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Currently, Baylor Research Institute is conducting more than 800 research projects. Studies open to enrollment are listed in the Table. To learn more about a study or to enroll patients, please call or e-mail the contact person listed.

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<td>At risk for heart attack/stroke; previous heart attack/stroke/PAD; cholesterol disorders; atrial fibrillation; overweight/obese; other heart-related conditions</td>
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Baylor Research Institute is dedicated to providing the support and tools needed for successful clinical research. To learn more about Baylor Research Institute, please contact Kristine Hughes at 214-820-7556 or Kristine.Hughes@BaylorHealth.edu.
Acute myelogenous leukemia at Baylor Charles A. Sammons Cancer Center, 2010 to 2012: retrospective analysis of molecular genetic evaluation

Catherine Jones, MD, Temekka V. LeDay, MD, and Alan M. Miller, MD, PhD

Over the last several decades, advancements in the understanding of genetic and molecular origins of acute myeloid leukemia (AML) have brought about significant changes in how the disease is classified, diagnosed, and treated. The change from the traditional French-American-British classification system to that of the World Health Organization redefined how the disease is diagnosed not only morphologically but genetically. With genetic information proving to have prognostic value, the newer classification system, which incorporates results of cytogenetic and molecular analyses, allows better definition of disease and risk stratification, ultimately guiding treatment choices. As understanding and advancements in the molecular basis of AML continue to grow and influence patient management, the importance of an accurate and thorough initial patient evaluation is paramount. We performed a review of AML cases diagnosed at Baylor Charles A. Sammons Cancer Center from February 2010 to December 2012 to assess the thoroughness of initial diagnostic evaluations based on current guidelines, including up-to-date molecular analyses for mutations in \textit{NPM1}, \textit{CEBPA}, \textit{FLT3}, and \textit{C-KIT}. Results showed that patients newly diagnosed with AML undergo thorough diagnostic evaluation in keeping with current recommendations, and many had further genetic and molecular evaluations, which although considered optional or investigational, have prognostic significance. We identified potential areas of improvement for making this diagnostic evaluation more specific to the patient and the patient’s disease. Currently, we are investigating having patients undergo reflex genetic testing if they meet certain criteria to better define their specific disease while avoiding unnecessary genetic evaluations that come at increased cost.

According to the American Cancer Society, in 2014 there will be an estimated 18,860 new cases of acute myelogenous leukemia (AML), and 10,460 patients will die from their disease (1). While the 5-year relative survival of patients with AML is only 24%, there are large differences in prognoses influenced by patient-specific factors and perhaps most importantly by the genetics of the disease. Initially classified by the French-American-British system, which categorized the disease based on cell morphology and cytochemical stains (2), AML is currently classified using a newer system developed by the World Health Organization (WHO). This system combines the traditional clinical and morphologic features with immunophenotypic criteria as well as cytogenetic and molecular analyses (3–5). This specific genetic and molecular information has altered criteria by which AML is diagnosed, allowing a lower blast percentage for AML diagnosis in the setting of specific genetic abnormalities as well as providing important prognostic information regarding remission rates, risk of relapse, and overall survival (6–8).

Based on cytogenetic results, patients can now be stratified among risk groups that provide important prognostic information regarding treatment response and survival (6–8).

In addition to the WHO classification system for AML, the international European LeukemiaNet (ELN) guidelines for reporting genetic alterations in AML were recently published, further delineating AML patients based on genetics as well as age (9). These guidelines, combined with the frequently updated National Comprehensive Cancer Network guidelines, serve as a reference and guide for the diagnosis and risk stratification of newly diagnosed cases of AML. We performed a review of AML cases diagnosed at Baylor Charles A. Sammons Cancer Center (Baylor Sammons) to assess the thoroughness of initial diagnostic evaluations based on current guidelines at our cancer center, including up-to-date molecular analyses for mutations in the \textit{NPM1}, \textit{CEBPA}, \textit{FLT3}, and \textit{C-KIT} genes.

**METHODS**

Cases of AML diagnosed at Baylor Sammons, a tertiary referral center in Dallas, were identified through the tumor registry for the period of February 2010 to December 2012 and then reviewed for demographic information, initial laboratory assessments and pathologic evaluations performed at presentation, as well as cytogenetic and molecular studies performed.

