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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>
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<tbody>
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<td>Anesthesiology</td>
<td>Various device trials, measuring oxygenation levels; EEG algorithms of sedation, Sobo and fluid volume levels, delivery of various anesthesia medications</td>
<td>Zhang Zhang 214-865-3128 <a href="mailto:Zhang.Zhang@BSWHealth.org">Zhang.Zhang@BSWHealth.org</a></td>
</tr>
<tr>
<td>Asthma and pulmonary disease</td>
<td>Chronic obstructive pulmonary disease, asthma (adult), lung transplant, pulmonary hypertension, diaphragm impairment, nebulizer, inhalation</td>
<td>Francie Crockett, RRT 214-820-5829 <a href="mailto:Francie.Crockett@BSWHealth.org">Francie.Crockett@BSWHealth.org</a>; Courteney Kinney, BS 214-818-7898 <a href="mailto:Courteney.Kinney@BSWHealth.org">Courteney.Kinney@BSWHealth.org</a></td>
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<tr>
<td>Cancer</td>
<td>Breast, ovarian, endometrial, prostate, brain, lung, bladder, colorectal, pancreatic, and head and neck cancer; hemato logical malignancies, leukemia, multiple myeloma, non-Hodgkin's lymphoma; melanoma vaccine; bone marrow transplant</td>
<td>Grace Townsend 214-818-8472 <a href="mailto:cancer.trials@baylorhealth.edu">cancer.trials@baylorhealth.edu</a></td>
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<tr>
<td>Central Texas</td>
<td>Cancer, cardiology, family medicine, gastroenterology, infectious disease, kidney, neurology, obstetrics, ophthalmology, orthopedics, pathology, pediatrics, plastic surgery, pediatrics, psychiatry, pulmonary, radiology, rheumatology, surgery, transplant, urology</td>
<td>Vanessa Hoescher 1-888-863-3675</td>
</tr>
<tr>
<td>Diabetes (Dallas)</td>
<td>Type 1 and Type 2 diabetes, cardiovascular events</td>
<td>Lisa Mamo, RN 214-818-7874 <a href="mailto:Lisa.Mamo@BSWHealth.org">Lisa.Mamo@BSWHealth.org</a>; Anne Marie Jones 214-818-7823 <a href="mailto:Anne.Jones@BSWHealth.org">Anne.Jones@BSWHealth.org</a></td>
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<tr>
<td>Emergency Medicine</td>
<td>Traumatic brain injury</td>
<td>Jon Thammavong 214-818-9687 <a href="mailto:Jon.Thammavong@BSWHealth.org">Jon.Thammavong@BSWHealth.org</a></td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>Inflammatory bowel disease</td>
<td>Sandra Kirby, RN 214-818-9792 <a href="mailto:Sandra.Kirby@BSWHealth.org">Sandra.Kirby@BSWHealth.org</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Dallas)</td>
<td>Aortic aneurysms, coronary artery disease, hypertension, poor leg circulation, heart attack, heart disease, congestive heart failure, angina, cardiac artery disease, familial hypercholesterolemia, renal denervation for hypertension, diabetes in heart disease, cholesterol disorders, heart valves, thoracotomy pain, stem cells, critical limb ischemia, cardiac surgery associated with kidney injury, pulmonary hypertension</td>
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</tr>
<tr>
<td>Heart and vascular disease (Fort Worth)</td>
<td>Heart and lung transplant, mechanical assist device such as LVAD</td>
<td>Anima Chowdhury 214-818-2569 <a href="mailto:Anima.Chowdhury@BSWHealth.org">Anima.Chowdhury@BSWHealth.org</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Fort Worth)</td>
<td>Atrial fibrillation, atrial fibrillation post PCI</td>
<td>Vicki Stokes, BS 214-818-2529 <a href="mailto:victoria.stokes@BSWHealth.org">victoria.stokes@BSWHealth.org</a></td>
</tr>
<tr>
<td>Heart and vascular disease (Legacy Heart)</td>
<td>At risk for heart attack/stroke; previous heart attack/stroke/PAD; cholesterol disorders; atrial fibrillation; overweight/obese; other related conditions</td>
<td>Mary Cao 817-922-2574 <a href="mailto:Mary.Cao@BSWHealth.org">Mary.Cao@BSWHealth.org</a>; Angela Germany 469-603-6409 <a href="mailto:hcresearch@baylorhealth.edu">hcresearch@baylorhealth.edu</a></td>
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<tr>
<td>Heart and vascular disease (McKinney)</td>
<td>Medication affordability and antiprurient treatment effectiveness after MI</td>
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</tr>
<tr>
<td>Heart and vascular disease (Plano)</td>
<td>Aortic aneurysm, coronary artery disease, renal stent for uncontrolled hypertension; poor leg circulation; heart attack; heart disease; heart valve repair and replacement; critical limb ischemia; repair of aortic diseases with endograft; surgical leak repair; atrial fibrillation; heart rhythm disorders; cardiac artery disease; congestive heart failure; gene profiling</td>
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<td></td>
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<tr>
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<tr>
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<td>Abdominal, solid organs, liver/kidney</td>
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</tr>
<tr>
<td>Waco</td>
<td>Patient outcomes, PTSD, pain management with chest tubes, damage control surgery, readmission, trauma activation, critical care, acute care surgery</td>
<td>Evan Elizabeth Rainey 214-865-2410 <a href="mailto:Evan.Rainey@BSWHealth.org">Evan.Rainey@BSWHealth.org</a></td>
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<tr>
<td>Weight management</td>
<td>Obesity</td>
<td>Lisa Mamo, RN 214-818-7974 <a href="mailto:Lisa.Mamo@BSWHealth.org">Lisa.Mamo@BSWHealth.org</a></td>
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<tr>
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<td>Mary Cao 817-922-2574 <a href="mailto:Mary.Cao@BSWHealth.org">Mary.Cao@BSWHealth.org</a></td>
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Improving the quality of patient care requires a culture attuned to safety. We describe the development, implementation, and psychometric evaluation of the Attitudes and Practices of Patient Safety Survey (APPSS) within the Baylor Scott & White Health system. The APPSS was designed to enable safety culture data to be collected and aggregated at the unit level to identify high-priority needs. The survey, with 27 Likert-scale core questions divided into 4 concept domains and 2 open-ended questions, was administered electronically to employees with direct patient care responsibilities (n = 16,950). The 2015 response rate was 50.4%. The Cronbach’s α values for the four domains ranged from 0.78 to 0.90, indicating strong internal consistency. Confirmatory factor analysis results were mixed but were comparable to those of established safety culture surveys. Over the years, the adaptability of the APPSS has proven helpful to administrative and clinical leaders alike, and the survey responses have led to the creation of programs to improve the organization’s patient safety culture. In conclusion, the APPSS provides a reliable measure of patient safety culture and may be useful to other health care organizations seeking to improve the quality and safety of the care they provide.

Patient safety culture is a key element of health care quality and safety (1, 2). Since 2007, hospitals seeking Joint Commission accreditation have been required to demonstrate that “leaders regularly evaluate the culture of safety using reliable tools” (3). Thus, it was not surprising that tools to measure patient safety culture proliferated. By 2006, 12 distinct surveys were used by health care organizations to assess safety culture (4, 5). Most surveys showed substantial limitations in psychometric properties (4) and, as a result, more recent research tends to rely on one of four safety culture questionnaires that have demonstrated acceptable psychometric properties: the Hospital Survey on Patient Safety Culture (HSOPSC), the Safety Attitudes Questionnaire (SAQ), the Patient Safety Climate in Healthcare Organizations, and the Hospital Safety Climate Scale (6). Such consistency offers the advantage of comparability between hospitals; however, in the context of operational quality improvement, these surveys may not meet the needs of health care organizations. Such was the situation that the Baylor Health Care System (now part of Baylor Scott & White Health [BSWH]) encountered in 2002. There was a need for a tailored tool to collect data that organizational leaders could use to develop improvement initiatives by identifying high-priority patient safety needs. Here we describe the development, psychometric evaluation, and deployment of the Attitudes and Practices of Patient Safety Survey (APPSS).

METHODS

BSWH, formed through the 2013 merger of Baylor Health Care System and Scott & White Healthcare, is the largest not-for-profit health care system in Texas and one of the largest in the United States. It includes 49 owned, operated, joint-ventured, and affiliated hospitals, >500 patient care sites, >6000 affiliated physicians, >38,000 employees, an accountable care organization, and the Scott & White health plan. The data presented here are from the 23 acute care hospitals BSWH fully owned in the summer of 2015.

The first version of the APPSS in 2002 sought to incorporate domains that were thought to contribute to safety. Domains were derived from the general safety science and patient safety literature. A draft item list was constructed, incorporating both items used in existing survey instruments (that did not have copyright or intellectual property limitations) and newly developed items. The draft item list was reviewed for clarity and relevance by quality and safety professionals as well as hospital employees who provide direct patient care. Revisions were made based on their feedback to provide face and content validity to the survey items. After revision, each item was assigned to a primary concept domain by a content expert panel. Additionally, a summary item intended to represent the respondent’s overall assessment of patient safety in his or her hospital was included: “I would feel safe being treated in my facility as a patient.” A job satisfaction item...
was also included ("How satisfied are you with your work at Baylor?") to investigate whether a link exists between patient safety culture and professional satisfaction.

A frequency scale ("always," "most of the time," "sometimes," "rarely," and "never") was used for as many items as possible. This approach was based on the idea that individuals vary widely in how they rate their agreement, but tend to favor positive responses. Furthermore, it was thought that employees would be more responsive to a quantitative rating scale describing how often a desirable activity took place. For example, knowing that good professional teamwork took place only "sometimes" (the central option of the 5-point frequency Likert scale) was thought to raise more concern than a "neutral" response (the midpoint of the level of agreement response options). Frontline staff indicated that making a selection on a frequency scale was easier than selecting among agreement options.

Following pilot testing in 2003, the APPSS was revised to reduce the number of items in order to alleviate the time burden associated with completing the survey. In 2008, the acquisition of eSurvey design software (SNAP Surveys, Portsmouth, NH) facilitated the use of additional survey methods such as branched chain items. Other changes were made based on results of cognitive testing and focus groups conducted following the first few deployments of the survey. By 2013, a core set of 27 standard Likert-scale items (17 of which have response-triggered follow-up items) and 2 open-ended questions covering four domains had been established (Table 1). A limited number of custom questions to investigate contemporary issues impacting safety (e.g., implementation of electronic medical records) can be added in each deployment.

The APPSS forms part of a 2-year patient safety monitoring and improvement cycle, with patient safety site visits being conducted in the years it is not deployed (7). It is deployed electronically to enhance data integrity (8) and enable more efficient data management. During each deployment, employees with direct patient care responsibilities receive an email inviting them to participate in the online survey; the invitation includes a URL link that takes them directly to the survey. Employee data from the human resources databases are linked to the URL, eliminating the need for respondents to enter data related to their role, location, tenure, or other relevant characteristics. The survey period lasts for 3 weeks, during which the eSurvey software e-mails weekly reminders to employees who have not yet submitted their response.

The internal consistency of the instrument was assessed using Cronbach’s α coefficient of reliability. We also assessed convergent and divergent validity of the survey items, checking that the corrected item-to-domain correlation (which indicates the item’s correlation to the concept domain to which it is assigned) was higher than the item-to-nondomain correlation (which indicates the item’s correlation to the other concept domains). We used the corrected item-total correlation, meaning that the item was removed from the domain score before the correlation was calculated. Correlations among the concept domains were also examined to ensure that the domains were sufficiently unique to be considered separate constructs. Finally, we fit a confirmatory factor model to examine the four predefined domains of leadership, teamwork, resources, and reporting and feedback. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

<table>
<thead>
<tr>
<th>Table 1. Items in the Attitudes and Practices of Patient Safety Survey by concept domain</th>
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<td><strong>Domain</strong></td>
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<tr>
<td>Leadership</td>
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<tr>
<td>Reporting and feedback</td>
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*Composite of four items asking individually about physicians, nurses, managers, and other staff.
RESULTS

In the 2015 deployment, 16,950 employees were invited to participate, and 8548 responses were received (response rate = 50.4%) across 23 facilities. The Cronbach’s $\alpha$ value for the APPSS domains indicated strong internal consistency, as shown in Table 2: all values fell in the 0.75 to 0.80 range (very good) or ≥0.80 range (excellent) (9). Table 2 also shows the corrected item-to-domain and item-to-nondomain correlations for each concept domain (8). For each domain, the former was larger than the latter, indicating that the items within each domain measured the same underlying concept. Based on the moderate to strong corrected item-to-domain and the smaller, moderate corrected item-to-nondomain correlations observed, the survey had desirable construct validity. This confirms the face and content validity observed via focus groups in the early years of development and deployment. Table 3 shows the correlations among the patient safety concept domains; all were <0.80, indicating that the domains were sufficiently different to be considered unique and to avoid problems with multicollinearity (10). The results shown in Tables 2 and 3 together support the use of the four concept domains and the assignment of items to them.

Table 4 shows the correlation between the concept domains and the overall patient safety rating at the individual respondent level, at the unit level, and at the hospital level. The concept domains that were the strongest predictors of an employee’s overall view of the safety of care were “Resources” and “Teamwork.” The highest level of analysis (i.e., the hospital level) showed the highest correlations; however, the correlations for the unit analysis and the individual analysis were very similar.

DISCUSSION

The APPSS satisfies this organization’s need for a safety culture survey because it provides meaningful data that enables leaders to make informed decisions regarding the implementation of improvement initiatives targeting patient safety. Our evaluation shows it to have acceptable psychometric properties, making it a feasible alternative to the safety culture questionnaires that have dominated the safety culture research literature.

The reliability of the APPSS was comparable to that reported for the 12 dimensions of the HSOPSC, whose Cronbach’s $\alpha$ values range from 0.44 to 0.84 (7, 12). The overall model fit for the HSOPSC was superior to that of the APPSS, with goodness-of-fit and normalized-fit index values >0.90 and an RMSEA of 0.04 (7). The SAQ also shows better model fit, with a comparative fit index of 0.90 and RMSEA of 0.03, but only

<table>
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<th>Concept domain</th>
<th>Leadership</th>
<th>Reporting and feedback</th>
<th>Resources</th>
<th>Teamwork</th>
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<td>Teamwork</td>
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<td>–</td>
<td>–</td>
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Table 5. Results of confirmatory factor analysis for the Attitudes and Practices of Patient Safety Survey (2013 version)

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<td>Goodness of fit index</td>
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<td>Bentler-Bonett normalized fit index</td>
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</table>
after 10 items were dropped to obtain satisfactory model fit \(^{(13)}\). The intercorrelation between concept domains was more consistent for the APPSS than the SAQ, ranging from 0.60 to 0.68, compared to the range of −0.28 to 0.95 \(^{(13)}\).

The APPSS was developed prior to the availability of the HSOPSC and its comparative database. While using the HSOPSC would enable comparison to other hospitals, BSWH has chosen to continue using the APPSS. Factors influencing this decision include the “deeper dive” that the APPSS provides through the use of response-dependent “breakout” items, the use of the frequency scale responses, the avoidance of negatively worded items, and the inclusion of questions asking for free-text responses through which respondents can address specific issues. Additionally, with the APPSS, hospital leaders have the ability to add, delete, and/or revise question items as necessary for the evaluation of current safety issues. Further, while the APPSS contains a similar number of items to the HSOPSC, they are divided into four concept domains rather than 12 dimensions \(^{(7)}\), and this reduced number of domains is felt to be more manageable and actionable for leaders without expertise in patient safety culture.

The “breakout” survey items have been particularly helpful within BSWH in pointing to actionable deficits as perceived by frontline staff. For example, one facility that showed poor responses on a question addressing senior leaders’ promotion of patient safety initiated regular patient safety leader rounding that both increased the visibility of the leadership’s involvement in patient safety and offered staff an opportunity to speak up about their concerns. Another system-level example comes from the inclusion of a question, with a breakout, about the patient safety implications of the adoption of electronic medical records in BSWH hospitals in the 2013 version of the APPSS. Responses indicated staff had concerns about the use of electronic medical records that warranted further exploration, which led to the development of a separate survey to measure user experience with the electronic medical record \(^{(14)}\).

The major limitation of our evaluation of the APPSS is that this instrument has been exclusively developed and used within BSWH and operates with a response rate of approximately 50%, so generalizability to other institutions has not been demonstrated. Given that terminology can be very specific to a particular region or institution, further work is needed to ensure respondents in organizations other than BSWH interpret the APPSS items in the same way. A related limitation is that comparison data to other institutions are not readily available.

**ACKNOWLEDGMENTS**

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Safety and efficacy of 2-octyl-cyanoacrylate in the management of patients with gastric and duodenal varices who are not candidates for transjugular intrahepatic portosystemic shunts

Luis Lizardo-Sanchez, MD, James Burdick, MD, and James F. Trotter, MD

Gastric variceal bleeding is associated with significant morbidity and mortality in patients with portal hypertension and cirrhosis. Options are limited for patients who are not candidates for transjugular intrahepatic portosystemic shunts (TIPS). Cyanoacrylate injections have been reported to be efficacious in previous case series. The aim of this retrospective study was to report our single-center experience with the safety and efficacy of 2-octyl-cyanoacrylate in patients who were not TIPS candidates. Electronic medical records were reviewed for 16 patients who underwent a total of 18 esophagogastroduodenoscopies for acute gastric or duodenal variceal bleeding and secondary prophylaxis of gastric varices; 14 patients had cirrhosis with an average Model for End-Stage Liver Disease score of 16, and 2 patients had noncirrhotic portal hypertension. Primary endpoints of the study included early and delayed rebleeding rate, complications, and death or liver transplantation. The rebleeding rate (early or delayed) was 7%, and no complications were found. One death was reported (unrelated to the procedure). In conclusion, 2-octyl-cyanoacrylate is a safe and effective alternative for non-TIPS candidates who present with acute gastric variceal bleeding given its low rebleeding and complication rate.

In general, management of acute gastric variceal bleeding consists of a combination of pharmacological therapy (octreotide bolus, followed by infusion), endoscopic therapy (banding ligation in the case of gastroesophageal varices type 1), bridge therapy (balloon tamponade), and rescue therapy (transjugular intrahepatic portosystemic shunts [TIPS]) in cases of high risk of rebleed or refractory bleeding. However, patients with severe decompensation of liver disease or significant thrombus of hepatic vasculature are not ideal candidates for TIPS or balloon-occluded retrograde transvenous obliteration (1, 2), therefore limiting their therapeutic options to the use of tissue glues. 2-Octyl-cyanoacrylate is a monomer that rapidly polymerizes when it comes into contact with weak bases (blood and water). Several trials have demonstrated a similar hemostasis rate compared with alcohol and ethanolamine, a lower rate of rebleeding compared with band ligation, and a reduced rebleeding rate compared with beta-blockers (3–5). However, most studies of cyanoacrylate have been performed outside of the United States, mainly in Asia and Europe. The purpose of our study was to report our experience with 2-octyl-cyanoacrylate in the management of patients with gastric and duodenal variceal bleeding who were not candidates for alternative procedures such as TIPS.

METHODS

This was a retrospective analysis of 16 patients who presented to our institution with gastric or duodenal variceal bleeding with high-risk stigmata (defined as nipple sign, red wale sign, or size >10 mm). Most patients had decompensated cirrhosis and were not candidates for TIPS. Patients were treated with 2-octyl-cyanoacrylate between July 2012 and October 2014 for active bleeding or secondary prophylaxis of bleeding. The study was approved by the Baylor University Medical Center institutional review board. After explaining risks, benefits, and alternatives of the procedure, we obtained informed consent from patients, or family members if the patient could not provide consent, prior to each procedure.

Patients’ deidentified data were obtained through review of electronic medical records. The information obtained included age, gender, liver disease (i.e., cirrhosis or portal vein thrombus), TIPS candidacy, esophagogastroduodenoscopy reports, progress notes, laboratory data for Model for End-Stage Liver Disease (MELD) score calculation (complete blood count, comprehensive metabolic panel, prothrombin time), and details regarding administration of cyanoacrylate (milliliters administered, number of sessions). Varices were classified according to location (gastric or duodenal). The Sarin anatomic classification system was used to characterize gastric varices. Dates were noted for death, liver transplantation, or last clinic or hospital follow-up.

Patients with gastric or duodenal varices underwent endoscopy for active bleeding or secondary prophylaxis in the hospital setting (Figure). Two experienced endoscopists (JB, JT) administered the 2-octyl-cyanoacrylate with anesthesia assistance. Olympus GF 160 and 180 therapeutic endoscopes were utilized. Marcon-Haber metallic injector sclerotherapy

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needles (Cook-Medical, Winston-Salem, NC) were used for procedures. All patients received 2-octyl-cyanoacrylate for variceal obliteration. The varices were targeted both in a forward view and retroflex fashion, depending on endoscopic preference and varix angle. The rate of cyanoacrylate administered was 1 to 2 mL/minute. The amount and sessions of glue injections varied according to endoscopists’ assessment of variceal obliteration and clinical evidence of active bleeding.

The study had four primary endpoints:

• Early rebleeding rate, defined as percentage of patients with evidence of overt gastrointestinal bleeding 7 days after the procedure
• Delayed rebleeding rate, defined as percentage of patients with evidence of overt bleeding 8 to 90 days after the procedure
• Complications, including pulmonary embolism, stroke, perforation, infection, or failure to achieve hemostasis requiring urgent TIPS
• Death from any cause

RESULTS

During the study period of July 2012 to February 2014, 16 patients were identified who underwent a total of 18 esophagogastroduodenoscopies with cyanoacrylate injection. Fourteen of the 16 patients had cirrhosis, with predominant etiologies including cryptogenic, chronic hepatitis C, and alcoholic liver disease (Table). Two patients had noncirrhotic portal hypertension associated with portal vein thrombosis.

Most patients (78%) underwent cyanoacrylate injection for active gastrointestinal bleeding; 22% who underwent this procedure were referred for secondary prophylaxis after experiencing an episode of gastric variceal bleeding. Based on Sarin’s classification, most varices were classified as GOV-2 (50%), followed by IGV-1 (38%) and duodenal varices (19%). The average MELD score was 16 (standard deviation [SD], 9).

A total of 18 procedures were performed on 16 patients. The mean number of injections was 1.5. The median amount of the injection used for the procedure was 4.2 mL (SD, 1.3 mL). Immediate postprocedure hemostasis was accomplished in 93% of patients who presented with acute gastric variceal bleeding (Table).

The median follow-up for our patients was 461 days (SD, 224 days). Among the patients who presented with active

| Table. Baseline characteristics, procedure data, and outcome data for 16 patients undergoing 18 cyanoacrylate injections |
|---|---|
| Variable | Value |
| **Baseline** | |
| Age (years), mean | 53 ± 13 |
| Males | 9 (56%) |
| Females | 7 (44%) |
| Cirrhosis | 14 |
| Etiology | |
| Alcohol | 4 |
| Chronic hepatitis C | 4 |
| Cryptogenic | 5 |
| Other (biliary atresia) | 1 |
| Portal vein thrombosis | 2 |
| MELD score, mean | 16 ± 9 |
| **Procedure** | |
| Indication | |
| Active bleeding | 14 (78%) |
| Secondary prophylaxis | 4 (22%) |
| Varix type | |
| IGV-1 | 6 |
| IGV-2 | 0 |
| GOV-1 | 1 |
| GOV-2 | 8 |
| Duodenal | 3 |
| Number of injections (mean) | 1.5 ± 0.7 |
| Amount of injection used (mL; mean) | 4.2 ± 1.3 |
| **Outcomes** | |
| Follow-up (days), median | 461 ± 224 |
| Early rebleeding rate | 1 (7%) |
| Delayed rebleeding rate | 1 (7%) |
| Complication rate | 0 (0%) |
| Death or transplant | 1 (6%) |
| Postprocedure immediate hemostasis | 13 (93%) |

*Death from sepsis unrelated to the procedure.
GOV indicates gastroesophageal varices; IGV, isolated gastric varices; MELD, Model for End-Stage Liver Disease.
bleeding, one experienced early rebleeding at day 2 and another was found to have delayed rebleeding at day 9. Although one of these patients was not deemed to be an ideal candidate for TIPS placement, he was able to undergo this procedure as a salvage therapy. One technical complication was reported due to catheter malfunction (glue not deployed), but no pulmonary embolism or thrombotic phenomena related to the cyanoacrylate injection were reported. One patient died of sepsis during an admission 7 months later. This death was deemed to be unrelated to the procedure but was included in the analysis.

**DISCUSSION**

Treating gastric and duodenal variceal bleeding in patients who are deemed to be ineligible for TIPS placement is a challenging therapeutic dilemma for the gastroenterologist; high-risk decompensated patients with cirrhosis have limited options for treatment. The findings of our single-center retrospective study confirm results reported by Rengstorff et al (6) and Monsanto et al (7), where the use of cyanoacrylate injection is very effective in controlling gastric variceal bleeding with an acceptable safety profile. Studies from China, Portugal, and the United States have reported rebleeding rates in the range of 4% to 14.4% (6–8). Our patient population consisted of subjects with active gastric variceal bleeding, and we were able to achieve hemostasis in 93% of them. Previous studies have shown cyanoacrylate injection to have better efficacy than variceal ligation (7) and results equivalent to those of TIPS (9). A minority of patients were referred for glue injection for secondary prophylaxis. No patients in this group developed rebleeding, although we recognize this was a small portion of patients in our study. In addition, our study included 3 patients who underwent injection of duodenal varices with successful hemostasis without subsequent evidence of bleeding.

Complications associated with glue injection include fever, abdominal pain, bacteremia, and thrombotic phenomena such as pulmonary embolism and stroke. The rate of complications appears to be mitigated by slowing the infusion rate as well as using a smaller amount of cyanoacrylate. No patients in our study developed procedure-related complications. There was one technical complication related to the deployment of cyanoacrylate, which may be related to the priming of the catheter. There was only one death in our study, which occurred 7 months after the procedure on a separate admission to the hospital, which we did not think was related to endoscopic therapy.

The limitations of our study include its retrospective nature and the small size of our patient population. The procedures were performed by experienced endoscopists; thus, results may not be generalizable. Although we followed patients for more than 1 year, we cannot guarantee that in our tertiary referral center no patients were lost to follow up. In this particular high-risk population, the use of tissue adhesives should still be considered when options are scarce for decompensated cirrhotics requiring management of gastric variceal bleeding.

Usefulness of ultrasonographic measurement of the diameter of the inferior vena cava to predict responsiveness to intravascular fluid administration in patients with cancer

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We conducted an observational, longitudinal prospective study in which we measured the diameters of the inferior vena cava (IVC) of 47 patients using ultrasonography. The aim of our study was to assess the state of blood volume and to determine the percentage of patients who responded to intravascular volume expansion. Only 17 patients (36%) responded to fluid management. A higher number of responding patients had cardiovascular failure compared with nonresponders (82% vs. 50%, P = 0.03). Among the patients with cardiovascular failure, the probability of finding responders was 4.6 times higher than that of not finding responders (odds ratio, 4.66; 95% confidence interval, 1.10–19.6; P = 0.04). No significant difference was observed in the mortality rate between the two groups (11% vs. 23%, P = 0.46). In conclusion, responding to intravascular volume expansion had no impact on patient survival in the intensive care unit.

The main objective of this study was to use ultrasonography to determine the percentage of patients who responded to fluid administration. As secondary objectives, we determined the mortality rates and the differences in hemodynamic variables between responders and nonresponders among the patients admitted to the intensive care unit (ICU) of the Instituto Nacional de Cancerología, México.

METHODS

We performed an observational, longitudinal, prospective study on the oncologic patients admitted to the ICU of Instituto Nacional de Cancerología, México, between January 2015 and June 2015. During this period, we measured the patients’ inferior vena cava (IVC) diameters using ultrasonography before beginning fluid reanimation. The sample size was calculated using the proportion formula \[ n = Z_a^2 \cdot p \cdot q \cdot d^2, \] where \( p \) is the possibility of finding a patient who responds to volume expansion (50%), and \( q = p - 1 \), with a significance level of 0.05% that corresponds to a Z value of 1.96 and has a 12% accuracy (d). Using this formula, the required sample size for the study was determined to be at least 34 patients.

The IVC diameter was measured in the subxiphoid window using transthoracic echocardiography operating in the M mode, 2 to 3 cm from the junction of the IVC and the right atrium. We determined the maximum and minimum diameters of the IVC during the patients’ respiratory cycles. In patients with spontaneous ventilation, the collapsibility index of the IVC (cIVC) values were calculated using the following formula: \[ [(\text{maximum diameter} - \text{minimum diameter}) / \text{maximum diameter}] \times 100 \], and in patients with positive-pressure mechanical ventilation, the distensibility index of IVC (dIVC) values were calculated using the formula \[ [(\text{maximum diameter} - \text{minimum diameter}) / \text{minimum diameter}] \times 100 \]. If the dIVC index was >18% or the cIVC index was >40%, the patient was determined to be responsive to intravascular volume expansion. Doctors trained in basic critical care ultrasonography performed the measurements to reduce bias and decrease the error margins.

We followed the guidelines outlined in the Declaration of Helsinki and its modifications as outlined in the Declaration of Tokyo for biomedical research in humans, along with the ethical considerations formulated in the “Ley General de Salud de los Estados Unidos Mexicanos” (General Law of Health in United Mexican States) for health research. The investigation is classified under the 17th article of the health research regulations as category I. This was a research study involving minimal risk because ultrasonography is a noninvasive diagnostic method with minimal risks for the participants.

This study included patients over 18 years old with positive-pressure mechanical ventilation whose dIVC indices were measured. This study also included patients over 18 years old with spontaneous ventilation whose cIVC indices were measured. We excluded patients who were treated with fluid reanimation at the time of ICU admission prior to IVC measurements. Patient data were collected immediately after the patients were admitted to the ICU. We collected information regarding patients’...
demographic characteristics, comorbidities, hemodynamic variables, type of oncological illness, and diagnosis at the time of admission. We calculated APACHE II (Acute Physiology and Chronic Health Evaluation II), SOFA (Sequential Organ Failure Assessment), and MEXSOFA (Mexican Sequential Organ Failure Assessment) scores to assess the severity of patients’ organ failure. APACHE II, SOFA, and MEXSOFA scores were calculated using each patient’s worst clinical and laboratory values during the first 24 hours of their stay in the ICU. The rate of organ failure was determined using the SOFA score, and severity of organ failure was determined using the patients’ laboratory and clinical data, as well as information about their vasopressor or inotropic doses (1–4). We documented the number of volume-responsive patients.

