawabe et al discussed safety guidelines for extravasation of strontium, which included four steps: documenting the site with a photograph, warming the region to promote vasodilation and alleviate pain, considering topical or intralesional steroids, and imaging the area to measure the dose of radiation absorbed by the skin (4). They also recommended consulting a dermatologist to treat the associated symptoms. Iddins et al recommended considering hyperbaric oxygen or 400 mg of pentoxifylline and δ-tocopherol (a form of vitamin E) for the treatment of local radiation injury (10).

The true incidence of adverse effects due to the extravasation of radioisotopes is likely underreported. Physicians involved in the care of these patients may not be aware that extravasation occurred. Furthermore, skin cancers are very common on the dorsal hands and forearms, where intravenous catheters are commonly placed. Due to the prolonged and protracted nature of radiation-induced injuries and the delayed development of cutaneous complications such as nonmelanoma skin cancer, the physicians and patients may not connect the two events. We recommend that patients who experience extravasation of radiotherapies be monitored by a dermatologist for the development of possible aggressive skin cancers. These measures in prevention, prompt detection, and treatment can decrease morbidity associated with extravasation of intravenous radiotherapeutics such as radium-223.

8. Surgeons have done wonders for Dr. Stover. *Weekly Courier* (Fort Collins, Colorado) 1909;4:3.
A nodular-ulcerative form of secondary syphilis in AIDS

Ofelya Gevorgyan, MD, Benjamin D. Owen, MD, Arvind Balavenkataraman, MD, and Mitchell R. Weinstein, MD

An uncommon variant in the pre-AIDS era, lues maligna is a nodular-ulcerative form of secondary syphilis. We present a case of a 41-year-old man with HIV infection who developed fever, chills, nausea, vomiting, right upper quadrant abdominal pain, weight loss, watery diarrhea, and a painless, nonpruritic rash. He had diffuse nodular-ulcerative lesions in various stages of development. He was found to have a CD4 count of 101 cells/mm³ (22%), an HIV viral load of 2,735,060 copies/mL, and a positive rapid plasma reagin at 1:64. He was started on emtricitabine, tenofovir, and dolutegravir, as well as doxycycline. He was given benzathine penicillin 2.4 million units intramuscularly and within hours developed a Jarisch-Herxheimer reaction. Skin lesions showed signs of healing, and constitutional symptoms improved 48 hours later.

We describe a nodular-ulcerative form of secondary syphilis in a patient with AIDS, characterized by some remarkable clinical and laboratory features. The alarming resurgence of syphilis and high coinfection rates with HIV necessitate clinicians’ familiarity with this manifestation of “the great imitator.”

CASE PRESENTATION

A 41-year-old man with a history of intravenous drug abuse and untreated HIV infection presented to his primary care physician with complaints of fever, chills, nausea, vomiting, right upper quadrant abdominal pain, weight loss, watery diarrhea, and a diffuse painless, nonpruritic nodular-ulcerative rash. He was malnourished, febrile (101.2°F), tachycardic, and in mild respiratory distress, with tender and enlarged cervical lymph nodes and mild right upper quadrant tenderness. A diffuse nodulo-ulcerative rash was present, with lesions in various stages of development involving the extremities, back, chest, face, and scalp, as well as a few lesions on his soles, but sparing the palms and the oral mucosa (Figure).

The patient was found to have a CD4 count of 101 cells/mm³ (22%), an HIV viral load of 2,735,060 copies/mL, a reactive treponemal antibody, and a positive rapid plasma reagin (RPR) titer at 1:64. He reported an unprotected sexual encounter with a male partner 4 months prior to the appearance of the rash. He was started on combination antiretroviral therapy with emtricitabine, tenofovir, and dolutegravir, trimethoprim-sulfamethoxazole for Pneumocystis jirovecii pneumonia prophylaxis, as well as doxycycline for presumptive secondary syphilis, given a reported allergy to penicillin.

He was admitted to the hospital a few days later with worsening constitutional symptoms. His white blood cell count was 3.3 k/mm³; hemoglobin, 9.6 k/mm³; aspartate aminotransferase, 81 IU/L; alanine aminotransferase, 64 IU/L; and alkaline phosphatase, 644 IU/L. Right upper quadrant ultrasound was unremarkable.

The patient had had a nonanaphylactic cutaneous reaction to penicillin previously. In the hospital he was given benzathine penicillin 2.4 million units intramuscularly. Within hours he developed worsening fever, tachycardia, and tachypnea, thought to be a Jarisch-Herxheimer reaction. Within 48 hours of treatment, his skin lesions showed signs of healing, and significant improvement was noted by the time of hospital discharge 5 days later. He received 2 more weekly penicillin injections as an outpatient, and 1 week after the third injection he reported almost complete resolution of the rash. At that time, his RPR titer was 1:512. He was subsequently lost to follow-up.

DISCUSSION

Syphilis is well known for its protean cutaneous manifestations, which led early clinicians to christen the disease “the great imitator.” Lues maligna, or nodular-ulcerative syphilis, is a rare but severe manifestation of secondary syphilis first described by Bazin in 1859, with early systematic studies by Haslund and Neisser in the late 1800s (1, 2). The term “malignant” has been used to describe its grotesque clinical features (3).

Lues maligna is characterized by marked prodromal constitutional symptoms, as observed in our patient. This is followed by the development of multiple irregularly distributed, erythematous papules that subsequently evolve into well-defined round or oval, necrotic ulcerated plaques on the scalp, face, trunk, and extremities. Lesions in various stages of development, including papules, nodules, pustules, and ulcerations covered...
A nodular-ulcerative form of secondary syphilis in AIDS

January 2017

with laminated, brown-black rupioid crusts are present, and mucosal surfaces may be affected (1). The trunk, palms of the hands, soles of the feet, and mucosal membranes can be involved, but to a lesser degree than in typical secondary syphilis (3). Our patient had a few lesions on the soles, but his palms and mucosal membranes were spared.

The liver is the most commonly involved extracutaneous organ (3). Our patient had right upper quadrant abdominal pain and elevation of liver enzymes, likely due to syphilis.

Fisher's criteria are usually used for diagnosing malignant syphilis: 1) compatible gross morphology; 2) a high-titer serologic test for syphilis; 3) a Jarisch-Herxheimer reaction following treatment; and 4) a dramatic response to antibiotic therapy (3). All of these manifestations were present in our patient.

The histologic findings in secondary syphilis are as varied as the clinical presentations. Features mimicking persistent gyrate erythema, lichen planus, parapsoriasis lichenoides and varioliformis acuta, erythema exudativum, psoriasis, pustular psoriasis, histiocytoma, and sarcoidosis have been described (4). Lues maligna is characterized by occlusion of the blood vessels with resultant fibrinoid necrosis at the dermal-subcutaneous junction. Treponemes are not readily identified in the lesions but have been described in the dermis using a Warthin-Starry stain (3).

The incidence of primary and secondary syphilis has been increasing in the USA in the last several years, especially in men who have sex with men, with the largest increases among Hispanic and white men. Despite this shift in epidemiology, the highest rates continue to occur in black men (5). The prevalence of lues maligna was 0.36% in Haslund’s original series (2). In the pre-AIDS era, lues maligna was associated with severe malnutrition, alcoholism, and intravenous drug use (6). Following the AIDS epidemic, the incidence of malignant syphilis significantly increased (6). According to a 1996 multicenter retrospective study, patients with HIV were 60 times more likely to present with ulcerative syphilis compared to historic case series (2).

The reasons for atypical manifestations in the setting of HIV are not entirely understood. It is known that the pathogenesis of lues maligna is less dependent on specific treponemal virulence
factors and more influenced by the host’s immune state, as patients can acquire the disease from persons with typical manifestations of syphilis (1).

There are also important clinical interactions between syphilis and HIV, as syphilis is associated with the transmission and acquisition of HIV infection. Syphilitic ulcers facilitate transmission of HIV, and syphilis stimulates the immune system, which can lead to an increase in HIV replication and lower CD4 counts (7).

An increase in the incidence of Jarisch-Herxheimer reactions has been described among patients with malignant syphilis and patients coinfected with HIV in general. Yang et al described a rate as high as 34.6% in HIV-infected patients (8). The Jarisch-Herxheimer reaction is a transient immunological phenomenon seen commonly in patients during treatment of secondary syphilis; it manifests with constitutional symptoms such as fever, chills, headache, and myalgias in addition to exacerbation of existing cutaneous lesions (9). The reaction usually occurs soon after the administration of an appropriate antibiotic (2–24 hours) and usually resolves without any intervention, generally within 24 hours. Jarisch-Herxheimer reaction is more severe when the number of organisms is abundant (9). No specific tests are available to diagnose Jarisch-Herxheimer reaction. It should be managed symptomatically and does not require discontinuation of the appropriate antimicrobial treatment (9). Corticosteroids have been used to offset the reaction with no conclusive evidence of their benefit (9). Pretreatment with anti–tumor necrosis factor-alfa Fab has been shown to reduce the incidence and severity of the reaction in louse-borne relapsing fever (10), but its role in syphilis and its potential therapeutic value is unknown.

The Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines recommend a follow-up nontreponemal serologic test of syphilis patients 6 and 12 months after therapy (11). Repeat syphilis testing before these specified times can create confusion, as the RPR may increase immediately after therapy of early syphilis, and the initial RPR may underestimate the maximal titer (12). In our case, the early rise in RPR posttherapy was uninterpretable, but likely was not significant. Unfortunately, the patient was lost to follow-up, so the subsequent response is unknown.

We present an approach for safe management of a patient with an oral endotracheal tube who required conversion to a nasal endotracheal tube. A 35-year-old man presented for mandibular fracture repair after multiple injuries sustained in a motor vehicle accident. The patient already had an oral endotracheal tube, and the surgical team requested a nasal endotracheal tube to facilitate surgical exposure and postoperative airway management in anticipation of a wired jaw. A nasal endotracheal tube was inserted through the naris and a video laryngoscope was used to visualize the glottis. A tracheal tube introducer was inserted through the oral endotracheal tube, and the oral endotracheal tube was then withdrawn approximately 5 cm. The nasal endotracheal tube was advanced through the vocal cords alongside the tracheal tube introducer. The nasal endotracheal tube cuff was then inflated and the tracheal tube introducer was withdrawn.

Occasionally, anesthesiologists are requested to convert an oral endotracheal tube to a nasal endotracheal tube. Unlike the relatively straightforward oral to oral endotracheal tube exchange that uses a modification of the Seldinger technique (1), an oral to nasal endotracheal tube conversion is complicated by head and neck anatomy. The foremost concern in performing such a tube exchange is maintaining secure control of the airway. We present a technique for converting an oral endotracheal tube to a nasal endotracheal tube while continuously maintaining reliable access to the airway.

CASE DESCRIPTION

A 35-year-old man sustained multiple injuries in a motor vehicle accident that necessitated emergent endotracheal intubation and admission to the intensive care unit. On hospital day 4, the patient was scheduled to undergo open repair of a mandibular fracture. A tracheostomy was considered, but the attending surgical critical care intensivist believed that the patient had a chance to be extubated within 3 to 4 days after the operation. A multidisciplinary decision was made to convert the oral endotracheal tube to a nasal endotracheal tube for surgical exposure and postoperative airway management.

The patient arrived intubated with an 8.0 mm oral endotracheal tube and was anesthetized with inhaled desflurane, paralyzed with rocuronium 40 mg intravenous, and preoxygenated with 100% oxygen. The left naris was topicalized with oxymetazoline. A lubricated 8.0 mm nasal endotracheal tube (Hudson RCI Sheridan Preformed, DRE Medical, Louisville, KY) was then inserted. A video laryngoscope (C-MAC D-blade, Karl Storz Endoskope, Beirut, Lebanon) was used to visualize the glottis. A Venn Reusable Tracheal Tube Introducer (Smiths Medical, St. Paul, MN) was inserted through the oral endotracheal tube as an airway exchange catheter. Under direct visualization with the video laryngoscope, the oral endotracheal tube cuff was deflated and withdrawn approximately 5 cm, leaving the tracheal tube introducer through the vocal cords. The nasal endotracheal tube was then carefully advanced to the glottis using Magill forceps. For illustrative purposes, this configuration was recreated using an airway mannequin (AirSim, TruCorp, Belfast, N. Ireland), and a picture taken using the camera of the video laryngoscope is included in Figure 1. A simple schematic representation of our technique is included in Figure 2.
There was difficulty advancing the nasal endotracheal tube through the vocal cords, and an additional Venn Reusable Tracheal Tube Introducer (Smiths Medical, St. Paul, MN) facilitated placement of the endotracheal tube using a modified Seldinger technique (1). The balloon of the nasal endotracheal tube was inflated, breath sounds were auscultated bilaterally in the axillae, and expired end-tidal carbon dioxide was confirmed. Finally, the tracheal tube introducer associated with the oral endotracheal tube was withdrawn past the inflated cuff of the nasal endotracheal tube.

**DISCUSSION**

Oral to nasal endotracheal tube exchanges have been described using various techniques. Dutta and colleagues inserted a bronchoscope through the naris, delivered it through the mouth, and used the bronchoscope as a guide to withdraw an existing oral endotracheal tube back through the naris (2). Similarly, Hoffman and colleagues used a urethral exchange catheter wire inserted through the naris and delivered through the mouth that was subsequently taped to an oral airway exchange catheter; the connected components acted as a guide (3). Nakata and Niimi designed a proprietary commercial device to facilitate oral to nasal endotracheal tube exchange where a two-part airway exchange catheter is used; the distal portion is inserted through the oral endotracheal tube, and the oral endotracheal tube is then withdrawn, the proximal portion is inserted through the nares, and then the two parts are connected, forming an intact airway exchange catheter to facilitate passage of a nasal endotracheal tube (4). Uria and colleagues reported using downward pressure on an existing oral endotracheal tube to bring the glottis into view, and a nasally placed bougie was inserted through the vocal cords to allow passage of an endotracheal tube (5). Monclus and colleagues inserted an airway exchange catheter that could be used for oxygenation during apnea through an oral endotracheal tube and then performed a nasal fiberoptic intubation, using the airway exchange catheter as a guide to the glottis (6).

Nasal to oral endotracheal tube exchanges have also been described. Using a video laryngoscope, Galgon and Ketzler advanced an oral endotracheal tube over a rigid stylet to the glottis, deflated the cuff of an existing nasal endotracheal tube before withdrawing it, and then inserted the oral endotracheal tube through the glottis (7). Lee and colleagues inserted an airway exchange catheter through an existing nasal endotracheal tube, removed the endotracheal tube, and delivered the proximal end of the airway exchange catheter through the mouth, allowing an oral endotracheal tube to be placed (8).

An advantage to our technique is that access to the airway is continuously maintained; we always had the ability to replace the existing oral endotracheal tube if our technique failed and the patient became hypoxic. Additionally, we used equipment that is commonly available in operating rooms. This technique took less than 2 minutes to complete and was accomplished on the first attempt. Disadvantages of this technique are that the oropharynx can get crowded with the two endotracheal tubes, particularly with abnormal anatomy, and that an airway with copious amounts of blood or vomitus would impair the view of the video laryngoscope during the endotracheal tube exchange. We anticipated this complication and had a trauma surgeon available to perform an emergency tracheostomy if indicated. We believe that our technique is a reasonable first-line approach for the uncommon request of oral to nasal endotracheal tube exchange.

---

Ingestion of computer circuit boards causing esophageal impaction and small bowel obstruction

Nizar H. Senussi, MD, and Nasir Saleem, MD

Foreign body ingestion is common in patients with psychiatric diagnoses. Ingested objects can become impacted in the upper and lower gastrointestinal tract, causing serious complications. We report a case of a schizophrenic who ingested large pieces of computer circuit boards, which impacted at the mid-esophagus, in the stomach, and in the cecum. Endoscopic removal of the esophageal object was unsuccessful, and the foreign objects were removed by esophagotomy and laparotomy. Expedient removal through endoscopic or surgical means is extremely important, as complications can be life-threatening. This is the first report of ingestion of a computer printed circuit board.

We report a case of the deliberate ingestion of fragments of a computer printed circuit board (PCB) leading to esophageal impaction of one fragment and multiple retained gastric and colonic fragments. This posed a risk for esophageal, gastric, and large bowel perforation and exposed the patient to complications unique to computer PCBs.

CASE DESCRIPTION

A 48-year-old man with schizophrenia was transferred to the emergency department from a skilled nursing facility after chewing and swallowing a circuit board from a personal computer 4 days earlier. At presentation, he reported only mild substernal chest pain and had been tolerating oral intake over the past several days. His vital signs were stable. He had normal breath sounds bilaterally, no crepitus, and a nontender abdomen. His affect was depressed, and there was no evidence of drug intoxication. Laboratory tests revealed a leukocytosis of 16,000/mm³. Chest and abdominal plain films showed a 2.5 × 2.5 cm metallic object impacted in the esophagus at the level of the carina (Figure 1a) and two radio-opaque foreign bodies measuring 4 × 4 cm and 2 × 2.3 cm in the stomach and cecum (Figure 1b). A noncontrast computed tomography (CT) scan of the chest, abdomen, and pelvis confirmed the presence of multiple foreign bodies and showed no evidence of mediastinitis or bowel perforation.

Emergent endoscopy to remove the esophageal object was unsuccessful. The object was flat shaped and embedded in the esophageal wall (Figure 2). A nasogastric tube was placed at the time of endoscopy in anticipation of postoperative needs. The patient was taken for right thoracotomy, esophagotomy, and removal of the foreign body with primary esophageal closure with intercostal muscle flap. At operation, the esophageal wall was thickened but no perforation was seen, and the foreign body was removed from the esophagus. The following day, the patient underwent exploratory laparotomy for removal of the gastric and cecal metallic bodies as well as several plastic pieces via gastrotomy and colotomy (Figure 3). Fluoroscopic localization of the foreign bodies was performed with the aid of a needle localization technique.

Figure 1. Initial x-ray plain film of esophageal, gastric, and cecal foreign bodies. (a) Chest radiograph showing a 2.5 × 2.5 cm object in the esophagus at the level of the carina. (b) Abdominal x-ray showing a 4 × 4 cm object in the stomach and a 2 × 2.3 cm object in the area overlying the small bowel.
for the retained colonic fragments was used, and a feeding jejunostomy tube was also placed.

The postoperative course was complicated by respiratory failure requiring continued ventilator support for 6 days. A postoperative contrast esophagram showed contrast extravasation at the esophagotomy site. It was managed with antibiotics and continued chest tube drainage. Seven days after the operation, CT of the chest showed fluid and gas collections in the paraesophageal and right lower hemithorax that were not being drained by the chest tubes. Thoracentesis confirmed empyema with pleural fluid growing Actinomyces meyeri and Streptococcus mitis. Antibiotics were switched to piperacillin-tazobactam and fluconazole and given for 14 days. The patient also developed agitation and delirium, which were treated with antipsychotics. A follow-up chest x-ray 25 days after the operation showed resolution of empyema. A repeat esophagram at 29 days showed no leak. The patient was discharged to a nursing home 53 days after admission.

**DISCUSSION**

Foreign body ingestion is the emergent consequence of a unique constellation of behaviors and patterns in adults and children. As many as 1500 people die in the United States each year as a result of foreign body ingestion (1). In adults, risk factors for ingestion include accidental swallowing of bones, dental surgery, visual impairment, and bulimia nervosa (2). However, a portion of ingestions in adults are deliberate, with about 85% of these patients having a prior psychiatric diagnosis and 84% of patients having had prior ingestions. Thus, deliberate foreign body ingestion can have a significant health and economic impact. While most ingested objects will pass per rectum spontaneously, 10% to 20% of cases require endoscopic removal, and about 1% require surgery (3). The risk for gastrointestinal perforation is greater with sharp objects and ranges from 15% to 35% (4, 5). Other complications include bowel ischemia, fistulization, and metal toxicity from coin ingestion (6).

Our case describes the deliberate ingestion of fragments of a computer circuit board with sharp edges. The patient was able to tolerate oral intake in the intervening 4 days before presenting to the hospital. He developed a complicated postoperative course with paraesophageal empyema requiring a prolonged course of antibiotics. We found no comparable studies of delayed esophageal repair for impacted foreign bodies. However, in the case of spontaneous esophageal rupture, one report showed no significant increase in mortality with delayed esophageal repair (7).

Computer PCBs are planar, high-hardness, epoxy- and fiberglass-bound boards. While items past the ileocecal valve are generally expected to pass spontaneously, fractured PCBs have the potential to create splintered points and sharp edges. This increases the risk of colonic perforation with spontaneous passage, and therefore surgical extraction was indicated to reduce this risk. Computer boards may also carry on-board batteries. The distal fragments had an appearance that was thought to possibly contain batteries, and this contributed to the rationale for surgical removal. Furthermore, PCBs are frequently plated with copper and lead solder. The possibility of acute lead poisoning was raised, but this was felt to be an insignificant risk and not a contributor to the patient's clinical scenario. Nonetheless, this may warrant further investigation in computer hardware ingestions that are treated nonoperatively.

---

**Avocations**

Cape buffalo. Photo copyright © Jed Rosenthal, MD. Dr. Rosenthal is a cardiologist in Dallas, Texas (e-mail: jedr2@sbcglobal.net).
Lead foreign bodies in joint spaces, often due to projectiles such as bullets, may cause localized arthropathy. There are no reports of joint fracture related to lead arthropathy. Additionally, lead foreign bodies embedded in the joint space may be a source of systemic lead absorption, causing elevated blood lead levels and toxicity to other organs. We present a young adult patient with retained left hip joint bullet fragments who developed suspected lead arthropathy and subsequent acute left hip fracture, as well as systemic lead absorption demonstrated by elevated blood lead levels.