**RESULTS**

From February 2010 to December 2012, AML was diagnosed in 77 patients. The mean age of patients in our cohort was 58 years (range, 20–83 years). Males represented 57% of
The cases had histologic evaluation of the bone marrow accompanied by flow cytometric analysis. Mean blast percentage in bone marrow was 60% (range, 9%-98%).

Conventional cytogenetic analysis was completed in 74 patients (96%). Based on these results, 17 patients (22%) were given a prognostic classification of favorable, 34 patients (44%) were classified as intermediate risk, and 23 patients (30%) were classified as adverse risk; three patients were not classified.

Human leukocyte antigen (HLA) typing at presentation was completed in 24 patients (49%). Of those patients in the intermediate and adverse risk categories, 58.8% and 56.5%, respectively, were tested, and of those below age 60, 60% had HLA testing.

In our cohort, conventional cytogenetics was performed in only 96% of patients; however, of the three patients without conventional cytogenetics, molecular cytogenetics was performed in two, giving the necessary diagnostic genetic information. These two patients were diagnosed with AML with recurrent cytogenetic abnormalities having acute promyelocytic leukemia (APL) with t(15;17) and AML with t(8;21) as detected by fluorescence in situ hybridization (FISH).

Overall, complete cytogenetic evaluation was performed in 98.6% of our patients. For the single patient who did not have cytogenetic evaluation, the reason is not clear.

Additional cytogenetic evaluation via FISH was performed in 66 patients (85.7%). The presence of the PML/RARA gene rearrangement was identified in 11 patients. Of those 11 patients, all but one had conventional cytogenetic evaluation. Of the remaining 10 patients, the additional cytogenetic evaluation by FISH correlated with conventional cytogenetics, which demonstrated the presence of t(15;17)(q22;q21), consistent with a diagnosis of APL. Overall, patients with APL accounted for 11% of our new AML diagnoses. Four patients had inv(16)(p13.1;q22) by conventional cytogenetics. In three of these, further cytogenetic evaluation by FISH was performed, and all demonstrated the presence of the CBFB-MYH11 gene rearrangement. Thus, patients with inv(16)(p13.1;q22) accounted for 5.2% of our new AML diagnoses. Mutations in the RUNXI gene were detected in nine patients by FISH. Three of the nine patients had the gene rearrangement RUNXI-RUNXI, which was consistent with the conventional cytogenetic finding of t(8;21)(q22;q22) in two of the patients. Mutations in RUNXI were present in 11.7% of our patient cohort, with 2.6% occurring in association with t(8;21)(q22;q22). The t(6;9)(p23;q34) DEK NUP214 was diagnosed in one patient by conventional cytogenetics. One additional patient with multiple cytogenetic abnormalities demonstrated the presence of DEK(6p23) and NUP214(9q34).

Among the 24 patients with a normal karyotype (CN-AML) by conventional cytogenetics, 13 (54.2%) had further cytogenetic evaluation by FISH and 20 (83%) had mutation analysis. Mutation analysis among patients with a normal karyotype included evaluation for the presence of FLT-3, which was performed in 19 patients (77%) and was positive in 11 (50%); NPM1, performed in 17 patients (79.2%) and positive in 12 (50%); and CEBPA, performed in three patients (12.5%) and negative in all of them. Five patients had isolated NPM1 mutations, while seven patients had mutations of both NPM1 and FLT-3. This additional information obtained by mutation analysis allowed for the reclassification of the five patients with an isolated NPM1 mutation from the intermediate-risk group to the favorable-risk group. Four patients with CN-AML did not undergo any mutation analysis for further risk stratification.

---

1One patient in our study was diagnosed with AML with <20% blasts in the marrow. This was a case of erythroleukemia with >50% erythroid precursors. Per WHO classification, erythroleukemia is defined as ≥20% myeloblasts in the nonerythroid cell population with ≥50% erythroid precursors in the bone marrow. In this case, blasts comprised 9% of the total cell population in the marrow, with 58% erythroid precursors (21.4% of nonerythroids). The case was classified as AML with myelodysplasia-related changes, as it arose from a previously diagnosed refractory anemia with excess blasts.

2No data were available on chart review as to why cytogenetic evaluation was not performed on these three cases, and review of pathology suggested in one case that there was not enough tissue for testing.
Further investigational mutation analysis was performed for the presence of the C-KIT mutation in 20 patients (26.0%). It was positive in only one patient (1.3%). In total, 53 patients (68.8%) underwent additional analysis for mutations in NPM1, CEBPA, FLT3, or C-KIT.