The numerical values were expressed as the mean ± standard deviation if the distribution was normal or as the median ± the interquartile range if the distribution was nonnormal. Data distribution was evaluated using the Kolmogorov-Smirnov test. Nominal variables were expressed using percentages. Numerical variables were compared using a Student’s $t$ test, Mann-Whitney $U$ test, and chi-square test. Fisher’s exact test was used to analyze the nominal variables. To establish an association between cardiovascular failure and volume responsiveness, we used the $X^2$ value from the Mantel-Haenszel test and expressed it as an odds ratio with a confidence interval of 95%. A $P$ value $< 0.05$ was considered statistically significant. The heart rate needed to predict the response to intravascular volume expansion was calculated using the area under the receiver operating characteristic curve. We also calculated the values for specificity, sensitivity, positive predictive value, and negative predictive value. All data were analyzed using SPSS version 22.0 for Windows.

**RESULTS**

This study included 47 critically ill oncologic patients who had been previously administered intravenous crystalloids. We measured the IVC diameters and calculated the dIVC or cIVC for each patient. Table 1 shows the general characteristics of the patient population. Less than half of the patients admitted to the ICU responded to the administration of intravascular volume expansion ($n = 17, 36.2\%$). Table 2 shows the clinical characteristics of the critically ill oncologic patients admitted to the ICU who were classified according to their volume expansion responsiveness. In patients with heart rates $> 88$ beats per minute, the minimum parameters required to predict volume responsiveness were a sensitivity of $82.4\%$, a specificity of $53.3\%$, a positive predictive value of $50\%$, and a negative predictive value of $84.2\%$. In patients with heart rate $> 88$ beats per minute, the rate of unnecessary crystalloid administration was $15.8\%$ (Figure 1).

**DISCUSSION**

This study had three main findings:

- Only $36\%$ of the critically ill oncologic patients who were admitted to the ICU responded to intravascular volume expansion.
- Patients with cardiovascular failure and tachycardia were more likely to respond to volume expansion.

- There was no significant difference in mortality rates between responders and nonresponders.

In patients with circulatory shock, fluid reanimation with crystalloids is one of the main treatment options to increase cardiac output and improve tissue perfusion (5–9). The clinical parameters used to evaluate blood volume in patients experiencing shock have poor specificity (10–12). Currently, the recommended procedure is to determine dynamic variables such as IVC measurements using ultrasonography in patients with mechanical ventilation during the respiratory cycle to predict their responsiveness to volume expansion. This procedure is also useful in patients with spontaneous ventilation (13). Muller et al reported that in patients with spontaneous ventilation, a cIVC index $>40\%$ is usually associated with volume responsiveness (14).
According to Michard et al, up to 72% of critically ill patients will respond to volume expansion with a significant increase in stroke volume or cardiac output (15). This contrasts significantly with our study, because only 36% of the patients admitted to the ICU in our institution were volume responders. VASST study data demonstrated that maintaining a positive water balance for 12 hours to 4 days after beginning the fluid reanimation can increase mortality in critically ill patients (16). Therefore, it is important to evaluate the volume responsiveness prior to the administration of intravenous liquids to determine if patients would benefit from it (17). We are not aware of any clinical studies that compare the mortality rates of volume responders and nonresponders. In our study, we did not find statistically significant differences in mortality rates between these two groups of critically ill patients. With respect to organ failure, we observed that the patients with cardiovascular failure, as determined by SOFA scores, were more likely to respond to the administration of intravenous fluids. With the above data, we can infer that the patients admitted to the ICU with hemodynamic instability and evaluated for volume responsiveness using their clinical and laboratory data of tissue hypoperfusion are those who can benefit from fluid reanimation, which results in increased cardiac output and, thus, increased oxygen supply to the tissues (3).

In the hemodynamic evaluation and monitoring described by Pinsky, he reported that the heart rate increases in patients with shock due to the increase of sympathetic tone; in short, “tachycardia is never good” (5). In our study, we found that a heart rate of 88 beats per minute was a threshold that helps determine the responsiveness of a patient to fluid administration, with a sensitivity of 88.4% and a specificity of 53.3%.

In the present study, only a third of the patients evaluated at the time of ICU admission using ultrasonography responded to volume expansion. One limitation of our study is that the measurements taken using ultrasonography can be operator dependent. It is important to evaluate who will benefit from fluid administration to avoid complications related to fluid overload. It must also be stressed that finding a volume responder is not the only parameter to be considered when deciding if fluid reanimation is needed, unless there are clinical and laboratory data of hypovolemic and tissue hypoperfusion that warrant intravascular volume expansion.

### Table 2. Clinical and hemodynamic characteristics of critically ill oncologic patients who were admitted to the ICU classified according to their volume response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responder (n = 17)</th>
<th>Nonresponder (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)**</td>
<td>46.2 ± 18.9</td>
<td>48.8 ± 16.1</td>
<td>0.63</td>
</tr>
<tr>
<td>SOFA (points)**</td>
<td>7 ± 3.5</td>
<td>6.6 ± 3.9</td>
<td>0.72</td>
</tr>
<tr>
<td>APACHE (points)*</td>
<td>16 (10–20)</td>
<td>12 (10–19)</td>
<td>0.63</td>
</tr>
<tr>
<td>MEXSOFA (points)**</td>
<td>8.3 ± 5.6</td>
<td>7.4 ± 4.0</td>
<td>0.52</td>
</tr>
<tr>
<td>SAP (mm Hg)*</td>
<td>92 (90–108)</td>
<td>100 (100–110)</td>
<td>0.05</td>
</tr>
<tr>
<td>DAP (mm Hg)*</td>
<td>60 (50–70)</td>
<td>67.5 (60–70)</td>
<td>0.18</td>
</tr>
<tr>
<td>Heart rate (bpm)*</td>
<td>99 (90–120)</td>
<td>88 (78–100)</td>
<td>0.047</td>
</tr>
<tr>
<td>Central venous saturation (%)*</td>
<td>76 (69–80)</td>
<td>74 (69–79)</td>
<td>0.59</td>
</tr>
<tr>
<td>Lactate (mmol/L)*</td>
<td>2.7 (1.2–6.2)</td>
<td>1.8 (1–3.7)</td>
<td>0.31</td>
</tr>
<tr>
<td>Base excess (mmol/L)*</td>
<td>−5.7 (−2.9 to −9)</td>
<td>−4.5 (−2 to −6.3)</td>
<td>0.71</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)**</td>
<td>19.8 ± 5.51</td>
<td>19.9 ± 6.68</td>
<td>0.97</td>
</tr>
<tr>
<td>Organ failures ≤ 2</td>
<td>10 (58.8)</td>
<td>14 (46.6)</td>
<td>0.42</td>
</tr>
<tr>
<td>Organ failures ≥ 3</td>
<td>7 (41.2)</td>
<td>16 (53.4)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular failure</td>
<td>14 (82.3%)</td>
<td>15 (50%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>13 (76.4%)</td>
<td>27 (90%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hematologic failure</td>
<td>8 (47%)</td>
<td>22 (73.3%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>4 (23.5%)</td>
<td>8 (26.6%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5 (29.4%)</td>
<td>9 (30%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Neurologic failure</td>
<td>3 (17.6%)</td>
<td>2 (6.6%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Mechanical ventilation requirement</td>
<td>10 (58.8%)</td>
<td>16 (53.3%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Hypovolemic shock</td>
<td>8 (47%)</td>
<td>8 (26%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Septic shock</td>
<td>6 (35.2%)</td>
<td>10 (33.3%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Death in ICU</td>
<td>2 (11%)</td>
<td>7 (23.3%)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*Median and interquartile range.
**Mean ± standard deviation.
DAP indicates diastolic arterial pressure; ICU, intensive care unit; SAP, systolic arterial pressure.

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The 4th Annual Research Days in Central Texas successfully came together on May 4–5, 2016. This multi- and cross-disciplinary event showcases the breadth of research at Baylor Scott & White Health. Medical residents and fellows, postdoctoral research fellows, medical students, nurses, research staff, and faculty represented the diverse group of investigators presenting research. This year, 86 abstracts were accepted from varying aspects of research, including basic/translational science, clinical effectiveness/delivery, case studies, and quality improvement. Abstract peer review resulted in the selection of 10 podium presentations and 76 posters. Departmentally nominated podium presentations were given by Di Ai, MD, Chad Hall, MD, and Matthew McMillin, PhD, and research podium presentations were given by Laura Hargrove, MS, Matthew Gestaut, MD, Connie Barker, PhD, Gurkarminder Sandhu, MD, Emily Wu, MD, Eric Sparks, MD, and David Olek, MD. Poster presentation winners included Bella Mogaka, PharmD, Christopher Johnson, MD, PhD, Ryang Hwa Lee, PhD, and Zachary Burke, BS. Selected abstracts are presented below.

**Activation of the apelin–apelin receptor axis promotes cholangiocarcinoma growth and angiogenesis**

Chad Hall, MD,* Laurent Ehrlich, BA, Tori Sheppard, April O’Brien, BS, Terry C. Lairmore, MD, Gianfranco Alpini, PhD, and Shannon Glaser, PhD (*e-mail: chad.hall@BSWHealth.org*)

The apelin receptor (APLNR), a G-protein coupled receptor, is involved in benign and malignant pathologies, including diabetes, obesity, and colon, prostate, and breast cancer. Cholangiocarcinoma (CCA) is an often fatal malignancy of intra- and extrahepatic cholangiocytes. We tested the hypothesis that the apelin–APLNR axis regulates CCA growth by autocrine/paracrine mechanisms. CCA cell lines (CCLP, HuH-28, HuCCT-1, SG231, TFK, and Mz-ChA-1) and nonmalignant cholangiocytes (H69) were used to measure the expression of APLNR via immunoblots. Immunohistochemistry was also used to measure APLNR expression in human CCA tissue arrays. Apelin secretion from CCA and H69 cell lines was measured by enzyme-linked immunosorbent assay (ELISA). CCA cell lines were treated with apelin in the presence and absence of APLNR antagonist over various timepoints. Changes in proliferation were measured through quantitative polymerase chain reaction (qPCR) for Ki-67 and proliferating cell nuclear antigen. Angiogenesis markers, including vascular endothelial growth factor-A and -C, were measured by qPCR. The Muse MAPK Dual Detection kit was used to measure phosphorylation of ERK1/2, a known pathway for cholangiocyte proliferation. Results showed that APLNR was upregulated in CCA cell lines and human CCA tissue arrays compared with nonmalignant controls. By ELISA, there was enhanced secretion of apelin in CCA lines compared with H69. Treatment of CCA cells with apelin increased CCA growth, whereas the APLNR antagonist significantly decreased basal proliferation and expression of angiogenesis markers. Treatment of CCA cells with apelin increased ERK1/2 phosphorylation compared with untreated cells. In conclusion, apelin and APLNR are up-regulated in CCA compared with normal controls. Apelin promotes CCA proliferation through activation of the ERK1/2 pathway. Inhibition of APLNR decreases basal proliferation, suggesting an autocrine mechanism of CCA growth. Modulation of the apelin–APLNR axis may serve as a novel therapeutic strategy to inhibit CCA tumorigenesis.

**Ursodeoxycholic acid treatment reverses biliary proliferation and hepatic fibrosis in Mdr2−/− mice and human primary sclerosing cholangitis by decreasing mast cell infiltration and histamine release**

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Ursodeoxycholic acid (UDCA) is used to treat biliary disorders. Bile acids alter histamine release from mast cells (MCs), which infiltrate the liver in the Mdr2−/− mouse model of primary sclerosing cholangitis (PSC). This study aimed to determine the effects of UDCA treatment on MC infiltration and liver pathology in PSC. Wild-type and Mdr2−/− mice were fed a...
control diet or UDCA. Human samples were collected from control and PSC patients treated with placebo or UDCA. MC infiltration was measured by immunofluorescence for FcεRI and quantitative polymerase chain reaction (qPCR) for c-kit, chymase, and tryptase. Intrahepatic bile duct mass was evaluated by CK-19. Fibrosis was detected by qPCR for α-SMA, fibronectin, and collagen-type 1α. In vitro, MCs were treated with UDCA prior to measuring histamine secretion and co-culturing with cholangiocytes. Biliary proliferation was measured in co-cultured cells. In PSC, the MC number increased and MCs were found close to bile ducts. UDCA treatment decreased MC number, marker expression, intrahepatic bile duct mass, and fibrosis. In vitro, UDCA decreased MC histamine release and proliferation in cholangiocytes co-cultured with UDCA-treated MCs. In conclusion, during PSC, MCs infiltrate the liver, inducing fibrosis. UDCA reduces MC histamine, thereby decreasing fibrosis. Inhibition of MCs’ migration/infiltration may be a therapeutic option for PSC.

Behavior of prostate cancer in patients with very low risk disease but an isolated high risk prostate-specific antigen level
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(*e-mail: matthew.gestaut@BSWHealth.org)

Rarely, a subset of patients with prostate cancer presents with biochemically divergent risk stratification. Other than markedly elevated prostate-specific antigen (PSA) scores (>20 ng/mL), these patients meet very low-risk criteria for Gleason scores (GS), stage, and number/percent cores involved with cancer. Oncologists debate whether malignancies in these patients behave more comparably to low-risk or high-risk disease. From 2000 to 2013, a retrospective chart review was completed of very low-risk disease: T1a–T2a, GS ≤ 6, ≤ 3 cores positive, ≤50% involvement of any core, and PSA < 10. The divergent-risk group met low-risk criteria except for PSA scores of 20 to 80 ng/mL. The high-risk, low-volume group had T1c–T2a, PSA < 20, GS of 4+4 only, and ≤4 cores positive. Failure was defined as PSA nadir + 2 ng/mL. Eighteen, 60, and 19 patients were in the divergent, low-risk, and high-risk groups, respectively. The mean PSA follow-up was 56 months (divergent), 74 months (low-risk), and 63.6 months (high-risk), and 61%, 2%, and 73% of patients in the divergent, low-, and high-risk groups received androgen deprivation therapy. Resulting biochemical failure rates were 22.2%, 11.7%, and 30% for divergent, low-, and high-risk patients. The biochemical failure rate differed significantly between the divergent group and the low-risk group (P = 0.021) and between the low-risk group and the high-risk group (P = 0.025), but not between the divergent group and the high-risk group (P = 0.53). Biochemical progression-free survival at 5 years was 71.3% for the divergent group, 68.8% for the high-risk group, and 98.3% for the low-risk group. Thus, divergent disease did not appear to behave differently from low-volume, high-risk disease. These findings are relevant when counseling patients with low-risk/low-volume but divergent PSA disease. Both oncologists and patients should be aware that outcomes for divergent patients are poor, similar to those for their low-volume, classically high-risk counterparts.

Variation in use of prophylactic antibiotics in gynecologic procedures before and after an education intervention
Emily Wu, MD,* Jessica Langsjoen, MD, Jessica Pruszynski, PhD, Thomas Kuehl, PhD, and Wilma Larsen, MD (*e-mail: Emily.Wu@bswhealth.org)

Guidelines for prophylactic antibiotic use in gynecology procedures are put forth by the American College of Obstetricians and Gynecologists. Despite clear guidelines, there is a high rate of use of nonindicated prophylactic antibiotics. The objective was to examine variations in use of prophylactic antibiotics in patients undergoing gynecology surgery at Scott and White Memorial Hospital. A secondary aim was to determine if an educational intervention to gynecology physicians was associated with a significant decrease in nonindicated prophylactic antibiotics. A retrospective chart review was performed for women undergoing gynecology surgery over a 1-year period. An educational intervention regarding prophylactic antibiotic use was held for the obstetrics and gynecology physicians in the middle of this time period. Subjects were included if they had CPT codes corresponding with a procedure that did not require prophylactic antibiotics. Subjects were excluded if they had concurrent procedures for which antibiotics were recommended. A total of 500 subjects were included, 243 before the educational intervention and 257 after. A significant decrease (P < 0.0001) in nonindicated prophylactic antibiotic use was demonstrated, from 45.7% (111/243) before the intervention to 24.9% (64/257) after the intervention. A simple educational intervention was associated with a significant decrease in use of nonindicated prophylactic antibiotics in gynecology procedures.

Medication reconciliation in the emergency department performed by pharmacy personnel: a prospective cohort comparison study
Bella Mogaka, PharmD,* Darren Clary, PharmD, Chau Le Bao Hong, PharmD, Charlotte Farris, PharmD, and Sebastian Perez, PharmD (*e-mail: bella.mogaka@BSWHealth.org)

Admission to an emergency department (ED) is a key moment when patients are at risk of medication discrepancies. Medication histories are an effective way of ensuring that fewer errors are made. The objective of this study was to determine the role of pharmacy personnel in obtaining best possible medication histories and performing reconciliation at the admission interface of care from the ED to the inpatient setting, therefore maximizing transition of care opportunities. The intervention group consisted of pharmacists conducting medication histories and reconciliations on patients 18 years or older admitted through the Scott & White Memorial Hospital ED to general medicine floors from February 15 to March 13, 2016. The control group consisted of a retrospective chart review between November 23 and December 20, 2015, of reconciliations done by ED providers (physicians, physician assistants, nurse practitioners, nurses, and medical students). Both groups then received a second standardized reconciliation by trained pharmacy personnel, and all discrepancies were recorded. The primary outcome of this study was to compare the number of discrepancies identified in each group. No medication discrepancies were noted after pharmacist-led medication reconciliations, compared with 561...
discrepancies reported with the admitting personnel reconciliations. The most frequent discrepancies included unnecessary drug therapy, medication omission, and wrong frequency. In conclusion, medication histories and reconciliations performed in the ED by pharmacy personnel led to fewer discrepancies during admission.

The epithelioid granuloma as a biomarker of severity in Crohn’s disease

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The epithelioid granuloma is considered a histologic hallmark of Crohn’s disease. However, controversy remains regarding the significance of this finding with relation to disease severity and behavior. In this retrospective analysis of 1466 patients followed over a 5-year period from 2009 to 2014 at a tertiary inflammatory bowel disease referral center, we examined the relationship of the epithelioid granuloma with various markers of disease severity as well as the effect of treatment with biologic therapies targeting TNF-alpha. Data were collected on various parameters measuring disease activity and behavior, quality of life, medication use, and health care utilization. The entire cohort and the subset of patients undergoing surgical resection were analyzed with regard to granuloma rates. Both univariate and multivariate analyses were conducted. The overall rate of epithelioid granulomas in our cohort was 12.8% (187/1466). In the subset of surgical patients, the rate was 21.0% (126/600). The presence of granuloma was associated with elevated inflammatory markers (C-reactive protein odds ratio = 2.9 [2.078–4.208], \(P < 0.0001\)), younger age at diagnosis (23.6 ± 11.3 years vs 27.9 ± 13.3 years, \(P = 0.0005\)), higher rates of steroid and narcotic use, higher rates of stricturing/penetrating disease phenotype, and higher health care utilization. Among the surgical cohort, the presence of granulomas was associated with need for repeat surgery (odds ratio = 2.5 [1.54–4.02], \(P = 0.0002\)). Patients using infliximab had a significantly lower granuloma rate compared with biologically naïve patients (odds ratio = 0.22 [0.05–0.97], \(P = 0.03\)), but this trend was not observed for either adalimumab or certolizumab pegol. In conclusion, epithelioid granulomas are detected in a minority of Crohn’s disease patients and are associated with a more aggressive disease phenotype. Infliximab use is associated with lower granuloma rates, suggesting that this drug may work to destroy granulomas or prevent their formation in Crohn’s disease.

Adapting cognitive work analysis for creating usable standardized work procedures: the case of a telemetry unit

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Every set of standardized work procedures in health care is a model of the processes through which a given unit contributes to the overall goal of patient care. However, to be useful, standardized work procedures need to strike a delicate balance between minimizing unnecessary process variability while still allowing flexibility to adapt to unexpected events inherent in a system as complex as a hospital unit. Unfortunately, little progress has been made towards developing a design methodology capable of striking this balance in a system often marked by seemingly conflicting priorities. To fill this gap, a cognitive work analysis was adapted to structure the design of an effective set of standardized work procedures. It was tested by creating a set of standardized work procedures for a small telemetry monitoring unit responsible for monitoring patients located across several floors of a hospital. The cognitive work analysis was able to be completed by a single experienced member of the telemetry unit, at which point it was validated and expanded upon through unstructured interviews with the unit’s four other members. The result was the completion of the background design work needed to create a set of procedures that is both accurate and appropriately specific. It is believed that, with further development, this framework will be valuable in creating an evidence-based practice framework that also accounts for the unique structure of an individual hospital unit.
Early cholecystectomy for patients with acute cholecystitis may not be possible in some clinical settings. Percutaneous gallbladder aspiration (PGBA) offers an alternative approach, but the benefits and risks of this procedure are unclear. We synthesized data on the outcomes of PGBA in acute cholecystitis patients using data sources from online databases, including MEDLINE and EMBASE, and bibliographies of included studies from January 2000 through December 2015. Two reviewers independently reviewed and critiqued the quality of each study. Seven eligible studies met our criteria. The success rates in single PGBA and repetitive PGBA (2–4 times) were 50% to 93% and 76% to 96%, respectively. Complication rates were 0% to 8% and were unrelated to the size of needle gauge used for aspiration and the number of aspirations. Salvage percutaneous cholecystostomy (PC) and urgent surgery were required in 0% to 43% of patients and 0% to 4% of patients, respectively. Two studies with antibiotic instillation had clinical success rates of 95% and 96%. In conclusion, repetitive PGBA combined with antibiotic instillation and salvage PC are useful alternatives to early cholecystectomy in patients with acute cholecystitis.

Acute cholecystitis is a common cause of acute abdominal pain. Up to 90% of these cases have calculous cholecystitis, which is caused by obstruction of the cystic duct or the neck of the gallbladder by gallstones (1). Acalculous cholecystitis has a multifactorial pathogenesis, including bile stasis and/or ischemia of gallbladder, and occurs in 0.2% to 0.4% of all critically ill patients (2). The standard management approach for acute cholecystitis is an early cholecystectomy (2). However, some patients in both the calculous and acalculous cholecystitis groups are high-risk surgical candidates because of comorbid medical conditions or presentations with severe sepsis or septic shock. Percutaneous cholecystostomy (PC) is frequently used in these patients and has a relatively high technical and clinical success rate (3, 4). Percutaneous gallbladder aspiration (PGBA) is an alternative nonsurgical gallbladder drainage method used in some patients. It is a minimally invasive procedure that can be performed at the bedside under ultrasound guidance with a 14- to 21-gauge needle used for puncture (1, 5). Drainage of bile improves the overall condition of patients by decompressing the gallbladder and reducing edema and inflammation of the gallbladder wall and reduces the possibility of secondary infection of the gallbladder (3–11). Several studies have been published on the outcomes and complications associated with PGBA, but the number of patients in these studies is typically small. We reviewed recent reports on the efficacy of PGBA to provide a better overview of this procedure and its potential role in critically ill patients with acute cholecystitis.

METHODS

We searched MEDLINE and EMBASE from January 2000 through December 2015 using “percutaneous gallbladder aspiration” as a search term. We screened all articles and reviewed the reference lists from each included article and relevant review articles. Two independent reviewers (S.R. and P.T.) performed article selection, data extraction, and assessment of the risk of bias. Disagreements were resolved through consensus. Studies were included if they 1) were reported in English, 2) provided adequate data, and 3) were either a controlled clinical study or an observational study that assessed the outcomes of PGBA on acute cholecystitis, including clinical success rates on single aspiration and repetitive aspiration and complications. We excluded studies with <10 patients. If multiple updates of the same data were found, we used the most recent version for analysis.

From each study, we abstracted the study design, setting, patients’ status and risk of surgery, inclusion and exclusion criteria, number of patients, number of gallbladder aspirations, and method of outcome determination. Two reviewers (S.R. and P.T.) independently assessed the quality of each trial by using a tool developed by the Cochrane Collaboration (12). Each trial was given an overall summary assessment of low, unclear, or high risk of bias. We adapted existing tools to assess the quality of observational studies. The strength of evidence for outcomes was graded as high, moderate, low, or very low according to the approach of the GRADE working group (13).

The methods used in these studies included single and repetitive PGBA with needle gauges ranging from 18 to 21 (3, 4, 9, 10, 11). From the Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas.

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6–10). This limited our ability to make specific comparisons. Two studies used antibiotic instillation in addition to PGBA (7, 8). We report the comparison of effectiveness and complications between PGBA and PC, the comparison of effectiveness and complications between single PGBA and repetitive PGBA, and other outcomes, including salvage PC, urgent surgery, and pain control. We did not perform a meta-analysis given the small number of heterogeneous studies.

**RESULTS**

The electronic and manual literature search identified 84 total citations (Figure 1). We identified 9 potentially relevant articles and analyzed 7 published articles, published as full papers, which met our inclusion criteria.

We identified one randomized controlled study (4) and one observational study (3) that compared PGBA with PC and had an unclear risk of bias and low strength of evidence. The randomized controlled clinical study by Ito et al compared the effectiveness of PGBA using 21-gauge needles with PC using 6.5- or 7-French catheters (4). This study recruited 58 patients with acute cholecystitis who did not respond to cefoperazone-sulbactam or ceftazidime within 24 hours and excluded patients with pericholecystic liver abscess or severe coagulopathy and patients who did not give consent for the procedure. The technical success rates in PGBA and PC were 82% and 100%. All unsuccessful PGBA were due to dense biliary sludge or pus. In the technically successful groups, a good clinical response was obtained in 90% of the PC group and in 61% of the PGBA group ($P < 0.05$). Thirty percent of patients who did not have good clinical response after PGBA underwent PC. No major complications were reported in either group.

Chopra et al compared the effectiveness of PGBA using 18-gauge needles with PC using 6- to 10-French catheters (3). They retrospectively identified 53 non–critically ill patients with acute cholecystitis and a high risk for surgery who underwent either PGBA or PC. The technical success rates in PGBA and PC were 97% and 95%, respectively. Unsuccessful PGBA were

![Figure 1. Identification of studies for the review.](image)

### Table 1. Summary of seven eligible studies

<table>
<thead>
<tr>
<th>Author, study year</th>
<th>Type of study</th>
<th>n</th>
<th>Patients' surgical risk</th>
<th>Needle gauge</th>
<th>Antibiotic installation</th>
<th>Single aspiration</th>
<th>Repetitive aspiration</th>
<th>Required PC/urgent surgery</th>
<th>Complication rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haas et al, 2015</td>
<td>Observational (prospective)</td>
<td>33</td>
<td>High</td>
<td>20</td>
<td>None</td>
<td>54.5% (18/33)</td>
<td>75.7% (18+7/33)</td>
<td>PC: 24% (8/33)</td>
<td>None</td>
</tr>
<tr>
<td>Komatsu et al, 2014</td>
<td>Observational (retrospective)</td>
<td>147</td>
<td>Unspecified</td>
<td>20</td>
<td>Isepanicin sulfate 200 mg</td>
<td>65.3% (96/147)</td>
<td>94.5% (96+43/147)</td>
<td>PC: 5.4% (8/147)</td>
<td>3.4% (5/147)</td>
</tr>
<tr>
<td>Chung et al, 2013</td>
<td>Observational (prospective)</td>
<td>67</td>
<td>High</td>
<td>21/18</td>
<td>None</td>
<td>92.5% (62/67)</td>
<td>None</td>
<td>PC: 4.4% (3/67)</td>
<td>4.4% (3/67)</td>
</tr>
<tr>
<td>Tsutsui et al, 2007</td>
<td>Observational (prospective)</td>
<td>45</td>
<td>Unspecified</td>
<td>21/18</td>
<td>Amikacin sulfate 100 mg</td>
<td>71.1% (32/45)</td>
<td>95.5% (32+11/45)</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Tazawa et al, 2005</td>
<td>Observational (retrospective)</td>
<td>79</td>
<td>Average</td>
<td>21</td>
<td>None</td>
<td>70.8% (56/79)</td>
<td>92.4% (56+17/79)</td>
<td>PC: 5% (4/79)</td>
<td>1.2% (1/79)</td>
</tr>
<tr>
<td>Ito et al, 2004</td>
<td>Randomized controlled study of PC vs PGBA</td>
<td>28 (PGBA group)</td>
<td>Unspecified</td>
<td>21</td>
<td>None</td>
<td>50% (14/28)</td>
<td>None</td>
<td>PC: 42.8% (12/28)</td>
<td>3.5% (1/28)</td>
</tr>
<tr>
<td>Chopra et al, 2001</td>
<td>Observational (retrospective)</td>
<td>31 (PGBA group)</td>
<td>High; non–critically ill</td>
<td>18</td>
<td>None</td>
<td>74.2% (23/31)</td>
<td>None</td>
<td>PC: 22.5% (7/31)</td>
<td>None</td>
</tr>
</tbody>
</table>

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**Notes:**
- Two patients had intraabdominal hemorrhage, two had bile leakage, and one had gallbladder hemorrhage. The patient who had gallbladder hemorrhage underwent emergent surgery.
- Two patients experienced dull pain at the injection site, and one patient with cirrhosis had hematoma in the skin area injected by an 18-gauge needle. Two patients died from heart failure.
- Two patients did not undergo repetitive PGBA due to deteriorating basal illness.
- One patient had bile leakage and suffered from peritonitis, which required emergent surgery.
- One patient with liver cirrhosis had mild bleeding.
- One patient in the PGBA group who technically failed gallbladder aspiration was excluded from the outcome study. PC indicates percutaneous cholecystostomy; PGBA, percutaneous gallbladder aspiration.
due to biliary sludge. In the technically successful groups, good clinical responses were obtained in 90% of the PC group and in 77% of the PGBA group. Ninety percent of patients who did not have good clinical response after PGBA underwent PC. No significant difference in clinical response was seen between the two groups treated with these two approaches ($P > 0.6$). No complications related to PGBA were reported.

We identified four observational studies with repetitive PGBA (7–10)(304 patients), two observational studies with single PGBA (3, 6), and one randomized controlled study with single PGBA (4) (126 patients) (Table 1). All observational studies had a low strength of evidence. Single PGBA had success rates of 50% to 93% and complication rates of 0% to 4%. Two single PGBA studies reported serious adverse events from gallbladder aspiration, which included intraabdominal hemorrhage, bile leakage, gallbladder hemorrhage, and peritonitis (8, 10). Repetitive PGBA (2–4 times) was reported in four studies, including two that used antibiotic instillation, and had clinical success rates of 76% to 96% and complication rates of 0% to 3%. The two studies with antibiotic instillation had clinical success rates of 95% and 96% (7, 8), and the other two studies without antibiotic instillation had clinical success rates of 76% and 92% (9, 10). Repetitive PGBAs had success rates of 47% to 96% in patients who did not improve with a single PGBA (7–10).

Three studies reported results in high-risk surgical patients, as defined by the authors. The studies included 131 patients who underwent 106 successful PGBAs (81%); 18 required salvage PC. The complication rate was 0% (3, 6, 9). One randomized controlled study and six observational studies reported that 0% to 43% of patients required salvage PC and 0% to 7% of patients required surgery, either due to lack of improvement of symptoms, patient preference, or procedure-related complications (3, 4, 6–10). Two observational studies reported immediate pain control rates of 99% to 100% (9, 10).