Lead toxicity is the most common cause of heavy metal poisoning. Historically, common sources of lead toxicity have varied, but internally sequestered lead from traumatic projectiles remains a consistent concern. Lead projectiles lodged within joint spaces from gunshot wounds and explosive devices may cause localized joint damage, known as lead arthropathy. Additionally, systemic lead toxicity may occur as solubilized lead gains access to the circulation through the damaged joint. Systemic lead toxicity symptoms vary widely by organ system involved, but may prompt consideration for surgical removal of the lead source and lead chelation therapy. We discuss a patient with bullet lead arthropathy, subsequent fracture of the involved joint, and evidence of systemic lead absorption.

CASE DESCRIPTION

A 32-year-old man was previously evaluated at our hospital for a gunshot wound to the right buttckock, which crossed midline and lodged in the subcutaneous tissue of the left proximal thigh. Initial imaging demonstrated fractures of the left posterior acetabulum and coccyx, a large bullet fragment in the left subcutaneous thigh, and tiny bullet fragments overlying the left hip joint (Figure 1a). The fractures were nonoperative. Traumatic sequelae included left hip pain, left sciatic neuropathy, decreased sensation to the left S1 dermatome, and left foot drop. The left thigh bullet was removed without incident 1 week later.

Four months after the injury, the patient presented with acute-on-chronic left leg pain. Radiographs demonstrated left hip (Figure 1b) and ankle arthropathy—advanced for age—with retained left hip joint lead fragments likely in contact with the synovium. A blood lead level was ordered and days later showed an elevated level of 16 mcg/dL (normal, <10). The patient was contacted with the results, but had no known follow up.

The patient presented again to the emergency department 1 month later for acute-on-chronic left leg pain. Additionally, the patient complained of recent-onset nausea, anorexia, and constipation. The blood hemoglobin was 13.2 g/dL (normal, 14–18). Eight months after the gunshot wound, the patient presented to our emergency department with increasing left hip pain after a reported seizure 2 days earlier. He had no new hip trauma. The patient reported only a remote seizure many years ago. He reported no other new symptoms. Imaging of the left hip demonstrated an acute displaced subcapital femoral neck fracture, along with the old, stable acetabular fracture and retained hip bullet fragments (Figure 1c). The patient underwent open reduction internal fixation with hip screw placement. Despite multiple patient contact attempts, we were unable to assess further symptoms of lead toxicity or arrange for repeat lead levels.

DISCUSSION

Lead toxicity is the most common form of heavy metal poisoning. Significant lead exposure may occur through occupational sources, such as battery processing, car radiators, glassmaking, brass-making, and de-leading of older facilities with lead-containing paint. Ingestion of lead-containing substances may occur in children exposed to paint chips in older housing. Toxicity may result from internal exposure of lead-containing foreign bodies, such as lead-containing bullets, buckshot, fishing sinkers, and some herbal preparations (1, 2).

Lead sources that embed in the joint space, such as bullets and buckshot, are often introduced traumatically. Normally, lead foreign bodies in the soft tissue are encapsulated by an...
immune-mediated fibrous reaction, limiting adjacent and systemic lead exposure. However, lead foreign bodies in the joint space may cause localized tissue destruction, known as lead arthropathy, and in some cases may be a source for leaking of lead into the systemic circulation (3, 4).

Lead arthropathy has been associated with localized degenerative joint disease, synovitis, and gout (5, 6). Degenerative joint disease may develop secondary to interaction of both irregular joint surfaces from fractures and from intraarticular bone and lead fragments sustained during the initial injury (5, 7).

Our patient's initial injury resulted in left acetabular fracture with associated joint bullet fragments. Later x-rays showed signs of arthropathy, likely due to both lead and posttraumatic etiologies. Subsequently, the patient sustained a new, acute left subcapital femoral neck fracture after a reported seizure. There were no reported signs of external left hip trauma to suggest another precipitant for hip fracture. There were no other known metabolic or structural risk factors for fracture. Therefore, it is reasonable to suggest the acute left hip fracture was precipitated by preexisting lead and posttraumatic joint arthropathy. We were unable to locate previous reports of fracture directly associated with lead arthropathy.

In addition, systemic absorption of lead from the joint space may occur due to multiple factors. Mechanical fragmentation of implanted lead projectiles, in addition to the acidic synovial fluid, increases lead solubilization. Absorption of lead through an inflamed synovium introduces lead into the systemic circulation (3–5, 7, 8). Subsequent systemic lead toxicity symptoms may occur as soon as weeks after, but more typically symptoms manifest years or decades following the initial injury.

### Table 1. Lead toxicity symptoms by organ system

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous</td>
<td>Acute toxicity manifested by encephalopathy, ataxia, seizures. Chronic central nervous system toxicity is hallmarked by vague symptoms, such as mood disturbances, headaches, fatigue, and cognitive impairment in children. Paresthesias may be present, along with progressive motor weakness and decreased deep tendon reflexes.</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Hemolytic anemia, chronic microcytic anemia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Elevated blood pressure</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Chronic abdominal pain, constipation, diarrhea, anorexia</td>
</tr>
<tr>
<td>Renal</td>
<td>Interstitial nephritis, Fanconi-like syndrome, uric acid retention (saturnine gout)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Reduced thyroid function</td>
</tr>
<tr>
<td>Bone/Joint</td>
<td>Degenerative joint disease, synovitis, reduced bone growth, increased metaphysis calcium deposition (lead lines on x-ray)</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Chromosomal abnormalities, abnormal sperm motility, premature rupture of membranes</td>
</tr>
</tbody>
</table>

Figure 1. Gunshot wound injury on initial presentation, 4 months later, and 8 months later. (a) After the injury, a dominant bullet fragment is seen in the subcutaneous soft tissues. Debris and bone islands are seen in the region of the acetabular fracture. Contrast is present in the bladder. (b) Four months later, retained metallic fragments remain in the left hip, likely in contact with the synovial fluid. The radiologist noted a slightly asymmetric age advanced left hip subchondral acetabular irregularity, progressed compared to prior x-rays, suggestive of posttraumatic arthritis and lead arthropathy. (c) Eight months after the gunshot wound, an acute comminuted fracture of the left femoral neck is present. Metallic fragments from the prior gunshot injury are again seen.
initial injury (3, 5, 7, 8). Symptoms of lead toxicity vary by organ system (Table 1). Evaluation for systemic lead toxicity was difficult in our patient due to multiple unplanned hospital visits with different providers and lack of follow-up. The patient presented on different occasions with nonspecific complaints and a reported seizure. There was no reported ongoing mental status change to strongly suggest worsening nervous system lead toxicity. However, retained joint foreign bodies in such patients may possibly contribute to developing systemic lead toxicity in the future.

Blood lead level measurements are an important variable in treatment of lead toxicity. However, they do not always correlate with severity of toxicity. A blood lead level >10 mcg/dL in adults and >5 mcg/dL in children is considered elevated (9, 10). However, adults and children may not show clinical signs or symptoms until blood lead levels are >70 mcg/dL in adults and >45 mcg/dL in children (11). Central nervous system (CNS) manifestations, such as encephalopathy, are rare, but occur in toddlers aged 15 to 30 months with blood lead levels >100 mcg/dL. However, similar effects in this age group may occur with blood lead levels ≤70 mcg/dL (11).

When blood lead levels are not available, lead toxicity may be considered presumptively based on a history of lead exposure, the presence of anemia, and radiographic evidence of lead. Black-blue lines (Burton’s line) may be seen on gums in chronic lead toxicity. Anemia, which may be microcytic or normocytic, is often present with or without basophilic stippling. Hemolytic anemia may be present. Blood chemistries, creatinine level, liver function tests, and urinalysis should be assessed for toxic effects and in preparation for possible chelation therapy options (1, 9, 11–13).

Radiographic diagnosis of lead arthropathy involves manifestations of the initial traumatic insult and subsequent sequelae (7, 14). Possible radiographic identification includes evidence of joint effusion, synovial thickening, synovial deposition of lead particles, lead arthrogram, joint space narrowing, evidence of metallic particles present in the tendon sheaths of affected joints, and lead arthrogram where the entire joint cavity can be outlined by lead (3, 8). Joint effusion, synovial thickening, synovial lead particle deposition, lead arthrogram, and joint space narrowing are the most frequently manifested radiographic findings (3, 8). X-rays in children with a history of heavy lead exposure may have increased metaphyseal density of long bones (lead lines) (11, 12).

Treatment for lead toxicity includes removal of/from the lead source and, if indicated, lead chelation therapy. Due to the known possibility of joint pathology and systemic lead toxicity, all cases of lead arthropathy should be considered for removal of the source of lead exposure, unless it is embedded in soft tissue and not exposed to body fluids or is adjacent to neurovascular structures. An orthopedic surgery consultation is needed for consideration of removal of the joint space lead products, usually by synovectomy or arthroplasty. In addition, lead chelation therapy should be considered. Lead chelation therapy with dimercaprol plus edetate calcium disodium is indicated for lead toxicity with severe CNS symptoms, such as encephalopathy, irrespective of blood lead level. CNS lead is chelated by dimercaprol (British anti-Lewisite), which is an intramuscular medication that crosses the blood-brain barrier. Edetate calcium disodium (CaNa2-EDTA), given intravenously or intramuscularly, does not cross the brain barrier and is used concurrently to chelate lead outside of the CNS (13, 15). Importantly, edetate disodium, used for hypercalcemia treatment, should not be mistakenly ordered instead of edetate calcium disodium, as it may cause life-threatening hypocalcemia.

Chelation therapy for lead toxicity that does not include severe CNS toxicity should be considered for symptomatic adults with a lead level >100 mcg/dL and symptomatic children with a lead level >69 mcg/dL, and possibly for asymptomatic adults with a lead level >70 mcg/dL and asymptomatic children with a lead level of >45 mcg/dL (11). Chelating agents for non-CNS system toxicity include dimercaprol plus edetate calcium disodium, succimer, or d-penicillamine (3, 4). As with lead encephalopathy, dimercaprol and edetate calcium disodium are used as combination therapy. Edetate calcium disodium is generally not recommended as a solo therapy due to its inability to bind newly mobilized yet not chelated lead entering the CNS, which may lead to encephalopathy. Alternatively, succimer, an oral analog of dimercaprol, may be used as a solo lead chelating agent for 2 to 3 weeks (6, 15). Finally, d-penicillamine is considered a third-line agent for lead poisoning by the American Academy of Pediatrics (10, 14). Ascorbic acid may be helpful in reducing serum lead levels (2, 12). Patients who are asymptomatic and have low blood lead levels (adults <90 mcg/dL and children <45 mcg/dL) are treated by removal of the lead source alone, without chelation therapy. Ultimately, consultation with a toxicology specialist is recommended for consideration of lead chelation therapy. Generally, patients should be admitted to the hospital for initial chelation therapy.

Identification of foramen of Huschke with reversible herniation of temporomandibular joint soft tissue into the external auditory canal on multidetector computed tomography

Shallini Mittal, DMRD, Samita Singal, MD, Amit Mittal, MD, Rikki Singal, MS, and Gunjan Jindal, MD

The foramen of Huschke, or foramen tympanicum, is a developmental defect in the bony part of the external auditory canal (EAC) due to a defect in ossification of normal bone in the first 5 years of life. Seen in the anteroinferior part of the EAC, it can be asymptomatic or present with salivary discharge into the EAC during mastication or as soft tissue swelling in the EAC in the absence of any inflammation, tumor, or trauma. We present a case of a man who presented with herniation of soft tissues of the temporomandibular joint into the EAC through a persistent foramen tympanicum.

This article brings attention to a specific anatomical defect in the external auditory canal (EAC) that may affect the diagnosis and treatment protocol for oral and maxillofacial surgeons who deal with temporomandibular joint (TMJ) soft tissue issues, as well as otolaryngologists in their assessment of otological symptomatology. In addition, the article should make radiologists more aware of this particular defect in assessing imaging involving TMJ or otological factors. Radiology can be very helpful in determining the size and extent of the defect and tissue herniation to aid in decisions regarding whether biopsy or surgical intervention is advantageous or harmful.

CASE PRESENTATION

A 70-year-old man was referred to us for high-resolution computed tomography (HRCT) of both temporal bones. He presented with left-sided otalgia. There was associated fullness in the left ear but no discharge and no previous history of trauma, ear surgery, or instrumentation. Clinical examination revealed a pulsatile polypoidal mass bulging into the EAC on the left side.

A biopsy was planned, and prebiopsy HRCT was performed on a 128-slice Philips Ingenuity Multidetector CT (Philips Medical Systems, The Netherlands) on 120 kV, 200 mAs, an ultra-high-resolution filter, 1-mm section thickness, 0.3-mm section increment, 512 × 512 matrix, and 160-mm field of view. HRCT of the temporal bone demonstrated a bony defect in the anteroinferior part of the EAC (Figure 1a). Through this defect, soft tissue protrusion was seen into the EAC, along with a few air specks. An open mouth view was used, which demonstrated that the herniated soft tissue retracted back into the TMJ with a few air pockets (Figure 1b). This mass was diagnosed as a soft tissue protrusion.

Figure 1. Axial closed-mouth high-resolution computed tomography sections showing (a) defect in anteroinferior part of bony external auditory canal with protrusion of the temporomandibular joint soft tissue into the external auditory canal; and (b) complete retraction of the soft tissue and air specks into the temporomandibular joint.

From the Department of Radiodiagnosis and Imaging, M. M. Institute of Medical Sciences and Research, Mullana (Distt-Ambala), Haryana, India.

Corresponding author: Shallini Mittal, DMRD, Department of Radiodiagnosis and Imaging, M. M. Institute of Medical Sciences and Research, Mullana, Ambala Pin Code - 133203, Haryana, India (e-mail: shallini_mittal@yahoo.com).
Identification of foramen of Huschke with reversible herniation of temporomandibular joint soft tissue

January 2017

Identification of foramen of Huschke with reversible herniation of temporomandibular joint soft tissue

from foramen tympanicum. The planned biopsy was abandoned, and no further treatment was given.

DISCUSSION

The temporal bone is complex and comprises squamous, petrous, mastoid, and tympanic parts and the styloid process. The EAC and tympanic cavity develop from the tympanic portion of the temporal bone. Foramen tympanicum occurs due to a congenital defect during the ossification process that leaves a bony defect that is anteriorly related to the TMJ (1). The EAC is incompletely formed at birth. Further development occurs postnatally through two bony processes, anterior and posterior, growing towards each other and forming the superior EAC and the inferior foramen tympanicum (1, 2). The term foramen is a misnomer, as no nerves or vessels pass through it.

In adults, the persistence of foramen of Huschke defines an anatomical variation that may produce clinical and otological symptoms. The incidence of persistent foramen of Huschke has ranged from 3% to 25% in various studies and is now considered a normal developmental variant. Herniation of TMJ soft tissue into the EAC is also seen in one-fourth of cases and is directly related to the size of the defect. The opening can be enlarged with softening of the bony structures around the foramen of Huschke due to mastication, with greater soft tissue herniation over the years (2–5).

Patients with persistent foramen tympanicum can be asymptomatic or can present with complaints of otalgia, otorrhea (during mastication), and soft tissue mass protruding through the EAC. The mass may be visible only with a closed mouth and may completely disappear when the mouth is open because the soft tissues retract. During mastication, ear discharge occurs because of connection of the foramen with the TMJ or connection of the fistula with the parotid gland. Minor trauma or surgical insult can result in destruction of the tympanic bone at this level.

HRCT is an excellent technique to detect foramen tympanicum because of its high spatial resolution, sharp bony algorithm, and thin sections. Although the typical location of the bony defect is considered diagnostic, if there is clinical suspicion, a variable degree of retraction of the soft tissue into the TMJ can be demonstrated on open mouth CT.

In symptomatic patients, surgical closure of the foramen may be required (2). Foramen tympanicum can cause complications during otoscopy as the endoscope can go into the opening of the foramen and cause injury to the TMJ. If inadvertent biopsy is attempted at otoscopy, it can cause TMJ damage and fistula formation. In our case, due to the patient’s advanced age and minor symptoms, no surgical intervention was pursued.

Anticonvulsant hypersensitivity syndrome secondary to carbamazepine

Shannon C. Brown, MD, and Robin L. Dauterive, MD

Anticonvulsant hypersensitivity syndrome (AHS) is a potentially fatal multiorgan drug reaction that presents with various cutaneous eruptions. There is a genetic predisposition to such reactions. We present a young woman with AHS due to carbamazepine that presented as an atypical erythema multiforme with elevated liver enzymes.

CASE DESCRIPTION

A 30-year-old white woman with a history of bipolar disorder, congenital heart disease, and migraines was admitted to the hospital with complaints of a generalized, painful rash, nausea, vomiting, facial edema, and malaise. The lesions started on her ears and arms and progressed to involve her entire body. Approximately 6 days prior to the onset of the rash, she was started on carbamazepine for bipolar disorder. She was seen 2 days later at an outside facility for a migraine and prescribed propranolol and an oral methylprednisolone 6-day taper starting at 24 mg a day. A few days later, she presented to the emergency department for urinary retention and nausea and was found to have a nondescript rash on her chest and upper extremities. The rash produced a burning sensation and was hypersensitive to touch. She was instructed to discontinue carbamazepine and was given a dose of diphenhydramine, ondansetron, and morphine and discharged on propoxyphene and ondansetron. Her rash continued to progress to involve her face, lips, abdomen, back, hands, and feet. She was seen again by her primary care provider, who instructed her to go to the emergency room to be admitted.

On the day of admission, she developed facial edema and worsening xerosis of the lips. Examination revealed multiple, deep red macules that coalesced into patches, predominantly on the upper extremities, chest, upper back, face, and ears. Some of the patches had dusky centers and developed edematous vesicles (Figure 1). There were more dispersed erythematous 3- to 5-mm macules located on her abdomen, lower back, upper thighs, distal fingertips, palms, and soles (Figure 2). There were no mucosal ulcerations or lymphadenopathy. Associated symptoms included nausea, nonbloody emesis, arthralgia, back pain, dyspnea, and nonproductive cough. She denied fevers but reported chills. She was afebrile throughout her hospitalization.

Laboratory abnormalities included a mild thrombocytopenia (platelets of 133,000/mcL) and a mild increase in liver enzymes (aspartate transaminase, 57 U/L [normal, 0–40 U/L]; alanine transaminase, 75 U/L [normal, 0–69 U/L]). Dermatology performed a 4-mm punch biopsy from the left upper extremity that showed interface dermatitis with areas of full-thickness epidermal necrosis. Given the lack of mucosal involvement and typical targetoid lesions on exam, she was diagnosed with an atypical erythema multiforme, likely secondary to carbamazepine. She was treated with methylprednisolone 60 mg intravenously every 6 hours for 2 days, then changed to oral prednisone 60 mg daily. Her prednisone was tapered over 6 days and discontinued upon discharge. She was also prescribed topical triamcinolone 0.1% ointment twice a day from the neck down and daily to her face for a total of 14 days. Her rash significantly improved over the next 2 weeks. Desquamation, specifically of the ears, palms, and soles, occurred with resolution of the rash.

From the Department of Internal Medicine, Baylor Scott & White Hospital, Temple, Texas.

Corresponding author: Robin L. Dauterive, MD, FHM, Clinical Assistant Professor, Texas A&M Health Science Center, Department of Internal Medicine, Baylor Scott & White Hospital, 2401 South 31st Street, Temple, TX 76508 (e-mail: Robin.Dauterive@BSWHealth.org).
Her half-sister and her father also had bipolar disorder. When her sister was visiting, she reported a similar reaction to carbamazepine, and her father noted the same reaction when asked. This incidentally acquired family history led to the diagnosis of AHS. Using the World Health Organization’s classification for adverse drug reactions, this case would be categorized as a “probable” causal relationship, given the family history of similar responses to the same medication and her response to withdrawal of the medication. The patient and her family were instructed to avoid all cross-reactive medications in the future.

DISCUSSION

AHS was first described in 1950. Recently, there has been a movement to reclassify AHS under the broad term “drug-induced hypersensitivity syndrome,” which would also include drug reaction with eosinophilia and systemic symptoms, hypersensitivity syndrome, and drug-induced delayed multiorgan hypersensitivity syndrome. Eosinophilia is not a requirement for any of these conditions. Fever and malaise frequently precede the skin lesions. The skin eruption of AHS is nonspecific and can range from a morbilliform eruption to toxic epidermal necrolysis (1).

Hypersensitivity reactions are common with anticonvulsants. The mechanism of these reactions is thought to be secondary to toxic drug metabolites. Aromatic anticonvulsants are metabolized by cytochrome P-450 to intermediate metabolites such as arene oxides, which are detoxified by epoxide hydroxylase. If there are defects in metabolism, these toxic metabolites may cause cell necrosis or apoptosis and induce secondary immunological responses (2). Patients should be advised to avoid all aromatic anticonvulsants and tricyclic antidepressants, as cross-reactivity may be as high as 75%.

Patients may be predisposed to hypersensitivity reactions through various genetic factors. The genetic allele HLA-A*3101 has been associated with carbamazepine-induced cutaneous drug reactions in many different populations (3). For example, >15% of Japanese, Native American, and Southern Indian patients are thought to carry this allele (3). Unfortunately, testing for HLA-A*3101 yields a high false-positive rate (2).

Treatment for hypersensitivity syndromes is primarily supportive after discontinuation of the offending agent. Systemic corticosteroids are frequently used, although there have been no clinical trials to prove efficacy. Steroid-sparing agents have also been used with success in other hypersensitivity reactions. Relapse is common given the high cross-reactivity among anticonvulsants.
While hypersensitivity drug reactions are well known, the hereditary component of AHS remains unfamiliar to physicians who prescribe anticonvulsants, as demonstrated by our case. Given the high rate of HLA-A*3101 carriers worldwide, improving physician awareness of AHS is essential in decreasing the preventable serious morbidity in family members of affected patients.