Molecular genetics studies, considered to be investigational, evaluating for the presence of fusion genes were performed in 15 patients (19.5%); 13 patients were assessed for PML/RARA and two patients for BCR-ABL. Of those evaluated, eight patients had the PML/RARA fusion gene, and both analyses for BCR-ABL were negative.

Overall, rates of conventional cytogenetics and cytogenetic evaluation by FISH of patients presenting to Baylor Sammons from year to year were consistent. In 2010, of 25 new AML patients, 24 had conventional cytogenetics performed and 20 had cytogenetics by FISH. In 2011, of 25 new AML cases, 24 had conventional cytogenetic analysis and 23 had cytogenetic evaluation by FISH. The results were again similar in 2012, with 21 of 22 patients having conventional cytogenetics and 18 of 22 having cytogenetic evaluation by FISH.

Patient evaluation and characterization by molecular diagnostics was compared from year to year with a noted increase in use of cytogenetics by FISH from 2010 to 2012. Of newly diagnosed AML patients in 2010, 8% had cytogenetics by FISH. Of those cases evaluated in 2011 and 2012, 16% and 27% of the cases had cytogenetics by FISH, respectively. Similar to cytogenetic evaluation, rates of mutation analyses over this time were fairly consistent, being performed in 72% of cases in 2010 and in 68% of cases in 2012. Per expert recommendations on behalf of the ELN published in January 2010, mutation analyses for the presence of mutations in the NPM1, CEBPA, and FLT-3 genes were considered an optional assessment at the time of diagnosis for all patients in our cohort (9). More specifically, these mutation analyses were only considered of prognostic significance, and therefore were only recommended as an optional assessment in patients with CN-AML (10, 11). Among our patient cohort, 24 patients had a normal karyotype, warranting further mutation analyses for the NPM1, CEBPA, and FLT-3 genes, but these mutation analyses were performed only in 18 of the 24 patients. Moreover, these analyses were also performed in 31 patients without CN-AML.

Based on ELN 2010 guidelines, in addition to mutation testing of the NPM1, CEBPA, and FLT-3 genes, testing for the presence of mutations in other genes such as C-KIT was considered investigational (10). Of the 20 patients who underwent C-KIT mutation analysis, the testing was only relevant in one patient. In one other patient in whom the analysis was relevant as a prognostic factor, testing was not performed. Overall in our cohort, of the 55 patients who had mutation analyses performed, 39 patients had testing that would not be considered standard or optional and should be restricted to investigation.

**DISCUSSION**

Based on the WHO categorization, AML is defined as the presence of 20% or more blasts in the peripheral blood or bone marrow occurring de novo, or in a patient with a prior diagnosis of myelodysplastic syndrome or myeloproliferative neoplasm.

<table>
<thead>
<tr>
<th>Table 2. Laboratory results of 77 patients with acute myelogenous leukemia treated at Baylor Sammons Cancer Center</th>
</tr>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Diagnostic CBC (mean, range)</td>
</tr>
<tr>
<td>White blood cells (1000/μL)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
</tr>
<tr>
<td>Platelets (K/μL)</td>
</tr>
<tr>
<td>Risk group by karyotype</td>
</tr>
<tr>
<td>Favorable risk</td>
</tr>
<tr>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Adverse risk</td>
</tr>
<tr>
<td>Not done</td>
</tr>
<tr>
<td>Molecular cytogenetics performed</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>HLA typing performed</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

*Normal values provided for diagnostic CBC as mean; total values provided for other categories. CBC indicates complete blood count; HLA, human leukocyte antigen.

<table>
<thead>
<tr>
<th>Table 3. Performance of HLA typing by risk group and age for 77 patients with acute myelogenous leukemia treated at Baylor Sammons Cancer Center</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Risk group</td>
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<tr>
<td>Favorable</td>
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<tr>
<td>Intermediate</td>
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<td>Adverse</td>
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<tr>
<td>Age</td>
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<tr>
<td>&lt;60 years</td>
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<tr>
<td>≥60 years</td>
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</table>
However, in the setting of specific genetic abnormalities, t(8;21) (q22;q22), inv(16)(p13.1q22) or t(16;16)(p13.1;q22), t(15;17) (q22;q12), a blast count of ≥20% is not required for diagnosis.