We found insufficient data to determine recurrence rates in patients who were successfully treated with PGBA and decided not to have cholecystectomy due to their preference or underlying diseases. Only two studies in our review reported recurrent cholecystitis rates during follow-up periods (9, 10). Two patients in the Haas study did not have cholecystectomy; one developed recurrent cholecystitis requiring PGBA and the other remained asymptomatic after 16-month follow-up. Out of the 22 patients in the study reported by Tazawa who did not have cholecystectomy, 2 patients developed recurrent cholecystitis at 4-month and 31-month follow-up.

**DISCUSSION**

Patients who develop acute cholecystitis but have life-threatening clinical presentations or severe chronic medical disorders are candidates for percutaneous gallbladder drainage. The standard approach to this drainage is PC performed by an interventional radiologist. However, this approach has complications, including pneumothorax, hemorrhage, bile peritonitis, and patient discomfort secondary to the cholecystostomy tube. An alternate approach to gallbladder drainage is ultrasound-directed aspiration. This approach reduces the pressure in the gallbladder and, in turn, reduces ischemia and the associated inflammatory response. One argument against this approach is that an infected focus needs continuous drainage until the

![Figure 2](image-url)
patient has a chance to respond to antibiotics and medical management. However, the culture positivity rate for gallbladder aspirates ranges from 30% to 78%, with an average of 33% in four recent studies, and many patients with acute cholecystitis do not have a bacterial infection in their gallbladder (3, 4, 7, 10). Consequently, it would seem that PGBA is an underutilized approach in the management of these patients. Our literature review suggests that this approach has good technical success, good clinical success, and a low complication rate. One approach to the management of these patients is outlined in Figure 2.

We identified seven recent articles with 430 patients reporting results with PGBA. The overall success rate was 98%. Forty-two patients (10%) required PC, five patients (1%) required urgent surgery, and 10 patients (2%) had complications. These studies indicate that PC had higher success rates than PGBA and that PGBA had lower complication rates. Patients in high-risk surgical categories did well and had no complications. We think that repetitive PGBA could produce higher clinical success rates than single PGBA without increasing the complication rate, but we could not determine whether increased volumes of aspirated bile from repetitive PGBA increased the clinical success rate based on the available studies. Two observational studies in this review found no statistically significant difference between volumes of aspirated bile in the successful and unsuccessful groups after single PGBA (7, 8). Two observational studies used larger needle gauges to improve the technical success rate when the bile was too thick to aspirate (6, 7). We also suspect that antibiotic instillation after PGBA may increase the clinical success rate, but there were no trials comparing PGBA and antibiotic instillation with PGBA alone. We did not find enough information to calculate recurrent rates of cholecystitis in patients who were successfully treated with PGBA or PC and decided not to have cholecystectomy. Therefore, the role of PGBA as definitive treatment for acute cholecystitis remains unclear.

Our review has several methodological limitations within the evidence base. Most studies included in our review were observational studies, which had low-strength evidence and did not provide sufficient data to conduct a meta-analysis. Substantial clinical heterogeneity precluded precise summary estimates.

Epidural analgesia complicated by dural ectasia in the Marfan syndrome

Benjamin B. Vacula, MD, Chelsea Gray, MD, Michael P. Hofkamp, MD, Patrick T. Noonan Jr., MD, Russell K. McAllister, MD, Kimberly A. Pilkinton, MD, MPH, and Zhiying Diao

Patients with the Marfan syndrome are considered to be high risk during pregnancy and warrant a complete multidisciplinary evaluation. One goal is to minimize hemodynamic fluctuations during labor since hypertensive episodes may result in aortic dissection or rupture. Although they may prevent these complications, neuraxial techniques may be complicated by dural ectasia. The case of a parturient with the Marfan syndrome and mild dural ectasia is presented. During attempted labor epidural placement, unintentional dural puncture occurred. A spinal catheter was used for adequate labor analgesia, and a resultant postdural puncture headache was alleviated by an epidural blood patch under fluoroscopic guidance.

Cardiovascular complications increase the risk of pregnancy for patients with the Marfan syndrome. The goal is to minimize hemodynamic fluctuations. Anesthetic management of a parturient with the Marfan syndrome can be challenging, and neuraxial blocks are preferred. Dural ectasia, a widening of the dural sac surrounding the spinal cord, is present in 63% to 92% of patients with the Marfan syndrome and complicates epidural placement (1). This case reports unintentional dural puncture during attempted labor epidural placement for vaginal delivery in a patient with mild dural ectasia.

CASE DESCRIPTION

An 18-year-old G1P0 parturient with the Marfan syndrome was followed closely during her pregnancy by her obstetrician and cardiologist with serial transthoracic echocardiograms (TTEs). Prior to pregnancy, a TTE revealed aortic root dilation of 4.34 cm, mild mitral valve regurgitation, and no prolapse. By term, the TTE revealed aortic root dilation of 4.42 cm with no evidence of dissection and no change in the severity of mitral valve regurgitation. Throughout the pregnancy, the patient remained asymptomatic. At 39 weeks and 4 days, she was admitted for induction of labor. On arrival to the labor and delivery suite, magnetic resonance imaging (MRI) of the lumbar spine was performed. Mild dural ectasia was present in the lower lumbar region below the L2–3 interspace. In the sitting position, a 17-gauge Tuohy needle was inserted at the L2–3 level. Unintentional dural puncture with clear spinal fluid occurred, and an intrathecal catheter was placed. The spinal catheter was bolused with 1 mL of ropivacaine 0.2% and fentanyl 25 μg.

A continuous infusion of ropivacaine 0.2% at 1.6 mL/h was started. Over the subsequent 6 hours, three separate 1 mL boluses of ropivacaine 0.2% were administered through the spinal catheter. Hemodynamic stability was maintained throughout labor. Uneventful passive vaginal delivery with forceps was accomplished with no significant elevation in heart rate or blood pressure. The spinal catheter infusion was discontinued, and the spinal catheter was left in place for 24 hours to possibly decrease the risk of postdural puncture headache. After removing the catheter, a trace amount of clear fluid was found at the catheter entry site.

Several hours after catheter removal, the patient complained of a postural headache rated as a 7 on the 10-point Likert scale for severity. Conservative management with fluids, caffeine, and analgesics was not successful, and the headache persisted. Interventional radiology performed an epidural blood patch under fluoroscopic guidance in the prone position. The patient had immediate headache relief and reported no recurrence at 2-month follow-up.

DISCUSSION

Instrumented vaginal delivery can be safely performed in patients with Marfan syndrome who have no cardiovascular involvement or stable aortic dilation <4 cm. Epidural analgesia is strongly recommended to minimize aortic wall stress associated with labor pain. Patients with an aortic root <4 cm in diameter at the time of delivery have a similar outcome for vaginal or cesarean delivery (1). Cesarean delivery is indicated in patients who have contraindications to epidural analgesia, an aortic diameter >4.5 cm, aortic dissection, severe aortic regurgitation, or heart failure. For patients with an aortic root diameter of 4.0 to 4.5 cm, delivery should be individualized and involve a multidisciplinary team (2). Both regional and general anesthesia techniques have been used successfully for cesarean section.

Dural ectasia may complicate neuraxial techniques. Moderate to severe dural ectasia may be a relative contraindication to

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epidural placement due to increased risk of dural puncture (3). General or continuous spinal anesthesia has been recommended. However, Lacassie et al reported two cases of failed continuous spinals. Continuous spinal anesthesia was performed with incremental doses of bupivacaine, but further administration was stopped after 21 mL for fear of potential neurologic injury. It was postulated that dural ectasia with an associated increase in cerebrospinal fluid volume may have caused erratic spread of spinal local anesthetics (4, 5). Therefore, combined spinal epidural may be recommended for cesarean delivery (3).

Positioning may have contributed to unintentional dural puncture in this patient. Prelabor MRI was performed in the supine position, demonstrating mild dural ectasia with progressively more pronounced scalloping of the L4 through S1 vertebra, a progressively enlarged dural sac diameter from L4 through S1, and elevated dural sac ratios at L3 through S1 (Figure). These findings are included in known criteria for the radiologic diagnosis of dural ectasia (6, 7). The subsequent labor epidural placement attempt was performed in the sitting position at the L2–3 interspace above the dural ectasia, but resulted in unintentional dural puncture. It is possible that severity of the dural ectasia was affected by positional changes from the supine position of the MRI to the sitting position during the epidural placement attempt.

After unintentional dural puncture, one option has been to thread a spinal catheter in the intrathecal space to provide labor analgesia and possibly decrease the risk of subsequent postdural puncture headache and the need for an epidural blood patch. After delivery in this patient, the spinal catheter was left in place for 24 hours. However, Russell et al, in a prospective controlled study in 2012, demonstrated no benefit to leaving an intrathecal catheter in place (8). Today, we routinely remove spinal catheters shortly after vaginal or cesarean delivery.

If a similar patient with the Marfan syndrome were to present in the future to labor and delivery, we would again offer epidural labor analgesia, counsel the patient on the possible increased risk of unintentional dural puncture due to dural ectasia, and consider placement in a lateral position.

Acknowledgments
The authors wish to thank the Departments of Obstetrics and Gynecology and Interventional Radiology at Scott & White Memorial Hospital for their assistance in the care of this patient.

Bilateral congenital pseudoarthrosis of the clavicles in a newborn

Ram R. Kalagiri, MD, Vinayak Govande, MD, Martha Hemingway, DNP, NNP-BC, and Madhava R. Beeram, MD

Bilateral congenital pseudoarthrosis of the clavicles is extremely rare. We report a case of this entity presenting in the neonatal period. We highlight the importance of the differential diagnosis when clavicular fracture shows no evidence of healing or occurs bilaterally.

Fracture of the clavicle in the newborn is not unusual and invariably is unilateral and heals well (Figure 1). In contrast, congenital pseudoarthrosis is nontraumatic but may be confused with the more common traumatic clavicular fracture (Figure 2). In congenital pseudoarthrosis of the clavicle, the two primary ossification centers in the developing clavicle fail to unite in utero during embryogenesis. The etiology is unknown. The two portions of the clavicle are connected by a fibrous bridge that is contiguous with the periosteum, and a synovial membrane develops. Most commonly this disorder is seen on the right side and presents with a clavicular mass/protuberance often beyond the newborn period. Bilateral clavicular pseudoarthrosis is very rare (1) and is often associated with other congenital malformations, e.g., trisomy 22. We report a case of bilateral pseudoarthrosis of the clavicle diagnosed in the nursery soon after birth. Recognition of this condition and its nontraumatic etiology is important since the workup and outcome are very different from traumatic clavicular fracture (2).

CASE HISTORY

A 34-week 2.11-kg female preterm infant was born to a white, married (nonconsanguineous) 21-year-old G1, HIV-, syphilis- and hepatitis B–negative mother who had an uncomplicated pregnancy except for the premature onset of labor. No antenatal steroids were given. The family history was noncontributory. Delivery was vaginal without forceps, and Apgar scores were 9 and 9. Minimal resuscitation in the delivery room was required. The infant had immediate onset of respiratory distress. Her birth weight was 2110 g; length, 47 cm; and head circumference, 29 cm. All measurements were appropriate for the gestational age. Vital parameters were stable. There was a 1 × 2 cm cystic, nontender mass in the left anterior neck that caused no airway obstruction. The rest of the physical examination was unremarkable.

The baby was admitted to the neonatal intensive care unit secondary to prematurity and respiratory distress. A chest radiograph (Figure 2a) performed for respiratory distress revealed findings of respiratory distress syndrome along with findings consistent with bilateral pseudoarthrosis of the clavicles. The infant was treated with surfactant and oxygen therapy. An osseous survey revealed 11 rib-bearing thoracic vertebral bodies and 6 lumbar-type vertebral bodies. Renal and brain sonograms were unremarkable. An ultrasound of the neck showed a cystic lesion with possible diagnosis of third branchial cleft cyst versus thyroglossal duct cyst. The cyst did not cause feeding or respiratory difficulty. The neck mass gradually became smaller and was unrecognizable at the time of discharge. The baby was discharged home after a few weeks. A genetic evaluation showed normal chromosomes. There is a high likelihood of congenital bilateral pseudoarthrosis of the clavicles, as there was no evidence of fracture healing on sequential imaging (Figure 2b).

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DISCUSSION

Congenital pseudoarthrosis is an uncommon congenital anomaly of the clavicles (1), right-sided being the most common (3–5). It is often asymptomatic (6). Our case of bilateral pseudoarthrosis of the clavicles presenting in the neonatal period is very rare. The baby was admitted to the neonatal intensive care unit due to respiratory distress; otherwise, this diagnosis would have been missed. It was associated with possible branchial cleft cyst versus thyroglossal duct cyst, 11 rib-bearing thoracic vertebral bodies, and 6 lumbar-type vertebral bodies. We did not find cervical ribs, cranio-cleido dysostosis, or dextrocardia, as described by Lloyds-Roberts and colleagues (7).

The clavicle is the first bone to ossify in the fetal period. There are two ossification centers in the clavicle, a medial and a lateral. A bridge forms between them, which gets ossified to form the clavicle (8). As per Cadilhac and colleagues, failure of ossification of the bridge that connects these two ossification centers may lead to pseudoarthrosis (3). While fracture of the clavicle and congenital pseudoarthrosis have a similar radiological appearance, they have different etiologies and outcomes. One should consider a diagnosis of pseudoarthrosis if the clavicular fracture does not show evidence of healing. Table 1 shows key differences between clavicular fracture and unilateral and bilateral pseudoarthrosis of the clavicle. A fractured clavicle heals well without any sequelae, while pseudoarthrosis persists throughout life. Often corrective surgeries are done at a later age (1). Surgical repair is indicated when symptoms limit daily activities and for aesthetic reasons. Open reduction and internal fixation result in good outcomes (9).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
<th>Key features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clavicular fracture</td>
<td>0.3% to 2.9% (2)</td>
<td>History of birth trauma</td>
<td>Heals well without sequelae</td>
</tr>
<tr>
<td>Unilateral pseudoarthrosis of clavicle</td>
<td>Rare; exact incidence unknown</td>
<td>Nonhealing fracture on one side, without antecedent trauma</td>
<td>Surgical repair if symptomatic</td>
</tr>
<tr>
<td>Bilateral pseudoarthrosis of clavicle</td>
<td>Extremely rare</td>
<td>Bilateral clavicular fractures without signs of healing on sequential radiographs</td>
<td>Surgical repair if symptomatic</td>
</tr>
</tbody>
</table>

Wedgie-associated radiculitis in a quinquagenarian

Courtney E. Sutherland, MD, MBA, Toban Dvoretzky, BA, and Nicholas J. Solomos, MD

Wedgies—the upward yanking of another’s underpants from the rear to wedge them between the buttocks—can be administered playfully, maliciously, or adventurously; at forces ranging from gentle to “atomic”; and with or without the foreknowledge or consent of the recipient. Wedgies have been documented anecdotally in the popular Internet literature, with chief emphasis on their sensation-seeking or momentary entertainment value to the giver and recipient. Most participants are typically young; however, we report the case of a 50-year-old man who sustained chronic, painless radiculitis after he received an unanticipated wedgie of moderate force. This report—apparently the first of its kind in the medical literature—serves as notice that exchanging wedgies is not merely a juvenile act or immature prank: the outcome can be injurious.

CASE REPORT

In September 2009, a 50-year-old man presented with a 7-day history of acute low-back pain, accompanied by numbness and tingling down his left leg and into all 5 toes. The symptoms had begun immediately after his 34-year-old wife had given him an unanticipated playful wedgie of moderate force as he was arising from a sofa. Heat therapy and analgesics had provided pain relief, but putting equal or heavier weight on his left leg rapidly reproduced the numbness and tingling, as did sitting in certain positions and lying on his left side. Examination revealed no loss of strength, function, or mobility in the affected limb. We anticipated eventual symptomatic improvement and recommended conservative measures (1).

During clinic visits throughout the next 6 years, the patient said that standing with all weight on the left leg evoked the same distinct symptoms. The symptoms were bothersome rather than disabling, and imaging studies were not deemed necessary (2).

In February 2016, the patient, now 56 years old, said that his wedgie-associated radicular symptoms had disappeared. He added that his wife had been so disturbed by the index event in 2009 that she had stopped giving him wedgies.

DISCUSSION

We monitored this patient over several years for a chronic problem that we think resulted from a wedgie. Our search of PubMed for “wedgie” and the Spanish term “calzoncillo chino” yielded no previous descriptions; indeed, some languages and cultures seem to have no word or concept for the wedgie. Accordingly, ours appears to be the first report in the medical literature about the adverse sequelae of this action.

The exchange of wedgies is anecdotally viewed as an immature act or juvenile prank, without consequences other than possible gratification and potential retribution. However, as reported in one news article (3), a 10-year-old English boy needed surgery in 2004 to reattach his testicle to the scrotal lining after he was given a wedgie. In December 2013, a man in Oklahoma confessed to police during a homicide investigation that he had maliciously given his stepfather an “atomic” wedgie; the next month, coroners ruled that this wedgie had caused the stepfather’s death by asphyxiation (4). (Of note, atomic wedgies differ from standard wedgies in that the underpants are pulled up at least to the recipient’s scapulae and optimally over the head, with strong or so-called “atomic” force.)

Our patient is far older than most people who typically engage in wedgies, and he was thus more likely to report his symptoms as a medical issue. Adolescents and college-aged individuals might take risks (including those inherent to atomic wedgies) for the sake of novel experience or to seek sensation, without prudent awareness of potentially negative outcomes beyond the entertainment of the moment (5). The prevalent perception among youths of their own invincibility (6) also might suppress their reporting of pain or injury after an exchange of wedgies. We therefore speculate that impairment from wedgies occurs more often than has been publicized.

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Although our patient presented to a family physician, other injured patients might present to neurologists, orthopedists, pediatricians, chiropractors, acupuncturists, nurse practitioners, or emergency departments. To patients in the highest-risk groups, preventive counseling can be offered that wedgies can be physically deleterious and that the outcome of exchanging them is not always benign or purely of sensation-seeking value.


Avocations

Neurology of a Poem

During lapsed conscious hours, I have often wondered and received mutable counsel in varied tongues—at times uninvited. This time it was a virtual dream.

I sensed caress of a woolly presence
While the pen was stitching strewn patches of similes, metaphors, rhythm and rhyme.
“Am I watching you from a vantage point.
“Your skull offers no barrier.”
He went on: “As I watch the marauding stampede of lines on the slopes of your mind, I see that you are trying to create.
“Innovation is not forethought or a whim.
It hails down from sky.
Gains access through the cranium and hacked mind slips into reverie.
“Chatter in corpus callosum rises,
untapped cerebral sectors are recruited—
some transmitters are kept at bay. Mind hoes what is known and jumps terrestrial fences.
“Prefrontal shackles are banished.
Societal reins are left dangling.
No more sentries! No more walls! No checkpoints!
Silence zone is in effect for the critic’s megaphone.
“Unleashed limbic flow is nourished
by the Gamma spike in brain.
There! You pirouette with the lines
and feel the Aha moment.”

Copyright © 2016 by Amanullah Khan, MD, PhD. Dr. Khan (e-mail: aman1963@gmail.com) is treasurer of the Poetry Society of Texas and an oncologist on the medical staff of Baylor Medical Center at McKinney.
Synchronous colorectal cancers (SCRCs) have been increasingly diagnosed due to emerging diagnostic modalities. The presence of three or more synchronous colorectal cancers has, however, only rarely been reported. A 76-year-old white man presented for management of two concurrent colorectal adenocarcinomas in the left colon evidenced on total colonoscopy. Preoperative abdominal ultrasonography and thoracoabdominal computed tomography were negative for metastatic disease. The patient underwent an elective left hemicolectomy. The pathology report ultimately showed the presence of three moderately differentiated, distinct colorectal cancers. The patient experienced an uneventful recovery.

Although uncommon, synchronous colorectal cancers (SCRCs) have been increasingly diagnosed due to emerging diagnostic modalities. Most patients with SCRCs present with two concurrent lesions. The incidence of SCRCs among colorectal cancers ranges from 2% to 11% in recent publications (1–14) (Table). The presence of three or more SCRCs has only rarely been reported.

CASE PRESENTATION
A 76-year-old white man presented for management of two concurrent colorectal adenocarcinomas in the left colon (one near the splenic flexure and one in the sigmoid colon), evidenced on total colonoscopy performed due to change of bowel habits and intermittent rectal bleeding during the past 2 months. A third polypoid lesion was encountered between these two lesions; it showed benign macroscopic features and had therefore not been biopsied. The colon proximal to the splenic flexure was free of lesions. The patient had undergone no screening colonoscopy in the past, and his family history was negative for colorectal adenomas/cancer or hereditary nonpolyposis colorectal cancer–associated tumors. He had arterial hypertension under medication and had had a radical prostatectomy for prostate cancer 10 years earlier. Preoperative abdominal ultrasonography and thoracoabdominal computed tomography were negative for metastatic disease. The patient underwent an elective left hemicolectomy with a transverserectal anastomosis. The histological study showed the presence of three moderately differentiated, distinct colorectal cancers: two of the lesions were Union for International Cancer Control (UICC) stage IIa (pT3N0), while the third exhibited UICC stage I (pT1N0) histology, presumably developed on a colorectal adenoma. Proximal and distal resection margins were clear, and all 19 dissected lymph nodes were negative. A retrospective analysis to check for possible Lynch syndrome was negative. The patient experienced an uneventful recovery, and his colonoscopy 1 year later showed no recurrent lesions.

DISCUSSION
Little is known about risk factors associated with SCRCs. It has been assumed recently that older men represent a high-risk

Table. Incidence of multiple colorectal primaries in published reports

<table>
<thead>
<tr>
<th>First author</th>
<th>Publication date</th>
<th>Multiple primaries</th>
<th>Synchronous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welch (1)</td>
<td>1981</td>
<td>101</td>
<td>1.7%</td>
</tr>
<tr>
<td>Kaibara (2)</td>
<td>1984</td>
<td>24,871</td>
<td>3.2%</td>
</tr>
<tr>
<td>Cunliffe (3)</td>
<td>1984</td>
<td>223</td>
<td>10.7%</td>
</tr>
<tr>
<td>Evers (4)</td>
<td>1988</td>
<td>320</td>
<td>7%</td>
</tr>
<tr>
<td>Kimura (5)</td>
<td>1994</td>
<td>358</td>
<td>5%</td>
</tr>
<tr>
<td>Passman (6)</td>
<td>1996</td>
<td>4,878</td>
<td>3.3%</td>
</tr>
<tr>
<td>Takeuchi (7)</td>
<td>1997</td>
<td>225</td>
<td>4%</td>
</tr>
<tr>
<td>Chen (8)</td>
<td>2000</td>
<td>1,780</td>
<td>3%</td>
</tr>
<tr>
<td>Oya (9)</td>
<td>2003</td>
<td>876</td>
<td>4.8%</td>
</tr>
<tr>
<td>Papadopoulos (10)</td>
<td>2004</td>
<td>1,160</td>
<td>4.3%</td>
</tr>
<tr>
<td>Latournerie (11)</td>
<td>2008</td>
<td>15,562</td>
<td>3.8%</td>
</tr>
<tr>
<td>Tziris (12)</td>
<td>2008</td>
<td>268</td>
<td>4.3%</td>
</tr>
<tr>
<td>Mulder (13)</td>
<td>2011</td>
<td>13,683</td>
<td>3.9%</td>
</tr>
<tr>
<td>van Leersum (14)</td>
<td>2014</td>
<td>25,413</td>
<td>3.5%</td>
</tr>
</tbody>
</table>
group for SCRC development (12, 15). Colonoscopy is more effective than barium enema in detecting SCRCs, and its widespread application has coincided with an increased diagnosis rate. Nonetheless, the most current estimates of incidence are still considered to be inaccurate since not all tumors are discovered clinically and the number of related population studies is still relatively low. Genetic and molecular pathways associated with colorectal cancer synchronicity, such as microsatellite instability, altered expression of p53, and gene promoter methylation have received increasing attention in the pertinent literature (15–20). In addition, distinct clinical features of patients with multiple colorectal lesions (such as age, male gender, metastasis rates) have been studied, yet their prognostic significance remains inconclusive.

The surgical treatment of synchronous lesions in separate colonic segments remains controversial. Total or subtotal colectomy has been advocated, because if synchronous lesions are overlooked at the time of surgery, the patient may soon have to undergo repeated surgery and the lesions are likely to have advanced in their pathological stage. On the other hand, multiple colonic segmentectomies have also been proposed (21). The argument in favor of this more conservative approach is that a subtotal colectomy may increase stool frequency, and synchronous colon anastomoses are not necessarily associated with an increased risk of complications (22).

Extreme anemia (hemoglobin 1.8 g/dL) secondary to colon cancer

Rob E. Schmitt, MD, and Clifford J. Buckley II, MD, MBA

We present the case of a 34-year-old man who presented to the emergency department with complaints of generalized fatigue and palpitations, with a heart rate of approximately 100 beats per minute and an orthostatic blood pressure of 80/30 mm Hg upon standing. A hemoglobin of 1.8 g/dL was discovered. A positive fecal occult blood test led to the diagnosis of colon cancer. Once the cancer was resected, the patient’s anemia resolved.

Emergency department management of lower gastrointestinal bleeding, anemia, fatigue, and orthostasis are common (1–5). We report the lowest hemoglobin of which we are aware, at 1.8 g/dL, in a patient with lower gastrointestinal bleeding.

CASE REPORT

A 34-year-old previously healthy black man presented to the emergency department with a complaint of generalized fatigue and palpitations that had progressively increased over the last 6 months. The patient’s heart rate was 100 to 105 beats/minute, and his blood pressure was 110/74 mm Hg when supine but 80/30 mm Hg upon standing. He was found to have marked conjunctival pallor with moist mucous membranes. He had generalized abdominal tenderness and a briskly positive fecal occult blood test absent of melena or overt blood. Electrocardiogram analysis showed Q waves in V1 to V3 with inverted T waves in V4 and lead III.

The patient had had anemia as a child. He had no history of sickle cell or other hematopoietic disorders. He denied melenic or bloody stools. He indicated that he had been intermittently homeless over the prior 6 months. He denied a history of hepatitis, intravenous drug use, prosthetic valves, or hemoptysis.

Initial laboratory evaluation was complicated by standard laboratory protocols rejecting the patient’s complete blood count due to machine error, citing a “dilute” specimen. A call by the emergency physician requesting the release of the results after two rejected attempts showed on the third specimen severe anemia with a hemoglobin of 1.8 g/dL (Tables 1 and 2).

He was transfused with a total of 5 units of blood over 2 days, reaching a hemoglobin level of 7.6 g/dL, and provided with intravenous and oral iron and cholecalciferol supplementation. He underwent esophagogastroduodenoscopy as well as colonoscopy with biopsies showing extensive carcinoma of the colon. This was followed by a right hemi- and transverse colectomy with an ileostomy placement. Ultimately, the surgical specimen revealed a 13 × 11 × 4 cm 100% encircling high-grade, poorly differentiated adenocarcinoma. The patient, now 36 years old, had complete resolution of his anemia, with the most recent hemoglobin level being 14.0 g/dL just under 2 years after his colectomy.

Table 1. Complete iron studies

<table>
<thead>
<tr>
<th>Hematopoietic studies</th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>1.8</td>
<td>14–18</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>7.7</td>
<td>42–52</td>
</tr>
<tr>
<td>Mean corpuscular volume (fL)</td>
<td>51</td>
<td>80–94</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin (pg)</td>
<td>11.9</td>
<td>27–34.5</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration (g/dL)</td>
<td>23.4</td>
<td>32–36.5</td>
</tr>
<tr>
<td>Iron (μg/dL)</td>
<td>21</td>
<td>39–150</td>
</tr>
<tr>
<td>Total iron binding capacity (μg/dL)</td>
<td>454</td>
<td>241–421</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>5%</td>
<td>20%–50%</td>
</tr>
<tr>
<td>Transferrin (mg/dL)</td>
<td>289</td>
<td>200–360</td>
</tr>
<tr>
<td>Haptoglobin (mg/dL)</td>
<td>182</td>
<td>62–197</td>
</tr>
<tr>
<td>Reticulocyte count (%)</td>
<td>0</td>
<td>0.5–2.2</td>
</tr>
<tr>
<td>Vitamin D 25 hydroxy (ng/mL)</td>
<td>16</td>
<td>30–80</td>
</tr>
<tr>
<td>Vitamin D 1,25 hydroxy (ng/mL)</td>
<td>35</td>
<td>15–75</td>
</tr>
<tr>
<td>Vitamin B1 (nmol/L)</td>
<td>47</td>
<td>70–180</td>
</tr>
<tr>
<td>Vitamin B6 (nmol/L)</td>
<td>20</td>
<td>20–120</td>
</tr>
<tr>
<td>Vitamin B12 (nmol/L)</td>
<td>447</td>
<td>180–914</td>
</tr>
</tbody>
</table>

From the Department of Emergency Medicine, Scott & White Healthcare, Temple, Texas.

Corresponding author: Rob E. Schmitt, MD, Department of Emergency Medicine, Scott & White Healthcare, MS-11-AG062, 2401 S. 31st Street, Temple, TX 76508 (e-mail: r.eli.schmitt@gmail.com).
DISCUSSION

Our patient had the lowest hemoglobin of which we are aware in an ambulatory patient with lower gastrointestinal bleeding. Severe anemia at a level <4 g/dL is uncommonly seen in the hospital setting. In the ambulatory setting, it has been reported in other case reports (6, 7). Only one other case has been reported of an ambulatory patient with a hemoglobin value of 1.8 g/dL, and this was due to chronic urinary bleeding (7). The most common source of blood loss that leads to such severe anemia is from the gastrointestinal tract (8, 9). This case adds to other case reports of patient survival with a hemoglobin level of <2 g/dL (6, 7, 10).

<table>
<thead>
<tr>
<th>Hemoglobin electrophoresis</th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A</td>
<td>98.6%</td>
<td>96.0%–98.5%</td>
</tr>
<tr>
<td>Hemoglobin A2</td>
<td>1.4%</td>
<td>1.5%–3.5%</td>
</tr>
<tr>
<td>Hemoglobin F</td>
<td>0%</td>
<td>0%–2.0%</td>
</tr>
<tr>
<td>Hemoglobin S</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Hemoglobin Other</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 2. Hemoglobin electrophoresis

Acute myeloid leukemia presenting as galactorrhea

K. Rakul Nambiar, MD, Sreejith G. Nair, DM, and R. Nandini Devi, MD

Acute myeloid leukemia (AML) presents with symptoms related to pancytopenia (weakness, infections, bleeding diathesis) and organ infiltration with leukemic cells. Galactorrhea is an uncommon manifestation of AML. We report a case of AML presenting with galactorrhea.