Avocations

“Nesting egret.” This image was taken in March 2016 at the egret nesting ground in the northwest corner of the Southwestern Medical Center campus in Dallas, Texas. Photo © Rolando M. Solis (rmsolis@mac.com), an interventional cardiologist at Baylor Scott and White Health Garland and The Heart Hospital Baylor Plano.
Ruptured ectopic pregnancy with a negative urine pregnancy test

Mallory Hughes, MD, Andrew Lupo, and Adrianne Browning, MD

Ectopic pregnancy is commonly seen as a differential diagnosis of first-trimester vaginal bleeding. Often the diagnosis is made based on a combination of exam findings, transvaginal ultrasound, and a positive pregnancy test. Our case describes a patient with a history of ectopic pregnancy treated with methotrexate and serial human chorionic gonadotropin measurements that were decreasing appropriately. At the time of evaluation, her urine pregnancy test was negative; however, she was confirmed to have a ruptured tubal ectopic pregnancy. This case highlights the variable presentation of ectopic pregnancies and the importance of combining exam findings with ultrasound and laboratory results.

Ruptured ectopic pregnancies are gynecologic emergencies that require prompt surgical evaluation. Diagnosis of an ectopic pregnancy includes history and exam findings, ultrasound evidence, and an elevated beta–human chorionic gonadotropin (hCG) level. This case of a ruptured ectopic pregnancy without an elevated beta-hCG is presented to emphasize the importance of clinical judgment in acute gynecologic settings.

CASE DESCRIPTION

A 25-year-old gravida 2 para 0 female with a history of ectopic pregnancy presented to the emergency department with sharp, right lower abdominal pain for 24 hours associated with near syncope. Three weeks earlier she was diagnosed with possible ectopic pregnancy. Due to an inappropriate rise in hCG, she had been given methotrexate. During the 2 weeks before admission, her hCG levels had gradually declined but had not reached zero. She had been sexually active after her diagnosis and took oral contraceptives, and her partner wore condoms.

On exam she was awake, alert, and in no distress. Her temperature was 98.6°F; heart rate, 99 beats per minute; blood pressure, 124/60 mm Hg; respiratory rate, 14 breaths per minute; and oxygen saturation, 99% on room air. There was tenderness to palpation in the left and right lower quadrants with voluntary guarding, but no distension or rebound tenderness. Bimanual examination revealed cervical motion tenderness and right adnexal and uterine tenderness. The uterus was small and anteverted. The speculum examination revealed scant white discharge without bleeding. The cervical os was closed.

Laboratory studies showed a white blood cell count of 5.9 K/uL; hemoglobin, 10.9 g/dL; and hematocrit, 33.8%. A urine pregnancy test was negative, and a serum hCG of 15 mIU/mL was within normal limits. An ultrasound showed a normal uterus and a 4 × 2.6 × 4.6 cm heterogeneous right adnexal mass with free fluid (Figure 1). Ruptured ectopic pregnancy was suspected despite a negative pregnancy test.

The patient was taken to the operating room for a diagnostic laparoscopy. Exam under anesthesia disclosed a fluid wave on the abdomen. On entry to the abdomen, 500 mL of blood was found. The right fallopian tube was disrupted, and a clot with products of conception was extruding through the opening (Figure 2). A right salpingectomy was performed with excellent hemostasis. The ovaries and uterus were normal. The patient tolerated the procedure well and was discharged home on the day of surgery in stable condition. An ectopic pregnancy was confirmed by pathologic examination.

DISCUSSION

Ectopic pregnancies in which the zygote is implanted outside the endometrial cavity comprise 2% of all pregnancies (1) and often present with vaginal bleeding or abdominal pain. The condition is diagnosed by a transvaginal ultrasound and elevated hCG, as recommended by the American Congress of Obstetricians and Gynecologists (2, 3). A combination of ultrasound and hCG has a 96% sensitivity and 97% specificity for ectopic pregnancy (1). Commonly in ectopic pregnancy, the hCG is elevated and increases abnormally, rising <53% in 48 hours (4). In the case described herein, however, ultrasound findings were concerning for hemoperitoneum. The patient’s history of ectopic pregnancy and physical exam prompted surgical management despite a negative pregnancy test.
Daniilidis et al described similar findings. Since 1987, eight cases of ruptured ectopic pregnancy have been reported with a negative urine pregnancy test. These patients were taken to the operating room for suspected hemoperitoneum (5). These cases and ours suggest that ectopic pregnancy should be considered even with a negative pregnancy test.

Our patient previously had methotrexate. Current recommendations for methotrexate therapy in ectopic pregnancy include a single or multidose regimen in patients who are hemodynamically stable and have no medical contraindications for methotrexate. Surveillance after methotrexate includes serial hCG levels. Treatment failure is defined as failure of hCG to decrease by at least 15% from day 4 to day 7 after treatment (2). Recommendations include following hCG weekly after 7 days until levels are negative. Our patient had regular follow-up with reported decreasing hCG levels, but they did not reach zero.

This highlights the importance of combining physical exam findings with hCG levels to ensure successful management of ectopic pregnancies.

Electromyogram-evoked focal myositis

Avery Smith, MD, George Snipes, MD, and Carolyn Quan, MD

Focal myositis is a rarely reported inflammatory disease of skeletal muscle, particularly of an extremity. It is often misinterpreted as an infectious syndrome, leading to prolonged antibiotic use and a delay in immunosuppressive therapy. Without a confirmed etiology to date, we present a case of recurrent focal myositis following an electromyogram.

A 74-year-old black man with prior chronic obstructive pulmonary disease and hypertension presented with a 3-day history of right calf swelling, dark discoloration, and pain. These symptoms began abruptly and were independent of any inciting trauma, fever, chills, or skin breakdown. The pain was localized within the calf muscle and worsened with dorsiflexion of the foot. He was hemodynamically stable and afebrile. Physical examination was unremarkable with no additional lesions or apparent muscle weakness. The erythrocyte sedimentation rate was 40 mm/hr with a C-reactive protein level of 7 mg/dL. The white blood cell count and creatinine kinase level were within normal limits. Magnetic resonance imaging demonstrated inflammation of the gastrocnemius muscle concerning for myositis (Figure 1a). Antibiotics were initiated but blood cultures returned negative. The right calf swelling, discoloration, and tenderness persisted. Antinuclear antibody was positive at a titer of 1:1280, and a myositis-specific antibody panel was performed. It revealed negative anti-Mi-2, PL-7, PL-12, EJ, OJ, Ku, and U2 snRNP antibodies. In addition, antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase were not present. Muscle biopsy disclosed superficial necrosis but normal muscle tissue and fascia within centimeters of exploration. Extracellular edema was present without overt signs of infection or hematoma formation. Microscopic examination of the muscle tissue revealed viable muscle and small numbers of lymphocytes that stained negative for IgG4 (1). In addition, scattered eosinophils were present but not in significant numbers. Gram stain and acid-fast and fungal stains were negative. There was marked variation in myofiber size (Figure 1d) along with CD163-positive macrophages located within the perimysium (Figure 1c).

Given his positive antinuclear antibody, methylprednisolone was started. Rheumatoid factor, ANCA, anti-Jo, anti-Ro, anti-La, anti-Smith, anti-RNP, anti-Scl70, anti-smooth muscle and anti-striated muscle antibodies were all within normal limits or negative. However, there was a positive result for an anticentromere antibody.

A potential neoplasm was ruled out with negative esophagogastroduodenoscopy, colonoscopy, serum and urine electrophoresis, and computed tomography scans of the chest, abdomen, and pelvis. An electromyogram revealed slightly increased polyphasic potentials and abnormal spontaneous activity in the left anterior tibialis and gastrocnemius muscles. Otherwise, all remaining muscles showed no evidence of electrical instability or conductive disorders. Following the electromyogram, the patient developed three new focal lesions. These were similar in appearance to the initial lesion on admission but were not as severely swollen. They were located in the left gastrocnemius, left deltoid (Figure 1b), and left abductor pollicis brevis muscles. Each of these muscles had overlying skin discoloration and a pain that worsened by muscle contraction. His erythrocyte sedimentation rate was 100 mm/hr despite the high-dose methylprednisolone. Rituximab infusions were initiated with subsequent resolution of the lesions. Ultimately, he was discharged to a skilled nursing facility and has not had recurrent lesions after 2 years.

CASE DESCRIPTION

A 74-year-old black man with prior chronic obstructive pulmonary disease and hypertension presented with a 3-day history of right calf swelling, dark discoloration, and pain. These symptoms began abruptly and were independent of any inciting trauma, fever, chills, or skin breakdown. The pain was localized within the calf muscle and worsened with dorsiflexion of the foot. He was hemodynamically stable and afebrile. Physical examination was unremarkable with no additional lesions or apparent muscle weakness. The erythrocyte sedimentation rate was 40 mm/hr with a C-reactive protein level of 7 mg/dL. The white blood cell count and creatinine kinase level were within normal limits. Magnetic resonance imaging demonstrated inflammation of the gastrocnemius muscle concerning for myositis (Figure 1a). Antibiotics were initiated but blood cultures returned negative. The right calf swelling, discoloration, and tenderness persisted. Antinuclear antibody was positive at a titer of 1:1280, and a myositis-specific antibody panel was performed. It revealed negative anti-Mi-2, PL-7, PL-12, EJ, OJ, Ku, and U2 snRNP antibodies. In addition, antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase were not present. Muscle biopsy disclosed superficial necrosis but normal muscle tissue and fascia within centimeters of exploration. Extracellular edema was present without overt signs of infection or hematoma formation. Microscopic examination of the muscle tissue revealed viable muscle and small numbers of lymphocytes that stained negative for IgG4 (1). In addition, scattered eosinophils were present but not in significant numbers. Gram stain and acid-fast and fungal stains were negative. There was marked variation in myofiber size (Figure 1d) along with CD163-positive macrophages located within the perimysium (Figure 1c).

Given his positive antinuclear antibody, methylprednisolone was started. Rheumatoid factor, ANCA, anti-Jo, anti-Ro, anti-La, anti-Smith, anti-RNP, anti-Scl70, anti-smooth muscle and anti-striated muscle antibodies were all within normal limits or negative. However, there was a positive result for an anticentromere antibody.

A potential neoplasm was ruled out with negative esophagogastroduodenoscopy, colonoscopy, serum and urine electrophoresis, and computed tomography scans of the chest, abdomen, and pelvis. An electromyogram revealed slightly increased polyphasic potentials and abnormal spontaneous activity in the left anterior tibialis and gastrocnemius muscles. Otherwise, all remaining muscles showed no evidence of electrical instability or conductive disorders. Following the electromyogram, the patient developed three new focal lesions. These were similar in appearance to the initial lesion on admission but were not as severely swollen. They were located in the left gastrocnemius, left deltoid (Figure 1b), and left abductor pollicis brevis muscles. Each of these muscles had overlying skin discoloration and a pain that worsened by muscle contraction. His erythrocyte sedimentation rate was 100 mm/hr despite the high-dose methylprednisolone. Rituximab infusions were initiated with subsequent resolution of the lesions. Ultimately, he was discharged to a skilled nursing facility and has not had recurrent lesions after 2 years.

DISCUSSION

Focal myositis was first described in 1977 by Reid Heffner Jr. He described 16 cases of myositis within a muscle group of an extremity. The myositis was not preceded by trauma or related to...
infection, but appeared to be a benign pseudotumor of skeletal muscle. Creatinine phosphokinase and lactate dehydrogenase levels were within normal limits, and the erythrocyte sedimentation rate was normal in 10 of the 16 patients. The muscle demonstrated no significant areas of necrosis, hemorrhage, or calcification. However, a “pale, ovoid and poorly defined area” of muscle was described in 11 of the 16 cases. Histologically, there was striking variation in muscle fiber size, with no predominance of fiber type. Phagocytic activity within the muscle fibers was often intense, and inflammatory infiltrates, particularly lymphocytes, were overshadowed by the myopathic fiber changes. Treatment in Heffner’s study was primarily surgical, but 8 cases simply had a muscle biopsy alone. None of the patients developed signs of systemic disease or diffuse muscle involvement. Based on these findings, Heffner speculated that, despite no obvious trauma, a subclinical internal injury was responsible for the condition (2).

Diagnosis of focal myositis in our patient was based upon the clinical manifestation of focal inflammation of a muscle group (3), elevated erythrocyte sedimentation rate, and exclusion of an alternative process. He did not have any proximal or distal muscle weakness to suggest polymyositis, dermatomyositis, or inclusion myositis. Furthermore, the myositis-specific antibody panel ruled out those syndromes. Antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase evaluated for a potential necrotizing myopathy associated with statin exposure (4), but was negative.

A unique aspect of our patient’s myositis was the provoked recurrence of the disease. The electromyogram revealed focal muscle irritability, but there was no evidence of a diffuse myopathic disorder. Nonetheless, the micro trauma of the procedure potentially provided a stimulus for a myositic event. Other case reports of focal myositis mentioned the use of an electromyogram (5), but did not report an incidence of induced myositic changes. Thus, it is unclear why a recurrence of myositis was seen in our patient and if his autoimmune process increased the immune sensitivity to a specific muscular antigen. However, this incident at least reopens the discussion concerning Dr. Heffner’s suspicion that subclinical trauma played a role in inciting focal myositis.

Henry Barton Jacobs, William Osler’s intimate friend

Charles S. Bryan, MD

William Osler was considered a universal friend by physicians of his era but, as with most people, his intimate friends were few. Henry Barton Jacobs became a close friend as one of the “latchkeyers” who lived next door to the Oslers in Baltimore, and the friendship intensified after Jacobs married Mary Sloan Frick Garrett, the fabulously wealthy widow of a former patient. The couples stayed close after the Oslers moved to Oxford, vacationing together and corresponding frequently. The couple friendship between the Oslers and the Jacobses benefited American medicine in specific ways, including the care of patients with tuberculosis and the care of children.

William Osler (1849–1919) was considered a universal friend by physicians of his era but, like most people, chose his personal friends carefully. Likewise, William and Grace Revere Osler as a couple entertained often but, like most couples, had few close couple friends. Three observations about Dr. Henry Barton Jacobs (1858–1939) prompted this study: 1) Jacobs was among the three “latchkeyers” who lived next door to the Oslers (1); 2) Harvey Cushing relied heavily on Osler’s letters to Jacobs for the second volume of The Life of Sir William Osler (2, 3); and 3) the Oslers and Jacobses often vacationed together (4). Archival material sheds light on this friendship and on the nature of couple friendships (5).

THE GARRETTES

The story begins with a Robert Garrett (1783–1857), who came to America from County Down, Ireland, in 1790 at age 7. At age 16, he joined his older brother in a trading expedition among the Indians, which took him over the Alleghenies and into the Ohio River Valley, where he spent a cold winter in an Indian hut. In 1801 he moved to Baltimore and took a job as a clerk. As the Conestoga wagon trails morphed into railroads, Robert Garrett foresaw that Baltimore’s competitive advantage lay beyond the Alleghenies, rather than north–west in competition with Philadelphia and New York. His enterprises made him one of Baltimore’s wealthiest and most useful citizens, but he was surpassed in both respects by his third son, John Work Garrett (1820–1884). After joining his father’s firm, John Work Garrett bought shares in the Baltimore and Ohio Railroad (B&O) and was elected to the board of directors in the midst of the financial crisis known as the Panic of 1857. The directors debated the troubled railroad’s future. Garrett offered a bold vision and was elected president by a narrow vote after a motion by the largest shareholder, Johns Hopkins. John Work Garrett became the most powerful man in Maryland, and it was later said that “no American ever did more for his city” than he did for Baltimore (6). It was John Work Garrett who enlisted George Peabody to persuade Hopkins to establish through his will a university and hospital, eventuating in the Johns Hopkins University in the Homewood section of Baltimore and the Johns Hopkins Medical Institutions on what was formerly known as Loudenslager’s Hill (7). John Work Garrett died in 1884, leaving an estate valued at $3.7 billion in today’s currency.

The second Robert Garrett (1847–1896) succeeded his father as president of the B&O, endeared himself to the employees (unlike his father, who had exploited them), and did much for his city. But by the mid-1890s the second Robert Garrett was a sick man, apparently from kidney disease. In 1886 his physician advised an extended trip. Garrett went west with a group of friends in private rail cars. Reaching San Francisco, he decided to extend the trip around the world, for which he needed a personal physician (6). Enter Henry Barton Jacobs.

HENRY BARTON JACOBS

Henry Barton Jacobs (1858–1939) (Figure 1) was born in a small village on Cape Cod, attended Phillips Exeter Academy and then Harvard College and Harvard Medical School, interned at Massachusetts General Hospital, and practiced briefly in Boston before becoming personal physician to Robert Garrett. In 1897, after the entourage returned to Baltimore from their world tour, Jacobs chose to stay on and moved in with the Garretts. It was the ultimate concierge practice—a single, ultra–rich patient—but not an easy one, as Garrett by then had mental as well as physical illness. After Garrett died in 1896, Jacobs, who had become especially interested in tuberculosis, became more closely associated with the Johns Hopkins Hospital and its medical school.


Corresponding author: Charles S. Bryan, MD, 6222 Westshore Road, Columbia, SC 29206-2121 (e-mail: cboslerian@gmail.com).
Jacobs and William Sydney Thayer moved into the four-story house at 3 West Franklin Street, next door to the Oslers, and thus became the original “latchkeyers”—young physician-bachelors to whom Osler gave keys to his home at 1 West Franklin Street so that they could access his library as they pleased. After Thayer married, Harvey Cushing and Thomas Barnes Futcher moved in. A hole was cut in the fence between the two houses so that Osler could use the latchkeyers’ telephone, as he resisted the nuisance of having one himself (8). Futcher and Cushing knew Jacobs as “Jake” or “the Bearded One” (1). Osler nicknamed him “Baron von Jacobus,” which Grace Osler shortened to “Jacobus.” In 1902 wedding bells, first for Jacobs and then for Cushing, broke up the latchkeyers. Jacobs married Robert Garrett’s widow. Cushing married Kate Crowell and commandeered 3 West Franklin Street.

THE OSLERS AND THE JACOBSES
Jacobs’s marriage to Mary Sloan Frick Garrett (Figure 2) evokes Osler’s marriage to Grace Revere Gross a decade earlier: a physician remained a bachelor until his early 40s and then married to his great advantage the widow of a former patient in a private ceremony that caught most of their friends by surprise. In Jacobs’s case, shockwaves rippled up and down the Eastern Seaboard, for Mary Sloan Frick Garrett was among the wealthiest and most socially prominent women in the United States. Daughter of “the Nestor of the Maryland bar,” she enjoyed a sheltered upbringing, became one of the most popular girls in Baltimore and Newport, Rhode Island, and, as an adult, was known as “the Mrs. Astor of Baltimore’s 400,” the ultimate social arbiter. To have her bow to one at the opera, at the races, or at any other social event was to have one’s social position acknowledged; to have her show up at a party for even a few minutes declared the evening a success; and to be invited to her home proved that one had “arrived.” She epitomized the excesses of America’s Gilded Age. Whenever she took a transatlantic steamer she had her suite fitted with draperies and other furnishings from one of her three homes: a 39,200-square-foot mansion in Mt. Vernon Place (the finest in Baltimore, containing among other things a world-class art collection and a ballroom); a country estate; and a second mansion in Newport. She also kept at various times an apartment in New York’s Plaza Hotel and a chateau in France. The prenuptial contract specified that neither husband nor wife could lay claim to the other’s property and that each could dispose of their properties as they saw fit. Despite, or perhaps because of, this stipulation, it was reported in a gossip column that “Dr. Henry Barton Jacobs is the most devoted husband in Newport. He seems unable to do enough for his wife, and waits on her hand and foot” (9).

Archival records document a quadrangular relationship among the two couples well before Jacobs’s marriage to Mary Sloan Frick Garrett. Thus, Osler sent condolences to Mrs. Garrett upon the death of her first husband (10) and thanked...
her for strawberries that “came just in time to astonish two northerners who were breakfasting with us” (11). Grace Osler wrote Jacobs in 1895, before he became a latchkeyer: “You have been so indulgent and good. I hardly know how to thank you” (12). And in 1901 Grace wrote Jacobs, “Do give my love to Mrs. Garrett if at home” (13).

The strongest bond was naturally between the two men, both well-educated physicians with special interest in tuberculosis. Jacobs like Osler was energetic, extroverted, colorful, athletic (having rowed on an 1883 Harvard crew that defeated Yale), thoughtful, and moved easily and gracefully whatever the social setting. Both men enjoyed golf, tourism, and book collecting. They informed each other of rare books and of sales at Sotheby’s in their areas of concentration, which for Jacobs included everything about tuberculosis and about Laennec, and nearly everything about Samuel Johnson, Edward Jenner, and Louis Pasteur (14). In 1903, when Osler and Jacobs were in Paris, Jacobs commissioned Frederic Charles Victor de Vernon (1858‒1912) to make a bronze medallion of Osler, resulting in the relief widely known as the Vernon plaque (15). Jacobs recalled that Osler became “boyish” on vacations (4), which was no doubt encouraged by Jacobs’s own playfulness. He belonged, for example, to an exclusive fishing club in Newport where, being out of sight of the mainland, the men “could swim as they did when they were boys” (16).

Typical of male friendships, Osler and Jacobs focused on activities rather than feelings. Grace Osler, as women are wont to do, showed less restraint. Whereas Osler’s salutations to Jacobs usually read “Dear Jacobs,” Grace confided to “Jacobus” frustrations with her husband’s bibliomania and propensity to charge large fees so that he could buy expensive books. Thus in July 1901 she wrote Jacobs, “He [Dr. Osler] has a consultation in the country next week and the fee will cover many indiscretions” (17), and 3 weeks later she expressed annoyance that her husband “became utterly disgusted at every place where old books were not forthcoming and promptly wanted to leave” (18).