Conventional cytogenetic evaluation is considered standard in the diagnosis and workup of new cases of AML. In comparison to cytogenetic evaluation by FISH, conventional karyotyping provides a more complete cytogenetic profile, assessing all structural and numerical chromosomal abnormalities (translocations, duplications, deletions) above the limits of detection by FISH. FISH studies at time of diagnosis are designed to rapidly target specific chromosomal abnormalities that define an AML with recurrent cytogenetic abnormalities (e.g., APL, AML with t(8;21), etc.). FISH tends to have a more rapid turnaround than conventional karyotyping, as it can be performed on interphase nuclei and it assesses a greater number of cells (200 per probe as compared to 20 metaphases in a conventional karyotype). Overall, conventional karyotyping and cytogenetic evaluation by FISH are complementary assessments of chromosomal abnormalities at diagnosis that can provide useful markers of disease that can be followed.

Cytogenetic information not only influences the diagnosis and classification of AML but also provides important prognostic information regarding remission rates, risk of relapse, and overall survival (6–8). Patients with favorable, intermediate, or adverse cytogenetics have 5-year survival rates of 65%, 41%, and 14%, respectively (7, 12). Table 4 lists the mutations related to each prognostic group. Classification among risk groups provides information regarding treatment response in addition to survival. Those classified as favorable show complete response rates to treatment of >80%, while those in the adverse or unfavorable group have complete response rates ranging from 32% to 55% (6, 8).

Further risk stratification among the intermediate-risk group of patients with normal cytogenetics is possible with molecular analysis for mutations of the FLT-3, NPM1, CEPBA, RUNX1, MLL, and EVI1 genes. Results of this molecular examination contribute important prognostic information, potentially influencing treatment and treatment response (13–15). Due to the significant progress that has been made in identifying these molecular markers and their role in pathogenesis, new recommendations have been developed that define general practice guidelines for the diagnosis of AML (13).

### Current recommendations and practice guidelines

Currently, consistent with prior guidelines, morphologic assessment of blood and bone marrow aspirates using Wright-Giemsa stains and assessment of the bone marrow aspirate remain fundamental to the routine diagnostic workup for AML. Specifically, when evaluating blood and bone marrow aspirates, it is recommended that 200 leukocytes be counted on blood smears and 500 nucleated cells counted on bone marrow aspirate smears containing adequate spicules (9). With the exception of cases with t(8;21), t(15;17), inv(16), or t(16;16), the diagnosis of AML through morphologic assessment requires the presence of a blood or marrow leukemic blast count of at least 20%. Blast counts should include all blast forms with the exception of erythroblasts, though in the case of pure erythroid leukemia these should be counted (9). As well as assessment of blood and bone marrow aspirate smears, assessment of a bone marrow trephine biopsy may provide valuable information regarding cellularity, cell maturation, and bone marrow stroma; however, expert panel recommendations consider this evaluation optional, except in the setting of a “dry tap,” where no material is obtained in the biopsy (9).

Besides morphologic assessment, immunophenotyping, using multiparameter flow cytometry or immunohistochemistry, is essential in new AML diagnoses for determination of cell lineage, with a preference towards use of flow cytometry (5, 9, 16). While consensus data do not give a specific cutoff point for considering a specific marker to be positive, expression of specific markers in ≥20% of leukemic cells is commonly used.

For all patients with a new or suspected AML diagnosis, cytogenetic analysis is considered mandatory as part of the diagnostic evaluation. Cytogenetic abnormalities are present in approximately 55% of adult AML cases, and they provide the most important prognostic information (7, 17). Additionally, they allow, in cases of t(8;21), t(15;17), inv(16), or t(16;16), AML diagnosis to be made with <20% blasts in the peripheral blood or bone marrow aspirate (9). As the results of the karyotype are the strongest prognostic factor for predicting response to therapy and overall survival, recommendations suggest that a minimum of 20 metaphase cells be analyzed to define an abnormal karyotype, and this cell number must be assessed before diagnosing a normal karyotype (5, 9). For cases with inadequate