Galactorrhea can result from excess prolactin secretion secondary to interference of the hypothalamic pituitary axis by neurologic disorders, neoplastic processes, medications, hypothyroidism, and chest wall irritation. Pituitary prolactinoma is the most common cause of galactorrhea, while nonpituitary malignancies such as bronchogenic carcinoma, Hodgkin’s lymphoma, and T-cell lymphomas have also been implicated. Infiltrative disorders and craniopharyngioma inhibit dopamine and induce galactorrhea. Galactorrhea is an uncommon presenting feature of acute myeloid leukemia (AML). To our knowledge, there have been only two prior reports of galactorrhea in patients with AML (1, 2).

CASE HISTORY
A 36-year-old-woman presented with a 2-week history of galactorrhea. She was otherwise asymptomatic and was not on any medications. Her serum prolactin level was 598 ng/mL (reference range, 0–25). Peripheral blood showed 35% atypical cells, which were peroxidase positive. A bone marrow evaluation confirmed the diagnosis of AML-M4 subtype. Results of magnetic resonance imaging of the brain and analysis of cerebrospinal fluid were within normal limits. After receiving standard induction chemotherapy with cytarabine and daunorubicin, her galactorrhea and serum prolactin levels normalized within 2 weeks (19 ng/mL). A bone marrow examination confirmed remission, and she subsequently received consolidation with three cycles of high-dose cytarabine. She has been asymptomatic for the past 4 years of follow up.

DISCUSSION
Symptomatic galactorrhea as the presenting feature of AML-M5 has been documented by Ales et al (1) and Muslahi et al (2). In both cases, the blasts had monocytic differentiation, and serum prolactin levels normalized after the patient attained remission. Since AML with monocytic differentiation has a high propensity to infiltrate normal tissues, and prolactin levels normalized after remission, we feel that leukemic blasts were the source of exogenous prolactin. This hypothesis has been substantiated by the documentation of bioactive prolactin in the cytoplasm of leukemic cells by immunological methods and the expression of prolactin mRNA in leukemic cell lines (3). Lymphoid cells produce prolactin (4), and stromal cells have basal levels of prolactin synthesis, which can be increased in response to cytokines (5). These findings suggest an up-regulation of prolactin secretion as a result of interaction between the myeloid blasts and normal marrow cells. This hypothesis could account for the observation of hyperprolactinemia in a wide variety of AML subtypes (6). Symptomatic hyperprolactinemia is a rare complication of AML, which may occur in cases with monocytic differentiation. The relation between prolactin synthesis and hematopoiesis in AML remains unclear.

Acute promyelocytic leukemia after renal transplant and filgrastim treatment for neutropenia

Jaime A. Campbell, MD, MS, and John R. Krause, MD

Prolonged immunosuppression in solid organ transplant recipients has been considered a risk for developing opportunistic infections and malignancies. Acute leukemia is a rare complication. We report a case of acute promyelocytic leukemia (APL) (FAB M3) after cadaveric renal transplant for focal segmental glomerulosclerosis in a 24-year-old woman. Her immunosuppressive therapy included tacrolimus, mycophenolate mofetil, and prednisone. Approximately 2 years after transplant, she became pancytopenic, prompting administration of filgrastim. A few doses caused a markedly increased blast count, resulting in a diagnosis of APL. She was successfully treated with all-trans-retinoic acid and arsenic trioxide.

Immunosuppressants offer prolonged survival and improve the quality of life in solid organ transplant recipients. However, long-term administration of immunosuppressants can increase the risk for opportunistic infections and malignancies such as lymphoproliferative disorders, epithelial tumors, and therapy-related myeloid neoplasms (1, 2). Granulocyte colony-stimulating factors (G-CSF), like filgrastim, are effective in increasing white blood cell counts and thus help protect against opportunistic infections (3). Effects of G-CSF are transient and rarely result in markedly increased numbers of blasts or leukemia. We present the case of a 24-year-old female renal transplant patient under chronic immunosuppressive therapy who was diagnosed with acute promyelocytic leukemia (APL) (FAB M3) after a few doses of filgrastim were given for new-onset neutropenia.

CASE REPORT

In October 2013, a 24-year-old woman received a cadaveric right kidney transplant for focal segmental glomerulosclerosis. Her posttransplant immunosuppressant regimen included tacrolimus (5 mg twice daily), mycophenolate mofetil (1080 mg twice daily), and prednisone (10 mg twice daily). A few months after transplant, she was admitted for recurrent urinary tract infections and elevated white blood cell (WBC) counts and was given long-term sulfamethoxazole/trimethoprim (Bactrim). A renal biopsy performed 8 months after transplant showed rejection, and her serum tacrolimus level had risen to 14.0 ng/mL. She was given additional doses of methylprednisolone, and tacrolimus was decreased to 3 mg twice daily. At a subsequent hospital admission 1 year later for a urinary tract infection, she was found to have *Clostridium difficile*, sepsis, and a brief upper gastrointestinal bleed diagnosed as a Mallory-Weiss tear. She was pancytopenic compared to her baseline values (WBC 0.5 K/μL, hemoglobin 7.7 g/dL, hematocrit 21.6%, platelets 47 K/μL), thought to be secondary to her sepsis and marrow suppression from long-term administration of Bactrim and mycophenolate (at a reported dose of 720 mg twice daily). Bactrim and mycophenolate were discontinued, while tacrolimus (4 mg twice daily) and prednisone (10 mg once daily) were continued. Filgrastim (Neupogen 480 mcg subcutaneous once daily) was administered to increase WBC recovery. There was an appropriate response in her WBC count with resulting bandemia, followed by an unexpected marked elevation in blast count after three doses.

Evaluation of the peripheral blood showed marked pancytopenia and 27% circulating immature cells with convoluted and bilobed nuclei, nucleoli, cytoplasmic blebbing, and occasional cytoplasmic granules (Figure 1a). Flow cytometry of the peripheral blood showed 47% immature cells characteristic of promyelocytes. Fluorescence in situ hybridization was positive for the PML/RARα t(15;17) fusion transcripts (Figure 1b), diagnostic for acute promyelocytic leukemia. No other cytogenetic abnormalities were detected.

Evaluation of the bone marrow revealed 85% cellularity (Figure 1c) with 55% immature cells positive for myeloperoxidase and partially positive for CD34, granulocyte maturation arrest, and decreased numbers of megakaryocytes and erythroid precursors. Flow cytometry of the bone marrow detected 55% small to medium-sized immature cells expressing similar markers as in the peripheral blood. Overall, the findings were diagnostic for APL. The patient was started on
all-trans-retinoic acid and arsenic trioxide, which allowed for current remission.

**DISCUSSION**

Our patient presented with pancytopenia; suspicion for a myelodysplastic disorder (MDS) or posttransplant lymphoproliferative disease was low due to her young age and lack of adenopathy or other symptoms. Acute myeloid leukemia as a posttransplant complication is rare (0.2%–2.5%) (1) and was suspected only after G-CSF treatment resulted in the proliferation of blast-like cells in the circulation. This patient most likely developed a therapy-related myeloid neoplasm as a late complication of chronic immunosuppression administered for renal transplant maintenance.

G-CSF is a hematopoietic cytokine produced by monocytes, fibroblasts, and endothelial cells whose role is to regulate the production, differentiation, and activation of neutrophils (3, 4). It stimulates the development of primitive hematopoietic stem cells and the release of CD34+ progenitors from the marrow into the circulation. As such, it is helpful in reducing febrile neutropenia in immunocompromised patients to protect against opportunistic infections (5). Transient effects of G-CSF include a shift towards earlier granulocyte progenitor cells (left shift) with the appearance of promyelocytes and myeloblasts, Döhle bodies, increased granulocyte granulation, as well as hypersegmented neutrophils. The peak incidence of CD34+ cells is in the range of 15- to 35-fold and usually occurs on day 5 (4).

There is controversy regarding G-CSF’s role in enhancing or accelerating leukemogenesis and causing MDS or a myeloproliferative neoplasm. Patients receiving long-term treatment or those already at risk of a secondary MDS and/or acute myeloid leukemia, such as those with severe congenital neutropenia (Kostmann’s syndrome), have increased susceptibility to develop MDS and AML. This is believed to be due to mutations in the G-CSF receptor gene and appears to increase with the duration of G-CSF therapy (3, 4, 6), with a cumulative incidence of 36% after 12 years of treatment (4). The effect of G-CSF on the development of abnormal cytogenetics and the effect of continued G-CSF administration in patients with abnormal cytogenetics or MDS are unknown. Although it is unlikely that filgrastim caused APL in our patient, it is conceivable that it augmented proliferation of the preexisting clone. APL cells are exquisitely responsive to G-CSF because they highly express the G-CSF receptor compared with leukemic cells in other types of AML (7).

Chronic immunosuppression for renal transplant maintenance likely played a role in the pathogenesis of leukemia in this patient. Therapy-related APLs have been reported in chronically immunosuppressed patients, including a patient with Crohn’s disease and liver and kidney transplant recipients (8–12). Cytotoxic antimetabolites such as mycophenolate, used in many immunosuppressive regimens, have been implicated in the development of secondary APL following renal transplantation (1, 8, 10). These secondary APLs seem to have similar clinical, morphologic, and pathologic features as de novo APL in the cases reported, including a good prognosis (8).


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**Avocations**

A photograph of the Andromeda Galaxy, taken with an Orion 80 mm refractor telescope from Troy, Texas. The closest spiral galaxy to the Milky Way, Andromeda is 2½ million light years away—so the photo reflects the appearance of the galaxy 2½ million years ago. Photo by John L. Manning, MD (John.Manning@BSWHealth.org), program director of the Family Medicine Residency at Baylor Scott & White – Temple.
Giant bullae often mimic pneumothorax on radiographic appearance. We present the case of a 55-year-old man admitted to a referring hospital with dyspnea, cough, and increasing sputum production; he refused thoracotomy for tension pneumothorax and presented to our hospital for a second opinion. A computed tomography (CT) scan at our hospital revealed a giant bulla, which was managed conservatively as an exacerbation of chronic obstructive pulmonary disease. Thoracic surgery was consulted but advised against bullectomy. Giant bullae can easily be misdiagnosed as a pneumothorax, but the management of the two conditions is vastly different. Distinguishing between the two may require CT scan. Symptomatic giant bullae are managed surgically. We highlight the etiology, presentation, diagnosis, and treatment of bullous lung disease, especially in comparison to pneumothorax.

CASE DISCUSSION

A 55-year-old man presented to a referring hospital with shortness of breath, cough, and increased sputum production for 3 days without fever or chills. His past medical history was significant for coronary artery disease and chronic obstructive pulmonary disease (COPD). He was not on home oxygen, and his baseline New York Heart Association functional class was I. He had smoked for many years and currently smoked half a pack per day. The patient had no occupational exposures or family history of lung disease. His initial chest x-ray suggested a tension pneumothorax, for which he was offered thoracotomy tube placement. However, he declined it and came to our hospital for a second opinion.

On presentation to our hospital, he was not in respiratory distress and was not cyanotic. His heart rate was 104 beats/minute and his blood pressure was 117/82 mm Hg, and he required 3 L/min oxygen via nasal cannula to achieve a peripheral capillary oxygen saturation of 93%. Chest examination revealed diminished breath sounds on the right with faint wheezing at the apex. He had moderate air movement without wheezing or rales on his left lung. Arterial gas analysis was not done. Computed tomography (CT) of the chest demonstrated a giant bulla occupying approximately 90% of the right hemithorax, mildly displacing his upper mediastinum to the left. There was compression atelectasis on the remainder of the right lung as well as advanced emphysema (Figures 1 and 2). His alpha-1-antitrypsin level was 181 mg/dL (normal range, 90–200 mg/dL).

Thoracic surgery was consulted and recommended against surgical management, as the patient had minimal residual lung and would be at high risk for developing a bronchopulmonary fistula. He was treated for a COPD exacerbation with systemic steroids, antibiotics, and nebulized bronchodilators with symptomatic improvement and was discharged home with oxygen. He was scheduled for pulmonary clinic follow-up at 1 week but was lost to follow up.

DISCUSSION

COPD affects >15 million Americans and is the third leading cause of death, with a mortality rate of 36.4 to 47.6 per 100,000 in the United States (1). COPD is a group of
Although some patients have none (3), with emphysema have moderate to severe airflow obstruction, although some patients have none (3).

Bullous emphysema refers to emphysematous lung with bullae, which are air-filled spaces within the parenchyma that are 1 cm or larger in diameter and consist of a thin wall of visceral pleura with remnants of alveolar and interlobular septa inside (4). Bullae are formed by destruction of interalveolar walls by chronic or less commonly acute stretch injury with increased intraalveolar pressure (5). The natural history of bullous lung disease is usually progressive enlargement as the bullae fill with air and loss of lung function because the irregular, fibrous membranes result in poor gas exchange. If bullae occupy >30% of a hemithorax, they are termed giant bullae. These typically form slowly by gradual filling with air, but rapid enlargement and spontaneous deflation are also possible. As giant bullae occupy spaces in the thorax, they can compress other lung parenchyma and affect gas exchange (4). Distribution of giant bullae is usually unilateral and asymmetric; however, bullous emphysema has bilateral involvement. There are no known factors that determine whether formation is unilateral or bilateral (6).

The major cause of giant bullae formation is cigarette smoking, but they are also associated with intravenous use of methadone, methylphenidate, or talc-containing drugs. Patients with Marfan’s syndrome, Ehlers-Danlos type IV, polyangitis with granulomatosis, Sjogren’s syndrome, and sarcoidosis can develop bullae but not typically giant bullae.

Giant bullae can present asymptptomatically, with dyspnea, or rarely with hemoptysis (7, 8). Diagnosis is made radiographically by plain chest x-ray demonstrating a bulla occupying more than 50% of a hemithorax. CT scan of the chest is sometimes needed to distinguish giant bullae from a pneumothorax.

In contrast to bullae, a pneumothorax is defined as the presence of air in the pleural space and is classified clinically by whether it developed spontaneously or traumatically. Furthermore, a spontaneous pneumothorax is classified as a primary spontaneous pneumothorax (PSP) if there is no known lung disease or as secondary in the background of chronic lung disease. It is referred to as a tension pneumothorax when associated with varying degrees of hypotension, hypoxia, chest pain, and dyspnea (9). After bullous lung disease is diagnosed, it is recommended that the team check antitrypsin levels and order pulmonary function tests to guide therapy. Stapled bullectomy, excision, ligation, and endocavitary drainage are different operative techniques to treat bullae or giant bullae (10). Indications for bullectomy include severe dyspnea, pneumothorax, pain, infection, or hemoptysis (11). Contraindications include significant comorbid disease, pulmonary hypertension, and poorly defined bullae. Based primarily on data regarding lung volume reduction surgery (12, 13), relative contraindications for bullectomy include poor forced expiratory volume in 1 second (<30%), hypercapnia, cor pulmonale, and severe hypoxemia.

A few longitudinal studies have reported on outcomes with surgical management. Cooper et al (14) followed patients after resection of giant emphysematous bullae and found significant improvements in pulmonary function, lung volume, and 6-minute walk distance, but most of these improvements began diminishing at 3-year follow-up. Giuntini et al (15) completed a 5-year follow-up of patients who underwent surgery for giant emphysematous bullae and also found improvement in pulmonary function, lung volume, and dyspnea score. They also noted increasing improvement for the first few years with a tapering of this effect beginning around 3 years. Both found surgical management to be fairly safe with low operative mortality, and most postoperative complications involved prolonged air leak (10).

Although surgery is the preferred approach for dealing with symptomatic giant bullae, one case report discussed treating a giant emphysematous bulla with bronchoscopic placement of one-way endobronchial valves (16). These valves are currently being investigated as a way to perform lung volume reduction without an operation in select emphysema patients.


Partial annular pancreas

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

Annular pancreas is an uncommon and infrequently reported anomaly. The malformation was given its descriptive name in 1862 by Ecker (1). The prevalence ranged from 5 to 15 per 100,000 adults in a cadaveric case series and was 1 in 250 on an endoscopic retrograde cholangiopancreatography (ERCP) study (2). Annular pancreas presents differently in neonates and adults. In neonates, it usually causes duodenal obstruction and may be associated with other congenital abnormalities such as Down syndrome. In adults, however, it can present as pancreatitis and associated biliary obstruction. Symptoms can occur when either a complete or incomplete ring of pancreatic tissue encircles the second portion of the duodenum. We report a case of annular pancreas that was diagnosed in an adult based on radiologic tests and was treated surgically. If the condition is not diagnosed quickly, it can lead to severe morbidity and mortality. Contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography, and laparoscopic ultrasonography are used as advanced imaging techniques even in asymptomatic patients (3).

CASE REPORT

A 42-year-old man presented with severe epigastric pain, vomiting after meals, and significant weight loss. Abdominal ultrasound showed gross dilatation of the stomach and duodenum with suspicion of annular pancreas (Figure 1). Contrast-enhanced CT revealed pancreatic tissue partially encircling the duodenum with gastric outlet obstruction (Figure 2). On axial T1-weighted MRI, partial annular pancreas was seen with a

Figure 1. Axial ultrasound images showing (a) a grossly dilated stomach and (b) at the inferior level, pancreatic tissue encircling the duodenum.
“crocodile jaw” appearance (Figure 3). Based on the imaging findings, partial annular pancreas with gastric outlet obstruction was diagnosed. The patient underwent duodenoduodenostomy with relief of symptoms. At 6-month follow-up, he had no complaints.

DISCUSSION

Pancreatic development starts with two ventral buds and one dorsal bud, which appear at about the fifth week of gestation. The two ventral buds unite and then rotate with the duodenum at about the seventh week of gestation. The ventral bud forms the uncinate process and the head of the pancreas, and the dorsal bud forms the body and tail of the pancreas. Failure of the ventral and dorsal buds to fuse results in entrapment of the duodenum (mostly the posterior part) by the pancreas and leads to formation of annular pancreas (1, 2, 4).

Annular pancreas can be complete or incomplete. In complete annular pancreas, a complete ring of pancreatic tissue surrounds the duodenum. In incomplete annular pancreas, an incomplete ring of pancreatic tissue surrounds a portion of the circumference of the duodenum, giving a “crocodile jaw” appearance. Complete annular pancreas is a well-known entity; however, incomplete annular pancreas is often poorly recognized and may be undetected, especially in patients who do not present with duodenal obstruction (2).

Preoperative diagnosis has improved considerably with the development of newer techniques such as ERCP and magnetic resonance cholangiopancreatography (MRCP). MRCP has superseded ERCP, as it is noninvasive (3). Annular pancreas can be diagnosed when pancreatic tissue is seen encircling the second part of duodenum. On CT and MRCP, a complete ring of pancreatic tissue surrounding the duodenum suggests complete annular pancreas, and posterolateral extension of pancreatic tissue to the duodenum suggests incomplete annular pancreas. Both MRI and multidetector CT reveal pancreatic tissue encircling the duodenum, which retains the signal intensity and density of normal pancreas even after contrast administration. Treatment consists of bypassing the duodenal obstruction by duodenoduodenostomy or laparoscopic gastrojejunostomy.

Abdominal apoplexy is a rare hemorrhagic condition involving the small arteries or veins within the abdominal cavity. A high degree of clinical suspicion, followed by appropriate diagnostic workup and therapeutic intervention, is critical, as nonoperative mortality approaches 100%. Contrary to most previously reported cases, which were associated with hemoperitoneum, we present a patient in which gastroduodenal artery dissection resulted in an organized retroperitoneal hematoma with local compression of the duodenum and subsequent bowel obstruction, resulting in vomiting, aspiration, and death.

In 1931, William Green and John Powers proposed the term “abdominal apoplexy” to describe five cases of intraperitoneal hemorrhage secondary to the idiopathic rupture of gastrointestinal arteries (1). Since then, the definition of abdominal apoplexy has been refined to encompass nontraumatic, spontaneous hemorrhage due to rupture of one of the smaller abdominal arteries or veins, and the definition excludes hemorrhage from aortic aneurysm or dissection, gynecological lesions, ectopic pregnancy, or visceral malignancy (2). As defined, the condition is exceedingly rare. Nonetheless, abdominal apoplexy is a surgical emergency with a high risk of fatal exsanguination (3). Clinical and radiographic diagnosis is difficult, and the majority of cases are diagnosed intraoperatively or postmortem. We present the case of an organizing spontaneous gastroduodenal artery dissection in which death was due to vomiting, aspiration, and respiratory failure due to gastric outlet obstruction caused by the compressing retroperitoneal hematoma.

CASE PRESENTATION
An active 84-year-old white woman with prior atrial fibrillation, normal pressure hydrocephalus, hypertension, and heart failure presented with 48 hours of nausea and vomiting. She denied abdominal discomfort, signs of gastrointestinal bleeding, or changes in bowel habits. A ventriculoperitoneal shunt had been placed 3 weeks earlier, but otherwise the patient had no previous abdominal operations. She was alert without distress. Her heart rhythm was irregular with a rate of 140 beats/min and a blood pressure of 123/77 mm Hg. She was afebrile. Her mucous membranes were dry, her lungs were clear to auscultation, and her abdomen was slightly distended but soft and non-tender. Her serum electrolytes and liver enzymes were normal. The serum creatinine was 2.64 mg/dL, hemoglobin was 11.5 g/dL, and leukocyte count was 16.6 K/μL.

She was placed on intravenous fluids and a diltiazem drip. She remained nauseated with slight abdominal distension. Her acute kidney injury resolved over 3 days, but the atrial fibrillation proved resistant to treatment. As a result, digoxin and a heparin drip were started on hospital day 5.

There was gradual slowing of her heart rate, but on day 10 her abdominal distension worsened and she vomited. An abdominal radiograph suggested gastric outlet obstruction. Subsequently, a 16 Fr Salem Sump nasogastric tube was placed with low-intermittent suction. Appropriate placement was confirmed by radiograph. On day 13, her nausea, vomiting, and abdominal distension increased. Computed tomography scan of the abdomen revealed a severely distended stomach, but the nasogastric tube remained in the body of the stomach (Figure 1). There was compression of the third portion of the duodenum by a complex fluid collection measuring 10 × 4 cm. This apparent hematoma was retroperitoneal and inferior to the head of the pancreas (Figure 1). There was no free air present to suggest a bowel perforation. Also, the pancreas, liver, gallbladder, kidneys, and remaining loops of bowel appeared normal. Anticoagulation was discontinued. She was started on total parenteral nutrition on day 15. Over the next 24 hours, 2 L of dark brown/black fluid was suctioned through the nasogastric tube. On day 16, she experienced multiple episodes of vomiting with aspiration of gastric material. Shortly after this, she became hypoxic and difficult to ventilate. She was transferred to the intensive care unit but had requested no intubation, and comfort measures were pursued. The patient died, and an “abdomen only” autopsy was requested.

Abdominal examination revealed normally positioned organs, and there was no free liquid or clotted blood within the peritoneal cavity. A 5 cm fibrous walled sac in the upper midline
of the abdominal cavity surrounded the end of the coiled ventriculoperitoneal shunt and contained a few milliliters of clear fluid. The cavity and shunt were free of associated hemorrhage. The pancreas had its usual firm, nodular texture. There was a 10 × 4 × 8 cm hematoma within the retroperitoneum, adjacent to the head of the pancreas, and it compressed the duodenum. The clotted blood surrounded the gastroduodenal artery as it entered the head of the pancreas. The proximal duodenum was dilated to 6 cm, but the remaining small bowel was unremarkable.

Microscopically, arterial cross-sections of the gastroduodenal artery revealed rupture of the internal elastic membrane with layered thrombus filling the arterial lumen and the surrounding false channel (Figure 2). In other sections, the false channel was organizing by fibroblastic proliferation. The overall pattern was consistent with a ruptured and partially organized arterial dissection. There was no evidence of acute arteritis, atherosclerosis of the gastroduodenal artery, or intrinsic pancreatitis. The patient’s death was the result of gastroduodenal artery dissection and rupture, associated with a retroperitoneal hematoma causing gastric outlet obstruction with subsequent vomiting and aspiration, although active bleeding had stopped.

DISCUSSION

In general, the clinical presentation of abdominal apoplexy is variable and nonspecific, but abdominal pain, nausea, vomiting, diarrhea, presyncope, and hypotension are typical. The diagnosis should always be considered in a patient with unexplained abdominal pain and hemodynamic instability. If suspected, the diagnostic gold standard is visceral angiography, given its combined diagnostic and therapeutic potential. Inconclusive
radiographic results or unsuccessful intervention should prompt surgical investigation. Open exploration has been reported to decrease the rate of mortality from 100% in nonoperative cases to 42% (4). However, the source of bleeding is often elusive due to the bloody operative field, decreased intravascular pressure, and small size of the involved vessel (3).

This case is unusual. First, gastroduodenal artery dissections are particularly rare. The artery arises within the hepatoduodenal ligament from the hepatic artery and courses inferiorly to give rise to gastroepiploic and pancreaticoduodenal branches (5). The authors have now seen several cases of arterial dissection involving the gastroduodenal artery and hypothesize that this anatomic area may be susceptible to mechanical stress contributing to small artery dissection in combination with other poorly defined predisposing conditions. Our patient had a history of systemic hypertension and there was significant renal hypertensive vasculopathy, but there was no significant atherosclerosis involving the gastroduodenal artery, and there was no convincing evidence of an infectious or “mycotic” component. She also had no evidence of a connective tissue disorder, systemic vasculitis, or portal hypertension.

Second, to our knowledge, this is the first reported case of abdominal apoplexy that had stopped bleeding, but, nevertheless, resulted in small bowel obstruction secondary to an organized hematoma. Compression of the pancreatic head by the hematoma may have ironically favored hemostasis, preventing further bleeding and exsanguination.

Severe ulcerative colitis is defined by more than six bloody stools daily and evidence of toxicity, demonstrated by fever, tachycardia, anemia, or an elevated erythrocyte sedimentation rate. Fulminant disease represents a subset of severe disease with signs and symptoms suggestive of increased toxicity. Treatment of severe colitis includes intravenous corticosteroid administration, with consideration of intravenous infliximab 5 mg/kg. Failure to show improvement after 3 to 5 days is an indication for colectomy or treatment with intravenous cyclosporine. We report a 23-year-old Hispanic woman with decompensated cirrhosis presenting with new-onset fulminant ulcerative colitis and resulting polymicrobial bacteremia, requiring colectomy for infection source control and colitis treatment.

Disease severity in ulcerative colitis (UC) is based on clinical and endoscopic findings and is classified as mild, moderate, severe, or fulminant. Fulminant colitis occurs in a portion of patients with severe UC who have more than 10 stools per day, continuous bleeding, abdominal pain, distention, and acute, severe toxic symptoms including fever and anorexia (1). In fulminant UC with extensive ulceration, the altered colonic mucosa may represent a potential source of infection, particularly in those with a preexisting state of increased intestinal permeability and impaired immune function such as cirrhosis. Patients with cirrhosis also have delayed intestinal motility, which can lead to intestinal bacterial overgrowth. In conjunction with portal hypertension, this overgrowth enables perpetuation of bacteria and can facilitate the spread of bacteria to extraintestinal sites (2). Forty-five percent of hospitalized patients with cirrhosis and gastrointestinal hemorrhage develop bacterial infections, the most common being spontaneous bacterial peritonitis (SBP) (2, 3).

CASE REPORT
A 23-year-old Hispanic woman with prior systemic lupus erythematosus and decompensated cirrhosis secondary to autoimmune hepatitis presented to an outlying facility with a 2-day history of hematochezia and intermittent abdominal pain. Esophagogastroduodenoscopy and colonoscopy revealed nonbleeding esophageal varices and pancolitis, respectively. The patient was discharged on prednisone 40 mg daily. She was readmitted to our facility because of an increase in the frequency of rectal bleeding and worsening abdominal pain. On examination, she was afebrile, with a heart rate of 118 beats per minute and a blood pressure of 110/70 mm Hg. Her mucous membranes were dry. Her abdomen was soft, mildly tender to palpation, and bowel sounds were present. The blood hemoglobin was 8.9 g/dL; platelets, 128,000/μL; and international normalized ratio, 2.1. Abdominal ultrasound showed a small amount of ascites, nonamenable to paracentesis. Following admission, she had several more episodes of hematochezia. Repeat colonoscopy revealed severe ulcerating lesions throughout the entire colon (Figure 1). Colon biopsies demonstrated chronic colitis, cryptitis with crypt abscess formation, basal cell plasmacytosis, and early glandular distortion. Stool was obtained during colonoscopy and was negative for infectious etiologies. Despite this therapy, hematochezia persisted with declining hemoglobin and persistent coagulopathy. Endotracheal intubation was performed.

Approximately 96 hours into admission, the patient’s temperature rose to 102°F, her heart rate rose to 140 beats per minute, and her blood pressure fell to 86/52 mm Hg. Due to suspicion of ensuing sepsis, immunosuppressive therapy with infliximab was decided against. A fecal management system collected 2000 mL of maroon-colored fluid over the following 24 hours. Aggressive blood product support continued. She was empirically started on piperacillin/tazobactam. Blood cultures revealed growth of gram-negative bacilli and gram-positive cocci. Vancomycin was added to the antibiotic regimen. Repeat blood cultures revealed gram-positive cocci in chains, gram-positive cocci in clusters, and two different gram-negative bacilli. Subsequent identification demonstrated Streptococcus pneumoniae, methicillin-sensitive Staphylococcus aureus, Escherichia coli, and an unidentifiable anaerobic gram-negative bacillus. The patient’s...
clinical condition progressively worsened, requiring increasing levels of vasopressor support and further administration of blood products. Despite adequate antimicrobial coverage, multispecies bacteremia failed to clear.

The patient underwent total abdominal colectomy with ileostomy. Postoperatively, she improved markedly. Restoration of hemodynamics, stabilization of blood counts, and clearance of bacteremia were achieved within 36 hours. Examination of the resected colon revealed numerous areas of cryptitis and crypt architectural distortion, as well as multiple foci of mucosal erosions with extravasation of erythrocytes through the length of the colon specimen. No obvious perforation was identified. At 1-month follow up after hospital discharge, the patient was doing well, with toleration of a normal diet, resumption of activities of daily living, and progression towards hepatic transplant evaluation.

DISCUSSION

Fulminant UC is uncommon and requires institution of potent intravenous immunosuppression or colectomy for adequate control. We present a patient with fulminant UC superimposed on decompensated cirrhosis, who developed resulting treatment-refractory polymicrobial bacteremia. Total abdominal colectomy was required to treat both bacteremia and fulminant colitis. Given the presence of ascites at the time of admission, it is postulated that severe mucosal friability, in combination with cirrhosis-associated immune dysfunction, led to the development of polymicrobial SBP and subsequent bacteremia. Pathogens isolated from blood cultures support this hypothesis. S. pneumoniae, E. coli, and anaerobic gram-negative bacilli represent usual gut flora and are among the most common causes of SBP. While S. aureus is not a typical cause of SBP, it has been demonstrated that the epidemiology of nosocomial SBP and bacteremia in hospitalized cirrhotic patients is characterized by a decreased prevalence of Enterobacteriaceae and a predominance of gram-positive cocci, namely S. aureus (4).