Osler seldom expressed feelings to the new Mrs. Jacobs, as would be appropriate since they were about the same age. She, on the other hand, sent Osler rare books for himself and for the libraries he supported. The two women corresponded often and warmly. Both liked to entertain large groups and were conservative in their worldviews, and in Grace Revere Osler the new Mrs. Jacobs no doubt recognized a fellow patrician.

Couple friendships sometimes necessitate choosing sides in family quarrels, which possibly explains why neither Osler nor his wife became close to Mary Elizabeth Garrett, who was the second Robert Garrett’s younger sister and therefore Mary Frick Jacobs’s sister-in-law. They could not have been more different. Mary Elizabeth Garrett had no interest in “society,” never married, and became a notable proto-feminist. As is well known, Mary Elizabeth Garrett led the Women’s Medical School Fund that made possible the opening of the Johns Hopkins University School of Medicine. Her sister-in-law did all she could to dissuade her wealthy friends from contributing to the Women’s Medical School Fund, and she later served as president of the Baltimore chapter of the Association Opposed to Woman Suffrage, thus countering another cause célèbre of Mary Elizabeth Garrett.

Osler appreciated Mary Elizabeth Garrett for spearheading the Women’s Medical School Fund and also for conceiving and funding John Singer Sargent’s portrait, The Four Doctors (1905). She apparently did not warm to Osler as much as she did to the other portrait-sitters: the pathologist William Henry Welch, the gynecologist Howard Atwood Kelly, and the surgeon William Stewart Halsted, who was her close personal friend and also one of her physicians. After Mary Elizabeth Garrett died, Jacobs joined a lawsuit brought by his wife and other Garrett family members against M. Carey Thomas, Mary Elizabeth Garrett’s longtime partner to whom she left most of her estate. They ultimately lost (19). Whether the Oslers would have been close to Mary Elizabeth Garrett had it not been for the feud among the siblings is, of course, speculative.

Mary Frick Jacobs had no children by her first marriage and, being 52 at her second marriage, was destined to be childless. She compensated by chatting frequently with children, whether rich or poor, by throwing an annual Christmas party for the messenger boys of Baltimore, and by establishing the Robert Garrett Hospital for Children. She paid for the children to recuperate in Mount Airy, Maryland, during the summer months, and she paid for railway fares for mothers to visit their children whenever they liked. She and her husband cherished their relationship with Edward Revere Osler, the Oslers’ only surviving child.

Jacobs served Revere as a quasi-godfather (the Canadian-born Tom Fitcher was the actual godfather) from cradle to grave and beyond. He sent Grace Osler roses and a picture frame at Revere’s birth; wrote letters to Revere from early childhood onwards, to which Revere replied when he became able to write (Figure 3); never failed to send a Christmas present; and stayed close to the end as evinced by a letter Revere sent from the trenches in Flanders just 2 months before he was killed by a German artillery shell. The letter reads in part:

We only came out of action the other day and this is really the first chance I have had to write any letters except those of course to Mum & Dad…. I am hoping to get home at the end of this month for ten days but at present all leave is on a standstill and I am beginning to fear that I will have to wait longer. It will be the greatest pleasure I have ever had to get home again after these last four nightmares of months…. I wish you could see my Waltoniana [books pertaining to Sir Izaak Walton] (20).

Two days after Revere’s death, Osler wrote the Jacobses that he wished he “could have spared them the grief the sad news would bring,” adding that after a life of good fortune the Fates had finally hit him, and saying of Revere that “he had not the heart to shoot a partridge” (21). The Oslers turned to Jacobs for assistance in carrying out their plans for the Tudor and Stuart Club at Johns Hopkins in their son’s memory (22).

The Great War interrupted the Jacobs’s summer trips to England and the Oslers’ trips to America where they had sometimes stayed at the Jacobs’s mansions in Baltimore or Newport. Still, they kept in close touch. When William Osler died on
December 29, 1919, Grace telegraphed the Jacobses at once and later informed them of the “funeral Thursday three fifteen Christ Church” (23). On overnight notice Jacobs arranged a memorial service for Osler at Old St. Paul’s Protestant Episcopal Church in Baltimore at the same time services were being held at Oxford. Three weeks later, Grace sent “Dearest Jacobus and Mary” a moving account of the funeral. She confided that she was “much fatigued” and felt like “a stranded ship” (24). A month later she wrote: “Some days I feel so oppressed with the struggle that I can hardly endure it. How I wish I could see you” (25). A year later she asked Jacobs:

Any chance of you two dear people coming over? I do not feel I can leave home while the books are still [here] but I may screw up courage some day. I am a poor old coward dear Jacobus—and hate being away from 13 Norham Gardens (26).

She never returned to the United States, feeling trapped at home by the need to get Osler’s books catalogued. She died in 1928 (27).

CONTRIBUTIONS TO MEDICINE

Henry Viets wrote in his obituary of Jacobs: “The enormous wealth of the Garrett family put him in a unique position in American medicine, a position he held with great charm and extraordinary tact” (16). Although Jacobs participated fully in Baltimore’s social and cultural life, supported the Garrett family philanthropies, and helped his wife in her art collecting and other interests, he remained committed to medicine, to Johns Hopkins, and, specifically, to the care of persons with tuberculosis. He was president of the Eudowood Sanatorium in what is now Towson, for which his wife funded and equipped a separate hospital for children with tuberculosis. He and Osler were among the organizers of the National Foundation for the Study and Prevention of Tuberculosis (now the American Lung Association), which he served as secretary (he was president of the Maryland chapter) (28); he wrote important papers on tuberculosis (16, 29, 30); he chaired a committee to standardize the tuberculosis emblem (31); he celebrated Osler’s work on the disease (32); and he collected everything he could about tuberculosis, including newspaper clippings that now fill two large boxes at the Alan Mason Chesney Archives. His social conscience is evinced by his role in raising funds for a new hospital for African American residents of Greater Baltimore (33).

Mary Frick Jacobs died in 1936 after a long illness. She left a collection of 65 paintings, including works by Rembrandt, Frans Hals, and others, to the Baltimore Museum of Art contingent upon the museum’s building a wing to house the...
collection, now the Mary Frick Jacobs Wing. Nobody “quite filled her place” as the doyen of Baltimore society (34). Her will stipulated that Jacobs would receive an annuity of $100,000 per year (or $1.7 million in today’s currency) and that after his death two-thirds of the residual estate would go to the Robert Garrett Fund for the Surgical Treatment of Children. This fund supported much of Alfred Blalock’s research that led to the Blalock-Taussig procedure and continues to fund a full professorship in pediatric surgery at Johns Hopkins. The rest of her estate went toward converting and maintaining her country estate into a “home for lonely churchwomen.”

Jacobs and the other members of his Harvard crew remained sufficiently fit to row on the 50th anniversary of their victory over Yale. His health eventually failed and he died in 1939 at age 77. His gave his collection of some 5000 books and numerous prints, medals, and other objects to the Institute of the History of Medicine at Johns Hopkins, where many of these items are now housed in the Henry Barton Jacobs Room (Figure 4).

ACKNOWLEDGMENTS

I thank Nancy McCall and Andrew Harrison of the Alan Mason Chesney Medical Archives, The Johns Hopkins Medical Institutions; and Zoe Gensheimer of the Baltimore Museum of Art.

10. William Osler to Mary Sloan Frick Garrett, undated, Jacobs Papers.
17. Grace Revere Osler to Henry Barton Jacobs, 14 July 1901, Jacobs Papers.
18. Grace Revere Osler to Henry Barton Jacobs, 7 August 1901, Jacobs Papers.
20. Edward Revere Osler to Henry Barton Jacobs, 6 March 1917, Jacobs Papers.
22. Grace Revere Osler to Mary Frick Garrett Jacobs, 18 November 1918, and Grace Revere Osler to Henry Barton Jacobs, 22 February 1921, Jacobs Papers.
23. Cable dated 31 December 1919, Jacobs Papers.
33. Newspaper clipping, untitled, undated, Jacobs Papers.
The purpose of this study was to describe the historical importance of a 1911 European hospital postcard sent from one American physician to another. In the late 19th and early 20th centuries, very few formal residency programs existed in America for training physicians. Most authors rightfully emphasize Johns Hopkins Hospital, founded in 1889, as the site of origin of the American medical residency, but these positions were for a chosen few. Many young physicians would go abroad to study medicine after completing medical school, a decision with many benefits and few drawbacks. At least 15,000 Americans took some kind of medical training in Austria-Hungary, Germany, and Switzerland between 1870 and 1914. Dr. Frank F. Hutchins took such a trip to Europe. On March 12, 1911, Dr. Hutchins wrote a postcard from Queen Square, London, to Dr. Allison Maxwell admiring the positive attributes of The National Hospital for the Paralysed and Epileptic. This trip would serve to shape Dr. Hutchins’ subsequent career and would influence the future of the Indiana University School of Medicine, neuropsychiatry in the US military, and the care of veterans.

In late 19th and early 20th century America, very few formal residency programs existed for training physicians. In the 1870s, there was no institution in the United States where a graduate physician could go to perfect his knowledge of any branch of medicine or learn the techniques required for medical research. No postgraduate education was available, and laboratories were sparse. The state of US medical practice in the late 19th century was underwhelming at best; there were scores of poorly trained physicians, and medical education was not standardized. Medical practice in America, in comparison to Europe, was practical and highly commercialized. Many of the problems surrounding American medicine were related to the nation’s sluggishness in developing a cultural climate in which scientific medicine could flourish (1).

Most authors rightfully emphasize Johns Hopkins Hospital, founded in 1889, as the site of origin of the American medical residency, but these positions were for a chosen few. Many young physicians would go abroad to study medicine after completing medical school, a decision with many benefits and few drawbacks. Entry to European universities was not difficult, especially for men with prior education, and travel costs were modest. Some ambitious students decided to pursue general medical training in the United States through an internship and follow that up with specialized postgraduate training abroad in Europe. A number took a “grand tour” of Europe, visiting numerous medical centers (2). At least 15,000 Americans took some kind of medical training in Austria-Hungary, Germany, and Switzerland between 1870 and 1914 (1). Although the German-speaking countries had more organized courses for American physicians, postgraduate education could also be obtained in London and Paris, among other cities (3, 4). In Honani Handbook to Medical Europe (published in 1912), over 50 pages describe postgraduate training opportunities in London, including those available at The National Hospital for the Paralysed and Epileptic (4).

On March 12, 1911, Dr. Frank F. Hutchins wrote a postcard from Queen Square, London, United Kingdom to Dr. Allison Maxwell, extolling the positive attributes of The National Hospital for the Paralysed and Epileptic (Figures 1 and 2). Dr. Hutchins (Figure 3) was on a trip to Europe alongside Dr. Burton D. Myers, professor of anatomy at Indiana University. This trip would shape Dr. Hutchins’ subsequent career. It also influenced the future of the Indiana University School of Medicine, neuropsychiatry in the US military, and the care of veterans.

HUTCHINS’ VISIT TO THE NATIONAL HOSPITAL FOR THE PARALYSED AND EPILEPTIC

Drs. Hutchins and Myers went to Europe on a grand tour with a particular focus on the study of neurologic conditions (5, 6). Hutchins visited Zurich, Berne, Vienna, Leipzig, Dresden, Paris, and London (7). On Hutchins’ trip, they stopped at The National Hospital for the Paralysed and Epileptic in Queen Square, London. Dr. Hutchins remarked that the National Hospital was “one of the few hospitals devoted exclusively to neurological disease” and that it had “large laboratories for research.” He mentioned that he had the opportunity to learn from the work of “such men as Sir Victor Horsley, Sir William Gowers, Sir David Ferrier, [John Hughlings] Jackson, [William Aldren] Turner, [Thomas Grainger] Stewart, [James Samuel Risien] Russell, [Howard] Tooth, [James Taylor, [Fredrick] Batten, [Gordon] Holmes.” Hutchins wrote in the postcard that “it is a great harvest for me, and I am trying
to improve every moment of the opportunity…. Everyone is very cordial to me, we are well, comfortable, and getting the full enjoyment and profit of our trip.”

At the birth of the National Hospital in 1860, the field of neurology was still in its infancy. Over the course of medical history, there were descriptions of neurological conditions by individuals such as Hippocrates, Aristotle, Vesalius, and Boerhaave, all of whom contributed to the field (8). However, great strides in neurology were undertaken in the late 19th and early 20th centuries by many of the physicians named by Dr. Hutchins in his postcard.

Sir William R. Gowers made noteworthy contributions to neurology, including epilepsy, and was renowned for his clinical abilities, insight into the nature of disease, and keen observational skills. He was adept at discovering evidence overlooked

Figure 1. Front of the postcard. From the author’s (CJB) collection.

Figure 2. Back of the postcard. From the author’s (CJB) collection.

Figure 3. Dr. Frank Hutchins. Reproduced with permission of the Indiana University–Purdue University Indianapolis University Library Special Collections and Archives.
by others and synthesized large amounts of facts to come to his conclusions. Sir David Ferrier was one of the pioneers of experimental research on the nervous system and played a crucial role in furthering brain physiology. Dr. John Hughlings Jackson was an astute clinician who made significant strides in the study of epilepsy as well as disorders of language. These individuals were products of the industrious, research-driven clinical practice that characterized the National Hospital (8).

HUTCHINS’ CAREER AFTER THE GRAND TOUR

Dr. Hutchins would return to the US in 1911 and continue to be involved in neuropsychiatric studies, being named professor of mental and nervous diseases at the Indiana University School of Medicine. He led classes entitled “Disease of the Brain, Cord, and Peripheral Nerves” for second-year students and “Clinic at Central Hospital for the Insane” for senior-level students (9). These courses drew on some of the lessons Dr. Hutchins learned while abroad in Europe at the National Hospital. His work at Indiana University would continue with greater emphasis on leadership. In light of his experience learning in Europe, coupled with teaching at the medical school, the trustees of Indiana University appointed Dr. Hutchins to a panel charged with building a new medical school.

Dr. Hutchins was an enlisted major in the army during World War I; he joined the medical reserve corps at Fort Benjamin Harrison in August of 1917 and was later assigned to Fort Oglethorpe, Georgia, in November 1917. From there he was transferred to Camp Freemont, Palo Alto, California, where all American soldiers involved in the Siberian expedition passed under his inspection. Eventually in September of 1918, he was deployed to Europe and worked on Major General Helmick’s staff, commander of the Eighth Division, as a neuropsychiatrist (10). During his time in the army, he played an important role in the medical treatment of soldiers, both allied and enemy forces. Towards the end of his service (1919), Dr. Hutchins was promoted to the grade of lieutenant-colonel in the American Expeditionary Forces (11).

After Dr. Hutchins’ return to the US following the war, he continued his career in neuropsychiatry as superintendent and medical director of the National Sanatorium at Marion, Indiana (12). This center was established to treat psychiatric patients coming back from the war and was the first institution of its kind in Indiana. His tenure was short, as he retired in 1920 and was replaced by Dr. William MacLake.

Although he resigned from the National Sanatorium, Dr. Hutchins continued to remain involved in medicine, becoming director of clinical neuropsychiatry at the US Veterans Bureau. As director he was in charge of supplying medical care and treatment to veterans of the war, as well as creating programs for training nurses and physicians in neuropsychiatry (13). He continued to work there until his death in December of 1924.

ALLISON MAXWELL AND BURTON MYERS

This postcard serves as a link between three men who impacted the history of medicine in Indiana. Dr. Allison Maxwell, the recipient of the postcard, was the first dean of the Indiana University School of Medicine and led it through difficult times. He served as dean until 1911, a few months after this postcard was received (14). Dr. Hutchins played an instrumental role in the further development of the Indiana University School of Medicine, as did his travel partner Dr. Burton Myers (9). Dr. Myers moved from his professor of anatomy post to become the dean of the medical school from 1927 to 1940.

DISCUSSION

A single postcard from the past can provide insight into European postgraduate medical education for Americans in the early 1900s. The trip to Europe served as an important step in Dr. Hutchins’ education and helped shape his subsequent career. He became very involved in neuropsychiatry, taking on important positions in both the war as well as the recovery period after. He was a pioneer in military neuropsychiatry here in the US and helped train future health care providers in the field.

These postgraduate medical education trips were not without their critics. Louis Wilson, MD, of the Mayo Clinic visited Europe in 1911 to assess the efficacy of graduate medical education and was not impressed. Most of the criticism was directed at those without prior internship and practice experience and those who stayed only a short time and did not speak the native language (15).

The trip was more than just an educational feather in Dr. Hutchins’ hat; the trip to Europe embodied an important principle, something that would change the standards of American medicine. The trip Drs. Hutchins and Myers took not only taught them about neuropsychiatry but also gave them insight into the teaching models of Europe and of the culture of scientific medicine practiced there, which was not readily available nor universally accepted in the United States. Their trip helped shape the future of the Indiana University School of Medicine, both through the doctors’ teaching of students and through the development of the curriculum and vision of the school. While two men took this trip, countless other medical students, nurses, and allied health staff benefited from the result.

On becoming a physician

Kenneth G. Swan, MD†

Ken Swan practiced surgery for 46 years, serving with the US Army Medical Corps in both Vietnam and Desert Storm. After his army service, he joined the faculty of Rutgers Medical School, where he was director of the clinical clerkships at the time of his sudden death in 2014. Among his papers after his death, his son, Kenneth Jr. ("K. G."), found this address to incoming third-year medical students. At a symposium and gala honoring his dad in Newark on May 15, 2015, K. G. read it as a tribute to his father.

In your last 2 years of medical school, you progress from books to bedside; you’re given the title clinical clerk, young physician, physician in training; your patients will even call you doctor. You may be on the bottom rung, but it’s a splendid ladder, and you will work your way up it. The respect you get will be what you deserve—the respect you earn. The advice I have for you I give myself, today, even though I have been a physician in practice for many years. My advice concerns four areas. These are professionalism, collegiality, patient care, and self-care. They are equally important.

PROFESSIONALISM

A professional is paid for what he or she does, whether it is throwing a ball, flying an airplane, or wielding a scalpel. The true professional would do any one of these activities without pay, if necessary, because it is that love of the profession that generates the enthusiasm for it, not the financial reward associated with it. Be a professional and be proud of your profession because, wherever you go, you will be looked upon as one who walks a little taller. In our country, physicians still top the list of most respected and admired. You have a reputation to uphold; you are a role model even before you receive your MD degree and certainly afterwards. You will be judged by your behavior, your speech, your dress and, yes, your knowledge, but knowledge will be assumed.

Wear a nametag and introduce yourself to your patients; they have a right to know who you are. They will expect much of you. Even though you have been up all night, you do not have the right to look tired when your patient needs you. And even though you have just come from a great case in the ER or the OR, you do not have the right to wear blood spattered on your attire in the presence of your patients. It may seem “cool” at first, but it’s unprofessional, as are four-letter words and addressing your adult patient by his or her first name, unless requested to do so by the patient. Remember on becoming a physician to avoid those things unbecoming a physician.

Your profession has, is, and always will be giving to you, probably more than you can ever give to it, but you must give back as much as you can. You do this by teaching others what you know and what they don’t know, by your charitable activities beyond your personal practice, and by giving from the earnings from your profession to the source of your education. We are all professors, whether we carry the title or not, and we must always find time to educate others, patients included, in some way, about our profession. We spend so much time and effort and, yes, money too, learning our profession; it would be a shame not to share some of it. Where it’s needed most is where it’s easiest to give away, as close as your own home, as far away as a distant continent. My experience isn’t extensive, but my wife and I have enjoyed teaching advanced trauma life support to physicians in Ghana and Nigeria on several trips to Africa in recent years. I encourage you to do likewise.

In addition, I support my medical school financially, and I recruit fellow alumni to join me. This too is an obligation. These activities are part of professionalism, and we are all professionals once we grab hold of the ladder. Be a professional wherever you travel in medicine.

COLLEGIALITY

Like all good things in life, you will take from and must give back to your colleagues. Because you are one and they are many, you cannot ever give back as much as you receive; thus, you must strive to be a good colleague, one who is always willing to lend a hand or an ear, even a shoulder to cry on. Remember, ours is the toughest of all jobs and for a very simple reason. If we make a mistake we may lose face, lose self-confidence, lose money, even lose a job. That makes us akin to the businessman, the lawyer, the professional athlete, and those in many other vocations. But where we differ is in the final outcome of our—but not their—mistakes. We may compromise the health, or even lose the life of our patient, who has entrusted his life to us.

†Deceased. Kenneth G. Swan Jr. can be reached at kage2336@gmail.com.
Daily we may make life-and-death decisions. Yes, this does make us special, and specially vulnerable: vulnerable to criticism from others and to self-criticism. It can get pretty lonely when your patient is not doing well, perhaps because of a decision you made. Such an eventuality is not easy to prepare for, nor to face on a continuing basis. How do we cope? We learn to turn to our colleagues for compassion, understanding, advice, and moral support. That’s why collegiality is so important. We don’t exist in a social or intellectual vacuum. We need each other. So be loyal to each other. Do not denigrate your colleague in front of others, or worse yet behind his or her back in the presence of other members of the health care delivery team; certainly not in front of patients. If you have a desperate need to be critical of a colleague for your own ego satisfaction, do so in private, with a friend who won’t repeat the incident. Remember, if a fellow physician asks you for help, you should have a good reason for not helping him or her, even if the request for help involves changing of a tire in the rain at night in the parking lot! Physicians need each other. Be collegial.

PATIENT CARE

Your patients come first, always. Your family will have to understand this, and you will have to learn the delicate balance between patients and family. Years later, when your children tell you that they are—or are not—interested in medicine as a career, you will know just how well your balancing act succeeded!

In caring for your patients, be a professional but also be a friend. It won’t hurt to lower your guard and to be human. A warm smile, the touch of a hand, a soft voice may be all that is necessary to convey a sense of compassion that every patient needs and deserves.

Avoid absurd statements like “just relax”; “it’s a simple procedure”; “it won’t hurt”; and “don’t worry.” Who are we kidding? In my opinion, the words “just relax” are the two most misused words in medicine!

Avoid talking about a patient in public places such as the hospital elevator. Patient confidentiality is a patient right. You and your patient form a partnership that is sacrosanct regarding confidences.

Educate yourself and others about your patient; it’s your obligation to your profession and it’s good medicine. Every patient is a lesson, and learning from your patients is part of continuing medical education. Know your patients; be familiar with their chart so that when you present their case to others, formally or informally, you won’t have to use notes. Advice we give to those physicians starting their first year of residency also applies to you, as you begin your clerkship: “Know your patient.” There are three questions you don’t want to respond to with the word “no” at morning report. They are 1) “Did you see the patient?” 2) “Did you write a note in the chart?” and 3) “Did you read about it?” Of these three, the most important is #1.

I believe that every patient is literally a gift, and it should be with a sense of gratitude that we treat a patient who seeks our professional opinion. You and I know there will be some patients and some times when we will be anything but grateful for the professional association, but these patients and these times will be the minority; if not, we are in the wrong profession.

I mentioned mistakes. Learn from your mistakes. You will make them; they are not to be forgotten nor worn on your sleeve. Remember that mistakes come from bad judgment; good judgment comes from mistakes. Recall George Santayana’s memorable statement: “Those who cannot remember the past are condemned to repeat it.”

Your closest colleague is yourself and you must talk to yourself because every physician makes decisions based upon what he or she thinks is the problem and its solution. You must learn to be comfortable with your assessment and your plan because they constitute your judgment. Next to integrity, your judgment is your most valuable professional attribute.

Look to your colleagues for advice; look up what you can’t otherwise deduce. Cultivate the sources that you will refer to for the rest of your professional life: texts, journals, and the Internet. And don’t forget to call upon your Higher Power for help. The orthopedic surgeon tells us that he is responsible for less than 50% of the success of knee reconstruction after an injury. The rest is patient rehabilitation. I would go a step further. I believe we, as physicians, are responsible for a small percentage of patient recovery from illness or injury; the major proportion belongs to God. We see examples of this phenomenon with regularity. Call on and share with your Higher Power. While there is great joy in patient recovery, there is great sorrow in therapeutic failure. Don’t be afraid to shed a tear, even in front of your patient’s family, when faced with failure. You can afford to be human.

I treated a policeman with a gunshot wound to his abdomen. Two days later, I was informed that the patient was in shock and that his abdomen was distended. The family, led by the father, confronted me and I speculated that the liver wound had hemorrhaged, that major resectional surgery might be necessary, and that survival was in question. At re-exploration we identified a small omental artery that was spurting blood. I clamped the artery and ligated it. The patient survived. I reported this to the father, and he asked me for an explanation. I told him we had made a mistake: either we didn’t see the injured artery or a tie had slipped off. He looked up at the ceiling and laughed! I asked him for an explanation! He said, “Pardon me, Doc, but that’s the first time I ever heard a doctor say he made a mistake!” Then we laughed; we also stayed friends for many years. When I related this story to my colleagues, some criticized my candor, but my gut feeling at the time was that I was on safe ground and I’ve never regretted it. Follow your hunches.

How far can I go without facing a lawsuit? You probably won’t travel far in medicine without hearing from the legal profession. Remember: if you believe that what you did or did not do for your patient was in the best interests of the patient, you need not be afraid of retribution. Even so, you must steel your pride and sensitivity toward the inevitable. You will make mistakes. They will be costly, and you may be held accountable. It may be painful, but never let it be the end of the road. With regards to lawyers, remember the ancient phrase, “Illegitimi non
“carborundum,” which literally translated means, “Don’t let the bastards wear you down.”

As I mentioned, befriend your patient and don’t hesitate to establish long-term relationships. It’s good clinical follow up. One of my patients was in jail for the murder of his girlfriend 10 years earlier. I had performed an emergency portacaval shunt to control his exsanguinating hemorrhage from esophageal varices in 1991. He recovered and was returned to jail. We communicated by phone every few weeks. He called collect and, I believe, I was his only friend! He finished his jail sentence and tried life outside. He borrowed money from me he was never able to repay and died 12 years later at University Hospital. We are an inner-city hospital; there are many similar examples.

Are such doctor-patient relations bizarre? They are extreme and I mention them only to reinforce what can easily be forgotten: We are not to judge our patients, other than in matters of health. The Geneva Convention says that in time of war we must provide the same care to our enemy as to our ally and our own. Once the enemy is wounded, he is no longer the enemy; he becomes a patient, if in the hands of a medic. The injured rapist or murderer is no different in civilian life. You may have trouble with this concept. If so, think it through. Remember the words of Louis Pasteur, so applicable to the practice of medicine: “Chance favors the prepared mind.”

I urge you to be accessible to your patients as much as possible. My calling card includes my home phone number, as well as my office phone number, and I tell my patients to call me, anytime, if they need me. Many colleagues criticize this practice of mine as unnecessary and potentially dangerous. I can assure you it has never caused me undue hardship; it has been the reverse, and I have been able to comfort, if not significantly help medically, many patients over the telephone. Their gratitude more than makes up for any inconvenience on my part. Take good care of your patients and be their friend as well.

SELF-CARE

My fourth and last concern is for you. You must learn to take care of yourself. If you don’t take good care of number one, you won’t be able to take care of number one’s patients! At your age there is a tendency to think you’re indestructible; most residency program directors think so too! Some may even think you’re expendable, but you’re not. You must somehow find time for rest and relaxation. When and how is up to you, but let not your colleagues say of you, “That physician works too hard and plays too hard.” We’ve all seen examples of that syndrome and some of us have been there. Remember, our profession has the longest work week and the highest number of work hours in that week. It also has among the highest incidences of divorce, alcoholism, and drug abuse, even suicide. Take good care of yourself and also look into the well-being of your colleagues.

As you enter the world of the physician, do so with confidence, however intimidating the atmosphere may appear. You have a great deal to be confident about. You are by definition highly intelligent, exceedingly diligent, and unusually conscientious. You are an achiever who has overcome many obstacles to get where you are. Look around you. I dare say you will never again be a member of such a distinguished and accomplished group of colleagues of the same age or level as your medical school class. So be confident of the future; be professional in all you do; be collegial; be a friend of, as well as a good physician to, your patients. And be good to yourself.
Improving health outcomes through patient education and partnerships with patients

Timothy E. Paterick, MD, JD, MBA, Nachiket Patel, MD, A. Jamil Tajik, MD, and Krishnaswamy Chandrasekaran, MD

“Each patient carries his own doctor inside him.”
—Norman Cousins, Anatomy of an Illness

To improve health care outcomes, physicians must spend more time with patients. The teaching physician’s interaction with the patient must be enthusiastic, motivated, and responsive to the individual patient’s needs. For individual members of our society to realize the benefits of physician health education, there is a need for a robust, hearty engagement between patients and physicians.

Interventions to improve self-care have led to documented improvements in self-efficacy. Self-efficacy is defined as one’s belief in one’s ability to succeed in specific situations, or accomplish certain tasks. One’s sense of self-efficacy plays a major role in how one approaches goals, tasks, and challenges regarding one’s health. Clinical benefits have been seen in trials of lifestyle intervention within a wide range of conditions such as diabetes, coronary heart disease, heart failure, and rheumatoid arthritis (1).

In the context of escalating health care costs and shocking future cost projections, the potential for improved health outcomes through patient education and self-management programs is immense. In the early 1990s, it was estimated that 50% of the annual mortality toll in the US was premature. Tobacco use, poor diet, a lack of physical exercise, alcohol consumption, exposure to microbial agents, use of firearms, risky sexual behavior, motor vehicle accidents, and illicit drug use were the culprits causing premature death. Approximately 80% of premature deaths were due to tobacco use, dietary patterns, and a low physical activity level (1). Clearly, these are all behaviors we could modify to reverse the trends. For those individuals who do not smoke, eat healthy food, and participate in regular exercise programs, the hazard ratio for diabetes, myocardial infarction, stroke or cancer was 0.22 (2).

There is a belief in the medical community that physical activity and diet can reduce the risk of developing coronary artery disease, hypertension, diabetes, and the metabolic syndrome. A comprehensive systematic review reinforced this notion by revealing that there is irrefutable, convincing evidence for the benefit of exercise in improving clinical outcomes in metabolic disorders, coronary heart disease, and heart failure (3).

Physicians must promote patient education and engagement through improvement in patients’ health literacy. Health literacy is defined as the capacity to seek, understand, and act on health information (4). The presumption has been that low health literacy means that physician communication is poorly understood, leading to incomplete self-health management and responsibility and incomplete health care utilization (5). It is the responsibility of physicians to proactively enable patients to have more accessible interactions and situations that promote health and well-being. Health literacy is the primary responsibility of physicians, given that it is physicians who determine the parameters of the health interaction, including physical setting, available time, communication style, content, modes of information provided, and concepts of sound health care decision crafting and acquiescence. There are communication methodologies and behaviors that physicians can implement to ameliorate the potential risks associated with limited patient health literacy, including avoiding medical jargon, engaging in patient questions, explaining unfamiliar forms, and using “teach back” as a method to ensure understanding (6).

Critical to any educational process is time. The development of patient health literacy is crucial to our proven health prevention measures of exercise and diet. Patients must have a deep understanding of the impact healthy interventions can have on their present and long-term health. Physicians will need to spend time and energy educating patients to see behavioral change that results in improved health outcomes and reduced morbidity and mortality due to preventable chronic diseases such as diabetes, obesity, and coronary and cerebrovascular disease. As physicians, we will know when we have reached the threshold of being an excellent teacher by observing responsible patients.

The partnership between a physician and patient requires dual responsibility. Physicians have a duty to inform patients how to achieve health and wellness, and patients have a
responsibility to act on the information provided in their best health interest. Medical informed consent is essential to the physician’s ability to diagnose and treat patients, as well as the patient’s right to accept or reject clinical evaluation, treatment, or both.

Medical informed consent should be an exchange of ideas that buttresses the patient-physician relationship. The consent process should be the foundation of the fiduciary relationship between a patient and a physician. Physicians must recognize that informed medical choice is an educational process and has the potential to affect the patient-physician alliance to their mutual benefit. Physicians must give patients equality in the covenant by educating them to make informed choices. Patients must use the educational process to make rational health choices.

When physicians and patients take medical informed consent seriously, the patient-physician relationship becomes a true partnership with shared decision-making authority and responsibility for outcomes. Physicians need to understand informed medical consent from an ethical foundation, as codified by statutory law in many states, and from a generalized common-law perspective requiring medical practice consistent with the standard of care. It is fundamental to the patient-physician relationship that each partner understands and accepts the degree of autonomy the patient desires in the decision-making process (7).

The political turmoil that has gripped our country for the past year or so should have largely subsided with the election of a new president. Its persistence, however, brings to mind a highly acclaimed bestseller published 26 years ago, titled *Parliament of Whores* (1). Its author, P. J. O’Rourke, a gifted conservative writer, uses wit, creativity, and humor in his thought-provoking attempt to explain the entire US government.

The book offers chapters on Congress, the president, the Supreme Court, domestic and foreign policy, the federal budget, and much more. A few quotations will give you the tone of his analysis:

- “Democrats are . . . the party of government activism, the party that says government can make you richer, smarter, taller and get the chickweed out of your lawn. Republicans are the party that says government doesn’t work, and then they get elected and prove it” (2).
- “It is a popular delusion that the government wastes vast amounts of money through inefficiency and sloth. Enormous effort and elaborate planning are required to waste this much money” (3).
- “Politicians are interested in people. Not that this is always a virtue. Fleas are interested in dogs” (4).
- “The mystery of government is not how Washington works but how to make it stop” (5).

Given his opinions of Washington’s “normal” political processes, we wonder what O’Rourke would say about the recent presidential election process. We do know that, at the end of September 2016, he introduced himself as a “political satirist in a campaign that’s self-satirizing” (6). Perhaps he felt that he had little to add to the circus.

No matter which candidate, if any, you supported in the 2016 presidential campaign, both the process and the results of the election were shocking and dismaying to a large number of people in the United States and around the world. Notably, several nations gave their citizens open access to the media streams and live debates between the candidates, with the implicit (and sometimes explicit) message that “this is why our people don’t want democracy.” An article in *The Diplomat*, a China-based newsletter, closed with this line from a US businessman, “Now the world is looking at us and laughing,’ he sighed. ‘What is going on?’” (7).

As readers will remember, this was going on:

One major party ran an experienced establishment figure who was perceived as wealthy and “entitled to be next,” who was being investigated for a variety of violations of laws (and common sense), who had ties to a foundation that received millions of dollars from foreign governments, and whose allies on the Democratic National Committee had clearly helped eliminate her closest rival.

The other major party ran a nonpolitician, alleged billionaire, semi-“reality” TV “personage” who said things that mocked the handicapped, were anti-Mexican, anti-Muslim, pro-nuclear proliferation, racist, and misogynist, and who made a number of other statements that would have gotten an eighth-grader grounded for months.

The third parties fielded candidates who were mostly running against the big parties and, in one case, didn’t know who or what Aleppo was.

By November 1, 2016, the two major candidates had managed during the course of their campaigns to become two of the most disliked presidential candidates ever. According to a *Washington Post* poll days before the election (8), only George W. Bush, Vladimir Putin, and white supremacist David Duke had worse popularity ratings than Hillary Clinton and Donald Trump. Each candidate was actually less popular than Communist China, the National Rifle Association, and even the Internal Revenue Service.

By Wednesday morning, hours after the polls had closed, Clinton had secured the popular vote, but because of the structure of the electoral college, Trump was the president-elect. This further confused people around the world who did not understand how a person could lose the popular vote and still win the election.

Perhaps O’Rourke’s opinion of the election process and its product is summed up in the final words of *Parliament of Whores*:

Authority has always attracted the lowest elements in the human race. All through history mankind has been bullied by scum. Those who lord it over their fellows and toss commands
in every direction and would boss the grass in the meadow about which way to bend in the wind are the most depraved kind of prostitutes. They will submit to any indignity, perform any vile act, do anything to achieve power. The worst off-soughings of the planet are the ingredients of sovereignty. Every government is a parliament of whores.

The trouble is, in a democracy the whores are us (9).

As a satirist, O’Rourke clearly paints a humorous—although ultimately very bleak—picture of democracy’s foibles and failures. However, even great politicians have been alleged to have expressed similar thoughts. Winston Churchill, for example, noted, “Indeed it has been said that democracy is the worst form of Government except for all those other forms that have been tried from time to time” (10).

Rather than ending this piece negatively, we (who were on adamantly opposite sides of the recent election) prefer to follow America’s long tradition of peaceful transition. In that light, we echo President Barack Obama’s words:

So I have instructed my team to follow the example that President Bush’s team set eight years ago, and work as hard as we can to make sure that this is a successful transition for the President-elect—because we are now all rooting for his success in uniting and leading the country. The peaceful transition of power is one of the hallmarks of our democracy. And over the next few months, we are going to show that to the world (11).

If we stop grieving or gloating and unite for the good of our country and the world, we could challenge O’Rourke’s claim that “the whores are us.”

2. O’Rourke PJ: 19.
3. O’Rourke PJ: 36.
From the seeds Dr. John W. Hyland planted in this institution just over half a century ago, the cardiology department of Baylor University Medical Center at Dallas (BUMC) has grown leaps and bounds into a mammoth organization with national recognition. In this context, I proudly and gratefully claim that I am a product of Dr. Hyland’s tutelage.

This is Jack’s 53rd year at Baylor and my 51st year. Out of respect and admiration, I will give him the honor of being the longest-serving cardiologist to retire from this institution.

I came to BUMC in 1966 as a resident in internal medicine. Two years later, I became Jack’s fourth fellow. Six months into the program, I did not believe he trusted me enough to help him with his cath lab procedures, since he relied solely on Rhoda Whitcomb, his efficient, longstanding cath lab nurse. Eventually, he allowed me to assist him hands on, which introduced me to the intricacies of cardiac catheterization. Teaching was done in baby steps, first by advancing the catheter into the right atrium, then a few days later to the right ventricle, and finally to the pulmonary wedge position. Sophistication followed later. It was his way of tutoring, which I facetiously label the “step-ladder technique”!

Other fellows came and went, and some did not finish the course. When his new partner, Dr. James Matson, was drafted into the Navy 6 months after joining his practice, the two of us worked together hand in hand almost daily until I finished my fellowship. I worked very hard to earn my keep, which Jack graciously reciprocated with an offer to join his practice after my first year of fellowship (Figure).

As a leader, he was rightfully demanding. Jack was as strict as he was kind. To him, a patient’s welfare was paramount. Professionally, he lived to the core the Hippocratic tenet of “do no harm.”

A quintessential teacher, he always made us fellows see, know, and examine our patients before we presented their data to him. This was followed by incisive questions and discussions about the cases. He was a preceptor par excellence, indeed! We wrote our cardiac catheterization reports long hand in ink, double spaced, on yellow legal pad paper. I still bear calluses in my right middle finger as a consequence. He went over these drafts meticulously and returned them with his corrections highlighted in red ink. His editing did not involve only format but also grammar, punctuation, and calculations.

After working with Jack for many years, I look up to him with respect, not only as a mentor but also as a good friend. His door was always open when I was in need. As an aside, he also taught me the nuances of life in general and the quirks of American culture—both always done in the most gentlemanly and subtle manner. To my advantage, he was always very supportive of new endeavors. This allowed me to innovate and start the BUMC pacemaker and coronary angioplasty programs.

Dr. John W. Hyland personifies a bygone era of cardiology at BUMC. Though he may no longer be around its halls, his teachings and examples will always be felt. His students have and will continue to carry the torch he lighted.

From the Division of Cardiology, Baylor Scott and White Health – Garland, Garland, Texas, and the Heart Hospital Baylor Plano, Plano, Texas.

Corresponding author: Rolando M. Solis, MD, 700 Walter Reed Boulevard, Suite 205, Garland, TX 75042 (e-mail: rmsolis@mac.com).
A century ago, my 18-year-old father (Figure 1) marched down the main street of Shawano, Wisconsin, with members of Company F, amid the cheers of hundreds of local citizens. The crowd may have sung the lyrics of “Over There,” by George Cohan, a great wartime propaganda song (“Send the word, the Yanks are coming…. And we won’t come back till it’s over there”), which also had to encourage our Allies and serve warning to the Germans. Dad’s unit took the train to Camp Douglas, Wisconsin, then on to Camp MacArthur in Waco, Texas, and eventually to Hoboken, New Jersey, where they would board the troop ship Tuscania. About 2 million American men were shipped to France to fight in World War I. Only one troop ship was torpedoe and sunk en route, my father’s ship. Fortunately, he survived.

THE SHIP

The Tuscania (Figure 2) was a British ship built by A. Stephen and Sons in Glasgow, Scotland. It was owned by the Anchor Line and served jointly with Cunard the route from Glasgow to New York via Liverpool. The Tuscania was 549 feet long and 66.5 feet wide and weighed over 14,000 tons. It was launched in September 1914 and made its maiden voyage in February 1915. In September 1915, it helped in the rescue of passengers from the Greek ship Athini, which caught fire in the Atlantic.

The captain of the Tuscania, Peter McLean, was from Britain, as were the crew members. The final voyage was from Hoboken, New Jersey, on January 24, 1918. According to Dad’s letters, “It sure was cold when we left. We were not allowed on deck, but I managed to see the old ‘goddess’ (Statue of Liberty) when we left. Sure will be glad to see her again.”

There were 2129 American troops on board, mostly National Guardsmen from Wisconsin and Michigan. Many of the men would reinforce the 32nd Division (the so-called “Red Arrow Division”). The ship and its crew of 384 joined a convoy at Halifax, Nova Scotia, bound for Le Havre, France (Figure 3).

THE U-BOAT

The Germans called their submarines U-boats, an abbreviation for “undersea boat.” Germany was the last major power to possess submarines. The first, U-1, completed sea trials in 1907. At the outbreak of World War I, Germany had only 24 such
boats. The number was eventually increased to 375 boats, which would sink a total of 5554 Allied and neutral merchant ships. The most famous was the Lusitania, a passenger ship sunk in 18 minutes in 1915, causing the deaths of 1198 people, including 124 Americans.

The submarine that sunk the Tuscania was UB-77 (Figure 4), built in the Blohm and Voss shipyard in Hamburg. It was launched in May 1917 and commissioned in October. A diesel-electric, it was captained by Wilhelm Meyer, aided by a crew of 34. It carried 10 torpedoes and no mines and could dive to a depth of 246 feet. Its range was 55 miles, and its top speed was 8 knots (9.2 miles) per hour.

THE ENCOUNTER

On February 5, 1918, at 5:40 pm, UB-77 spotted the Tuscania in its periscope (Figure 5) near the Scottish and Northern Irish coasts and fired two torpedoes. The first one missed, but the second scored a direct hit, killing six men instantly. By 7:00 pm, all lifeboats had been launched, but over 1000 men were still on board. According to one account (1), some 600 of them were lining the rail, waiting for the next development, smoking and talking quietly, “discussing their plight”:

The remarkable part of it all was that they took everything in a matter-of-fact way, with a sort of “well, what’s next” attitude. Occasionally a few would sing some little song, indicative of their feelings, such as “Where Do We Go From Here, Boys?” or “To Hell With the Kaiser.” The absence of panic . . . and time in prayer was remarkable (1).

The convoy’s escorting destroyers helped rescue most, including my father, who leaped onto an adjacent destroyer. The rescue was hampered by the continued presence of the UB-77 in the area.

The Tuscania sank at 10:00 pm (Figure 6) 7 miles southwest of the Scottish Isle of Islay (pronounced “eye-la”) in water
around 500 feet deep (Figure 7). A number of the men in lifeboats drowned when the ropes lowering the boats into the sea broke. The sinking made headlines, especially in Wisconsin newspapers, given the number of men on board from that state. Nearly 210 US soldiers were lost (the account varies according to different sources). The bodies of the majority were recovered, with others lost at sea.