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Isolated naratriptan-associated ischemic colitis

Asra Akbar, MD, George Nissan, DO, Priyanka Chaudhry, MD, Priya Rangasamy, MD, and Steven Mudrovich, MD

We report a 41-year-old woman who developed histology- and colonoscopy-proven ischemic colitis with the use of naratriptan not exceeding the maximum 2 doses a day and 3 days per week and without a known medical or cardiovascular history. By exclusion of other causes of colonic ischemia, naratriptan was considered the sole causal agent. Discontinuation of naratriptan resulted in a complete clinical recovery. To date, our patient is the youngest known patient to develop ischemic colitis on isolated naratriptan in the setting of no known medical risk factors or predisposing medical condition. Even though triptans are commonly used for the abortive treatment of migraine headaches, such a reported side effect is rare; however, careful assessment and individual patient-based treatment is advised.

Ischemic colitis, the most common form of intestinal ischemia, has been associated with advanced age, cardiovascular disease, drug therapy, and vascular surgery (1). It manifests as a spectrum of injury, from transient self-limited ischemia involving the mucosa and submucosa to acute fulminant ischemia with transmural infarction that may progress to necrosis and death. Although there are several causes, the most common mechanism is an acute, self-limited compromise in intestinal blood flow (2). We report a case of ischemic colitis due to a triptan, whose therapeutic effect is based on vasoconstriction of the cerebral circulation, which leads to cranial vessel constriction, inhibition of neuropeptide release, and reduced transmission in trigeminal pathways (3, 4).

CASE REPORT

A 41-year-old woman with a longstanding history of chronic migraines without aura presented to the emergency department with severe lower abdominal cramping pain with frequent episodes (12–20 episodes in 8–10 hours) of bloody diarrhea accompanied by nausea without vomiting. The patient’s headache history dated back to the age of 20 years. At that time, her headaches were less frequent and severe. At age 30, she sought medical attention from a neurologist and had preventive medications prescribed. At the time of presentation, she had been using naratriptan 2.5 mg for acute migraines for 2 years—no more than 3 days a week and not more than 2 doses a day; she did not combine naratriptan with any analgesic. Her last dose was about 12 hours prior to presentation. Other medications included desvenlafaxine, bupropion, lamotrigine, and clonazepam. Previous brain magnetic resonance imaging without contrast and a magnetic resonance angiogram with contrast were normal. She had tried topiramate, nadolol, and divalproex sodium in the past, with no response in headache frequency and severity.

The patient had not taken any oral contraceptive pills for over 4 years. She denied physical exercise, use of illicit drugs, and smoking; had no recent history of sick contacts, travel outside the United States, or antibiotic exposure; and denied the ingestion of shellfish or undercooked food. In addition, she had no history of hypertension, diabetes mellitus, or coronary artery disease and no evidence of an autoimmune or hypercoagulable state. Her laboratory findings were normal, as were cultures of urine, blood, and stool and hypercoagulability workup.

Computed tomography (CT) of the abdomen and pelvis with contrast showed colitis from the transverse colon to sigmoid colon. The patient was hydrated and a partial colonoscopy on the day following admission revealed patchy areas of moderate to severe congested, erythematous, and ulcerated mucosa in the left colon, extending from 20 to 35 cm consistent with ischemic colitis (Figure 1). A biopsy showed accumulation of fibrin in...
the interstitial exudate, with a pink smudgy character of the lamina propria, indicative of loss of tissue and ischemic damage (Figure 2). The patient was treated with intravenous levofloxacin and metronidazole, bowel rest, and intravenous hydration. She responded well, with resolution of the bloody stool and abdominal pain, and was discharged on the fifth hospital day. One month and 6 months later, repeat CT scans of the abdomen were normal, and her gastrointestinal symptoms had not recurred. She was followed at a multidisciplinary headache center, and her headache frequency and severity have improved with onabotulinum toxin A injections of 155 units every 3 months.

**DISCUSSION**

This case report demonstrates the occurrence of histology-proven ischemic colitis in the youngest patient to date on a triptan in the absence of major vascular obstruction, atrial fibrillation, blood dyscrasia, other medication use, or an intermittent low-flow state of the systemic circulation. We believe the segmental, self-limited colitis observed in this 41-year-old otherwise healthy patient was ischemic in nature. This hypothesis is supported by the onset and rapid spontaneous resolution of symptoms, as well as the characteristic distribution of colonic injury. She did not have any other known risk factors that would predispose to ischemic colitis and did not take prescription or illicit drugs commonly associated with gastrointestinal ischemia, such as conjugated estrogens, ergotamine derivatives, and other vasoconstrictive agents. It is therefore likely that the ischemic colitis is due to the naratriptan, even though the dose was within prescribed limit of no more than 2 doses a day and 3 days a week.

Naratriptan’s mode of action is through selective agonism of serotonin (5HT1B and 5HT1D receptors) in the cranial arteries; it causes vasoconstriction and reduces sterile inflammation associated with antidromic neuronal transmission correlating with relief of migraine. The onset of action is 1 to 2 hours; time to peak, 2 to 3 hours; and half-life, 6 hours. When prescribed to patients with a low risk of cardiovascular events, triptans have been proven to be safe without evidence of increased occurrence of ischemic conditions (3, 4). The frequency of ischemic colitis associated with naratriptan, according to the Netherlands Pharmacovigilance Centre, is rare (<1:1000). There have been four case reports to date of naratriptan-associated ischemic colitis. One involved naratriptan in conjunction with an oral contraceptive pill, which may have increased the risk of developing ischemia (4–6). The other cases reported patients older than 50 years (3–8). In addition, there have been reports of sumatriptan-associated ischemic colitis and naratriptan-associated ischemic colitis with concurrent use of oral contraceptives or other medications including quetiapine and topiramate (7, 8). While triptans have proven efficacious in relieving the pain of acute migraine headaches, predisposition to ischemic events, either on the basis of underlying vascular disease or concomitant drug/medication use, should be assessed in all patients in whom triptan therapy is being considered.

Acute renal failure due to vancomycin toxicity in the setting of unmonitored vancomycin infusion

Shagufta Vora, DO

Vancomycin-induced nephrotoxicity is a commonly feared and largely preventable adverse effect of vancomycin therapy. We present the case of a 56-year-old woman who developed acute renal failure requiring hemodialysis as a result of unmonitored vancomycin infusions for the treatment of osteomyelitis.

Vancomycin is valued for its effectiveness in the treatment of severe infections caused by methicillin-resistant *Staphylococcus aureus*. Vancomycin-associated nephrotoxicity can be avoided with attention to risk factors and with careful monitoring of patients receiving the antibiotic.

CASE DESCRIPTION

A 56-year-old woman presented to the emergency department from a skilled nursing facility with dyspnea. She had been discharged from the hospital to the nursing facility 18 days earlier for long-term intravenous antibiotic treatment with piperacillin-tazobactam and vancomycin for left middle toe osteomyelitis. She had hypertension, type 2 diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, irritable bowel syndrome, depression, anxiety, and osteomyelitis of her left first and second toes, which had been resected. In the emergency department, the patient indicated that her legs had been swollen for the past 10 days. She had decreased urination over the past week and was anuric since the day prior to presentation. She also had a dry cough, orthopnea, pleuritic pain, and a 43-pound weight increase since her previous admission. She had been given hydrochlorothiazide a few times for volume overload at the nursing home, but this did not improve her symptoms. The patient was sent to the emergency department for an acutely elevated creatinine of 4.0 mg/dL. She had been receiving scheduled intravenous vancomycin infusions without having her vancomycin trough levels monitored at the nursing facility.

At the emergency department, her blood pressure was 155/63 mm Hg; pulse, 70 beats/minute; temperature, 97.3°F; and respiratory rate, 19 breaths/minute. Her oxygen saturation was 82% on room air, which improved to 97% on 3 L oxygen via nasal cannula. Her height was 177.8 cm, weight was 152.86 kg, and body mass index was 48.3 kg/m². The patient was slightly somnolent. Her heart sounds were distant but regular and without murmurs. She had bilateral crackles upon auscultation of her lungs. The extremities had 3+ pitting edema up to her knees bilaterally. She had a slight tremor in her upper extremities bilaterally with asterixis. She had a well-healed skin ulcer of her left middle toe. Her creatinine was 6.8 mg/dL, and the vancomycin trough level was 74.6 μg/mL. Her creatinine during the previous hospitalization was 0.8 mg/dL.

Her antibiotics and hydrochlorothiazide were discontinued. Hemodialysis was initiated and her symptoms improved with daily dialysis over the next 7 days. Her urine was positive for eosinophils, and tests for antineutrophil cytoplasmic antibodies were positive. Renal biopsy revealed acute tubulointerstitial nephritis with severe acute tubular injury. She was given pulse-dose methylprednisolone and then was transitioned to oral prednisone for allergic nephritis. The patient’s symptoms continued to improve. She was started on intravenous daptomycin and meropenem, with plans to switch to oral antibiotics at outpatient follow-up after discharge. Her urinary function returned to normal, her creatinine stabilized to 4.0 mg/dL, and her vancomycin blood level returned to normal. The patient was discharged home with home health with plans for close outpatient follow-up.

DISCUSSION

Vancomycin has been used for over 60 years to treat methicillin-resistant *S. aureus* and various resistant gram-positive infections. This antibiotic is commonly linked to nephrotoxicity, leading to the need for aggressive monitoring with regularly measured vancomycin trough levels (1–3). There are various methods to assess for vancomycin-induced renal toxicity, and inconsistencies in defining renal toxicity make it difficult to compare studies. A standardized definition was proposed in the 2009 vancomycin consensus review, which defined vancomycin-induced nephrotoxicity as a minimum of two increases in serum creatinine of at least 0.5 mg/dL or a 50% or greater increase in

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the serum creatinine from baseline after several days of vancomycin therapy (4).

Vancomycin is eliminated primarily through glomerular filtration and active tubular secretion. The half-life in adults with normal renal function is 4 to 8 hours (5, 6). The exact mechanism of vancomycin-induced nephrotoxicity is not completely understood; however, current data suggest that use of the antibiotic causes oxidative effects on the proximal renal tubule resulting in renal tubular ischemia. The drug has also been shown to interfere with the normal reabsorption function of the proximal renal tubule epithelium and alter the mitochondrial function of these cells. Ultimately, vancomycin-induced renal toxicity is likely due to a combination of these oxidative effects and allergic interstitial nephritis. The incidence of nephrotoxicity varies widely from 5% to 43%, depending on study parameters.

Risk factors for vancomycin-associated nephrotoxicity can be divided into three classifications: vancomycin exposure-related factors, host-related factors, and the use of concurrent nephrotoxins (1, 2, 8). Vancomycin exposure-related factors include larger vancomycin exposures, such as troughs >15 mg/L and prolonged duration of treatment. Doses of vancomycin in excess of 4 g/day have been linked to increased toxicity. Metrics that incorporate patient trough levels in the monitoring of vancomycin dosing can be useful; however, it remains unclear whether the high trough levels are the cause or result of nephrotoxicity. The American Thoracic Society and the Infectious Diseases Society of America recommend vancomycin trough levels between 15 and 20 mg/L for hospital and ventilator-associated pneumonias, bacteremia, endocarditis, osteomyelitis, and meningitis (7). Treatment with vancomycin beyond 1 week increases the incidence of nephrotoxicity from 6% to 21%, and the incidence is close to 30% with more than 2 weeks of therapy (2). Once-weekly monitoring of trough concentration is recommended in stable patients (7).

Host-related factors include a previous history of acute kidney injury or preexisting renal insufficiency, as well as sepsis and critical illnesses. Medications that are associated with an increased risk of vancomycin-associated nephrotoxicity include loop diuretics, acyclovir, amphotericin B, and aminoglycosides. The concurrent use of aminoglycosides with vancomycin has been associated with a 20% to 30% increase in renal injury (1, 9). Piperacillin-tazobactam itself is rarely associated with renal toxicity; however, the medication is frequently given with vancomycin for enhanced activity against gram-negative and anaerobic bacteria. Studies show a twofold increase in nephrotoxicity frequency in patients receiving vancomycin plus piperacillin-tazobactam. Piperacillin-tazobactam decreases the renal clearance of vancomycin, resulting in vancomycin accumulation. The concurrent use of nephrotoxins should be avoided during vancomycin therapy, and when unavoidable, these therapies should be monitored daily to limit the duration and risk of adverse effects (5).

Most mild cases of vancomycin nephrotoxicity resolve upon discontinuation of the medication. Aggressive drug elimination is indicated in patients with severely elevated plasma vancomycin concentrations compounded by impaired clearance due to oliguria, as this further increases the risk of permanent renal damage. Standard membrane dialysis is ineffective in clearing large mass molecules such as vancomycin, but high-flux hemodialysis allows for improved elimination of large molecules, with a reported vancomycin removal rate of up to 79% (10).

Novel oral anticoagulants including the factor Xa inhibitor rivaroxaban are important alternatives to warfarin for the prevention of thromboembolic stroke in patients with nonvalvular atrial fibrillation. The pharmacology and metabolism of these agents differ from those of the vitamin K antagonists used over the decades preceding their introduction. We present a case of spontaneous hemopericardium and cardiac tamponade following administration of rivaroxaban. A review of the patient’s medications revealed a total of seven agents known to be metabolized through cytochrome P450 3A4 (CYP3A4), the major pathway for rivaroxaban metabolism. While most physicians are familiar with recommendations to monitor renal function in patients prescribed rivaroxaban, we suspect that many fail to evaluate possible interactions with other agents having CYP3A4 inhibitory or inducer activity.

We report a case of pericardial tamponade requiring emergent pericardiocentesis occurring soon after rivaroxaban therapy was started in a patient taking seven medications metabolized by the same cytochrome pathway as rivaroxaban. The potential for interference of rivaroxaban metabolism has not been appreciated to the same extent as the interference of multiple medications with warfarin metabolism.

**CASE REPORT**

A 69-year-old man with hypertension and hyperlipidemia presented to the emergency department with palpitations and chest discomfort and was found to have paroxysmal atrial fibrillation (AF) with a rapid ventricular response. The AF terminated spontaneously with rate control, and the patient had no further chest discomfort. Echocardiography showed normal cardiac structure and function. Coronary angiography revealed no significant coronary artery disease. The patient was treated with dronedarone 400 mg twice daily and rivaroxaban 20 mg daily based on a calculated CHADS\textsubscript{2}VASC\textsubscript{2} score of 3 (age, diabetes mellitus, and hypertension) and HAS-BLED score of 3. At the time of initiation of rivaroxaban, the patient’s serum creatinine level and glomerular filtration rate were 1.00 mg/dL and >60 mL/min/1.73 m\textsuperscript{2}, respectively.

Three days after starting rivaroxaban, the patient returned to the hospital with tachycardia, hypotension, and syncope. His electrocardiogram showed sinus tachycardia, and an echocardiogram revealed a large pericardial effusion with findings suggesting tamponade. Emergency pericardiocentesis was performed, during which 1400 mL of bloody fluid was removed with improvement in his hemodynamics. His rivaroxaban was discontinued. A pericardial drain was left in place, and over the next 48 hours there was minimal residual serosanguinous drainage. Cultures, including staining for acid-fast bacilli, were negative, as were cytological test results. Computed tomography imaging showed no evidence of pericardial thickening, granulomatous disease, or active bleeding into the pericardium. There was minimal inflammation, which was attributed to the indwelling drain. The computed tomography images also showed no evidence of pericarditis. The drain was removed and the patient was observed for 24 hours. Repeat echocardiography demonstrated a small residual pericardial effusion without evidence of tamponade. He was discharged to home and made a full recovery.

A review of the patient’s medical regimen revealed seven medications known to undergo metabolism via cytochrome P450 3A4 (CYP3A4), including rivaroxaban, omeprazole, atorvastatin, dronedarone, tamsulosin, and tadalafil (Table 1). The patient has been followed in the clinic monthly for the last 2 months to ensure resolution of pericardial effusion. At this time, he has opted to not reinitiate anticoagulation but rather to take aspirin 325 mg daily for stroke prevention in AF.

**DISCUSSION**

It appears that our patient experienced spontaneous pericardial bleeding associated with use of rivaroxaban. We found only one published report of unexplained spontaneous cardiac tamponade associated with rivaroxaban use (2). While renal excretion of rivaroxaban and other novel oral anticoagulants is well known, there is less appreciation of their hepatic metabolism. For rivaroxaban, hepatic metabolism primarily through CYP3A4 accounts for most (65%) of the drug’s elimination.
Reduction in rivaroxaban dosing is recommended in patients with mild to moderate renal impairment (3), and its use is not recommended in patients with severe renal impairment. There are no guidelines to assist patients or physicians in adjusting dosing based on patient use of other agents that undergo CYP3A4 metabolism.

Pharmacologic studies have demonstrated that single agents with CYP3A4 inhibitor activity such as ketoconazole can increase serum rivaroxaban levels by as much as 158% (4). Few studies have investigated the interaction of other CYP3A4 metabolized drugs with rivaroxaban in clinical practice. One of the few large studies investigating possible drug-drug interactions included 17,701 individuals receiving rivaroxaban for thromboprophylaxis after orthopedic surgery (5). This study reported no association but included few individuals taking medications that act as inhibitors of CYP3A4 (<3%). We suspect that patients receiving medical therapy for nonvalvular AF are more likely to be on agents with known CYP3A4 inhibitory activity. Diltiazem, verapamil, and dronedarone are potent inhibitors of CYP3A4 and are used with anticoagulants in patients with AF. Omeprazole, tadalafil, and tamsulosin are commonly used agents in older patients prone to develop AF.

We suspect that the coadministration of multiple drugs metabolized by CYP3A4 led to elevated serum levels of rivaroxaban, which in turn was the major causative factor for the patient’s pericardial bleeding. Novel oral anticoagulants have differing pharmacologic profiles (Table 2) (6), with both apixaban and rivaroxaban having significant hepatic metabolism through CYP3A4. We hope that our case can serve as a reminder that physicians should exercise caution when prescribing rivaroxaban in combination with other agents that share CYP3A4 metabolism.

We describe our management of an immunocompetent individual who developed obstructive uropathy and candidemia as a result of a fungal bezoar in the kidney. These sequelae arose from candiduria, provoked after several courses of antibiotics. Successful treatment included therapy with both culture-appropriate intravenous antifungals and operative intervention, including direct irrigation of the affected kidney with amphotericin B, relief of renal obstruction with a ureteral stent, a percutaneous nephrostomy tube, and ultimately endoscopic removal of the fungal bezoar. Our patient was successfully treated as evidenced by negative urine culture and lack of ongoing symptomatology.

Candiduria is a common problem. Risk factors include the use of Foley catheters, antibiotics, and immunosuppression, including diabetes mellitus (1). Candiduria can be complicated by ascending infection and the formation of fungal bezoars (2). The Infectious Diseases Society of America guidelines for management of fungal bezoars are predominantly based on case reports in infants with structural abnormalities of the genitourinary tract (2). In this case report, we describe the complex management of a woman with normal genitourinary anatomy treated in a multimodal fashion.

CASE REPORT

A 57-year-old woman with diabetes mellitus, a hemoglobin A1c of 6.7%, and a history of nephrolithiasis presented with emphysematous pyelonephritis due to Klebsiella pneumoniae. She was treated with intravenous antibiotics and placement of a right ureteral stent. The patient returned over the following month with nausea, vomiting, and flank pain, for which she received various intravenous and oral antibiotics. On her third presentation, she was admitted for acute kidney injury (creatinine of 4.73 mg/dL) and started on broad-spectrum antibiotics. Urinalysis showed white blood cells >50 × 10³/μL, nitrites negative, leukocyte esterase 2+, blood 2+, and protein 100 mg/dL. Additionally, yeast was identified on the urine culture. She was switched to micafungin, which had an MIC of 0.06 μg/mL.

The patient underwent right ureteroscopy and laser lithotripsy with ureteral stent exchange. During the procedure, a lesion of unusual appearance was suspicious for a fungal bezoar. After the procedure, she became septic with a temperature of 39.2°C, blood pressure of 75/39 mm Hg, and heart rate of 134 beats per minute. Blood cultures grew C. glabrata, which was now resistant to micafungin with an MIC of 1.0 μg/mL. Intravenous liposomal amphotericin B 5.0 mg/kg was initiated. A repeat CT confirmed a bezoar in the renal pelvis, as well as an obstructed collecting system, prompting placement of a right percutaneous nephrostomy (PCN). An antegrade nephrostogram demonstrated no extravasation of contrast. Administration of deoxycholate amphotericin B via PCN was initiated at 10 mg per liter of 5% dextrose in water infused by gravity.

After 5 days of combination therapy, the patient underwent endoscopic removal of the fungal bezoar via a percutaneous approach and ureteral stent exchange (Figure 1a). Intraoperatively, the bezoar was described as leathery and round (Figure 1b). On postoperative day 1, the PCN was removed at bedside, and the patient was transitioned to systemic deoxycholate amphotericin B 0.5 mg/kg for an additional 14 days. She was discharged to a long-term acute care hospital to complete this course of antifungals. She had microbiological cure with a negative urine culture at day 17 and no evidence of residual hydronephrosis.

DISCUSSION

To our knowledge, this is the first multidrug-resistant C. glabrata fungal bezoar reported in an adult with normal genitourinary anatomy. Although candiduria is a common problem, renal fungal bezoars are rare. Judicious and nonjudicious use of urinary catheters and antibiotics have led to an increase in candiduria and fungal bezoars. Patients with any degree of immunosuppression are at particular risk for developing complications associated with candiduria.
The most common causes of fungal bezoars are *C. albicans* and *C. tropicalis* (3–7). *C. glabrata* may have inherent resistance to azoles, which are typically first-line agents for treatment of candidal urinary tract infections. In this particular case, micafungin was chosen as first-line therapy because of fungemia. Two cultures obtained 14 days apart demonstrated increasing micafungin resistance, leading to the use of amphotericin B.

The Infectious Diseases Society of America treatment guidelines recommend selecting antimicrobials depending on sensitivities of the cultured organism and including different modalities of therapy, including systemic antifungal therapy and local irrigation through PCN. Scerpella and Alhalel used intravenous and direct irrigation with amphotericin B as well as urologic intervention with success (4). In regards to the irrigation of the kidney with amphotericin B, a 10 mg/L dose was used as detailed above. There are reports of using a dose of 50 mg/L for irrigation (8, 9), but in vitro studies demonstrate that most strains of Candida are susceptible to <1 μg/mL (8). The optimal duration of irrigation is unknown. One series mentioned an average duration of 6 days (range, 4–14) (10).

Surgical debridement and removal of the fungal bezoar is a key element in eradicating infection. While the exact timing of surgical intervention is unclear, endoscopic removal of the bezoar should be considered when irrigation fails to result in either clinical or radiographic improvement (8). We successfully treated our patient with a combination of three modalities: systemic amphotericin B, local renal irrigation with amphotericin B, and endoscopic removal of the renal bezoar.

We describe a 60-year-old man who presented with rectal pain and bleeding of a month’s duration. His presentation was highly suggestive of lymphogranuloma venereum (LGV) proctitis. Nucleic acid amplification for chlamydia and gonorrhea via rectal swab revealed evidence supportive of anorectal chlamydia. Treatment with doxycycline resulted in complete resolution of his symptoms.

Proctitis is defined as an inflammatory syndrome of the distal 10 to 12 cm of the anal canal (1). Etiologies of proctitis include inflammatory bowel disease (IBD), radiation, diversion colitis, ischemia, and infection. Infectious causes can be further expanded to include sexually transmitted illnesses (STIs) such as gonorrhea, chlamydia, lymphogranuloma venereum (LGV), herpes simplex virus (HSV), HIV, and syphilis. STI-related proctitis, especially LGV-related proctitis, has been increasing in prevalence due to physician unawareness and poor screening protocols, and outbreaks have been discovered in both Europe and North America among men who have sex with men (MSM) (2, 3). LGV should remain in the differential in the MSM population with suspected chronic IBD because of the overlap in clinical presentation and histopathological diagnosis (4). Early diagnosis is imperative, as delayed treatment can lead to irreversible sequelae.

**CASE REPORT**

A 60-year-old man presented with a complaint of hematochezia and rectal bleeding for 1 month. The stools occurred two to three times per day with associated symptoms of abdominal pain, bloating, constipation, loose stools, and rectal pain. He denied a history of Crohn’s disease or ulcerative colitis. He had a history of Crohn’s disease or ulcerative colitis. There was no recent travel and no family history of gastrointestinal disease.

The patient’s past medical history was significant for well-controlled HIV, pulmonary embolism, depression, chronic weight loss, chronic pain, and insomnia. The patient was sexually active with an HIV-positive partner and participated in receptive anal intercourse. Medications included lamivudine/zidovudine, warfarin, duloxetine, aripiprazole, hydrocodone/acetaminophen, vitamin D, zolpidem, and merino. He was allergic to sulfonamides.

His temperature was 97.9°F; heart rate, 92 beats per minute; blood pressure, 116/80 mm Hg; respiratory rate, 16 breaths per minute; and body mass index, 21 kg/m². Blood was present in the feces. The remainder of the examination was normal. Laboratory results from 3 months earlier showed a white blood cell count of 5.6 × 10⁹; hemoglobin, 13.6 g/dL; hematocrit, 41.8%; platelets, 278 × 10³; sodium, 142 mmol/L; potassium, 4.9 mmol/L; blood urea nitrogen, 10 mg/dL; creatinine, 0.94 mg/dL; aspartate transaminase, 31 U/L; alanine transaminase, 17 IU/L; and bilirubin, 0.2 mg/dL. HIV studies from 3 months prior showed a CD4 count of 1127 with an undetectable viral load. A repeat hemogram showed a white blood cell count of 7.3 × 10⁹ per liter, platelet count of 234 × 10⁹ per liter, hemoglobin of 14.1 g/dL, and hematocrit of 41.3%. The erythrocyte sedimentation rate was 74 mm/h.

A colonoscopy was completed 3 weeks after the patient’s presenting office visit. A rectal mass and two sigmoid sessile polyps measuring ≤6 cm each were detected. The remainder of the colon was normal. The sessile polyps were hyperplastic and the rectal mass revealed ulceration with numerous fragments of a necroinflammatory ulcer base. There was also evidence of reactive atypia of the surrounding colonic mucosa without definitive evidence of dysplasia.

Sigmoidoscopy revealed the continued presence of a rectal ulcer. Clostridium difficile testing was negative. The microscopic examination of the four biopsies found acute cryptitis with crypt abscess formation. Diffuse acute and chronic inflammatory cell infiltrate was present throughout the mucosa. Cytomegalovirus and HSV-1 and -2 testing were negative. The urine sample was negative for both diseases, but the rectal swab was positive for chlamydia and negative for gonorrhea. The patient was prescribed doxycycline 100 mg for 21 days for LGV proctitis. The symptoms had completely resolved following his antibiotic course. Follow-up sigmoidoscopy with biopsy performed 3 months after treatment showed a healing ulcer with return of normal microscopic architecture.

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**Lymphogranuloma venereum proctitis**

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The patient’s partner was seen for similar symptoms and also had severe proctitis with sparing of the remainder of the colon on endoscopy, with evidence of cryptitis and prominent ulceration. He was also treated with a 21-day course of doxycycline with complete resolution of his symptoms.

**DISCUSSION**

Chlamydia is one of the most common sexually acquired illnesses worldwide (5). Chlamydia is an obligate intracellular gram-negative bacterium. Serovars L1, L2, and L3 are known to cause LGV, a subtype of genital ulcer disease. It is transmitted through unprotected vaginal, anal, or oral sexual contact (3).

LGV can present in three stages. The first stage is characterized by a painless ulcer at the site of inoculation. Hemorrhagic proctitis is the primary manifestation of infection after direct transmission in the MSM population. These lesions typically heal within 1 week. The second stage involves extension to regional lymph nodes and occurs 2 to 6 weeks later. Those with primary involvement of the rectum may have deep iliac or perirectal node involvement, which may cause intraabdominal or retroperitoneal lymphadenopathy. The third stage involves destruction of surrounding tissues and is a result of chronic inflammation. Untreated, LGV proctitis may result in perirectal abscess, fistulas, strictures, and stenosis of the rectum, which can ultimately lead to chronic progressive lymphangitis with chronic edema and sclerosing fibrosis (3).

Based on clinical presentation, endoscopy is typically performed. LGV shares several common characteristics with IBD including findings of hyperemic, friable mucosa with multiple ulcers and erosions and granulation tissue in the rectum (4). Diagnosis of rectal LGV relies heavily on presentation and high clinical suspicion based on risk factors, including MSM and a sexual history suggestive of an STI. LGV in the MSM patient is associated with additional risk factors including using enemas, having sex at sex parties, using recreational drugs, having unprotected receptive anal intercourse, and having sex with HIV-positive partners and anonymous partners (6).

Laboratory diagnosis for LGV includes culture and nucleic acid amplification tests, followed by genotyping via polymerase chain reaction–based restriction fragment length polymorphism analysis and serologic testing. In the MSM population that reports anorectal intercourse, rectal chlamydia screening is indicated. Patients with proctoscopic findings of proctitis should be treated until rectal chlamydia tests are available. If anorectal findings do not confirm chlamydia, treatment should be discontinued after a minimum of 7 days. If anorectal testing confirms chlamydia, LGV testing should follow when available. If anorectal testing is positive for chlamydia, but LGV testing is unavailable, a full course of treatment should be administered with one of the following findings: proctitis noted during proctoscopic examination, >10 white blood cells per high-power field in the initial Gram-stained anorectal smear specimen, or HIV seropositivity (3). In addition, the Centers for Disease Control and Prevention recommends that patients with a clinical syndrome consistent with LGV, including proctocolitis, be treated (8).

Treatment should be offered to all patients due to the long-term sequelae of untreated disease. Doxycycline 100 mg twice daily for 21 days is currently the preferred regimen. Patients should be followed until resolution of symptoms. In addition, it is recommended that all partners in the past 6 months be warned about possible infection. Individuals who have come into sexual contact with the patient within 4 weeks of the onset of the patient’s symptoms, or the last 3 months if the patient was asymptomatic when LGV was detected, should be tested and initiated on treatment (3, 9).