THE AFTERMATH

Dad's first letter home was dated February 17, 12 days after the incident. He merely stated that he got off “in fine style, did not even get wet.” He was proud that he “kept cool,” and the experience made him “feel able to hold my own at any time.” After the armistice, his letters indicated that the destroyer deposited him in Ireland and that he went “on the rocky railroad to Dublin,” where he boarded a steamer for England. He stayed there for 6 weeks before returning to the war in France.

The UB-77 sank one other ship and survived the war, unlike 182 of the other 374 U-boats. The sub was surrendered on January 16, 1919, and later “broken up” at Swansea, Wales, in 1922. Lt. Wilhelm Meyer, skipper of the U-boat, was invited to the 20-year reunion of the Tuscania survivors. He politely declined but did correspond with several of the survivors and, as requested, added his account of the sinking for reunion members.

The American victims were temporarily buried in three different sites on the Isle of Islay and eventually reburied permanently in other cemeteries at home. In 1920, the American Red Cross erected a monument on Islay to those lost at sea. Years later, divers visited the sunken ship and retrieved the bell, which was donated to the Islay Museum.

Dad never said much about the experience, and I was too young and too involved in my own affairs to ask him much about it. I did find a piece of cardboard in the box of his war letters which his mother kept, with several items he had saved from the Tuscania (Figure 8). One was a card indicating his berth (bed No. 5 on the upper deck). It also included his meal ticket (first seating at 7:00 AM, noon, and 5:00 PM), so he was having dinner when the torpedo struck. There was also a piece of a curtain that one man who had been in the shower wrapped himself in. The survivors cut the curtain into small sections to keep as souvenirs.

Dad’s letters home reflected a certain fatalistic attitude about the war, perhaps a defense mechanism to allay the obvious anxiety that soldiers must feel. Perhaps he was right, that it just was not his time to die. If he had not been at dinner, in the first seating, when the torpedo struck, he might have gotten into a lifeboat and then been lost at sea.

Some years ago, I published an article about Dad’s war letters and mentioned the Tuscania. A physician from my hospital (Charles Hancock, MD), whom I had known for years, called me. His father, Boyd, from south Georgia, had also been on the Tuscania. He was in a lifeboat, being lowered into the Irish Sea, when the supports gave way, depositing the men in the cold water. Another lifeboat pulled his father to safety. His only possession was a water-sogged wallet with one dollar bills. He later gave each of his five children one, as a keepsake for his good fortune.

Dad’s 32nd Division entered the war at Château-Thierry, stopping the German advance on Paris. At nearby Soissons, the
fighting was fierce, where the Germans were desperately trying to hold a hill. The following day, while attacking that hill, Dad’s good friend and former football teammate, Eli Elefson, was “struck first with a machine gun bullet that pierced his abdomen. He raised up a little and was immediately hit by another machine gun bullet, this time in the forehead.” His body was placed in a pit with seven others. The site was marked for proper reburial later; however, with continued fighting in the area the marker was obscured, and Eli’s body was never recovered. His name is listed on the “Wall of the Missing” in the Oise-Aisne Cemetery, 14 miles northeast of Château-Thierry. He was one of 28 Shawano-area youths to pay the ultimate price in the war (Figure 9).

After their initial battle with the Germans at Château-Thierry, Dad’s 32nd Division continued to take the fight to them, culminating in the Meuse-Argonne encounter. After the armistice, Dad spent time in Germany with the Army of Occupation and eventually returned home to another parade down Main Street (Figure 10) to the tune of “When Johnny Comes Marching Home Again.” He then attended the University of Wisconsin. He worked in sales for a brief time and then decided to follow his father and brother into the medical field. While in medical training as an obstetrician/gynecologist, he married the nursing supervisor, Alice Davis, originally from Montana. They returned to Shawano, where Dad delivered most of the babies in his 36-year career and reared four of their own. He didn’t travel much after the war, convinced that “home” had all that he needed—friends, family, a nice house on the river, and a farm for his horses less than 2 miles away. He died suddenly at age 71. He never had an interest in returning to Europe, certainly not by ship.

Howard and Georgeanna: Sixty Years of Marriage and Medicine by Howard W. Jones Jr.; edited by Lucinda Veeck Gosden and Roger G. Gosden
Reviewed by Samuel P. Marynick, MD

A fter reaching the age of 100 years, Dr. Howard W. Jones Jr. published three books: this volume, along with In Vitro Fertilization Comes to America and Personhood Revisited. All of these writings are fundamental to understanding the history and reasoning that contributed to the development of current reproductive medical practices.

Howard and Georgeanna is a thoughtfully compiled history of how Georgeanna and Howard were reared, how they were introduced, how they were trained, how they courted, how their relationship developed, how they married, and how they continued being thoughtful and productive practitioners of medicine and science while rearing three children. This volume then informs us how Georgeanna and Howard continued developing their relationship after their children became adults and left home.

Howard did not live to see this autobiography completed, but the material was developed to the point that a couple close to the Jones, Lucinda Veeck and Roger Gosden, were able to organize the material into the final format for publication.

There are so many relationships and intertwinings in this book that it is not possible to sufficiently mention all that are pertinent in this brief review. I will list several highlights here and let this serve as the basis to interest the reader to study the complete work.

Howard W. Jones Jr. was delivered by his future father-in-law, gynecologist-obstetrician Dr. King Seager, in Baltimore, Maryland, in December 1910. Georgeanna Seager was born some 18 months later, on July 6, 1912. Howard’s father practiced internal medicine at St. Agnes Hospital, where King Seager practiced.

Howard and Georgeanna were friends from childhood. They would often play together on the St. Agnes Hospital lawn while their fathers were making hospital rounds. After Howard’s father died, when Howard was 13 years old, Howard and Georgeanna did not see each other for several years.

Their reunion occurred at the monthly meeting of the Johns Hopkins Medical Society. Dr. Harvey Cushing was presenting a lecture on pituitary gland basophilic adenomas. Howard was a 22-year-old freshman medical student at Hopkins and Georgeanna, a 20-year-old senior at Goucher College. Georgeanna was so moved by Dr. Cushing’s lecture that she felt this one evening directed her future career choice toward endocrinology. While Georgeanna developed interest in hormones, Howard developed interest in surgery.

Georgeanna deciphered that human chorionic gonadotropin (hCG), the pregnancy hormone, is a product of the uterus/placenta and not a pituitary hormone. This was quite a discovery for a researcher in her 20s. In a relationship that spanned several decades, I never heard one peep from Georgeanna about this fundamental observation but learned of her discovery from Dr. Griff Ross, who developed one of the earliest and most accurate immunoassays for hCG, when Dr. Ross and I were discussing the history of our understanding of hCG.

Howard Jones Jr. was an experienced battlefield trauma surgeon. The information presented of his experience in the European Theater in World War II helps the reader who has never experienced war and the severe injuries that result understand this horror and the problems encountered as maximal effort is mustered to save human life. Following World War II, the Joneses returned to Baltimore.

Much was accomplished during the Baltimore years. A relationship was established with Bob Edwards, an embryologist at Cambridge University in England, and a chapter on Dr. Edwards develops the special relationship that Howard and Georgeanna had with this truly remarkable scientist. This relationship was essential to the future development of human reproductive medicine. Daily life during this period of around 35 years consisted of work and family, establishing a rhythm for life conducive to their remarkable professional and personal productivity.

Georgeanna contributed a chapter on the recipe that she and Howard established to allow their marriage to be so productive. This serves as a possible template for young couples who are both busy professionals.

After retiring from Johns Hopkins, the Joneses began new careers at Eastern Virginia Medical College in Norfolk. This move began one of the more impressive medical stories of the last century. Although information is provided in this book, to better understand the dynamics of the first in vitro fertilization success in America and the development of the Jones Institute for Reproductive Medicine in Norfolk, the reader is directed to In Vitro Fertilization Comes to America, previously reviewed in this journal (1).

The gallery of photographs is very good in documenting the lives of these two remarkable individuals. The reader will enjoy this pictorial walk through time. Following the gallery is a chapter of tribute by Ms. Nancy Garcia, Dr. Howard’s secretary.
and right-hand person at the Jones Institute. Ms. Garcia was helpful to individuals who had dealings with the Joneses. She gets more accomplished in less time and is just an amazing person. The Joneses were fortunate to have Nancy’s help for over three decades.

In her chapter, Ms. Garcia discusses how Alzheimer’s disease slowly destroyed Georgeanna’s exceptional mind before her death on March 25, 2005. Howard lived 10 more productive years, dying from complications of a medical procedure in the summer of 2015.

The conclusion of Ms. Garcia’s chapter sums up the feelings of everyone who knew the Joneses: “But anyone who knew them really well will agree that their achievements in research and clinical medicine would be hollow without their generosity, kindness and joyful living which shown on everyone around them.”

Memories and tributes from 104 of the individuals who worked with, were patients of, or crossed paths with the Joneses in their long lives complete this volume—one tribute for each year Dr. Howard Jones Jr. spent on Earth. If the editors had sought 200, 300, or 1000 tributes, they would have had no difficulty finding individuals grateful to this couple and willing to record their debt to Howard and/or Georgeanna. This couple positively influenced a significant number of thankful individuals.

This book is highly recommended. Much thanks to Lucinda and Roger for their fine and diligent work to make this publication possible.


The reviewer, Samuel P. Marynick, MD, is medical director of the Texas Center for Reproductive Health in Dallas, Texas, and an attending physician at Baylor University Medical Center at Dallas.
Baylor Scott & White Health announces Jim Hinton as new president and CEO

Following a national search, the Baylor Scott & White Holdings Board of Trustees announced the appointment of James H. Hinton to president and chief executive officer of Baylor Scott & White—the largest not-for-profit health care system in Texas—effective January 16, 2017. Hinton, a recognized leader with more than two decades of CEO experience, comes to Baylor Scott & White from Presbyterian Healthcare Services, a private, not-for-profit healthcare system in New Mexico, the largest in the state.

Hinton has served in his current role at Presbyterian since 1995 and has been with the organization since 1983. Known for helping to build Presbyterian into a model statewide integrated delivery network, Hinton worked to grow the Presbyterian Health Plan, which now serves more than 470,000 lives, and was deeply involved in building the Presbyterian Medical Group, a practice of more than 800 providers. Also during his tenure, he drove clinical quality and disciplined management processes, and he developed new models of care, which garnered national attention.

“During this time of incredible change in health care, Jim brings exceptional experience that will help move us into the future,” said Jim L. Turner, chairman, Baylor Scott & White Holdings Board of Trustees. “He is one of the few health system leaders in the country who has successfully navigated an organization from a focus on volume to a focus on value, and beyond his impressive accomplishments, those he leads are quick to say he is best known for promoting a caring culture.”

Hinton is also recognized nationally for his exceptional leadership in the community. He served on the Board of Trustees of the American Hospital Association from 2011 through 2015. In 2014, he was the chair of the organization that represents nearly 5000 hospitals, health care systems, networks, and other providers of care through advocacy and public policy.

“I have always been impressed with Baylor Scott & White’s reputation for high-quality care, its dedication to its mission, its service to its communities, and its innovative strategies,” said Hinton. “I am honored to now be in a position to help continue to advance the organization and its move toward population health.”

Hinton will succeed retiring president and CEO Joel T. Allison, FACHE, whose servant leadership steered the organization for 23 years. Allison joined legacy Baylor Health Care System in 1993, was promoted to president and CEO in 2000, and became CEO of Baylor Scott & White Health following the 2013 merger with Scott & White Healthcare. Over more than two decades, he worked to grow the system to 47 hospitals and nearly 1000 patient access points across North and Central Texas. Allison will work with Hinton to ensure a seamless transition of responsibilities.

NIH awards Baylor Scott & White Research Institute $8.5 million for lupus research center

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH) recently announced that Baylor Scott & White Research Institute will be home to one of four new Centers of Research Translation (CORTs). NIAMS will fund $8.5 million over 5 years toward the center’s research, which aims to better understand the development of severe lupus in children and could ultimately lead to new personalized treatments.

Virginia Pascual, MD, will lead the CORT at the Baylor Institute for Immunology Research, part of Baylor Scott & White Research Institute, to understand how the changes in gene expression contribute to the development of lupus. She’ll build on her previous pioneering work to correlate lupus disease activity with certain gene expression profiles. The Center for Lupus Research will focus on novel genomic technologies and bioinformatic resources to monitor pediatric patients who suffer from severe forms of lupus, potentially leading to new interventional strategies and personalized treatments, Dr. Pascual said.

“Lupus is a complex autoimmune disease that can affect multiple organs,” Dr. Pascual said. “We expect that knowledge gained through the implementation of these studies will permit us to better understand what drives the disease in each individual patient in order to apply personalized treatments, which should have a greater chance of being successful.”

Baylor Scott & White nationally recognized for outstanding patient experience

Baylor Scott & White Health earned national recognition from Press Ganey, the leading provider of patient experience measurement, for outstanding performance in patient experience. The health system was also honored with Press Ganey’s newest accolade, The Community Response Award, for excellence in care during the Dallas shootings in July 2016.

The Pinnacle of Excellence Award is given to the three top-performing organizations by category that have maintained consistently high levels of excellence over 3 years in patient experience, employee engagement, physician engagement, or clinical quality. Two hospitals received the Pinnacle of Excellence Award in patient experience: The Heart Hospital Baylor Plano, for hospital care, and HealthTexas Provider Network, for medical practice.

The Guardian of Excellence Award recognizes top-performing health care organizations that have consistently achieved the 95th percentile or above in one of the four categories based on 1 year of data. Seven Baylor Scott & White hospitals received this award: Baylor Jack & Jane Hamilton Heart and Vascular Hospital, hospital experience; Baylor Scott & White Medical Center – Waxahachie, ambulatory surgery; Baylor Scott & White Medical Center – Irving, neonatal intensive care unit; Baylor Scott & White Medical Center – College Station, hospital experience; Baylor Scott & White Medical Center – Grapevine, neonatal intensive care unit; Baylor Scott & White Medical Center – McKinney, hospital experience and neonatal intensive care unit; The Heart Hospital Baylor Plano, hospital experience and emergency department.

In addition to the Community Response Award, Baylor Scott & White Health earned the Success Story Award for innovation and improvement in patient experience. The award was based on results from implementation of the Press Ganey eRounding and Point of Care platforms.

“These prestigious awards originate from the experience of our patients,” said John McWhorter, chief operating officer of Baylor Scott & White. “The awards speak to leadership visibility, focus on the patient, the humility to address our shortcomings, and adoption of improvement processes that drive results and promote patient-centered care.”
Baylor Scott & White Research Institute joins consortium awarded precision medicine funding

The White House and the NIH have announced that Baylor Scott & White Research Institute is joining a five-member research consortium to expand precision medicine research. The consortium is one of four regional medical center groups awarded funding under the NIH’s Precision Medicine Initiative (PMI) Cohort Program, a landmark research effort aimed at advancing personalized health care. Precision medicine tailors treatment and disease prevention to a person’s biological makeup, lifestyle, and socioeconomic factors.

Baylor Scott & White Research Institute is joining the Trans-American Consortium for the Health Care System Research Network, which includes four integrated health care systems representing a strikingly diverse community population totaling more than 9 million individuals across nine states. The consortium also includes scientists from Henry Ford Health System in Detroit, Essentia Health headquartered in Minnesota, Spectrum Health in Michigan, and the University of Massachusetts Medical School.

“We’re honored to have been chosen to collaborate with such a distinguished group of health care organizations,” said Jaime Walkowiak, senior vice president of research and chief operating officer of Baylor Scott & White Research Institute. “The data we collect could help answer important questions about a variety of health conditions.”

The consortium will enroll 10,000 participants in the first year, collect their health information and biospecimens, and provide input on developing plans for the cohort program. Baylor Scott & White Research Institute will recruit 2000 to 2500 patients in both North and Central Texas.

“We were chosen based upon our structure and model, including health records, clinic, and hospital integration,” said John E. Zeber, PhD, of Baylor Scott & White Health in Temple. “For our part, we will be getting some biometric data from the selected patients and with their permission we will get lab values to collect as part of overall data.”

The 3-year grant will provide $1.1 million for the first year, said Giovanni Filardo, PhD, principal investigator of the project for Baylor Scott & White Health.

The cohort program aims to collectively enroll 1 million participants nationally. Participants will provide diet and lifestyle information, provide blood and urine samples, undergo a physical evaluation, and share real-time information via smartphones or wearable devices. The NIH emphasized that collected data will be protected by privacy and security safeguards. Each participant’s data will be linked to their electronic medical record.

“This initiative has the potential to improve prevention and treatment of disease based on an individual’s lifestyle, environment, and genetics. Ultimately, this could lead to more effective preventive measures and treatments early on,” says Christine Cole Johnson, PhD, MPH, chair of Henry Ford’s Department of Public Health Sciences and co-principal investigator of the Trans-American Consortium. “We look forward to working with our consortium partners known for their medical and research expertise.”

Dallas researchers develop first-ever tuberculosis treatment regimen for children

Researchers at Baylor Scott & White Research Institute have developed a first-of-its-kind treatment regimen for children infected with tuberculosis (TB), tailored specifically for the way the disease spreads in their bodies. The research is outlined in seven papers published in the October 2016 special issue of Clinical Infectious Diseases.

“Treatment for children with any infectious disease is copied and adapted from how we treat adults, but TB in children is very different from TB in adults,” said Tawanda Gumbo, MD, investigator at Baylor Scott & White Research Institute and the director of the Center for Infectious Diseases Research and Experimental Therapeutics at Baylor Institute for Immunology Research. “In children, TB spreads to the brain and other parts of the body, while in adults it is usually confined to the lungs. Our research takes that difference into consideration. This is a first-of-its-kind in the world of children’s health.”

In addition to Dr. Gumbo, the Baylor Scott & White Research Institute team involved in the study includes Devyani Deshpande, MD, associate investigator; Jotam Pasipanodya, MD, PhD, assistant investigator; and Shashikant Srivastava, PhD, associate investigator. Dr. Soumya Swaminathan, Director General of the Indian Council of Medical Research, and Dr. Eric Nuernberger of Johns Hopkins University School of Medicine also participated in the initiative.

To develop a TB regimen for children from scratch, researchers conducted experiments with the hollow fiber system model of TB, created by Dr. Gumbo and approved by the European Medicines Agency in 2015 and editorially endorsed by the US Food and Drug Administration. The system is used to select and evaluate possible drugs and treatment regimens before they’re tested in clinical trials. Thousands of hollow fibers throughout the unit carry nutrients and antibiotics to multidrug-resistant Mycobacterium tuberculosis, the causative agent of TB, to test which drug concentrations and combinations effectively kill the bacteria.

The series of papers published in Clinical Infectious Diseases outlines the progression of research conducted by Dr. Gumbo and his team, from treatment design to the lab to children. The clinical data and pediatric input came from the team led by Dr. Swaminathan and her colleagues in Chennai, who measured drug levels and treatment response in children being treated for TB with standard regimens.

“We’re proud to share this important work that will make a difference in the health of millions of people worldwide,” Dr. Gumbo said.

Common asthma drug could prevent liver disease, reduce need for liver transplants

A drug commonly used for the prevention of allergies and asthma someday could find new use in preventing liver disease and reducing the need for transplants, according to new
research published in the October 2016 edition of *Hepatology*.

Led by a team of researchers at Baylor Scott & White Research Institute in conjunction with the Central Texas Veteran’s Health Care System and Texas A&M Health Science Center, the study found that cromolyn sodium successfully blocked a series of cells that trigger liver scarring (known as fibrosis), which in advanced cases can lead to cirrhosis. The finding could most impact patients with primary sclerosing cholangitis (PSC), a chronic disease that damages bile ducts and causes serious liver damage. The disease has no effective treatments and leaves patients with few options beyond a liver transplant.

In particular, the study evaluated mast cells, which are known to infiltrate and multiply after liver injury and release histamine, which causes fibrosis. Using a model that mimics human PSC, researchers found that the drug successfully
is to find drugs to target mast cells and render them inactive,” said Heather L. Bradley-Francis, PhD, an investigator at the Digestive Disease Research Center at Baylor Scott & White Health. “This particular study was a direct outgrowth of previous published work involving the same drug for bile duct damage and liver cancer. We were pleasantly surprised to find that our data and results matched what we had hypothesized about the drug’s effect on PSC, based on that previous work.”

“This paper is very important and opens new avenues for the treatment of cholangiopathies,” said Gianfranco Alpini, PhD, director of the Digestive Disease Research Center at Baylor Scott & White Health. “This particular study was a direct outgrowth of previous published work involving the same drug for bile duct damage and liver cancer. We were pleasantly surprised to find that our data and results matched what we had hypothesized about the drug’s effect on PSC, based on that previous work.”

PHILANTHROPY NOTES

- 17th annual Celebrating Women luncheon raises $1.8 million for the fight against breast cancer

On October 20, 2016, Baylor Health Care System Foundation celebrated the 17th annual Celebrating Women luncheon. The 2016 luncheon, presented by Tom Thumb for the 12th consecutive year, raised $1.8 million to benefit Baylor Scott & White Health’s fight against breast cancer in North Texas. Since the first Celebrating Women luncheon in 2000, more than $28 million has been raised to support breast cancer initiatives at Baylor Scott & White Health.

Breast cancer survivor and multitalented actress, producer, writer, and singer Rita Wilson was the featured speaker. During a Q&A session, in which she was interviewed by Rowland K. Robinson, president of Baylor Health Care System Foundation, she discussed her family, career highlights, and her breast cancer diagnosis and journey.

For those in the audience just starting their journey with the disease, Rita advised, “Trust your instincts and your gut. Don’t be afraid to ask for a second opinion, for your doctor or for your pathology. For those going through treatment or are about to go through treatment, I know it feels like it’s never going to end, but there is a light at the end of the tunnel. You’re going to be able to see that light sooner than you think.”

- Golfers tee off in support of medical education in 15th anniversary Grand Rounds® Golf Tournament

The 15th anniversary Baylor Health Care System Foundation Grand Rounds® Golf Tournament, held at the Northwood Club, had a record-breaking year, with 229 golfers raising more than $290,000. Since the first tournament, Grand Rounds has raised nearly $3 million toward Baylor’s medical education initiatives. Once again, Bank of Texas was the presenting sponsor.

Funds raised through the annual fall tournament support undergraduate and graduate medical education at Baylor University Medical Center at Dallas. A recognized leader in the training of medical professionals since 1903, Baylor Dallas trains nearly 240 residents and fellows in 31 specialties each year—ranging from internal medicine to vascular surgery to pathology. For Baylor to continue to offer high-quality medical educational programs that help secure the future health of our community, donor support is critical.

- 7th annual DHWI Healthy Harvest event a success

The seventh annual Diabetes Health and Wellness Institute (DHWI) Healthy Harvest Fun Walk/5K Run & Diabetes Expo brought together supporters to raise awareness and generate funding for the newly renamed Baylor Scott & White Health and Wellness Center at Juanita J. Craft Recreation Center. The event received support from many generous sponsors, including presenting sponsor Vizient and founding sponsor OTSL Charities, and raised more than $140,000 for the institute’s diabetes self-management and wellness programs, education initiatives, and outreach projects.

Prior to DHWI’s opening, the area lacked services that are essential to living healthy, such as access to doctors’ offices or hospitals, healthy food options and grocery stores, exercise programs, and affordable transportation. By providing access to a health care team, including a physician, nurses, care coordinators, and diabetes education specialists, the results speak for themselves. Since opening, more than 6000 community members have participated directly in DHWI programs, and as of September 30, 2016, 40% of the institute’s members who have diabetes have achieved optimal blood sugar levels and 75% have reached optimal blood pressure control.

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.

- The Scott & White Healthcare Foundation is now Baylor Scott & White – Central Texas Foundation

Much has changed in the health care industry since Drs. Arthur C. Scott Sr. and R. White Jr. established what is now Scott & White Medical Center more than a century ago in Temple, Texas. Their friendship sparked a series of relationships that has led to the creation and continued growth of the largest not-for-profit health care system in Texas—Baylor Scott & White Health. At the Scott & White Healthcare Foundation, our relationships with patients, staff, supporters, and our communities exist at the core of our mission to help meet the needs of those we serve through philanthropic resources.

Now, we are pleased to announce that our relationship with Baylor Scott & White Health has sparked one more change: the Scott & White Healthcare Foundation is now the Baylor Scott & White – Central Texas Foundation. This change identifies us as the philanthropic arm of our system in Central Texas and helps us build relationships in new markets using the Baylor Scott & White brand.

Although our name has changed, our mission and values remain the same. We are committed to the responsible stewardship of gifts to support enhanced clinical services, medical education for the next generation of health care professionals, innovative research, and state-of-the-art facilities in which to deliver care. As our new name suggests, gifts to the foundation still benefit the Central Texas entity chosen by the donor. We appreciate all the friendship and support our donors have shown through the years and look forward to an even brighter future.
Scott & White. “Given the limited treatment options for PSC patients, we are thrilled with these study insights.”

If more research supports the study’s initial findings, investigators see a future where patients could be given the cromolyn sodium drug, which is also used to treat the autoimmune disorder irritable bowel syndrome, for its histamine-blocking properties to prevent the progression of fibrosis. That ultimately could result in fewer liver transplants—and potentially shorter transplant waitlists.

■ Grant for cancer research means more cancer drugs in the pipeline faster

Dr. Jung-Hee Woo, director of Baylor Scott & White’s Central Texas cancer research facility, has been awarded a $3.56 million grant from the Cancer Prevention and Research Institute of Texas. The grant will support Baylor Scott & White Health Research Institute’s Investigational New Drug Production Core Facility.

“With this support, we have a great opportunity to expand cancer drug production capabilities and lower a financial barrier to test innovative new drugs in cancer patients,” Dr. Woo said, adding that researchers plan to produce at least four new cancer drugs in the next 3 years.

The Baylor Scott & White Central Texas cancer research facility was founded in 2005. Its main goal is to provide investigators with new drugs for effectiveness and safety testing in all types of cancer patients. It conducts preclinical research and development, process development and scale-up, good manufacturing practice (GMP) production, clinical pharmacology, and custom projects. It has produced eight investigational new drugs, received Food and Drug Administration approval for phase II clinical trials for three drugs, and out-licensed two drugs to biotech companies. To expand production capabilities and efficiently respond to the growing drug production need, the facility plans to convert a vacant $5 million GMP clean space (7,500 square feet) into a GMP 3 suite for drug production in mammalian cells. “As a result, more cancer drugs can be tested in clinical trials, leading to development of more effective therapies for cancer patients,” Dr. Woo said.

■ Sleep apnea in TBI rehabilitation study receives seven-figure award

In patients with traumatic brain injuries (TBI), several factors can affect recovery and rehabilitation. Among them are sleep apnea, which disrupts a person’s breathing while sleeping and can worsen brain damage—affecting thinking, functioning, and overall health. Early diagnosis and treatment is crucial to minimize brain damage and improve recovery, but published insights specific to TBI and sleep apnea are sparse. As researchers learn that at least one-third of patients with TBI have sleep apnea, a long-term project at the Baylor Institute for Rehabilitation could find new ways to identify and treat the sleep disorder among these patients. In light of this major finding, the North Texas Traumatic Brain Injury Model System was chosen to receive a $2.68 million funding award from the Patient-Centered Outcomes Research Institute for the study “Comparison of Sleep Apnea Assessment Strategies to Maximize TBI Rehabilitation Participation and Outcome.”

Led locally at the Baylor Institute for Rehabilitation by neuropsychologist Marie Dahdah, PhD, the study takes place at six TBI model system research centers around the country. At each research site, investigators will compare current screening and diagnostic tests of sleep dysfunction in patients who have experienced a TBI and are currently receiving inpatient rehabilitation. The results of the comparison will identify the most accurate screening tools, which will aid in establishing an early diagnosis method that increases accessibility to patients, thereby reducing negative TBI outcomes.
Operative management of dermatofibrosarcoma protuberans of the breast

In the July 2016 issue of Proceedings, Kinney and Knox described a case of dermatofibrosarcoma protuberans (DFSP) located on the breast of a 26-year-old woman (1). Two operations were required to obtain clear margins. The first operation consisted of a wide local excision with 2 cm margins. Interoperative frozen pathology revealed a positive deep margin, and another excision was taken at that time. Interoperative frozen pathology of the reexcised deep margin was clear of tumor. However, subsequent permanent pathology revealed a positive lateral margin and a focus of tumor within 2 mm of the deep margin. The patient underwent a second operation where an additional wide local excision with 2 cm margins was performed, resulting in clear margins. Thus, two operations and a combined 4 cm margin was required for complete extirpation. This is not an unusual course of events when DFSP is treated with wide local excision. There is another well-accepted treatment for DFSP that results in higher cure rates with the added benefit of sparing normal tissue: Mohs surgery.

Mohs surgery is an iterative surgical procedure that allows pathological examination of the entire surgical margin while maintaining exact orientation of the excision specimen. Positive margins are microscopically identified and precisely located clinically for subsequent excisions. Subsequent excisions are processed in the same manner as the initial excision: pathological examination of the complete surgical margin while maintaining strict orientation. In essence, the tumor is “tracked” until clear margins are obtained. In this manner, only diseased tissue is excised and normal tissue is spared. In order to make the precise translation from the microscopically positive margin to the clinical margin, it is required that a single physician act as the surgeon and pathologist. The majority of Mohs surgeons are board-certified dermatologists who have completed a fellowship in Mohs surgery.

Mohs surgery has been recognized internationally as a preferred treatment for DFSP. Mohs surgery is listed first in the National Comprehensive Cancer Network guidelines (and wide local excision with 2- to 4-cm margins is last in the list) (2). In 2015, the European consensus-based interdisciplinary guideline for the treatment of DFSP recommended Mohs surgery as the treatment of choice (3). The British Society for Dermatological Surgery position statement on the management of DFSP states that Mohs surgery is the initial treatment of choice for DFSP (4). The French Society of Otorhinolaryngology guidelines recommends Mohs surgery for the treatment of head and neck DFSP (5). Comparisons of Mohs surgery with wide local excision for treatment of DFSP have shown Mohs surgery to be superior in terms of lower recurrence rate (6–9). There are no published reports that wide local excision is superior to Mohs surgery for the treatment of DFSP. Not surprisingly, Mohs surgery has been shown to achieve tumor clearance with smaller margins and greater preservation of tissue and, as a consequence, a better aesthetic outcome in the majority of cases (10, 11). DFSP is a skin cancer. In this case, the DFSP arose on the skin of the breast. There is nothing unique about the skin of the breast that would make Mohs surgery less effective. DFSP is a rare malignancy and, as a consequence, it is unlikely that a randomized controlled trial will be performed to definitively demonstrate the superiority of Mohs surgery over wide local excision for DFSP. However, there is ample literature to justify the evidence-based treatment recommendations for Mohs surgery.

—FRANK Saporito, MD
Dallas Skin Cancer Center
E-mail: fsaporito@txmohs.com


Kinney and Knox (1) report on a case of a slow-growing dermatofibrosarcoma protuberans (DFSP) of the breast in a young woman which was managed by repeat wide local excisions to clear margins. We agree with the surgical approach and find that cosmesis was very satisfactory in this case, given the repeat excisions. Although Mohs micrography has been suggested for managing DFSP of the trunk (which represents the most common anatomical location for DFSP), there is a paucity of data on whether Mohs is superior to standard wide local excision for DFSP of the breast.

We feel that the authors could elaborate on the triple assessment during initial presentation of the lesion. We understand that mammography might be of limited value in this case, as breast density (in a 26-year-old patient) would likely preclude a proper evaluation of the extent of the lesion. Have the authors considered magnetic resonance imaging of the breasts in this case? DFSP can extend variably to the surrounding soft tissue; hence, accurate preoperative planning with nonconventional imaging of the breast (particularly in young patients) can potentially avoid repeat surgery to obtain clear margins (2).

Moreover, given the size of the lesion, the clinical presentation as a palpable superficial lump, and the fact that the disease was identified on preoperative ultrasound, we feel that an ultrasound-guided core biopsy could have been used instead of open surgical excision biopsy (which did not obtain clear margins), in order to establish a firm diagnosis.

Lastly, the authors do not comment on the follow-up planning of this patient. DFSP can recur locally and carries metastatic potential; therefore, we suggest an aggressive clinical follow-up, especially given the patient is young and has a long life expectancy.

—Petros Charalampoudis, MD, FRCS, FEBS
Breast Unit, Guy’s Hospital, London, UK
King’s College, London, UK
E-mail: petros.charalampoudis@gmail.com


THE AUTHORS REPLY:

Thank you for your comments, Dr. Saporito. While Mohs surgery for dermatofibrosarcoma protuberans (DFSP) of the trunk is a well-accepted approach, there is limited information on the treatment of such a lesion on the breast, and the technique might not be as easily applied to breast lesions. The dermal tissue of skin lesions is well suited to analysis by frozen section. In the breast, the underlying adipose tissue does not freeze well, making immediate frozen section problematic and inaccurate. Permanent sections where the adipose tissue can be firmly fixed and sectioned have proven more accurate. In this patient, frozen sections of the deep margin were performed and found to be clear at the time of surgery, but subsequently proved to be too close a margin for this type of tumor. The lateral margin was in dermal tissue, which could have been frozen and evaluated. Nonetheless, as Mohs surgery has afforded excellent results with DFSP on the trunk and extremities, it would be reasonable to consider multidisciplinary collaboration and further discussion with a Mohs surgeon for treatment of such lesions in the future.

Thank you, Dr. Charalampoudis, for comments on initial diagnosis as well as follow-up. The initial presentation of the patient was that of a skin cyst without clinical evidence of deeper involvement, in which case it would be difficult to justify diagnostic breast MRI, although in retrospect it may have added additional helpful information. This is a consideration for follow-up, with the known natural history of this lesion that of local recurrence. The plan for follow-up is careful breast examination every 6 months for the next 3 years and then annually. It is not felt that mammography would be helpful for a patient of this age. Thank you for your comments on this interesting patient.

—Melissa Kinney, MD, and Sally Knox, MD
Baylor University Medical Center at Dallas
E-mail: mkinneymd@yahoo.com; smknox37@gmail.com
NO MORE ANIMALS FOR MEDICAL STUDENTS

When I was a freshman in medical school in 1954, the students did experiments on dogs in each laboratory session of the physiology course. When the experiments were over, I remember picking up the dead dogs and putting them in large garbage disposals. The Physicians Committee for Responsible Medicine, led by Neal Barnard, MD, has now convinced every school in the USA and Canada that provides MD or DO degrees to discontinue use of nonhuman animals for medical instruction and experimentation (1). Medical students no longer will be able to study physiology or surgery on any animal. The same is not true, however, for higher levels of medical training. In some residency and trauma laboratories, instructors still use live animals. The National Institutes of Health this year ended its use of chimpanzees, our closest living relatives, for medical training.

In 1985, 87% of medical schools used dogs and other animals to teach physiology, pharmacology, and surgical skills. Students were instructed to inject the animals with various drugs and monitor their responses or to practice surgical procedures. After the training, of course, the animals were killed. Dr. Barnard said that he worked to stop these animal labs for medical students for two reasons: First, because of the obvious cruelty to animals, and second, because when medical students are trained to kill these animals, they come to believe that killing animals is somehow essential to medicine and science. He of course disagreed.

None of the 44 surveyed medical schools that have opened in the USA since 1979 have used animals to train students. In 1995, the Physicians Committee persuaded the medical schools of Harvard and Columbia to eliminate their physiology dog laboratory course. Duke University, Case Western Reserve, the Medical College of Wisconsin, and Oregon Health and Science University eventually followed suit. In 2010, the last medical school in Canada, the Memorial University of Newfoundland, ended the practice.

“Th e End of Animal Use in Medical Student Education: A Model for the Future of Medical Training 1985–2016” has detailed the history of the Physicians Committee’s campaign at www.PCRM.org/EndOfAnimalUse.

FREQUENCY OF FAMILIAL HYPERCHOLESTEROLEMIA

As a medical student (1954–1958), I was taught that atherosclerosis (hardening of the arteries; blockages) was a degenerative disease. I remember vividly one professor saying, “Boys [my class of only 66 students had only 1 woman], atherosclerosis is a consequence of living on planet Earth. If you live on this planet, you get it.” Of course, that viewpoint is absolutely incorrect. Many have believed that bad genes were the cause of atherosclerosis. Several decades ago, Michael Brown and Joseph Goldstein, here in Dallas, taught us that familial hypercholesterolemia occurred in 1 in 500 people, which meant that 499 out of 500 of us cannot blame our parents for our development of atherosclerosis.

A recent article in Circulation (2) described an analysis of 36,946 participants in the 1999 to 2012 National Health and Nutrition Examination Survey (NHANES) utilizing the Dutch Lipid Clinic criteria for familial hypercholesterolemia. The prevalence of probable/definite familial hypercholesterolemia was calculated for the population by age, sex, obesity status (body mass index \( \geq 30 \) kg/m\(^2\)), and race/ethnicity. The results
were extrapolated to the 210 million US adults ≥ 20 years of age. The estimated overall US prevalence of probable/definite familial hypercholesterolemia was 0.40%, or 1 in 250, indicating that 834,500 US adults have familial hypercholesterolemia.

HARMONICA HEALTH BENEFITS

Weekly harmonica classes for people with chronic lung conditions or breathing difficulties are popping up all over the country as pulmonary rehabilitation programs (3). The patients make music with the very thing that troubles them most—their breath. There is no scientific proof that playing the harmonica improves lung function. Still, harmonica classes, started at hospitals and clinics, may confer a variety of benefits. The harmonica is among the few instruments where breath is both inhaled and exhaled, thereby mimicking the breathing exercises used in pulmonary rehabilitation classes. It exercises the diaphragm, produces deeper breathing, increases strength, reduces anxiety, and helps clear phlegm from the lungs. One hypothesis is that breathing with pursed lips decreases the amount of air that remains in the lungs, thereby providing some relief from dyspnea. There are also social benefits. For some people, the harmonica classes are the only places they go outside their homes once they become dependent on cumbersome oxygen tanks. At the class occasions, the participants celebrate each other’s birthdays and other special occasions. The camaraderie is important for them.

LIMITING CERTAIN PROCEDURES BECAUSE OF OBESITY

The National Health Service is rationing some operations and treatments for patients who are obese (4). These include hip and knee surgery, in vitro fertilization, joint replacements, and, in the case of one trust, all routine operations. The National Health Service is extremely pinched for funds at the moment, and its effort to meet budget is requiring some rationing. The same will occur in the US, in my view; it’s just a matter of time. The USA is broke. Both Medicare and Medicaid are in trouble. We owe $20 trillion as a nation, and that amounts to $167,000 for every individual living in the USA, and our present population is just over 320 million.

DOGS LICKING HUMAN FACES

Don’t do it! Animals’ mouths are hosts to an enormous oral microbiome of bacteria, viruses, and yeast (5). A dog’s saliva has proteins that may help cleanse or heal its own wounds, but there are some organisms unique to dogs that humans are not meant to tolerate or combat. Some bacteria in dogs’ mouths are zoonotic, meaning the animals can pass them to humans and cause disease. Some common zoonotic bacteria, including Clostridium, Escherichia coli, Salmonella, and Campylobacter, can cause severe gastrointestinal disease in humans.

What about letting a dog lick you at all? When the dogs’ saliva touches intact human skin, especially in a healthy person, it is extremely unlikely to cause any problems because there will be little absorption through the skin. A dog’s saliva and pathogens can be absorbed, of course, more easily through the mucous membranes of a person’s nose, mouth, and eyes. Though illnesses transmitted this way are rare, it is best to avoid letting your dog lick those parts of your face. It is not just what is carried in the dogs’ saliva, but dogs spend half of their lives with their noses in nasty corners or hovering over dog droppings, and their muzzles are full of bacteria, viruses, and germs of all sorts.

Other infections, such as hookworm and roundworm, can be transmitted in a practice called coprophagia, in which animals ingest one another’s stool or lick each other’s anuses. The immediate past president of the American Veterinary Medical Association indicated that a puppy could have as many as 20 to 30 million roundworm eggs in its intestinal tract in 1 week, and a roundworm can destroy an eye. It is conceivable that a dog with fecal material in its mouth could transmit an intestinal parasite to a human through licking, but that is rare. More commonly, parasites are contracted by ingesting contaminated soil where pets have left their droppings. And, of course, kissing a dog’s face could lead to a bite on your face! What should we do? Make sure your pets are current on all vaccines. New pets should undergo deworming. Keep your pets away from other animals’ feces. Wash your hands regularly with soap and water.

THE GOLDWATER RULE

Mark Siegel, a professor at New York University Langone Medical Center and a Fox News medical correspondent, had a piece in The Wall Street Journal regarding some pseudopsychiatric diagnoses including “narcissistic sociopath” and “pathologic liar” used to describe our 2016 presidential candidates (6). Siegel suggested that phrases like that lack empathy, and he emphasized that in actuality we don’t know either presidential candidate except through the media and that it is unfair to draw conclusions, although we all do it, about public figures we don’t know.

Since 1973, in the wake of damaging speculation published in a survey of psychiatrists about the mental fitness of 1964 Republican presidential candidate Senator Barry Goldwater, the American Psychiatric Association has abided by a principle known as the Goldwater Rule, published in its “Principles of Medical Ethics with Annotations Especially Applicable to Psychiatry.” The Goldwater Rule states that “it is unethical for a psychiatrist to offer a professional opinion unless he or she has conducted an examination and has been granted proper authorization for such a statement.”

In August 2016, as the presidential election campaign was heating up, the president of the American Psychiatric Association, Maria A. Oquendo, published a warning that psychiatrists should resist any temptation to psychoanalyze the candidates. “Simply put,” she wrote, “breaking the Goldwater Rule is irresponsible, potentially stigmatizing, and definitely unethical.” The Goldwater Rule, however, does allow a psychiatrist to share with the public his or her expertise about psychiatric issues in general. Siegel ended his excellent column with the following:

This profoundly unsettling and destructive [presidential] election [2016] may still serve as a teaching tool about how we ought to behave as a society and as individuals. Evidently, we still have to learn how to treat each other with respect,
regardless of race, ethnicity or gender. We need to regain the ability to accept opposing points of view instead of vilifying anyone who doesn’t agree with us. Definitely no invasions of personal space without permission. No mocking of women in any way—if nothing else, let’s remember that they are the people who gave birth to all of us. Also, apologies are fine, but how about no lying or making fun of each other or talking one way in public and another in private.

TOUCHING ONE’S OWN HEART

I recently encountered the book *The Man Who Touched His Own Heart: True Tales of Science, Surgery, and Mystery* by Rob Dunn, who is an associate professor of ecology and evolution in the Department of Biological Sciences at the University of North Carolina (7). I was intrigued with his title because I have shown about 65 patients who have undergone heart transplantation at Baylor University Medical Center their own hearts and photographed them holding their hearts in front of their chests. Despite going through most pages of Dunn’s book, I was unable to find a section describing “the man who touched his own heart.” Nevertheless, the book describes many major events in heart disease, both good and bad, mostly good, primarily in the last 70 years. I found the author to be a good storyteller. He does have a few factual inaccuracies, but they did not, in my view, detract from the readability of the book.