Placement of the AbbVie PEG-J tube for the treatment of Parkinson’s disease in the interventional radiology suite

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The primary treatment for Parkinson’s disease is dopaminergic stimulation. Although levodopa has historically been administered orally, maintaining a predictable plasma concentration of the drug is challenging. As a result, enteral administration of carbidopa/levodopa (Duopa) has emerged as a promising tool in the treatment of the disease. This requires placement of an enteric catheter, two of which have been approved by the Food and Drug Administration for delivery of Duopa. The approved tubes are placed using the “peroral” or “pull” technique, a method traditionally requiring endoscopy. This technical note describes placement of the AbbVie PEG-J tube by means of the peroral route while utilizing only sonographic and fluoroscopic guidance. After placing an orogastric tube and achieving percutaneous access to the stomach under fluoroscopic visualization, a snare catheter is advanced through the percutaneous access into the stomach. The orogastric tube is engaged with the snare and retracted, bringing the attached snare with it to the mouth. The AbbVie PEG tube is attached to the snare, pulled back down the esophagus and into the stomach before being retracted through the percutaneous access to the skin. Finally, the AbbVie J tube is advanced through the gastrostomy tube into the proximal jejunum and attached with the provided connectors. As demonstrated, the AbbVie PEG-J tube can be placed safely and effectively using a percutaneous image-guided technique without the use of an endoscope.

BACKGROUND

In the United States, approximately 60,000 people are diagnosed with Parkinson’s disease each year, and as many as 1 million people are currently living with the disease. Oral levodopa, the mainstay of treatment, is absorbed in the proximal third of the small intestine. As such, its pharmacokinetics are largely dependent on gastric emptying, which can be delayed in these patients, resulting in an unpredictable levodopa plasma concentration (2, 4). Direct enteral administration of Duopa has been shown to decrease this variation in plasma concentration, resulting in reduced “off” time, improved motor performance, and a better quality of life (2, 3, 5).

TECHNIQUE

Our patient was seen in the interventional radiology clinic, where risks, benefits, and postprocedure care were explained. Informed consent was obtained. The patient was instructed to ingest barium (8 ounces) the night before the procedure and to fast for 6 hours prior to the procedure. On the day of the procedure, the patient was placed supine, and an oral bite block (EnCompas) was inserted. Sedation was achieved with intravenous midazolam, fentanyl, and diphenhydramine. One gram of intravenous cefazolin was given as antibiotic prophylaxis. The liver was marked on the skin with ultrasound to avoid its inadvertent transgression.

A Corpak orogastric tube (Corpak Medsystems, Buffalo Grove, IL) was placed through the oral bite block, advanced into the stomach, and used to insufflate the stomach with room air. Lidocaine (1%) was administered locally, and a 19-gauge Chiba needle (Cook Medical, Bloomington, IN) was advanced into the mid-body of the stomach directed toward the pylorus under intermittent fluoroscopic guidance. Care was taken to avoid inadvertent puncture of the liver or barium-filled colon. A small incision was made at the puncture site.

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The needle was exchanged for a 6 French Pinnacle sheath (Terumo Medical, Somerset, NJ) over a 0.035-inch Bentson wire (Boston Scientific, Marlborough, MA) using standard Seldinger technique. An EnSnare device (Merit Medical, South Jordan, UT) was advanced through the sheath and was used to snare the previously placed orogastric tube in the distal gastric antrum where the potential space was smallest. Next, the orogastric tube was retracted at the bite block, pulling the connected snare catheter up the esophagus and out of the mouth (Figure 1). The AbbVie PEG fixation loop was attached to the snare, which was pulled back into the stomach and out through the percutaneous gastric access site until the internal retention plate of the tube apposed the inner gastric wall.

The externalized tapered tip of the PEG tube was then cut off to allow the coaxial insertion of a 6 French Cobra catheter (Cook Medical, Bloomington, IN), which was advanced into the proximal jejunum over a 0.035-inch exchange length hydrophilic Glidewire (Terumo Medical, Somerset, NJ). The Cobra catheter was exchanged for the AbbVie J tube over the wire, facilitated by use of a small amount of nonpetroleum gel (Sterile Aquasonic, Parker Laboratories, Fairfield, NJ). The wire was removed, the position of the tube was confirmed fluoroscopically, and the J tube was attached to the gastrostomy tube using the supplied connectors, as per the manufacturer’s instructions (Figure 2). Fluoroscopy time was 10.5 minutes.

A small sterile dressing was applied. The patient was observed in the interventional radiology observation suite for 1 hour after the procedure and instructed to follow up in the interventional radiology clinic in 1 week in conjunction with a neurology appointment.

**DISCUSSION**

To our knowledge, this is the first described technique that allows for placement of the AbbVie PEG-J tube with an internal phalange without the use of endoscopy. Fluoroscopic visualization of the opacified bowel ensures that the large bowel will not be perforated. We have also found that using fluoroscopic guidance during percutaneous gastric access results in a favorable “downstream” orientation of the gastrostomy tube, which facilitates snaring of the orogastric tube in the gastric antrum. It also results in an optimal “lie” of the J tube, which courses naturally across the pylorus into the duodenum without the tendency to kink or coil in the stomach. The described technique can be performed very quickly without any identified increased risk.

Jejunal administration of dopaminergic agents for the treatment of Parkinson’s disease is a very promising potential treatment option for patients afflicted with this disease. As one of the two approved transgastric jejunal tubes, AbbVie PEG-J facilitates this treatment, as it is specifically designed to connect to the Duopa pump. Percutaneous gastrostomy placement has been proven to be a highly safe and effective technique (6). Although there is slight variation in the technique used to place the AbbVie PEG-J compared with previously described techniques, this particular tube can be placed with little difficulty in the interventional radiology suite. Placement of the AbbVie PEG-J tube under direct fluoroscopic guidance is a safe and effective procedure that is well suited for the skill set of an interventional radiologist.

Avocations

Pumpkins at the Dallas Arboretum. Photo copyright © Rolando M. Solis, MD. Dr. Solis (e-mail: rmsolis@mac.com) is an interventional cardiologist at Baylor Scott and White Health – Garland and The Heart Hospital Baylor Plano.
Origin of the left subclavian artery as the first branch and origin of the right subclavian artery as the fourth branch of the aortic arch with crisscrossing posterior to the common carotid arteries

Junlin Zhang, MD, PhD, Joseph M. Guileyardo, MD, and William C. Roberts, MD

We describe an aortic arch anomaly consisting of the origin of the left subclavian artery as the fourth branch and the right subclavian artery as the first branch off the aortic arch with crisscrossing of these two arteries anterior to the trachea without clinical consequences. This anomaly, to our knowledge, has not been reported previously.

Anomalous origin of one or more arteries from the aortic arch (AA) is frequent. Liechty and associates (1) studied 1000 adult cadavers and found “departures from the anatomic norm” in 350 cases (35%). Karacan and colleagues (2) studied 1000 adults by computed tomographic angiography and found “variations from the norm in aortic arch branching patterns” in 208 cases (21%). Origin of the right subclavian artery (RSA) from the fourth branch of the AA with coursing to the right arm posterior to the AA is a relatively common AA anomaly. Origin of the RSA as the fourth AA branch, however, combined with origin of the left subclavian artery (LSA) as the first branch of the AA with crisscrossing posterior to the AA must be an extremely rare anomaly.

CASE DESCRIPTION

A 69-year-old hypertensive, diabetic, and obese (body mass index 39 kg/m²) woman had cardiac arrest outside the hospital the day of death. Forty days earlier, she had a debilitating stroke. Necropsy disclosed no grossly visible myocardial lesions and minimally narrowed coronary arteries. Examination of the AA disclosed the LSA to be the first branch and the RSA to be the fourth branch of the AA, and both coursed posterior to the AA and anterior to the trachea. The RSA coursed posterior to the LSA, and both coursed posterior to the common carotid arteries. The lumen of all four arteries arising from the AA were wide open (Figure).

DISCUSSION

We have found no example of the anomaly described herein in any previously published report.
Described herein are findings in a 58-year-old man in whom necropsy disclosed origin of the left vertebral artery (or the arteria thryoidea ima) directly from the aortic arch. No functional consequences resulted. Study of previous publications disclosed the frequency of this anomaly in adults to be approximately 3.5%. Dissection has been reported to be more frequent in the left vertebral artery when it arises directly from the aorta than when it arises from the left subclavian artery.

We recently encountered, as an incidental autopsy finding, origin of the left vertebral artery (LVA) (or possibly the arteria thryoidea ima [ATI]) directly from the aortic arch (AA). Being unfamiliar with this variation, we studied previously published reports of its frequency and potential consequences. The results of that search and a brief description of the anomaly encountered in our patient is the purpose of this report.

CASE DESCRIPTION

A 58-year-old man died 10 years after bilateral lung transplantation for chronic obstructive lung disease. Figure 1 shows the AA with the anomalously arising artery between the left common carotid and the left subclavian arteries. The anomalous artery produced no apparent detrimental consequences.
This report has a major limitation. We were not able to follow the anomalously arising artery from the AA to its destination. Therefore, it is possible that the anomalously arising artery, rather than being the LVA, is the ATI. Both have been reported to arise directly from the AA, as in the present report. The LVA, however, appears to be the more common of the two to arise anomalously from the AA. No functional consequences have been reported when the ATI arises directly from the AA.

1. Liechty JD, Shields TW, Anson BJ. Variations pertaining to the aortic arches and their branches; with comments on surgically important types. Q Bull Northwest Univ Med Sch 1957;31(2):136–143.

### DISCUSSION

The reported frequency of origin of the LVA from the AA among large numbers of patients studied at necropsy or by angiography/computed tomography is summarized in Table 1. Of 1000 subjects studied at necropsy by Liechty et al (1), the LVA arose anomalously in 25 (2.5%). Of 6439 patients studied by angiography/computed tomography and reported by Komiyama et al (2), Uchino et al (3), Karacan et al (4), Lale et al (5), Huapaya et al (6), and Tapia et al (7), the LVA arose anomalously from the AA in 240 (3.7%). Additionally, four small necropsy studies (each ≤75 patients) found an abnormal LVA from the AA in 17 (8%) of 214 cases (8–11).

Only one reported study of origin of the LVA from the AA has reported any hazardous consequences, and that was by Komiyama and colleagues (2), who described by angiograms acute dissection in 4 of 21 patients (19%) having origin of the LVA from the AA. In contrast, these same authors described dissection by angiogram in 9 of 837 patients (1.1%) with LVA arising normally from the left subclavian artery.

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Number of patients</th>
<th>Age range (yrs)</th>
<th>Method of diagnosis</th>
<th>Frequency of the LVA arising from the AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liechty (1957)</td>
<td>1000</td>
<td>Adults</td>
<td>Autopsy</td>
<td>25 (2.5%)</td>
</tr>
<tr>
<td>Komiyama (2001)</td>
<td>860</td>
<td>—</td>
<td>Angio</td>
<td>21 (2.4%)</td>
</tr>
<tr>
<td>Uchino (2013)</td>
<td>2287</td>
<td>17–94</td>
<td>CT Angio</td>
<td>94 (4.1%)</td>
</tr>
<tr>
<td>Karacan (2014)</td>
<td>1000</td>
<td>17–94</td>
<td>CT Angio</td>
<td>41 (4.1%)</td>
</tr>
<tr>
<td>Lale (2014)</td>
<td>881</td>
<td>19–93</td>
<td>CT Angio</td>
<td>25 (2.8%)</td>
</tr>
<tr>
<td>Huapaya (2015)</td>
<td>361</td>
<td>—</td>
<td>CT Angio</td>
<td>8 (2.2%)</td>
</tr>
<tr>
<td>Tapia (2015)</td>
<td>1050</td>
<td>18–89</td>
<td>CT</td>
<td>51 (4.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>7439</td>
<td>17–94</td>
<td></td>
<td>265 (3.5%)</td>
</tr>
</tbody>
</table>

**Table 1. Summary of the frequency of the left vertebral artery arising from the aortic arch**

Angio indicates angiography; AA, aortic arch; CT, computed tomography; LVA, left vertebral artery; —, no information available.
Atrial myxoma is a rare cardiac tumor that may be diagnosed incidentally on cardiac imaging or may present with life-threatening cardiac symptoms. We present a case of giant left atrial myxoma that presented as a flulike illness.

Atrial myxoma is the most common primary neoplasm of the heart (1, 2). The prevalence of primary cardiac tumors is approximately 0.02% (200 tumors per million autopsies), with about 50% of them being myxomas (3). The surgical incidence of atrial myxomas according to an international registry from the Republic of Ireland is 0.50 atrial myxomas per million population per year. The clinical presentation can range from an asymptomatic incidental finding to a life-threatening cardiac emergency. Myxomas can also present with atypical generalized constitutional symptoms and cardiac symptoms such as arrhythmias and heart failure. Growth rate, location, consistency, and size can affect the presentation of atrial myxoma. Herewith, we present a case of a giant left atrial myxoma that presented initially with symptoms of a flulike illness and acute heart failure.

CASE PRESENTATION
A 42-year-old man with schizophrenia presented with symptoms of generalized fatigue, malaise, dry cough, and dyspnea of 1-week duration. Symptoms got worse 2 days prior to his hospitalization. His temperature was 100.4°F; blood pressure, 121/82 mm Hg; heart rate, 112 beats/minute; and oxygen saturation, 92% on ambient air. Examination revealed moderate jugular venous distension, coarse bilateral rales, and a rumbling diastolic murmur best heard at the apex. A chest radiograph revealed increased pulmonary vascularity and bilateral pulmonary edema. His hemoglobin level was 12 g/dL; white blood cell count, 6300/μL; platelet count, 166,000/μL; sodium, 140 mEq/L;
serum creatinine, 0.8 mg/dL; and pro B-type natriuretic peptide, 1814 pg/mL. A rapid flu test was negative. An echocardiogram (Figure 1) showed a large pedunculated left atrial mass measuring 8.0 × 5.5 cm, filling most of the left atrium. The mass protruded into the left ventricle, resulting in moderate mitral regurgitation and an estimated peak systolic pulmonary arterial pressure of 65 mm Hg. The surgically resected mass measured 8.5 × 9.3 cm and weighed 153 g (Figure 2). After surgical resection, the mitral annulus was dilated and a 36 mm Carpentier-Edwards Physio II annuloplasty ring was placed. The patient had an unremarkable recovery and was discharged home a week after his operation. At 4-week postoperative follow-up, he reported complete resolution of his symptoms.

**DISCUSSION**

Most myxomas are sporadic; in about 7% of cases, there can be a familial association with Carney complex, an inherited autosomal dominant disease characterized by multiple neoplasms including cardiac and extracardiac myxomas, endocrine tumors, and schwannomas (4). Most myxomas originate from the left atrium (82%), and the remainder originate from the right atrium (13%), left ventricle (6%), and right ventricle (2%) (5). The diagnosis of an atrial myxoma can be easily missed, especially in patients presenting with nonspecific symptoms. The symptoms of atrial myxoma can be attributed to the triad of blood flow obstruction (67%), systemic embolization (29%), and constitutional symptoms (34%), which may include fever, malaise, and weight loss (1). Constitutional symptoms are usually secondary to elevated interleukin-6 levels (6). The presentation of atrial myxomas also depends on the tumor growth rate, location, and integrity (7). When patients with a left atrial myxoma present with an embolic stroke, the stroke is usually related to the friability and mobility of the tumor rather than its size (1, 5, 8). Rarely, cardiac myxoma can be infected, and in these circumstances they are more prone to systemic embolization (7, 9).

Our case illustrates how the diagnosis of atrial myxoma can be challenging and may even be missed, especially if the patient presents with nonspecific symptoms. In our case, the patient reported flulike symptoms when indeed he had a cardiovascular emergency.

Melanoma to the heart
Charis G. Durham, MD, James A. Hall, DO, Erica J. Fidone, MD, Ryan Mack, MD, and Austin L. Metting, MD

Malignant melanoma is the third most common skin cancer yet has the highest mortality rate due to its predilection for metastasis. While the diagnosis of antemortem melanoma with cardiac metastasis is relatively uncommon, diagnosing malignant melanoma itself by first identifying a cardiac metastasis is even more rare. This vignette describes an antemortem diagnosis of melanoma in a 50-year-old woman through identification of metastasis to multiple sites, including the tricuspid valve.

In the US, skin cancer has the highest prevalence of any cancer (1). It is the most common type of cancer found in young women, with approximately 1 in 50 developing the disease within their lifetime (2). The median survival for patients with metastatic melanoma is just a few months (3).

CASE REPORT
A 50-year-old white woman presented with back pain during yoga. She endorsed lower extremity numbness and weakness, intermittent visual auras, handwriting changes, dyspnea on exertion, fever, fatigue, and a 10-pound weight loss of 2 months’ duration. She had been very active and recently stopped daily cardiovascular workouts in favor of yoga. On presentation she needed a cane to walk. She had a history of hypertension, hypothyroidism, and asthma. Her medications included levothyroxine, metoprolol succinate, montelukast, and an albuterol rescue inhaler. Physical examination disclosed an extra diastolic heart sound over the left fifth intercostal space. She had diminished sensation to fine touch distal to the left knee, reduced hip flexion, and marked weakness bilaterally with quadriceps extension, knee flexion, plantar extension, and flexion. She had no lesions in the skin or mucous membranes. Magnetic resonance imaging (MRI) of the brain and spine revealed a mass on the conus medullaris and multiple intraparenchymal lesions in the cerebral hemispheres bilaterally. Computed tomography (CT) of the chest, abdomen, and pelvis performed for staging purposes demonstrated an intracardiac mass (Figure). Transthoracic echocardiogram disclosed a 5.3 × 3.2 cm right atrial mass that prolapsed into the right ventricle during ventricular systole (video; see link at https://youtu.be/RH8JNKl0po). CT of the chest revealed a soft tissue density in the subcutaneous fat of the chest, a biopsy of which showed melanoma. The melanoma was BRAF positive, and vemurafenib was started along with radiation of the spine and brain. The size of the cardiac and cerebral masses 6 months later had decreased. However, the patient ultimately stopped therapy due to progression of disease and subsequently initiated hospice care.

DISCUSSION
A study that reviewed autopsies in 70 patients with melanoma demonstrated that cardiac metastases occurred in up to 65% of the cases (4). Although cardiac melanoma metastasis is not uncommon, a diagnosis of antemortem cardiac metastasis is unusual and has been described in <10% of melanoma cases (5).

Once metastasized to other organs, melanoma is by definition stage IV with poor survival rates; the 5-year survival is 15% to 20% (6). Currently, gold standard diagnostic imaging is positron emission tomography–computed tomography (7), which can be used concomitantly with MRI of the brain and CT of the chest, abdomen, and pelvis. One of the reasons that cardiac metastasis is so easily undiagnosed is that patients remain free of cardiac symptoms (8). Of the imaging modalities employed to identify cardiac masses, cardiac MRI has demonstrated the best utility (9).

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**BRAF** gene mutations are found in half of melanoma cases; therefore, all patients diagnosed with metastatic melanoma should be evaluated for a V600 **BRAF** mutation. Vemurafenib is a selective BRAF inhibitor that has led to a positive response in >60% of cases, as demonstrated by regression in tumor size, longer survival (13.6 months vs. 9.7 months with dacarbazine), and a median response time period of 5 months (10).

Our case is unique not only because cardiac metastasis was found at the time melanoma was diagnosed, but also because a primary was never found, which is a rare occurrence (11, 12).

A previously healthy 39-year-old male cigarette smoker came to the emergency department because of the new onset of retrosternal chest pressure. The electrocardiogram recorded on admission showed sinus rhythm at a rate of 64 beats per minute, nondiagnostic Q waves in the inferior leads (II, III, and aVF), and inferior ST-segment elevation of 0.5 mm (0.05 mV) when compared to the PR segment or the TP segment. The inferior ST segments were normally concave upward, and there was no reciprocal ST depression in lead I or lead aVL (Figure 1). While the electrocardiogram was not picture-perfect normal, it was not diagnostic of an acute myocardial infarct (1, 2). Importantly, however, it belonged to a man with the new onset of chest discomfort compatible with myocardial ischemia/injury, and that mandated further investigation. Serum cardiac markers can confirm myocardial injury, but often not immediately; echocardiography can show ischemic wall motion abnormalities; radionuclide studies at rest can demonstrate myocardial perfusion defects; and repeat electrocardiograms can document progression of ischemia/injury. A second electrocardiogram performed 30 minutes after the first one clearly documented an increase in inferior ST-segment elevation with the appearance of reciprocal ST depression in lead aVL. Furthermore, ST depression in leads V1 to V3 now indicated posterior ischemia/injury, and new ST elevation in leads V5, V6 signified lateral ischemia/injury (Figure 2).

The electrocardiogram, like all other laboratory data, must be interpreted in light of the patient’s symptoms and signs, and trying to rule out a myocardial infarct on the basis of a single electrocardiogram is often impossible.

Coronary arteriography in this man revealed an occlusive lesion in the mid portion of a dominant right coronary, and it was opened with balloon angioplasty and two stents. During admission, systemic hypertension and dyslipidemia were discovered.

Figure 1. Electrocardiogram recorded on the patient’s arrival in the emergency department. See text for explication.


Figure 2. Electrocardiogram recorded 30 minutes later, diagnostic of an acute inferoposterolateral myocardial infarct. See text for explication.
Epipericardial fat necrosis as a cause of acute chest pain

Ankit H. Shah, MD, Vivek Bogale, MD, David Hurst, MD, and Gregory dePrisco, MD

Acute chest pain is one of the most common reasons for presentation to the emergency department. Although most etiologies of chest pain are easy to clinically ascertain with routine history, physical, and laboratory examinations, we present an important benign cause of acute chest pain that may mimic acute coronary syndrome.

Epipericardial fat necrosis is a rare, non–life-threatening entity that presents as acute chest pain. The diagnosis requires imaging in conjunction with tests to exclude other more common life-threatening causes of chest pain.

CASE REPORT

A 57-year-old woman with prior overactive bladder, migraine headaches, and labyrinthitis presented to her primary care physician with 2 days of chest tightness and generalized chest pain. The patient had undergone bladder surgery 2 weeks prior to presentation. The chest tightness presented abruptly, and the chest pain prevented her from completing her normal physical activity. The pain worsened with deep inspiration. On physical examination, the patient was noted to be splinting on her left side during inspiration. Otherwise, her physical examination and vital signs were unremarkable. Her D-dimer was 1.32 mg/L (normal <0.59 mg/L). Computed tomography (CT) angiogram of the chest demonstrated no evidence of pulmonary embolism but did identify a heterogeneous appearance of the epipericardial fat overlying the right ventricle (Figure 1a). Repeat CT of the chest 8 weeks later demonstrated resolution of the anterior mediastinal CT findings (Figure 1b).

DISCUSSION

Acute chest pain is one of the most common presenting symptoms in the emergency department. Major differential considerations remain unstable angina, acute coronary syndrome, aortic dissection, and other noncardiac causes of chest pain.
pain such as gastroesophageal reflux disease and costochondritis (1). The differential is broad, but usually the workup is tailored towards diagnosing or ruling out cardiovascular etiologies for chest pain. One uncommon diagnosis that is helpful to keep in the differential is epipericardial fat necrosis, previously known as pericardial or mediastinal fat necrosis (1–3).

Imaging plays a pivotal role in ascertaining this diagnosis and preventing unnecessary workup or procedures. CT remains the modality of choice for diagnosing the necrotic changes in the epipericardial and pericardial fat tissue (3, 4). Magnetic resonance imaging may be utilized for diagnosis (5), but is typically unnecessary. Features of epipericardial fat necrosis include a self-limiting course and typical resolution of findings on repeat imaging (6, 7).

The largest case review series revealed 11 patients from a cohort of 426 patients with acute chest pain caused by epipericardial fat necrosis (4). However, diagnostic dilemmas may underrepresent the actual prevalence of the condition (4).

Invited Commentary

Epipericardial fat necrosis: a unique clinicoradiologic disease

In 1957, Jackson and colleagues (1) provided the first report on what they and subsequent authors called pericardial fat necrosis. In 2005, however, Pineda and associates (2) pointed out that the necrosis occurs in the mediastinal fat adjacent to the parietal pericardium and not between the two pericardial layers. Accordingly, they believed that the term “pericardial fat” is a misnomer and that it should be replaced by “epipericardial fat.” In 2013, Bhatt and coauthors (3) proposed “mediastinal fat,” because the lesion characteristically occurs in the mediastinum outside the pericardium. They also noted that mediastinal fat extends at times into the adjacent interlobar fissures, which explained the location of the necrosis in one of their two patients. In this commentary, I will use the term epipericardial fat necrosis (EPFN).

FREQUENCY

My painstaking search of the English-language medical literature yielded 57 cases of EPNF (1–18), including the case in this issue from Shah and associates (4). At first blush, this small number of reported cases supports the widely held concept that EPNF is infrequent to rare. In my view, however, it would be more appropriate to consider EPNF as infrequently or rarely recognized—and for good reason. Textbooks of internal medicine and cardiology do not acknowledge EPNF (5), and only one of three books devoted solely to the pericardium mentions it (19). Consequently, EPNF remains little known and poorly appreciated.

The first estimate of EPNF’s frequency is now available (6). Investigators in Brazil retrospectively reviewed 7263 computed tomographic (CT) examinations of the chest performed in the emergency department of a private hospital during a 42-month span. Of all the scans reviewed, 926 had been performed to evaluate acute chest pain. From that group, the investigators found 20 patients with EPNF—a frequency of 2.15%, or approximately one diagnosis every 2 months. They also concluded that EPNF is frequently overlooked by emergency room physicians and radiologists.

CLINICAL FEATURES

Classically, EPNF strikes suddenly and without warning. The victims—39 men, 17 women, and 1 patient whose sex was not reported (9)—ranged in age from 23 to 80 years. All were in good health when attacked by EPNF.

Excruciating chest pain, characteristically pleuritic and usually left-sided, is the initial manifestation. The pain is located anteriorly near the diaphragm and radiates at times to the neck, shoulder, upper arm, axilla, or back. It ordinarily subsides within a week or so, but it can recur with less intensity for up to a year. Fever and cough are not features of EPNF (5).

Early in the condition, the patient is dyspneic, with tachypnea, tachycardia, and diaphoresis. Several patients have had a pericardial friction rub (5, 10); others have shown marked tenderness to palpation over or near the precordium (5). After a few days, the physical examination yields normal results.

RADIOLOGIC AND IMAGING RESULTS

Radiographs of the chest obtained during the first day or two of illness might show no abnormality. Thereafter, an ovoid mass invariably develops in or near the cardiophrenic angle on the side of the chest pain. The mass is located anteriorly and almost always is contiguous with the cardiac silhouette. In one case, however, it extended between the lingula and left lower lobe (11); in another, it overlay the left hemidiaphragm in the area of the interlobar fissure (1); and in another, it was distinctly separate from the heart (12). Finding such a mass on the chest radiograph always raised concern for a pericardial cyst or a pericardial or pulmonary neoplasm.

Detailed descriptions of the CT findings are presented elsewhere (3, 6). Suffice it to say, CT determines the exact location and nature of the mass. The lesion itself can be precordial, diaphragmatic, or adherent to the anterior chest wall. It typically appears as an ovoid, encapsulated, fat-containing mass with varying degrees of stranding in and around the mass. Pericardial thickening and a small ipsilateral pleural effusion are frequent. In contrast to EPNF, other mediastinal fat-containing lesions such as lipoma, liposarcoma, and lipothymoma do not develop rapidly, do not have a characteristic clinical course, and do not resolve with conservative care.

Magnetic resonance imaging has been used infrequently in these cases but confirms the CT findings (5, 8, 13).

DIAGNOSIS

Awareness of EPNF and knowledge of its natural history can speed its recognition and avert unnecessary or inappropriate diagnostic and therapeutic actions. During the first 24 to 48 hours, the patient’s symptoms characteristically suggest myocardial infarction, pulmonary embolism, or acute pericarditis (6). Tests for these disorders are indicated but will give normal results. Even though the clinical picture improves, the imaging picture worsens as a new paracardiac lesion forms.

The lack of cross-sectional imaging before the 1970s necessitated surgical exploration to establish the correct diagnosis and to
exclude the suspicion of neoplasm, especially liposarcoma (10). The typical intraoperative finding was an inflammatory mass involving the parietal pericardial fat pad. The masses varied in size from 1.5 cm to 10 × 7.5 × 3 cm. Their pathologic features bore close resemblance to those of infarcted epiploic appendices and to fat necrosis in the breast. Lesions removed early in the clinical course showed a central focus of necrotic fat cells encompassed by macrophages with intense neutrophilic infiltration. Later in the clinical course, the specimen showed considerable fibrosis. Resection of the diseased tissue effected a cure in every case, with follow-up periods of as long as 19 years (5).

In 2005, Pineda and associates made a tentative diagnosis of EPFN purely on the basis of the patient’s clinicoradiologic picture (2). After 2 months of conservative care, and without tissue proof, the patient’s pericardial density disappeared from the chest radiograph and decreased markedly in size upon CT examination. Since then, only one reported patient with EPFN has needed surgical intervention for diagnosis (3). In all the other cases, the diagnosis has rested on the CT findings in conjunction with the typical clinical features. Follow-up chest radiographs and CT scans in these patients have uniformly shown substantial shrinkage or total resolution of the paracardiac mass, always within several months.

**PATHOGENESIS**

Despite almost 60 years of study, the cause of EPFN remains speculative. In two patients, the mass was attached to the heart by a pedicle, torsion of which might have triggered the necrosis (1, 14). Existing structural abnormalities of the involved adipose tissue, such as lipoma or hamartoma, might render the tissue vulnerable to the trauma of a beating heart and moving diaphragm (15, 16). Associated obesity—thought originally to be a probable prerequisite for the disease (1)—has been an inconsistent finding in subsequent cases. Extreme lifting efforts just before or during onset of the chest pain might raise intravascular pressure markedly, causing hemorrhage into and subsequent necrosis of the loosely supported pericardial adipose tissue (17, 18). Recent or concomitant infection, trauma, and acute pancreatitis have been absent in all cases.

**TAKE-HOME MESSAGE**

Epipericardial fat necrosis is the only disease known to cause sudden, excruciating, low anterior chest pain—typically pleuritic and without fever or cough—followed in a few days by a rapidly developing ovoid mass in or near the cardiophrenic angle. This sequence of events sets up the differential diagnosis: cardiopulmonary emergency early, neoplasm later.

Given the unique clinicoradiologic picture and benignity of EPFN, coupled with CT’s ability to verify the fatty nature of the paracardiac mass, a clinical diagnosis will suffice in most cases, and symptomatic conservative care is the recommended practice. Only when serious diagnostic questions persist, or the patient has intractable pain, should operative intervention be considered.

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Laparoscopic resection of rectal cancer in the elderly

L. August Clark, MD, and Walter R. Peters, MD, MBA

Recent published trials have failed to demonstrate that laparoscopic resection is not inferior to open resection of rectal cancer in terms of pathologic outcomes. However, there have been numerous studies showing the benefit of laparoscopic resection in terms of short-term complications and quality of life. Fewer complications and shorter hospital stays improve the chance of maintaining functional status, which is very important for the elderly population. Thus, laparoscopic resection of rectal cancer remains a viable option for the elderly.