In contrast, Robert R. Nesbit Jr., MD, professor emeritus of surgery at Augusta University Medical College of Georgia, found the book “simplistic,” found the title misleading, and would not recommend the book to anyone, whether layman or physician. Dunn’s chapters are stories covering a wide range of topics related to the heart, including cardiac surgery, diet, the development of medications, and more. Nesbit was quite offended, as was I, by the author’s reference to Sir William Osler—the ultimate physician and humanist of his time—as a brilliant pathologist who “didn’t care for medicine, for curing the living.”

ALCOHOL IN COLLEGES

Surveys find that more than 40% of college students binge drink, defined by the Centers for Disease Control and Prevention as consuming five or more drinks for a man and four or more for a woman in about 2 hours (8). Of those imbibers, many end their sessions on gurneys. The Subzero walk-in freezers are dangerous (9). A number of experts suggest alarms, cell phones, or an ax kept inside to help someone get out. Some of these safety upgrades unfortunately would cost hundreds or thousands of dollars, and that expense can be a big obstacle to improvements. Leave the door a bit open when you walk into one of these freezers.

AMERICAN SERVICEMEN BURIED ABROAD

The American Battle Monuments Commission maintains 25 military burial grounds around the globe and 400 or so employees worldwide (10). The sites are in the United Kingdom, France, Belgium, Italy, the Netherlands, Luxembourg, Philippines, Mexico, Tunisia, Panama, and a few others. Of the approximately 218,000 US service members in them, 172,200 died in World War II and most of the rest in World War I. After World War II ended, the US government offered families of the slain at federal expense the choice of having them buried abroad or in the USA. About 25% were interred overseas, according to the American Battle Monuments Commission. Many of us will be long forgotten 7 decades after we die, but many people still honor the fallen Americans buried in overseas military cemeteries where the deliberators and the liberated now “live” together.

THE CONSOLATIONS OF MORTALITY

Andrew Stark, professor of management and political science at The University of Toronto, has written an intriguing book entitled *The Consolations of Mortality: Making Sense of*
Death (11). The author has indicated that the wisdom of the ages has generated four great consolations for mortality, none of which relies on religious conviction or invokes the possibility of an afterlife. The four include that death is actually benign; that immortality would give us no more goods than mortality can provide; that immortality would be intolerable; and that life already contains all the bad things that death entails.

Epicurus said that so long as we are alive, death is not with us, and in death there is no self so we have nothing to worry about. Stark observes that this view is not much help because we still have to face the fact that this thing we love—life—will someday be snuffed out. Stark indicates that the fact that he will be no more is what bothers him, not the fear that he will be unhappy when dead. The existentialists claim that death is the great motivator: it galvanizes us by its presence, forcing us to make something of our lives. Then there are the Buddhists. Once we come to see that the self is unreal, we will recognize that there is no self to die—no real entity goes out of existence when death overtakes us. In Western philosophy, we have the views of David Hume and Derek Parfit, to the effect that persons are collections of connective mental states with no underlying ego; so long as the mental state continues in other people, nothing substantial has been lost when a particular individual dies.

Now to the perils of immortality and whether they might be as harrowing as those of death. This part describes the important work of the late Bernard Williams, whose argument takes the form of a dilemma: either immortality would lead inevitably to excruciating boredom, or it would lead to the perpetual reinvention of the self, in which case it is tantamount to repeated death. It would seem to inevitably lead to boredom because eternity is an awfully long time to keep repeating the same old pleasures and passions. Most things in the world will have been learned, with few new things to pique one’s interest. Even a delicious plate of oysters will pall after the millionth dozen. Immortality also might allow for a crushing accumulation of bitter memories of slights, failures, and betrayals. Memory is already cruel enough in our limited lifespans, but it would be crueler if it could store up pain and grievance over endless eons.

As Stark argues, “Yes, death is bad, very bad, but it is not as bad as the impossibility of death. We may prefer mortality to immortality but that is like preferring to be whipped than electrocuted—neither is remotely acceptable.”

There may be many deaths over anyone’s biologic lifetime. The childhood self, for example, no longer exists, having been replaced by a very different adult self. Maybe we can be consoled by the thought that an ordinary human life consists of a series of deaths of successive selves, the last death merely being the one that puts an end to the series.

KAROSHI

It means death by overwork. According to a story in the USA Today, employees at nearly 1 in 4 companies in Japan are at risk of dying from working too many hours (12). According to the Japanese Labor Ministry, about 100 suicides per year in Japan are due to karoshi, and it is believed that this number represents just the tip of the iceberg. The Japanese prime minister in September 2016 appointed an outside panel to recommend changes to Japan’s workplace environment. A cabinet office report in October 2016 found that employees at 23% of Japanese companies worked 80 hours or more of overtime per month in 2015. That number appears to be the threshold at which the risk of death from physical or psychological causes is quite significant.

HOW WHAT WE EAT DEFINES WHO WE ARE

Sophie Egan, the director of programs and culinary nutrition for the Strategic Initiatives Group at The Culinary Institute of America, has written Devoured: From Chicken Wings to Kale Smoothies—How What We Eat Defines Who We Are (13). She divides us into three buckets: 1) the healthy eaters, 2) the totally unhealthy eaters, and 3) the sometimes healthy and the sometimes very unhealthy eaters.

There are 42,214 items in the average American supermarket, and each year we add over 20,000 new items. Our nutrient-centric environment often makes us buy foods not because they contain worthwhile ingredients, but because they omit something (fat, calories, etc.). We now have a protein craze: Nearly 60% of Americans are actively trying to increase their protein intake. Protein is “the new low fat” or “the new low carb.” The four “foods” that have increased the fastest in the USA in the last 30 years are bottled water, snack bars, frozen sandwiches, and frozen entrees; the four that have decreased the most are carbonated soft drinks, beef, salads, and bread.

More and more, the US as a nation cooks less and less. For the first time, in March 2015, Americans spent more money at restaurants and bars than at grocery stores. Our national motto is “gobble, gulp, and go”—eat and run. Ease of preparation and consumption are the driving forces of 21st century food product development. The percentage of single-person households is at an all-time high. (Who likes cooking for one?) One of the core tenets of human evolution appears to be “find someone else to do the cooking.”

Fast food is the best known feature of our food culture and the one we have exported most widely. It is not only the food but the way it is consumed at drive-throughs or carry-out. When we watch movies we eat popcorn. At state fairs the food is fried. Foods you didn’t even know could be fried are fried. In the summer we invite friends over for BBQs. Unlike in Britain, Canada, or Ireland, bacon is supposed to be crispy. Eat pizza—all kinds, any time. We are united by food events. Thanksgiving is our biggest. Our second biggest meal of the year is the Super Bowl evening.

The US work clock is all out of whack—the starting and stopping of work is far less clear than it used to be. Americans now work 200 more hours per year than they did in 1970. Our workaholic culture is killing us. As a result of longer hours, we have had to bring food into the workplace. Forty percent of us dine at our desks, particularly while multitasking. We minimize the time we spend obtaining, preparing, and consuming food to maximize the time we spend doing other things, mostly working. Ironically, many of us gladly spend half of our Sundays in pursuit of brunch. That may involve waiting in line at a
restaurant or actually cooking. (Pancakes and French toast are among the most-searched recipes online.) Taking a day to make a weekend meal suggests a silent protest against our workaholic society. It also suggests a rejection of all of our solo dining and of the idea that food is fuel. Most of the time, we eat exactly what we want, where we want, when we want, and as fast as we want. We in the US can always find a better way to do something.

We cannot understand American food culture without understanding American work culture. When asked how important working hard is to getting ahead in life, 73% of Americans rated it a 10 or “very important” compared to a median of 50% among 44 other countries worldwide. Only 59% of Americans actually take all of their paid vacation. Indeed, Americans today take less vacation time than at any point in nearly 40 years. The USA ranks last for time off provided to new parents. Workers who take all of their vacation time are viewed as less dedicated by at least 15% of senior management. The American work ethic is second to none! There is an amount of work that has a negative impact on output (errors, duplications, and the like), but we refuse to accept it.

We are the supersized nation with the biggest portions, the biggest cars, the biggest homes, and home theaters. That more is better also applies to hours of work. Our industriousness is arguably our economic edge around the world.

Our American work ethic undermines our eating. Being so busy has brought two major changes in our food culture: our definitions of “what” a meal is and “when” a meal is. Today, 20% of snacking happens outside the home. When we think snacks, we think dashboard dining or keyboard munching. The snack food is becoming the meal. A whopping half of all eating occasions now in the US are snacks! Snacks account for 14% of all restaurant traffic (restaurant meaning food service outlet). A snack is anything small, increasingly nutritional, and portable that complements or replaces a meal. As a consequence, we eat more total food than before. Between 1970 and 2010, the average daily caloric intake in the US increased by 505 calories total, up to 2544, according to the Department of Agriculture. That is a 25% increase!

A snack used to be infrequent, a special occasion. Now it happens throughout the day, every day. Snacks are no longer just for kids but for adults of all ages. Snacking is now a social norm. The marketers have tapped into the snacking desire. They make an even larger array of snacks and portable foods each year. We want everything to be more convenient this week than it was last week! The result is that we eat throughout the day.

We never set out to have the craziest food system on the planet or crushing rates of obesity and type 2 diabetes. We never intended to be so guilt ridden and confused about food. There is plenty more information in this book.

HANDWRITING

Many believe that the handwriting of physicians is atrocious, and I agree. But I’m not convinced that it is worse than that of many chief executive officers, as Adrian Flatt, MD, pointed out several years ago. I once took a class on handwriting, and the teacher recommended that a person have his/her handwriting analyzed by an expert before tying the marriage knot. Leaning the letter forward was a good sign and leaning it backward was a bad sign. Whether the letters went below the bottom line or the tall letters above the upper line showed certain characteristics of the person. I really have little patience with a person signing his/her name and having it totally unreadable.

Ann Trubek has written a book, The History and Uncertain Future of Handwriting (14). She indicates that it was in ancient Greece and Rome that radical alphabets arose featuring characters representing not only consonants but also vowels. Over the next millennium, handwriting grew more refined, resulting in the eventual appearance of what the author calls the “human Xerox machines,” the scriptoria of the Middle Ages where dilligent monks cranked out page after page of handwritten text, combining art and commerce. In the 15th century, the printing press irrevocably changed humankind’s relation with the written word. Trained masters of handwriting, no longer vital, were forced to take their skills on the road. Instead of writing a few commissioned books a year, these scribes started teaching penmanship to others through tutoring, classes, and books. They established a cadre of well-paid professionals in the process.

The 19th century was their heyday, when handwriting blossomed with an emphasis on standardization. Curlicues and sweeping strokes were added to letters like fins on a mid-century Cadillac. Penmanship instructors were akin to our yoga teachers, with acolytes and disciples who fervently followed their decrees and believed that a “good hand” meant more than being adept at a simple motor skill; it also improved the quality of one’s mind and one’s life.

The century was bracketed by two lions of longhand: Platt Rogers Spencer and A. N. Palmer. Spencerian penmanship was the sort of flowing, billowing letters familiar to anyone who’s pondered the Coca-Cola logo. Spencer was “a true believer in the ennobling qualities of script,” which “refines our tastes, assists in cultivating our judgment, and thereby makes us better men.” Ms. Trubek writes, “In the second half of the 19th century in America, having a good Spencerian hand was an indicator that you were Christian, educated, and proper.”

Spencer’s style was supplanted by a leaner script advocated by A. N. Palmer, who thought an industrializing country needed a more efficient script. His learning process was no less rigorous than Spencer’s—“students practiced arm movements for 3 to 6 weeks alone before picking up a pen.” Lefties were required to use their right hand, and students were also encouraged to cut off their undersleeves for more fluid arm motion. The Palmer School held sway into the 1930s, when secretaries and typewriters made it less vital for aspiring professionals to demonstrate a good hand for ledgers and correspondence.

Trubek unearthed some captivating sidelights in the history of handwriting. Medieval scribes could burn through 60 quill pens a day. In the 16th and 17th centuries, educated citizens learned two scripts: one for professional communications and one for personal. And the Palmer Method was thought to have a “powerful hygienic effect” and so was pressed on immigrants.

When it comes to writing, we are increasingly all thumbs as smartphones take over. I still write manuscripts with a pencil.
and paper, but that mode is quickly passing. It is infrequent to see handwriting in a medical record now. The loss of elegant handwriting, however, may be more than the disappearance of a basic motor skill. Spencer died in 1864 holding a pen in hand, still advocating for handwriting as enlightenment: “By disciplining your hand you could also discipline your mind.”

**US SKILL SCORES**

Clive Crook summarized the first results from an exhaustive international survey of skills by the Organization for Economic Cooperation and Development (15). It is the most authoritative project of its kind—a huge undertaking—comparing adults’ proficiency in literacy, numeracy, and problem-solving across the organization’s 22 member countries. In effect, the survey measures the quality of human capital, one of the crucial drivers of long-term economic success. The US performance, unfortunately, is pitiful. The average literacy score for Americans aged 16 to 65 places the USA 18th out of 22 participating countries. In numeracy, the US ranks 20th out of 22. In problem-solving—a measure of the capacity to interact productively with computers—the US ranks 14th of 19. These results are actually quite good when compared to the performance of US adults aged 16 to 24. In literacy, young Americans rank 20th out of 22; in numeracy, 22nd out of 22; and in problem-solving, 19th out of 19. Young Americans have slid to the bottom of the rankings mainly because young adults in other countries are doing much better than their predecessors did, whereas the American counterparts are not. The result is this: the capacity of the US labor force is consistently well below average, and the younger segments rank (on 2 out of 3 measures) dead last. These findings are a clear and present danger to US prosperity and social cohesion!

**DALLAS COUNTY 2016**

An editorial in The Dallas Morning News on October 31, 2016, stated: “Education is the best way out of poverty. But if you can’t speak English, the paths to a prosperous future are very limited” (16). Literacy Instruction for Texas expects that by 2030, >1 million of Dallas County’s projected 3.5 million residents will not be literate in English. Even now in Dallas, >35% of adults in households that make <$12,000 annually did not complete high school; half of them read English below a basic level. Much of the illiteracy rate, which is expected to grow faster than the population rate, is believed to be driven by immigration.

**SENIOR ATHLETICS**

The Physical Activity Guidelines for Americans, published by the US Department of Health and Human Services, recommends that adults aged 65 and older engage each week in 150 minutes of moderate-intensity aerobic activity, or 75 minutes of vigorous aerobic activity, plus resistance training 2 days a week (17).

Staying active and avoiding injury are certainly two goals of older individuals. Ageism, it appears, holds many older folks back from exercising more often than any physical limitation. Many people view retirement as an excuse to slow down; others see it as an opportunity to become more active. Senior athletes appear to be the fittest and happiest members of their age cohorts.

**COLLEGE FOOTBALL COACHING AND COMPENSATION**

According to a piece in the USA Today, 36 (56%) of the 64 football head coaches at colleges in the five largest conferences (Atlantic Coast, Big 12, Big 10, Pac-12, and Southeastern) make annual salaries of $3 million or more (18). The head coaches at Michigan and Alabama make $7 million annually. And buyouts of head coach contracts are also lucrative. Florida State’s head coach will be owed $33 million in his buyout. Wow!

**ARNOLD PALMER (1929–2016)**

He was born in Latrobe, Pennsylvania, a working-class steel mill town. His father was the head professional and greenskeeper at Latrobe Country Club, where he learned about golf. He attended Wake Forest College on a golf scholarship but left after a year to enlist in the US Coast Guard, where he served for 3 years, after which he returned to college and competitive golf. In 1954, he won the US Amateur and turned professional. His first professional win was the 1955 Canadian Open. From early on, he was the most popular player on the professional golf tour and remained so for decades. He eventually won 95 professional golf tournaments, including 62 PGA tournaments, 2 European, 2 Australasia, and 10 Senior PGA championships, including 7 Majors (between 1958 and 1970). He was nicknamed “The King” because his impact on golf was unrivaled. His humble background and plain-spoken popularity helped change the perception of golf as an elite, upper-class pastime to a more popular sport accessible to the working and middle classes. He also was one of “The Big Three,” along with Jack Nicklaus and Gary Player, who are widely credited with popularizing and commercializing the sport around the world. Although his total prize money on the PGA circuit amounted to only $1.9 million, he made a fortune (nearly $900 million) in his business enterprises and annually was one (usually #1 or #2) of the highest paid retired professional athletes. In 2015 he accumulated $40 million. He is the only golfer to have received the Presidential Medal of Freedom. As a pilot for almost 55 years, he logged nearly 20,000 hours of flight time in various airplanes. He indicated that next to marrying his wife, Winnie, and deciding on a professional career in golf, there was only one decision he considered smarter: learning to fly an airplane. He is already greatly missed.

**William Clifford Roberts, MD**

November 10, 2016


15. Crook C. Skills deficit is the real crisis for US. *Dallas Morning News*, October 20, 2016.


Original Research

3 Repeat ablation and hospitalization following cryoblation ablation of atrial fibrillation at a single tertiary medical center by C. E. East et al
7 Causes of tumor necrosis during photodynamic therapy by C. Bristow et al
11 Interpretation of positive troponin results among patients with and without myocardial infarction by K. M. Tescio et al
16 Relation between proprotein convertase subtilisin/kexin type 9 and directly measured low-density lipoprotein cholesterol by K. M. Tescio et al
21 Factors associated with reduced radiation exposure, cost, and technical difficulty of inferior vena cava filter placement and retrieval by M. Noll et al
26 Optimizing laboratory test utilization in long-term acute care hospitals by A. Mora et al
30 Inappropriate use of antibiotics in patients undergoing gynecologic surgery by J. Joyce et al
33 Concussion knowledge among rehabilitation staff by V. Salaboy et al
36 Factors associated with performance in an internal medicine clerkship by C. Cobalt et al

Case Studies

41 Late presentation of fatal hyperammonemic encephalopathy after Roux-en-Y gastric bypass by A. Nagare and A. Z. Fenxes
44 Recurrent epigastic appendicitis mimicking appendicitis and cholecystitis by C. Lorente et al
47 Endovascular therapy using flow diversion for giant internal carotid artery pseudoaneurysm arising in the setting of an invasive plastic macroadenoma by A. F. Saad et al
50 Pulmonary artery aneurysm by M. D. Shaw et al
52 Understanding vascular-type Ehlers-Danlos syndrome and avoiding vascular complications by A. Carter and A. Z. Fenxes
54 Right atrial thrombus and its causes, complications, and therapy by M. M. Benjamin et al
57 Intrauterine surgery by R. L. Rosenthal and J. O. Franklin
59 ST-elevation acute myocardial infarction due to arterial thrombosis in a 29-year-old woman with normal coronary arteries by J. D. Cantwell
61 A variant of Brugada syndrome by A. F. Khan et al
64 Electrocardiogram after operation for a subarachnoid hemorrhage by D. L. Gancy
66 Primary spinal epidural B-lymphoblastic lymphoma by R. K. Nambiar et al
69 B-cell lymphoma, thiamine deficiency, and lactic acidosis by A. Mora et al
71 Dasatinib-induced chylothorax in chronic myeloid leukemia by Z. Q. Baloch et al
74 Blood group change in acute myeloid leukemia by R. K. Nambiar et al
76 Subcutaneous paniculitis-like T-cell lymphoma by M. S. Attwood et al

Focal cutaneous squamous cell carcinoma following radium-223 extravasation by K. E. Benjegerdes et al
80 A nodular-ulcerative form of secondary syphilis in AIDS by G. Cosgrove et al
83 An approach for safe conversion of an oral endotracheal tube to a nasal endotracheal tube by M. Hofkamp and N. Palev
85 Ingestion of computer circuit boards causing esophageal impaction and small bowel obstruction by R. M. Solis
88 Bullet fragment-induced lead arthropathy with subsequent fracture and elevated blood lead levels by S. C. Brown and R. L. Dauterive
92 Identification of teratomas of Hassel's with reversible herniation of temporomandibular joint soft tissue into the external auditory canal on multidetector computed tomography by K. E. Benjegerdes et al
94 Anticoagulant hypersensitivity syndrome secondary to carbamazepine by N. Brown and R. L. Dauterive
97 Ruptural ectopic pregnancy with a negative urine pregnancy test by M. Hughes et al
99 Electromyogram-ruled focal myasthenia by A. Smith et al

Historical Studies

101 Henry Barton Jacobs, William Osler’s intimate friend by C. Bryan
106 A 1911 postcard of the National Hospital for the Paralysed and Epileptic highlighting European medical specialty training by A. Beba and C. J. Boes

Editorials and Book Review

109 On becoming a physician by K. G. Swan
112 Improving health outcomes through patient education and partnerships by T. E. Paterick et al
114 Parliament of Whores, revisited by H. L. Fred and M. Scheid
116 Reflections on the retirement of John W. Hyland, MD, by R. M. Solis
117 Torpedoed en route to France and World War I: a father’s experience by J. D. Cantwell
121 Book review: Howard and Georganna: Sixty Years of Marriage and Medicine by S. P. Mayrick

From the Editor

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

Miscellany

2 Clinical research studies enrolling patients
29 Acknowledgment of reviewers for volume 29
56 Avocations: Photograph by J. L. Manning
65 Avocations: Photograph by R. M. Solis
87 Avocations: Photograph by J. Rosenthal
96 Avocations: Photograph by R. M. Solis
123 Baylor Scott & White Health news
128 Reader comments: Operative management of dermatofibromas by T. E. Paterick et al; “Ruptural ectopic pregnancy with a negative urine pregnancy test” by M. Hughes et al

The peer-reviewed journal of Baylor Scott & White

Baylor Scott & White Medical Center - College Station

The largest not-for-profit health care system in Texas, and one of the largest in the United States, Baylor Scott & White Health was born from the 2013 combination of Baylor Health Care System and Scott & White Healthcare. For more information on our nearly 50 hospitals and more than 950 patient care sites, please visit baylorhealth.com and www.sw.org.