While surgical resection remains the cornerstone of treatment for stage II or III colorectal cancer, there is some debate regarding the efficacy of a laparoscopic technique in patients with rectal cancer. The recently published ACOSOG Z6051 trial failed to demonstrate that laparoscopic resection of rectal cancer was not inferior to open resection in terms of pathologic outcomes. The concern is that while laparoscopic surgery might be beneficial in terms of short-term complications, it might sacrifice long-term recurrence prevention and survival. Since the incidence and death rates for colorectal cancer increase with age (1), determining the best approach to resection in elderly patients with rectal cancer is particularly important.

The Z6051 trial asked, “Is laparoscopic resection noninferior to open resection for the treatment of rectal cancer?” The trial consisted of 462 patients with clinical stage II or III rectal cancer within 12 cm of the anal verge who were randomized to laparoscopic or open low anterior or abdominoperineal resection of the rectum after receiving neoadjuvant therapy. Successful resection was defined as a negative distal margin, a circumferential radial margin (CRM) >1 mm between the deepest extent of tumor invasion into the mesorectal fat and inked surface on the fixed specimen, and a complete or nearly complete total mesorectal excision (TME). A 6% noninferiority margin was chosen for the study.1

A successful resection was achieved in 81.7% of the laparoscopic cases compared with 86.9% of the open cases. While the difference in success rates was less than the preset noninferiority margin of 6%, the 95% confidence limits extended to a possible difference of up to 10.8%, forcing the authors to acknowledge possible inferiority of the laparoscopic technique. While the authors admitted to using a “novel composite measure of resection quality,” tumor pathologic staging has been shown to be the most important prognostic determinant for the development of recurrent rectal cancer (2). The importance of negative margins also extends to survival data; the 5-year survival of patients with stage III rectal cancer decreased to 42% in those with CRM involvement compared with 81% in those with negative CRM (3). Because the Z6051 trial failed to show that laparoscopic resection was not inferior to open resection, the authors concluded that the data do not support the use of laparoscopic resection of rectal cancer (4).

The ALaCaRT trial from Australia and New Zealand was similar to Z6051, in which 402 patients with T1 to T3 rectal adenocarcinoma <15 cm from the anal verge were randomized to laparoscopic or open laparotomy for rectal resection. The noninferiority margin was set at 8%. A successful resection was accomplished in 82% of laparoscopic cases and 89% of open resections, but similarly, the confidence limits did not allow this study to reject inferiority (5).

The CLASICC trial from the United Kingdom studied 737 patients with colorectal cancer who were randomized to receive laparoscopic-assisted or open resection; this trial included both colon and rectal cancer and randomized patients at a 2-to-1 ratio in terms of laparoscopic or open resection to account for expected conversion rates to open surgery. A nonsignificant increase in CRM positivity was seen in patients who underwent laparoscopic anterior resection of the rectum. The small subset of patients (160) undergoing laparoscopic resection of rectal cancer and the high conversion rate (82) in the subset make the data difficult to interpret. The concern regarding laparoscopic

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1 Noninferiority trials are employed when equivalence trials would be impractical due to the larger number of patients required. The noninferiority margin is determined by the investigators prior to the trial and represents their opinion regarding the benefit of a novel treatment that is equal to its reduction in effectiveness. In this study, the noninferiority margin refers to the maximum decrease in successful resections with the laparoscopic technique for laparoscopic resection not to be considered inferior to open resection.
anterior resection was lessened when long-term data were later published demonstrating no difference in overall survival, disease-free survival, and local and distant recurrences between the two groups (6, 7).

The COREAN trial involved 340 patients with mid to low rectal cancer resected after chemoradiotherapy and actually found higher rates of complete TME and CRM negativity in laparoscopic proctectomy (92% and 97%, respectively) when compared with open surgery (88% and 96%). The 3-year local recurrence rate was 2.6% in patients who underwent laparoscopic resection and 4.9% in those who had open surgery. The average body mass index was <25 kg/m², which somewhat decreases the difficulty of the procedure. Furthermore, the non-inferiority margin was set at 15%, which gave the study more leeway to establish a statistical difference (8). This study, however, supported the use of laparoscopic surgery for rectal cancer.

These trials with somewhat contradictory conclusions do not definitively define the role of laparoscopic resection for rectal cancer. It is reasonable to consider this option, especially in the right patient population. The elderly represent a high-risk surgical group due to the usual presence of multiple medical comorbidities, decrease in reserve, and diminished functional capacity (9). Numerous studies have shown the benefit of laparoscopic resection in terms of short-term complications and quality of life. Furthermore, studies have shown that prolonged hospital stay is independently associated with a large reduction in functional status (10, 11). Therefore, fewer complications and shorter hospital stays improve the chance of maintaining functional status, which is very important for the elderly population.

A review of the Nationwide Inpatient Sample from 2008 to 2011 of 3,191 patients undergoing elective laparoscopic or open abdominoperineal resection showed that the laparoscopic resection group had lower in-hospital complication rates and a shorter length of stay when compared with the open resection group. The complication rates were 19% in the laparoscopic group and 29% in the open group, and the length of stay was 5.3 vs. 7 days for patients undergoing laparoscopic and open resections, respectively (12).

Boutros et al followed 234 patients who received open or laparoscopic TME for rectal cancer for almost 5 years. This study also showed less blood loss in the laparoscopic group as well as a 1-day shorter hospital stay. Thirty-day general morbidity, specifically the presence of surgical site infections, was less for patients undergoing laparoscopy (13).

Li and colleagues confirmed that the short-term benefits of laparoscopic surgery are also seen in the elderly population. Laparoscopic surgery reduced the length of hospital stay, intraoperative blood loss, time to return of bowel function, and incidence of postoperative pneumonia, wound infection, and postoperative ileus in their review of laparoscopic colorectal resection versus open surgery in octogenarians. Data were collected from 11 comparative studies that included a total of 1066 laparoscopic and 1034 open colorectal resections (9).

Many studies have reported better short-term quality of life in patients after laparoscopic versus open resection. Ng et al reported that Chinese patients with rectal cancer undergoing laparoscopic resection had better physical and cognitive function at 8 months, fewer micturition problems at 4 to 8 months, and fewer male sexual problems from 8 months onward than those undergoing open resection (14). Another study by Li et al specifically looked at the quality of life in patients with rectal cancer after laparoscopic resection and found that patients in the laparoscopic group had less pain, better global health status, and better body image (15).

The above benefits of laparoscopic surgery must be weighed against the potential reduction in cure. While 100% of patients undergoing laparoscopic resection stand to benefit from a faster recovery, up to 11% of patients might have an anticipated 5-year survival rate of approximately 42% instead of 81%, based on data from the Z6051 trial and survival data from the study by Luna-Perez. It is important to relay this concern for a potential decrease in cure rate to the elderly patient considering laparoscopic resection. Because laparoscopic surgery has shown a benefit in short-term complications and quality of life, it remains a viable option for the properly selected elderly patient. High-risk elderly patients may favor the known short-term and quality-of-life benefits of laparoscopic resection over concerns regarding the uncertainty surrounding oncologic outcomes. It is appropriate to discuss this approach with the elderly patient despite the uncertainty around the role of laparoscopic resection for the general population.


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**Avocations**

*Passion flower.* Photo copyright © Amanullah Khan, MD, PhD, 2016. Dr. Khan (e-mail: aman1963@gmail.com) is an oncologist on the medical staff of Baylor Medical Center at McKinney.
Dr. Carl Couch’s book takes us through the journey toward accountability in the Baylor Scott and White Quality Alliance (BSWQA), the accountable care organization (ACO) owned by Baylor Scott and White Health, which is the largest not-for-profit health care system in Texas. It is a great summary for someone who wants to understand the rationale behind accountability and wants to take a deep look at an organization that has operationalized many pieces of this journey. Dr. Couch clearly documents the planning and operational process as BSWQA continues to move toward value-based health care.

This book examines the term “accountable” and quantifies and qualifies it in reference to new health care delivery models and the transition from volume to value. It takes us into the population health arena, understanding the critical value of accountability for quality, cost, and outcomes as critical inputs into the population health transition. Dr. Couch details how the ACO fits into a population health–centric model and patient-centered medical home model. The emphasis is clearly on primary care; however, the book ensures that readers understand the importance of the specialist role in ACOs’ long-term success.

Accountable emphasizes the rearrangement of the six Institute of Medicine aims into a trademarked Baylor health program known as STEEEP. This stands for safe, timely, effective, efficient, equitable, and patient-centered care delivery (p. xxix). Pointing out that our health care system has been constructed to serve providers and is now transitioning to serve patients, the book takes us through some of the underlying demographics and cost drivers that are leading us toward the need for “accountability” and the role that physicians must play.

Chapter 3 addresses the organization of BSWQA and emphasizes what is, and is not, an ACO. It details the legal aspects of forming a clinically integrated network and an ACO. Of particular value are the tables on pages 52–58 and pages 64–69, which provide information on the legal complexities and safe havens of ACOs and clinically integrated networks. These user-friendly charts alone are worth exploring this book.

Accountable also lays out the BSWQA committee structure (Table 3.6), with detailed information on the flow of data and information through various subcommittees. These include:
- Membership and standards
- Best care/clinical integration
- Compliance
- Finance, contracting, and compensation
- Population health information technology

It notes the importance of data in managing “accountability”—including the different reports that are necessary for managing physician outcomes as well as the ACO (pp. 81–83). It also addresses issues of consumer expectations, access, and wellness and shares an overview of bonus distribution models in the context of a shared savings bonus system.

The importance of transitional care, and care transition nursing, is emphasized. This process includes carefully identifying different subsets of risk at the patient level, wherein high risk is the top 5%, rising risk is the next 15%, and low risk is the remaining 80%. The importance of identifying these populations and accurately assigning care processes and transitional care coaches is emphasized.

Chapter 6 discusses the financing of ACOs with an emphasis on the third part of the triple aim, which is reducing per capita costs. Discussing six forms of waste, i.e., non–value-added care—failure of care delivery, failure of care coordination, overtreatment, administrative complexity, pricing failures, and fraud and abuse—it explains how ACOs fit into this waste- and cost-reduction strategy.

Overall, the book excels in discussing the journey from volume to value in the context of creating accountability at the physician and the delivery system level. Accountable is highly valuable for anybody on the ACO journey who wants to understand operational steps in constructing committee structures, addressing legal hurdles, and developing financing and incentive programs.

The reviewer, George Mayzell, MD, MBA, is a consultant with Rx Health Partners and previously served as senior vice president/chief medical officer and chief clinical integration officer of a Chicago-based health care system. He is the author of Physician Alignment: Constructing Viable Roadmaps for the Future and Population Health: An Implementation Guide to Improve Outcomes and Lower Costs.
Baylor Scott & White Research Institute teams with Abzena to form Denceptor Therapeutics to develop novel immunotherapies

Baylor Scott & White Research Institute (BSWRI) and Abzena PLC announced the formation of a joint venture company, Denceptor Therapeutics Limited. Denceptor will develop Abzena Inside immunotherapeutic products to treat cancer and autoimmune diseases using BSWRI’s dendritic cell receptor-targeting antibodies. These antibodies will be humanized using Abzena’s Composite Human Antibody™ technology to reduce unwanted drug immunogenicity. Denceptor will operate as a virtual business and outsource its development and manufacturing activities. BSWRI and Abzena will be among the outsourced service providers.

Denceptor has been incorporated as a private limited company in Cambridge, UK. It will seek third-party funding to support the clinical development of the lead product, an HPV E6/E7 immunotherapy for head and neck cancer and other HPV-associated malignancies. Such funding will also be used to progress other preclinical-stage programs into clinical development and to cover the general running costs of the business. Abzena has the potential to receive future license income from the separately funded development of these Abzena Inside products.

Dr. Kevin FitzGerald has been appointed CEO of Denceptor and will be supported by Dr. Matthew Baker as chief scientific officer. Dr. FitzGerald previously held CEO positions at PhosImmune Inc., Activicomics Limited, F-star GmbH, and Isogenica Ltd. Dr. Baker was the founder of Antotope, which is part of the Abzena Group, and is currently the chief scientific officer at Abzena.

Dr. FitzGerald commented: “The dendritic cell-targeting technology that has been developed at BSWRI’s Immunology Research Program offers exciting opportunities for therapeutic intervention in a wide variety of life-limiting and life-threatening diseases. I look forward to progressing this approach to establish new treatment options that will improve patients’ lives.”

U.S. News & World Report recognizes 15 Baylor Scott & White Health hospitals

Baylor Scott & White Health and the Dallas Cowboys broke ground on June 15, 2016, in Richardson, Texas, to lay the foundation for their new state-of-the-art sports medicine, orthopedics, and rehabilitation center. The 212,000-square-foot facility will house a joint venture between the Dallas Cowboys and Baylor Scott & White, which is scheduled to open in 2018.

Baylor Scott & White hospitals received national rankings or high-performing ratings, more than any other health system in Texas. “We are honored to be recognized and thankful for the dedication of our team,” said Joel Allison, president and CEO, Baylor Scott & White Health. “Having so many of our hospitals on this list is a testament to the commitment of our many talented, compassionate caregivers and their calling to deliver excellent patient care.”

This year, for the first time, The Heart Hospital Baylor Plano was eligible to be recognized as one of the Best Hospitals for 2016–2017 by U.S. News & World Report, and it ranked #18 in the nation for cardiology and heart surgery. The Heart Hospital Baylor Plano joins Baylor University Medical Center at Dallas (BUMC), which has been included on the prestigious list for 24 years.

Once again, U.S. News ranked BUMC the #1 hospital in the Dallas metro area and #3 in Texas. The hospital was nationally ranked as a top hospital in four specialty areas: #16, gastroenterology and gastrointestinal surgery; #26, ear, nose, and throat; #31, diabetes and endocrinology; and #38, neurology and neurosurgery. It was recognized as high performing in seven other adult specialties: cancer, geriatrics, gynecology, nephrology, orthopedics, pulmonology, and urology.

Scott & White Memorial Hospital — Temple was also recognized as one of the state’s top hospitals, ranked #10, and was named high performing in five specialties: cancer, gastroenterology and gastrointestinal surgery, geriatrics, nephrology, and pulmonology.

Baylor Scott & White Medical Center — Grapevine was ranked #7 in the Dallas metro area and #19 in Texas. Baylor Institute for Rehabilitation was also recognized as high performing in the specialty of rehabilitation.

The U.S. News Best Hospitals rankings, now in its 27th year, help guide patients to hospitals that deliver outstanding care across 25 specialties, procedures, and conditions. The Best Hospitals methodologies include objective measures such as patient survival, the number of times a given procedure is performed, infection rates, and adequacy of nurse staffing. For 2016–2017, 153 hospitals were ranked in at least one specialty, while 1628 received a high-performing rating in one or more specialties, procedures, or conditions. In rankings by state and metro area, U.S. News recognized hospitals that were high-performing across multiple areas of care. In addition to 16 adult specialty rankings, U.S. News published hospital ratings for common adult procedures and conditions (previously referred to as “common care ratings”). The ratings evaluated more than 4500 hospitals nationwide on common inpatient procedures and conditions, recognizing them as high performing, average, or below average. This year, 12 Baylor Scott & White Health hospitals were recognized as high performing for at least one common care procedure or condition:

- Baylor Scott & White All Saints Medical Center – Fort Worth: Heart failure, chronic obstructive pulmonary disease (COPD)
- Baylor Scott & White Medical Center – Irving: Heart failure, COPD
- Baylor Scott & White Medical Center – Grapevine: Heart failure, colon cancer surgery, COPD, hip replacement, knee replacement
- Baylor Scott & White Medical Center – Plano: Heart failure, colon cancer surgery, COPD
- Scott & White Memorial Hospital: Heart failure, colon cancer surgery, COPD, hip replacement, knee replacement
- Baylor Jack and Jane Hamilton Heart and Vascular Hospital: Abdominal aortic aneurysm repair
- Baylor Scott & White Medical Center — Garland: Heart failure, COPD
- Baylor Scott & White Medical Center — Round Rock: Heart failure
- The Heart Hospital Baylor Plano: Abdominal aortic aneurysm repair, aortic valve surgery, heart bypass surgery, heart failure, lung cancer surgery
- Baylor Scott & White Medical Center – Carrollton: COPD
- Baylor Scott & White Medical Center – White Rock: COPD, heart failure
- Baylor Scott & White Medical Center – Hillcrest: COPD, heart failure
- Baylor Medical Center at Uptown: Hip replacement
- BUMC: Aortic valve surgery, heart bypass surgery, heart failure, colon cancer surgery, COPD, hip replacement, knee replacement, lung cancer surgery

Cowboys and Baylor Scott & White Health team up, unveil plans for sports health–centric facility

On June 15, 2016, Baylor Scott & White Health and the Dallas Cowboys broke ground
on a game-changing sports medicine, research, and performance facility that will be located at The Star in Frisco, home of the new Dallas Cowboys World Corporate Headquarters. The 300,000-square-foot campus, to be named Baylor Scott & White Sports Therapy & Research at The Star, will focus on injury prevention, research, and wellness for athletes of all levels and is expected to become a nationally recognized model for the holistic treatment of physically active individuals upon its completion in early 2018. It is also a first-of-its-kind collaboration between an NFL team, a health system, and a school district—Frisco Independent School District.

“With a focus on preventing injuries and keeping people healthy, the goal of Baylor Scott & White Sports Therapy & Research at The Star is to make North Texas the safest place in the country to play sports,” said Joel Allison, president and CEO, Baylor Scott & White Health. “This initiative is a perfect complement to Baylor Scott & White’s broader strategy of serving communities, with a focus on overall health and wellness.”

Baylor Scott & White Health announces agreement to acquire Lakeway Regional Medical Center

On July 7, 2016, Baylor Scott & White Health and Lakeway Regional Medical Center (LRMC) in Lakeway, Texas, announced an agreement for Baylor Scott & White to acquire the hospital operations. The agreement will facilitate the parties working toward a successful closing of the transaction by fall. Founded in 2012 to serve the Texas Hill Country, LRMC is a 106-bed, full-service, state-of-the-art medical campus with 300 affiliated physicians and 450 employees. It provides services in emergency medicine, neurosurgery, orthopedics, neurology, cardiology, general surgery, gastroenterology, and women’s health. LRMC is currently owned by independent investors.

Upon successful closing of the transaction, LRMC will join a strong contingent of Baylor Scott & White health care providers in a growing area. LRMC will become part of the Baylor Scott & White brand, to be named Baylor Scott & White Medical Center – Lakeway. “We are constantly looking for ways to improve access to quality care and the overall health of the communities we serve,” said Joel Allison, president and CEO, Baylor Scott & White Health. “This is about advancing our mission of population health for our great state.”

UPCOMING CME PROGRAMS

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

- Chest Cancer 2016, October 28, 2016, Baylor Charles A. Sammons Cancer Center, Dallas, Texas
- Spirituality at the End of Life, October 29, 2016, Dallas Theological Seminary, Dallas, Texas
- Scott & White Annual Neonatology Conference, September 29–30, 2016, Hilton Garden Inn, Temple, Texas
- 43rd Annual Williamsburg Conference on Heart Disease, December 4–6, 2016, Williamsburg Lodge, Williamsburg, Virginia
- Complex Care: Treatment Trends and Improved Outcomes (Internet CME), February 15, 2017

For more information, visit http://cmebaylor.org/conferences.

- Two Baylor Scott & White Health hospitals earn advanced palliative care certification
- The A. Webb Roberts Center for Continuing Education of Baylor Scott & White Health is offering the following programs: Chest Cancer 2016, October 28, 2016, Baylor Charles A. Sammons Cancer Center, Dallas, Texas
- Spirituality at the End of Life, October 29, 2016, Dallas Theological Seminary, Dallas, Texas
- Scott & White Annual Neonatology Conference, September 29–30, 2016, Hilton Garden Inn, Temple, Texas
- 43rd Annual Williamsburg Conference on Heart Disease, December 4–6, 2016, Williamsburg Lodge, Williamsburg, Virginia
- Complex Care: Treatment Trends and Improved Outcomes (Internet CME), February 15, 2017

- Baylor Scott & White hospitals earn “mother-friendly worksite” designation
- Several Baylor Scott & White Health hospitals earned a “Mother-Friendly Worksite” designation from the Texas Department of State Health Services, meaning employees are provided the time, space, and support to maintain breastfeeding after returning to work. The facilities with this designation include BUMC, Baylor Scott & White All Saints Medical Center – Fort Worth, Baylor Jack and Jane Hamilton Heart and Vascular Hospital, and Baylor Scott & White Medical Centers at Plano, Waxahachie, Carrollton, Grapevine, Irving, McKinney, Frisco, Garland, College Station, and White Rock.

- New clinical trial investigates minimally invasive treatment option for aortic stenosis patients with a larger valve size
- A clinical trial exploring a new minimally invasive treatment option for some patients with severe aortic stenosis recently launched at Baylor Jack and Jane Hamilton Heart and Vascular Hospital. The investigational treatment option is for patients who might have been previously deemed unable to have transcatheter aortic valve replacement (TAVR) due to the large size of their diseased valves. About 60 patients at up to 15 clinical sites will be enrolled in the prospective, single-arm trial.

- The Medtronic CoreValve® Evolut® R 34mm System, which features a larger TAVR technology than previous versions, replaces a diseased aortic heart valve through a minimally invasive procedure, without open-heart surgery and without surgical removal of the diseased valve. The device is typically inserted through

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an artery in the leg and then guided through the arteries into the heart. Once in place, the device expands and takes over the original valve’s function to enable oxygen-rich blood to flow efficiently out of the heart.

“Our rich history and tradition of being on the forefront of cardiac care continues with this new clinical trial,” said Robert Stoler, MD, co-medical director of cardiology and medical director of the cardiac catheterization laboratory at Baylor Heart and Vascular Hospital. “Our patient outcomes and quality care continue to garner national attention. We are pleased to be one of seven clinical sites chosen for this study.”

Residents doing research: program at BUMC provides resources, mentors

Before joining Baylor Scott & White Health, Philip Edmundson, MD, had limited exposure to the world of research. “I was a philosophy major in undergrad, so I didn’t do any research as an undergraduate,” the third-year resident from the University of Texas Southwestern Medical School said. “I’m pretty new to the game.” In just 3 years, Dr. Edmundson has found himself on the investigative fast track, having contributed to multiple studies, posters, and papers on BUMC’s trauma team. Much of this research has been the result of good timing. Dr. Edmundson’s residency coincided with the start of Baylor’s resident-research program, which since 2013 has required BUMC surgery residents to publish at least one manuscript in a national journal.

James Fleshman, MD, chairman of BUMC’s Department of Surgery, emphasizes this requirement among BUMC’s pool of 45 surgical residents. “Research has always been done here, but it’s usually been done by attending physicians and others,” said Dr. Fleshman, who helped spearhead the program 3 years ago. “We wanted to involve residents so they’d have the tools and skills to launch their own projects.”

In the 3 years since the program’s inception, resident-driven research has increased significantly, and the Department of Surgery has kept pace by offering special resources to support new and ongoing projects. These include several research coordinators and interns, a peer-review committee for surgical research, a statistician, a manuscript-writing resource, and a structured template that helps residents organize protocols into standardized article formats. Dr. Fleshman and others also serve as mentors. All told, these resources help reduce the time and stress imposed on the already busy residents.

Dr. Fleshman added that the process encourages ideation and strategic thinking and potentially fosters interests in research topics that go well beyond the 5-year residency. In addition, by the end residents not

### RECENT GRANTS

- **A novel function of Itch in controlling IL-17–induced inflammation in colon cancer**
  Principal investigator: Venuparasad Poojary, PhD
  Sponsor: Cancer Prevention Research Institute of Texas
  Funding: $900,000
  Award period: 8/1/2016–5/31/2019

- **Mandatory estimates of vaccine effectiveness against medically attended, PCR-confirmed influenza in West South Central US**
  Principal investigator: Manjusha Gaglani, MD
  Sponsor: Department of Health and Human Services/Centers for Disease Control and Prevention
  Funding: $800,000
  Award period: 8/1/2016–7/31/2017

- **Improving combination chemotherapy of tuberculosis: a computational approach**
  Principal investigator: Tawanda Gumbo, MD
  Sponsor: Colorado State University/National Institutes of Health
  Funding: $548,800
  Award period: 8/1/2016–7/31/2017

- **Emergency and trauma care education partnership program—graduate medical education**
  Principal investigator: Dorian Drigalla, MD
  Sponsor: Texas Higher Education Coordinating Board
  Funding: $528,000
  Award period: 5/1/2016–6/30/2018

- **Core_apt measure of PCR-based influenza vaccine effectiveness in inpatient adults**
  Principal investigator: Manjusha Gaglani, MD
  Sponsor: Department of Health and Human Services/Centers for Disease Control and Prevention
  Funding: $450,000
  Award period: 8/1/2016–7/31/2017

- **Familial and early onset colorectal cancer**
  Principal investigator: Ajay Goel, PhD
  Sponsor: National Institutes of Health
  Funding: $372,400
  Award period: 8/1/2016–7/31/2017

- **The paracrine regulation of mast cells during biliary/cholangiocyte repair and damage**
  Principal investigator: Heather Francis, PhD
  Sponsor: National Institutes of Health
  Funding: $252,123
  Award period: 4/1/2016–3/31/2017

- **Anti-DC-ASGPR antibody-based therapeutic approach for allergic asthma**
  Principal investigator: SangKon Oh, PhD
  Sponsor: American Asthma Foundation
  Funding: $175,000
  Award period: 7/1/2016–6/30/2017

- **Facilitating patient-reported outcome measurement for key conditions**
  Principal investigator: Peter McCullough, MD
  Sponsor: Trustees of Dartmouth College/ Patient-Centered Outcomes Research Institute
  Funding: $81,140
  Award period: 3/1/2016–9/30/2016

- **Advancing treatment for pancreatitis: a prospective observational study of TPIAT**
  Principal investigator: Bashoo Naziruddin, PhD
  Sponsor: University of Minnesota/National Institutes of Health
  Funding: $27,788
  Award period: 6/1/2016–3/31/2017

- **Affect regulation training (ART) for alcohol use disorder: a stage II efficacy trial**
  Principal investigator: Suzy Gulliver, PhD
  Sponsor: The Research Foundation for the State University of New York/National Institutes of Health
  Funding: $14,826
  Award period: 4/20/2016–3/31/2017
only have a published manuscript on their curriculum vitae, they’ve also learned critical thinking skills to discern which research applies to their clinical cases. “We want to make residents in surgery understand the impact of research on their practice and on their career,” Dr. Fleshman said. “But the other benefit is when they read an article that relates to a particular patient, they have to be able to understand whether or not it’s actually relevant and applicable—and whether they can trust the conclusions.”
Lipid therapy and plasmapheresis in tricyclic poisoning

We read with interest the recent report by Odigwe and colleagues regarding the use of intravenous lipid emulsion therapy and plasmapheresis in a patient with presumed tricyclic antidepressant overdose (1). While we commend the authors for their contribution, we have several serious concerns regarding their case report.

First, while there was a history of ingestion of amitriptyline and venlafaxine, there was no attempt to confirm the ingestion with either quantitative or qualitative testing. This omission was compounded when signs and symptoms were attributed to amitriptyline and the potential contribution of venlafaxine was ignored. An attempt to quantify the ingestion might have informed us that the clinical effects were preferentially attributable to one toxin over another, the combined effects of both toxins, or a third undisclosed ingestion. While we recognize that toxicological testing rarely contributes to clinical decision-making due to the delay in obtaining specific drug concentrations, we feel that confirmation is an essential requirement for contributions to the medical literature. The authors also failed to quantify the amount of drug removed by plasmapheresis. The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup provided a framework for reporting the efficacy of toxin removal by extracorporeal therapies (2), and almost none of the elements suggested in those recommendations were discussed or reported. Although the authors provided a citation that discusses a reduction in plasma concentration of a tricyclic antidepressant following plasmapheresis, they failed to recognize that given the very large volume of distribution of amitriptyline, even a massive reduction in plasma concentration only minimally reduces the total body burden of the drug. It is this fact that served as the basis for the EXTRIP group to recommend against attempts at any type of extracorporeal removal of tricyclic antidepressants (3).

Second, the patient’s urine was positive for opiates and phencyclidine, yet opiates were not discussed as a group of compounds that might be able to worsen the poisoning or contribute to lung injury. The manuscript did not specify nor discuss the specific analytical method used. Urine drug screens are well known to report false-positive results from cross-reactivity with the immunoassays of the urine drug screen tests such as phencyclidine and venlafaxine (4). Positive results from urine drug screen tests should be followed by a confirmatory laboratory assay to eliminate interference (4, 5).

Third, the attribution of a clinical outcome to any specific therapy or therapies in this case cannot be confirmed. The authors stated that following successful resuscitation with a number of therapies, the patient was then given intravenous lipid emulsion and later received plasmapheresis. No description was provided of dose, duration, and chronological clinical effect of either therapy. If the toxicity was primarily due to amitriptyline, this information, along with the clinical and electrocardiographic response, would be particularly useful for the reader to assess the role and value of the adjunctive treatments. The table presented by the authors is an incomplete list of references regarding TCA overdose, particularly with regard to the use of lipid emulsion treatment.

A recent experimental model suggests a detrimental effect of lipid in oral amitriptyline toxicity (6), and a systematic review sheds doubt on the overall efficacy of lipid in most cases of oral overdoses (7). Furthermore, while it is noted that the patient developed acute respiratory distress syndrome, there is no mention of the possibility that this complication could have either resulted from, or be exacerbated by, lipid administration (8).

In conclusion, while we commend the authors on the successful resuscitation of a severely poisoned patient, in reality it is unclear what poison or poisons harmed this patient and whether intravenous lipid emulsion or plasmapheresis was beneficial, neutral, or even harmful in this case.

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7. Levine M, Hoffman RS, Lavergne V, Graudins A, Chuang R,  information, lipid emulsion was administered as a 34 g dose, in our manuscript. With regard to the request for additional lipid emulsion treatment. Moreover, the association between the etiology in this case was likely aspiration rather than the suggested the presence of ARDS at the time of initial presentation. Additionally, serum levels seldom play a role in non-local aesthetics toxicity. Clin Toxicol (Phila) 2016;54(3): 194–221.


Although the clinical presentation was strongly suggestive of tricyclic antidepressant (TCA) poisoning, we acknowledge that a definitive diagnosis of TCA overdose should be made using appropriate and supportive laboratory measurements. Unfortunately, these assays carry a longer than desirable turnaround time in many community institutions, limiting the clinical utility of such laboratory data. Additionally, serum levels seldom play a role in patient management and prognosis (3).

While lipid emulsions are a potential cause of acute respiratory distress syndrome (ARDS), our patient’s presentation suggested the presence of ARDS at the time of initial presentation. The etiology in this case was likely aspiration rather than the lipid emulsion treatment. Moreover, the association between ARDS and TCA poisoning is well documented, as discussed in our manuscript. With regard to the request for additional information, lipid emulsion was administered as a 34 g dose, given once in a 170 mL 20% infusion prior to the initiation of plasmapheresis. Plasmapheresis was done for two consecutive days, with each treatment lasting for 2 hours using 5% albumin and 1 g of 10% calcium gluconate per liter of fluid removed.

Our patient had no history of substance abuse, raising the likelihood of false-positive urine toxicity, an effect that may be ascribed to venlafaxine (4). Further confirmatory testing was probably unwarranted; such information is unlikely to impact the clinical management in patients who present similarly.

Lastly, while there are many areas of overlap of symptoms and signs in suspected drug overdose cases, most of the life-threatening manifestations in our patient have largely been described with TCA overdose (3, 5, 6).

Few adjuvant therapies exist in the literature for treatment of life-threatening TCA overdose (5). The EXTRIP workgroup was formed to provide recommendations on the use of extracorporeal treatments in poisoning; however, only case reports, case series, and poor-quality observational studies were identified, yielding a very low quality of evidence for all recommendations (7).

As mentioned in our report, there have been no randomized trials on the role of extracorporeal therapy in life-threatening TCA overdose. Until randomized trials are available, extracorporeal therapy may still have some role in a subset of patients at high risk of death despite the lack of established evidence (8, 9). We hope our experience contributes to the body of existing literature that will ultimately guide the development of more definitive recommendations for the treatment of severe drug poisoning.

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BOOKS AUTHORED BY PHYSICIANS

Cardiologist Alfred A. Bove collected a number of books written by physicians and published the results in CardioSource World News in June 2016 (1, 2). He indicated that physician writers can be traced back to antiquity. Notable examples extend from Copernicus in the 13th century, Vesuvius in the 14th, Jenner in the 16th, and Conan Doyle in the 19th to the many contemporary writers in the 20th and 21st centuries. Some of the modern physicians include Michael Crichton, Robin Cook, Atul Gawande, Siddhartha Mukherjee, Tess Gerritsen, Khaled Hosseini, and Abraham Verghese. The term physician-writer or physician-author is usually used to describe physicians who write fiction rather than nonfiction.

General fiction. Abraham Verghese (Stanford University) was an early overachiever, board certified in internal medicine, pulmonary diseases, and infectious diseases. His novel Cutting for Stone, set in Ethiopia and New York City, is rich in medical detail and human emotion. It spent >2 years on The New York Times bestseller list. He has penned two memoirs: My Own Country (detailing his experiences as a young doctor in rural Tennessee at the beginning of the AIDS epidemic) and The Tennis Partner (tracing his friendship with a medical student dogged by drug addiction). Both were critically acclaimed, and the former became a TV movie.

Khaled Hosseini’s first success was The Kite Runner (2003) followed by A Thousand Splendid Suns. These two books together sold >38 million copies worldwide. Dr. Hosseini practiced internal medicine for >10 years until shortly after the release of The Kite Runner. In 2013, he published And the Mountains Echoed.

Mysteries, science fiction, thrillers. Dame Agatha Christie was an apothecary. So accurate was her description of thallium poisoning that on at least one occasion it helped solve a case that was baffling physicians. Sir Arthur Conan Doyle, the creator of Sherlock Holmes and Dr. Watson, was an ophthalmologist. He started penning fiction while waiting for patients to discover his newly opened private practice. Doyle continued to practice medicine even after achieving literary success, but in 1891, after a near-death experience with influenza, he stopped. Robert Brian “Robin” Cook authored The Year of the Intern (1972), Coma (1977), Death Benefit (2011), Nano (2013), Cell (2014), and Host (2015). An ophthalmologist, Dr. Cook has written 33 worldwide bestsellers to date. In each, Dr. Cook tries to elucidate various medical/biotech ethical issues. Dr. Cook’s subjects include such topics as genetic engineering, medical economics, in vitro fertilization, research funding, managed care, drug research, organ transplantation, stem cell research, concierge medicine, and physician-owned specialty hospitals.

Michael Crichton, Tess Gerritsen, and Michael Palmer also achieved chart-topping hits as physician-writers in the mystery, thriller, and sci-fi arenas. Dr. Crichton (1942–2008) trained at Harvard Medical School but never obtained a license to practice medicine, instead becoming a bestselling author (Jurassic Park, 1990, among others), producer, director, and screenwriter. Dr. Gerritsen wrote Vanish (2005), among others. She started writing during a maternity leave as an internist. She is now retired from medicine, but uses her knowledge and fame to help raise money for Alzheimer’s research. Many but not all of her books fall under the medical thriller category. She is the creator of pathologist Dr. Maura Isles and her colleague and close friend, Detective Jane Rizzoli, who both live in the pages Dr. Gerritsen has penned and on the small screen in the television series Rizzoli and Isles. Michael Palmer (1942–2013) never wanted to be a writer, but he was inspired to write after reading Robin Cook’s Coma. He wrote Extreme Measures (1991), among others. He spent 20 years as a full-time practitioner of internal and emergency medicine and served as an associate director of the Massachusetts Medical Society’s physician health program. Along the way, he wrote 19 novels, several of which were bestsellers.

Two cardiologists (electrophysiologists), Douglas Zipes and Peter R. Kowey, have written murder mysteries. He is “Douglas P” when writing as a physician and just “Doug” when writing creatively. He just published his third mystery titled Not Just a Game. The story takes place during the 2016 Rio Olympics. Dr. Kowey has published two books, Lethal Rhythm (2010)
and Deadly Rhythm (2012). He focuses on cardiac rhythm disturbances.

On living and dying. Death and illness are obvious topics for physician-writers, and some of the seminal works on death have been penned by physicians. Sherwin B. Nuland's How We Die: Reflections on Life's Final Chapter (1994) won a National Book Award and is considered one of the most important books on the topic. Dr. Nuland is a surgeon at Yale. In 1969, Elizabeth Kübler-Ross wrote the groundbreaking classic On Death and Dying, which massively reshaped the way we talk about mourning, the process of moving from anger to acceptance. It remains basic reading for those interested in life and living as well as death and dying. Many of Kübler-Ross's observations on living and dying are so much a part of popular parlance that their origin has been forgotten.

Some of the most powerful and even haunting writing to arise from the physician world is from physicians who have written about their own fatal diseases. When Breath Becomes Air (2016) by Paul Kalanithi, a budding neurosurgeon struck down by lung cancer at the age of 37, is a profoundly moving memoir. Dr. Kalanithi (formerly of Stanford Medical School) wrote about reading his own computed tomographic scan, seeing a new tumor, scrubbing for his last case, his last day practicing medicine. The New York Times called this book “a great, indelible book” that, once read, will never be forgotten.

Just down the list from Dr. Kalanithi's book at #4 on The New York Times hardcover nonfiction bestseller list (as of May 15, 2016) is Atul Gawande's Being Mortal (2014), at #11, which considers “the modern experience of mortality” and how medicine is failing the test of assisting patients to a good death. Along with his success as a surgeon, Dr. Gawande has received international renown for his insightful, honest, and sometimes highly critical looks at the practice of modern medicine. He has written four books and dozens of articles on the practice of medicine today.

And, there is the late Oliver Sacks, the poet laureate of contemporary medicine. Dr. Sacks wrote in 1984 about his experience recovering from muscle surgery and then, in 2006, about the loss of stereoscopic vision after radiation for uveal melanoma. In December 2014, in a New York Times op-ed piece, he revealed that he was dying from metastatic cancer. When he died in August 2015, Dr. Sacks was remembered not just as a gifted neurologist, but as one who was able to chronicle death and illness from the cool intellectual perspective of a physician and scientist, yet with profound sympathy. In his own words, he "bore witness" to the wealth of emotion felt by the sick and dying.

About medicine or disease. Siddhartha Mukherjee authored The Emperor of All Maladies: A Biography of Cancer (2010), which details the evolution of diagnosis and treatment of cancer from ancient Egypt to the latest breakthroughs. A large book detailing an exhaustive account, Emperor won a Pulitzer Prize in 2011 before becoming the basis of a PBS miniseries. It is unusual for a 600+-page book on cancer to be a bestseller. The New Yorker said of the book, "It's hard to think of many books for a general audience that have rendered any area of modern science and technology with such intelligence, accessibility, and compassion…. An extraordinary achievement." Dr. Mukherjee's second book, The Laws of Medicine: Field Notes from an Uncertain Science (2015), was shorter, addressing the issue of whether medicine is indeed a science. His third, The Gene: An Intimate History, weaves science, social history, and personal narrative to tell the story of one of the most important conceptual breakthroughs of modern times.

Eric Topel, from La Jolla, California, wrote The Creative Destruction of Medicine (2012) and The Patient Will See You Now (2015). The latter attempts to democratize and digitize and thereby improve medicine. The book was heralded by The New York Times as a “must-read manifesto for patients who feel helpless.”


History of medicine. W. Bruce Fye, the world's finest medical historian, wrote Caring for the Heart: Mayo Clinic and the Rise of Specialization (2015), which describes major developments in the diagnosis and treatment of heart disease in the 20th century and details how the Mayo Clinic evolved into one of the world's leading medical centers. The book also describes how scientific advances and technological innovations—along with national and international societies—helped create contemporary heart care and stimulate subspecialization. Fye's earlier book, American Cardiology: The History of a Specialty and Its College (1996), was also extremely well received.

James Forrester, a cardiologist at Cedars-Sinai Medical Center in Los Angeles, has written The Heart Healers: The Misfits, Mavericks, and Rebels Who Created the Greatest Medical Breakthrough of Our Lives (2015), a memoir of his personal relationships with pioneers who created cardiac surgery, defibrillators, pacemakers, cardiac care units, cardiovascular imaging, and percutaneous coronary intervention.

William L. Winters, Jr., of Houston has written Houston Hearts: A History of Cardiovascular Surgery and Medicine and the Methodist DeBakey Heart and Vascular Center at Houston Methodist Hospital (2014). In its first half, the book focuses on Michael E. DeBakey, who came to Houston in 1948 to chair the department of surgery at Baylor University School of Medicine. His six-decade relationship with Houston resulted in the establishment of the Methodist DeBakey Heart and Vascular Center in 2001.

Few physicians actually publish, whether in medical journals or lay publications, but good writing signifies good thinking. Since writing is required of all physicians, it is important for all of us to continually work on our writing skills.

SUICIDE RATES AMONG US VETERANS

The Department of Veterans Affairs (VA) recently examined the death records of 55 million veterans dating back to 1979 (3). The data for 2014 indicated that there were 7403 suicide deaths among US veterans. The VA found the worst suicide
pattern among male veterans aged 18 to 29, a rate of 86 per 100,000 people, nearly 4 times the rate among active-duty service members in 2015. By contrast, the overall US suicide rate is 13 per 100,000 people. The suicide rate among young female veterans, aged 18 to 29, was 33 per 100,000. In 2014, veterans accounted for 18% of all suicides in the USA, and they made up only 8.5% of the population.

US HEALTH CARE SPENDING IN 2016
The nation’s health care tab this year is expected to surpass $10,300 per person for the first time, for a total of $3.3 trillion (4). The annual health care spending growth rate is projected to average 5.8% from 2015 to 2025, a bit below the pace before 2007 to 2009, but faster than in recent years. A stronger economy, a faster growth in medical prices, and an aging population are driving the trend. Medicare and Medicaid are expected to grow more rapidly than private insurance as the baby-boom generation ages. By 2025, government at all levels will account for nearly 50% of health care spending.

About 5% of the population—those most frail or ill—account for nearly half the spending in a given year. About half of the population accounts for only 3% of health care costs. Of the total $3.35 trillion spending projected this year, hospital care accounts for about 32%; physicians and other healthcare personnel account for nearly 20%; and prescription drugs bought through pharmacies account for about 10%.

SOCIAL SECURITY AND MEDICARE
The Social Security and Medicare Trustee Reports were released in June 2016, and Scott Burns summarized some of the findings (5). The 2016 report showed that Social Security and Medicare have a combined surplus of $17.1 billion. In spite of employment taxes, taxes on Social Security benefits, trust fund interest, and premiums for Medicare Parts B and D, these programs were short $354.5 billion. This cash shortage represented 80% of the entire federal deficit for 2015! All other government programs, after tax collections, operated at a loss of $83.9 billion. The prices paid by Medicare for most health care services will fall increasingly short of the cost of providing such services. If the issue is not addressed by the legislature, it is likely that access to, and quality of, Medicare benefits will deteriorate over time for beneficiaries.

MEDICARE’S PRESCRIPTION COVERAGE
The cost of Medicare’s prescription coverage jumped 85% in 3 years from $28 billion in 2013 to $51 billion in 2015 (6). Of 2750 drugs covered by Medicare’s Part D benefit, two pills for hepatitis C infection—Harvoni and Sovaldi—accounted for nearly $7.5 billion in catastrophic drug costs, having doubled in 2 years from about $3.5 billion in 2014 to nearly $7.5 billion in 2015.

Medicare’s catastrophic coverage was designed to protect seniors with multiple chronic conditions from the cumulative high costs of taking many different pills. Beneficiaries pay 5% after they have spent $4850 of their own money. With some drugs now costing more than $1000 per pill, that threshold can be crossed quickly. Lawmakers who created Part D in 2003 also hoped the added protection would entice insurers to participate in the program. Medicare pays 80% of the cost of drugs above a catastrophic threshold that combines spending by the beneficiary and the insurer. That means taxpayers, not insurers, bear the exposure for the most expensive patients.

Revlimid, a cancer drug derived from the 1950s thalidomide, surpassed $1.7 billion in catastrophic costs in 2015, coming in second among high-cost drugs. Gleevec, a breakthrough drug introduced in 2001 to treat leukemia, was fifth among the top 10 pricey medications, with more than $1 billion spent in 2015. That was a 54% increase from 2013.

Catastrophic spending accounts for a growing share of Medicare’s drug costs, which totaled nearly $137 billion in 2015. The catastrophic share was 37%, yet only about 9% of beneficiaries reached the threshold for such costs. For those patients, average spending jumped 46%, from $9666 in 2013 to $14,100 in 2015.

Catastrophic coverage will soon cost as much as the entire prescription program did when it was launched in 2003. The rapid rise in spending for pricey drugs threatens to make the popular prescription benefit financially unsustainable. Most beneficiaries have not seen a drastic hit yet from rising drug costs, but that may be changing. This year, 2016, average premiums went up >15% in 5 of the top 8 drug plans.

DENTAL FLOSSING
The Associated Press examined 25 studies conducted over the last decade and found that the support for dental flossing is “weak, very unreliable,” of “very low” quality, and carries a “moderate to large potential for bias” (7). While the federal government has recommended flossing since 1979, that recommendation has now been removed from the latest Dietary Guidelines for Americans, which, as required by law, must be based on scientific evidence.

I have asked a number of dentists through the years: If one could do only tooth brushing or dental flossing, which would they consider the most healthful? The answer almost overwhelmingly has been dental flossing. I have been flossing religiously for the last 20 years (I wish I had done it the many previous decades) and find my mouth refreshed after doing so. One or more food fragments are usually dislodged from my mouth by the process. When I didn’t floss and went to the dental hygienist, my gums bled considerably. Since fl ossing daily would they consider the most healthful? The answer overwhelmingly has been dental flossing. I have been flossing religiously for the last 20 years (I wish I had done it the many previous decades) and find my mouth refreshed after doing so. One or more food fragments are usually dislodged from my mouth by the process. When I didn’t floss and went to the dental hygienist, my gums bled considerably. Since fl ossing daily

FOOD LABELS
Most food labels are confusing and most lack precise definitions. Joe Craven McGinty, writing in *The Wall Street Journal*, defined some of the terms (8):

*Whole grains:* Unless the label on a loaf of bread, box of crackers, or other cereal product explicitly says “100% whole grain” or “100% whole wheat,” it probably is not.
Made with: This phrase often means “made with very little.” Many consumers assume it means made only of whole grains; that is not true. The term “made with” has not been formally defined by the Food and Drug Administration. Items made with whole grains or whole wheat contain a substantial amount of refined flour.

Ingredients list: If the first item listed is enriched flour—which is refined but has had some nutrients added back in—the product probably is not made primarily of whole grains.

Cage-free: Most egg-laying hens in the USA are confined in wire cages measuring 67 x 86 square inches per hen. Cage-free birds are allowed to roam in a room or in an area, but they are not guaranteed access to the outdoors.

Free-range: These chickens, which are raised for meat, do not have outdoor access, although producers may use screened-in porches with floors made of concrete, dirt, or grass to provide access.

Hormones: Hormones are not allowed in poultry or hogs. Nonetheless, some producers label these products “no hormones added.” When they do, the claim is supposed to be followed by a statement that says “federal regulations prohibit the use of hormones.” Beef and lamb may be labeled “no hormones administered” only if the producer provides documentation showing steroids were not used in the livestock.

Organic: Only labels that say “100% organic” are sure to indicate products that are made exclusively of organic ingredients. When the label simply says the contents are “organic,” at least 95% of the ingredients, excluding salt and water, must fit that description. If it says the food is “made with” organic ingredients, at least 70% of the ingredients, excluding salt and water, must be organic. Organic meat and poultry recommendations require animals to be raised in living conditions that accommodate natural behaviors, such as grazing, and be fed 100% organic feed and forage and administered no antibiotics or hormones.

Natural: This word refers to the preparation of a product, not how a plant or animal was raised. The label is supposed to include a statement explaining what it means. For example, it might say the product contains no artificial ingredients and was minimally processed.

Free, low, reduced: “Free” means there is <0.5 g per serving of a nutrient that has a daily value, such as fat. “Low” means there are 3 g or less per serving. These thresholds vary depending on the nutrient. “Reduced” means there is at least 25% less of the nutrient compared with another food.

Gluten-free: Manufacturers may label foods “gluten free” if ingredients derived from grains have been processed to remove gluten and the food has <20 parts per million. Foods that inherently have no gluten—such as water—also may be labeled gluten-free, even though they never contained the substance.

The director of the Office of Nutrition and Food Labeling at the Food and Drug Administration was in charge of labeling these foods, with the objective of providing truthful and not misleading information, but the terms on food labels are infrequently defined. I think some of our federal officials could do a bit better.

A law signed in July 2016 by President Obama requires food companies to flag genetically modified organism (GMO) ingredients on labels, using either plain writing, an icon developed by regulators, or a digitally readable symbol known as a QR code (short for quick-response code) (9). The black-and-white code of shapes, squares, and lines provides product information when scanned using a smartphone app. The law lets companies make GMO disclosures using only QR codes and not words—something the food industry supported. That cumbersome process has drawn criticism from healthy food advocates who want to see ingredients derived from biotech crops flagged as explicitly as possible. Healthy food advocates oppose the use of QR codes to disclose GMOs as cumbersome. The industry’s position is that QR codes allow for the most up-to-date information and get around space constraints on labels. While QR codes are not widely used in the US, they have been common in Japan for nearly 2 decades. Containing data both horizontally and vertically, the codes pack in more information and convey it to a scanning device more quickly than barcodes do.

DECISIONS, DATA, CHOICES, AND FATIGUE

Jim Sollisch in a column in The Wall Street Journal estimated that the average American adult makes 35,000 decisions a day (10). No wonder we are tired and soul-weary. We may be suffering from decision fatigue. According to Sollisch, there is only one cure: Stop being the decider of everything. It sounds easy, but is not: we are all one Google search away from dozens of meaningless decisions. Decision fatigue is different from choice paradox, in which too many options paralyze one from making any decision. We can now decide on a physician based on rankings and reviews and might spend hours on a decision that used to be handled by asking a friend for a recommendation.

In their book Will Power: Rediscovering the Greatest Human Strength, John Tierney and Roy Baumeister wrote that judges have only a finite amount of willpower, a limited store of energy for adjudicating. As the day wears on, a judge’s decision-making abilities wear down and he or she reverts to the easy answer, which is often no. An analysis of 1100 decisions by an Israeli parole board disclosed that parole was granted about one-third of the time overall, but prisoners whose cases were heard early in the morning received parole about 70% of the time and prisoners appearing late in the afternoon were granted freedom only 10% of the time. These judges were deciding several dozen cases a day.

I understand the judge’s dilemma. As editor of a major cardiology journal and this Baylor journal, I review an average of 8 manuscripts every day of the week. I have found that I do more rejects late at night than I do early in the morning, and I frequently put aside those late manuscripts to look at them the next day when my thought processes are less fatigued.

Sollisch indicated that decision fatigue is the result of two things that have become abundantly available: data and choices. When everything is measurable, everything seems knowable. Decision making has the appearance of work. It can often, however, be a distraction disguised as productivity. Having data
feels like power. Having choices feels like freedom. Sometimes having both is having neither.

LOOSE DOGS

The chair of the Dallas Animal Commission some time ago raised money from six private foundations to hire the Boston Consulting Group to examine the problem of loose dogs in Dallas, nearly entirely in South Dallas (11, 12). The consulting firm has spent many days gathering data and has now concluded that there are about 8700 loose dogs in Dallas! The number of reported dog bites in Dallas increased 33% from 2013 to 2015, with 51% being attributed to “loose-but-owned dogs.” Since 2011, Dallas Animal Services’ dog intake has remained flat, with an increase in owner surrenders compensating for a slight decline in field intake. Eighty-five percent of dogs in southern Dallas have not been spayed or neutered. That means the population grows quickly. Despite all efforts, the population of intact dogs has not been reduced. The commission’s full report will be presented to the full city council in a few weeks. Obviously, loose and stray dogs are potentially dangerous. The bites can even be fatal, produce serious infection, and, heaven forbid, lead to rabies. Dallas can do better.

TATTOOS

I understand that slightly less than 25% of US adults have a tattoo. I am not in favor of tattoos. So many who get them regret them later and want them removed. That is an expensive and painful proposition. Each of the Armed Services has its own regulations regarding tattoos (13). The Army’s policy occupies a little less than 2 pages, and the Navy sums up its regulations in 4 paragraphs. The Marines, however, use 32 pages to describe their tattoo regulations, including glossaries. The new regulations for the Marines disallow enlisted personnel to have tattoos on the head, neck, hands, elbows, or knees. Marines can only have one tattoo on their lower arm or lower leg, and it cannot be bigger than the size of their hand unless that tattoo is a “band” that wraps around the whole limb. The new Marine policy, released in June 2016, also lets Marines know they have 120 days to document existing tattoos so they can be grandfathered in, and, as a reminder, policy violations can be punished by a court martial.

FALLING US STANDARD OF LIVING

Robert J. Gordon, probably the US’s best economic historian, has written a magnificent book entitled The Rise and Fall of American Growth: The US Standard of Living Since the Civil War, on the economic history of the US over the last 150 years (14). His study focuses on what he calls the “special century” from 1870 to 1970 in which living standards increased more rapidly than at any time before or after. The book is without peer in providing a statistical analysis of the uneven pace of growth and technological change, in describing the technologies that led to the remarkable progress during the special century, and concluding with a provocative hypothesis that the future is unlikely to bring anything approaching the economic gains of the earlier period.

The message of Rise and Fall is this: For most of human history, economic progress moved at a crawl. From the first rock tools used by humanoids 3 million years ago to the earliest cities 10,000 years ago, through the Middle Ages, to the beginning of the Industrial Revolution around 1800, living standards doubled (with a growth of 0.00002% per year). Another doubling took place from 1800 to 1870. Then the world economy took off. Gordon focuses on growth in the US. Living standards, as measured by gross domestic product per capita or real wages, accelerated after 1870. The growth rate looks like an inverted U. Productivity growth rose from the late 19th century and peaked in the 1950s, but has slowed to a crawl since 1970. In designating 1870 to 1970 as the special century, Gordon emphasizes that the period since 1970 has been less special. Indeed, the pace of innovation has slowed since 1970, and the gains from technological improvement have been shared less broadly.

A central aspect of Gordon’s thesis is that the conventional measures of economic growth omit some of the largest gains in living standards and therefore underestimate economic progress. The standard measurements of economic progress, for example, do not include gains in health and life expectancy, nor do they include the impact of revolutionary technological improvements such as the introduction of electricity or telephones or automobiles. Most of the book is devoted to describing many of history’s crucial technological revolutions, which, in Gordon’s view, took place in the special century. Moreover, he argues that the innovations of today are much narrower and contribute much less to improvements in living standards than did the innovations of the special century.

The first chapter summarizes his major arguments. Here is the basic thesis:

The century of revolution in the United States after the Civil War was economic, not political, freeing households from an unremitting daily grind of painful manual labor, household drudgery, darkness, isolation, and early death. Only one hundred years later, daily life had changed beyond recognition. Manual outdoor jobs were replaced by work in air-conditioned environments; housework was increasingly performed by electric appliances; darkness was replaced by light, and isolation was replaced not just by travel, but also by color television images bringing the world into the living room…. The economic revolution of 1870 to 1970 was unique in human history, unrepeatable because so many of its achievements could happen only once.

The series of “only once” economic revolutions behind this short summary makes up the next 14 chapters of the book. Most of the innovations are familiar, but Gordon tells their histories vividly. Among the most illuminating chapters are those on housing, transportation, health, and computers. The last two chapters are about the fall in Rise and Fall. Gordon sees two sources for his pessimistic outlook: 1) the long list of “only once” social and economic changes cannot be repeated; 2) “headwinds,” structural changes in the economy, reduce actual output below the country’s technological potential.
To summarize, Rise and Fall is a magnificent book on American economic history, including changes in health in the last 150 years!

LIFE LESSONS OF BYRON WIEN

He is now 83 years old and has been an investment manager or strategist on Wall Street for the last 57 years (15). The following are some of his life lessons that he has passed on.

Network intensely: Luck plays a big role in life, and there is no better way to increase your luck than by knowing as many people as possible. Treat those you meet as a friend: Assume they are a winner and will become a positive force in your life. Read all the time: Have a point of view before you start a book or article and see if what you think is confirmed or refuted by the author. Get enough sleep: Seven hours will do until you’re 60, eight from 60 to 70 years, and 9 thereafter, which might include 8 hours at night and a 1-hour nap. Travel extensively: Try to get everywhere before you wear out. Attempt to meet local interesting people where you travel and keep in contact with them throughout your life. In philanthropy, try to relieve pain rather than spread joy. Remember that the hard way is always the right way: Never take shortcuts. Shortcuts can be construed as sloppiness, a career killer. Don’t try to be better than your competitors; try to be different. There is always going to be someone smarter than you, but there may not be someone who is more imaginative. Take the job that looks like it will be the most enjoyable: This applies when leaving school or making a job change. If it pays the most, you’re lucky. If it doesn’t, take it anyway. Never retire: If you work forever, you can live forever.

GORDIE HOWE, “MR. HOCKEY” (1928–2016)

Gordie Howe was so skilled, prolific, durable, and ferocious that he scored 975 goals in 2186 hockey games for 4 teams in 2 leagues during a professional career that spanned 32 seasons from 1946 to 1980 (16, 17). The 23-time National Hockey League (NHL) All-Star also acquired 500 stitches in his face alone during that time. He was born in Saskatchewan, took up hockey at age 8, and at age 18 signed with the Detroit Redwings and quickly left his mark on the NHL. His toughness became legendary. Howe was inducted into the Hockey Hall of Fame in 1972, a year after he first retired at age 42 from the Redwings, with whom he played for 25 seasons and won 4 Stanley Cup championships. He also was the NHL’s most valuable player six times. But Howe was back on the ice a year later as a member of the Houston Aeros of the World Hockey Association (WHA). He resumed playing because his oldest sons, Marty (then 19) and Mark (then 18), had both signed with the Aeros. (Mark Howe went on to play 22 seasons and was inducted into the Hall of Fame in 2011.) The Howes helped the Aeros win the Avco Cup, the WHA’s equivalent of the Stanley Cup, in each of their first 2 seasons. With 31 goals and 69 assists in his first season, Gordie won the WHA’s most valuable player trophy, which was renamed for Howe a year later. Howe moved from the Aeros to the New England Whalers in 1977. When the WHA folded 2 years later, the Whalers were renamed the Hartford Whalers and joined the NHL. Howe played his final season for the Whalers at age 52. When he retired for good, Howe held the NHL record for most goals (801) and points (1850). Those records were broken by Wayne Gretzky. He also remains the oldest person to play in the league (52 years) and the first to play in 1500 games.

Howe met his wife, Colleen, in 1949, and she became known as Mrs. Hockey. They were married for 44 years. Howe is survived by 4 children and 9 grandchildren. Wayne Gretzky stated: “He was the nicest man I ever met.”

MUHAMMAD ALI (CASSIUS MARCELLUS CLAY, JR.) (1942–2016)

He was born in Louisville, Kentucky, and that is where he grew up. He began training as an amateur boxer when he was 12 years old, and at age 18 he won a gold medal in the light heavyweight division at the 1960 Summer Olympics in Rome (18). He converted to Islam shortly afterwards. At age 22 (1964), he won the World Boxing Association and World Boxing Council heavyweight titles from Sonny Liston. In 1966, he refused to be conscripted into the US military, citing his religious beliefs and opposition to American involvement in the Vietnam War. He was eventually arrested, found guilty of draft evasion, and stripped of his boxing titles. The US Supreme Court overturned his conviction in 1971, by which time he had not fought for nearly 4 years—losing a period of peak performance as an athlete. Ali’s actions as a conscientious objector to the war made him an icon for the larger counterculture generation.

He regained the heavyweight champion title in 1974 and defended it in 1978. He is the only boxer to be named The Ring Fighter of the Year six times. He was ranked as the greatest athlete of the 20th century by Sports Illustrated and the Sports Personality of the Century by the BBC. He was known for trash talking, rhyme schemes, and word poetry. As a musician, Ali recorded two spoken word albums and a rhythm and blues song and received two Grammy Award nominations. As an actor, he performed in several films and a Broadway musical. He wrote two autobiographies.

Kareem Abdul-Jabbar (19), the all-time National Basketball Association scorer and a well-regarded writer, wrote of Muhammad Ali: “In the ring, he was as much businessman as athlete. Out of the ring he was a champion of justice and a terrible businessman.” Regarding his refusal to submit to the draft during the Vietnam War, he said, “My conscience won’t let me go shoot my brother, or some darker people.” Ali also indicated, “I ain’t got anything against them Viet Cong” who “never called me nigger.” Half the world would chant his name in praise; the other half would sharpen pitch forks and light torches. Abdul Jabbar went on to say, “While I admired the athlete of action, it was the man of principle who was truly my role model.”

SKY DIVING

Luke Atkins, a 42-year-old skydiver with more than 18,000 jumps, in July 2016 became the first to leap from a plane (from
25,000 feet) without a parachute and land in a net that was 100 × 100 feet (20). His wife and 4-year-old son watched from the ground. Is that smart or otherwise?

William Clifford Roberts, MD
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438 Aversion: Photograph by A. Khan
440 Baylor Scott & White Health news
444 Reader comments: Lipid therapy and plasmapheresis in tricyclic poisoning by S. Gasselin et al, author reply by C. Odgren et al

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