### Table 4. Prognostic value of cytogenetics

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<tr>
<th>Prognostic group:</th>
<th>5-year survival</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable: 65%</td>
<td>t(8;21)(q22;q22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inv(16)(p13.1q22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(16;16)(p13.1q22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(15;17)(q22;q21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal karyotype with mutated CEPBA or mutated NPM1 without FLT-3</td>
<td></td>
</tr>
<tr>
<td>Intermediate: 41%</td>
<td>Normal</td>
<td>+8</td>
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<td></td>
<td></td>
<td>+21</td>
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<td>+22</td>
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<td></td>
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<tr>
<td></td>
<td>Abnormal (11q23)</td>
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<tr>
<td>Adverse: 14%</td>
<td>Complex cytogenetics</td>
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<td>−7</td>
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<td></td>
<td>Abnormal 3q</td>
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</tbody>
</table>
potential candidates for allogeneic stem cell transplant should for therapeutic recommendations (15, 25). Patients considered guidelines, age >60 is associated with a higher prevalence of associated with adverse prognostic outcomes. In the treatment recommendations (25). Documentation of these various factors to determine higher risk is important, as age >60 years and medi-cation among risk groups. Isolated mutations of the CN-AML group includes approximately 40% to 45% of young adults with AML (7, 17). Identifying the presence of these particular mutations has provided further prognostic information and allowed for stratification within the intermediate-risk group to intermediate-I and intermediate-II groups (10). Evaluation for the presence of specific isolated mutations has allowed for movement among risk groups. Isolated mutations of the NPM1 and CEBPA genes offer a favorable prognosis associated with higher complete response rates, reduced relapse risk, and longer overall survival (18, 19). In comparison, mutations of the FLT3 gene, whether present as a single mutation or in combination, are considered intermediate-I risk, conferring poorer prognosis due to inferior disease-free survival and overall survival rates (9, 20–22). Mutations in C-KIT have prognostic significance in patients with t(8;21)(q22;q22) or inv(16)(p13.1q22) (23, 24). Among this specific patient population, a mutation of C-KIT is associated with a worse prognosis, changing the risk status from favorable to intermediate (24, 25).

Testing for the presence of additional fusion genes via reverse transcriptase-polymerase chain reaction, such as RUNX1-RUNX1T1, CBFB-MYH11, DEK-NUP214, and PML-RARA, can be performed, but these tests are presently considered optional, although recent alterations in the WHO classification have categorized these as individual entities (5). Additional studies for mutations in the specific genes WT1, RUNX1, MLL, C-KIT, RAS, TP53, TET2, and IDH1 for prognostic assessment are currently considered investigational and only advised for use in clinical trials (9).

In addition to bone marrow examination and genetic studies to establish a diagnosis of AML, several further tests and assessments should be performed as standard in the initial patient evaluation. Review and documentation of a patient’s performance status, comorbidities, basic blood counts and chemistry profile, coagulation studies, hepatitis and HIV testing, chest x-ray and electrocardiogram, and transplant assessment should all be performed based on guidelines and expert panel recommendations (25). Documentation of these various factors to determine higher risk is important, as age >60 years and medical comorbidities, specifically diabetes, coronary artery disease, and chronic obstructive pulmonary disease (20), have been associated with adverse prognostic outcomes. In the treatment guidelines, age >60 is associated with a higher prevalence of other unfavorable factors and thus is considered a division point for therapeutic recommendations (15, 25). Patients considered potential candidates for allogeneic stem cell transplant should have HLA typing performed at diagnosis, along with typing of their first-degree relatives, an assessment of key importance particularly in patients with adverse cytogenetics (9, 20).


The aim of this study was to assess the nationwide use of epidural analgesia (EA) and the incidence of postoperative complications in patients undergoing major liver resections (MLR) with and without EA in the United States. The 2001 to 2010 Nationwide Inpatient Sample was queried to identify adult patients undergoing MLR. A 1:1 matched cohort of patients having MLR with and without EA was assembled using propensity-score matching techniques. Differences in the rate of postoperative complications were compared between the matched groups. We identified 68,028 MLR. Overall, 5.9% of patients in the database had procedural codes for postoperative EA. A matched cohort of 802 patients per group was derived from the propensity-matching algorithm. Although use of EA was associated with more blood transfusions (relative risk, 1.36; 95% confidence interval, 1.12–1.65; P = 0.001) and longer hospital stay (median [interquartile range], 6 [5–8] vs 6 [4–8] days), the use of coagulation factors and the incidence of postoperative hemorrhage/hematomas or other postoperative complications were not higher in patients receiving EA. In conclusion, the use of EA for MLR is low, and EA does not seem to influence the incidence of postoperative complications. EA, however, was associated with an increased use of blood transfusions and a longer hospital stay.

Liver resection is a major abdominal surgical procedure with a high risk of postoperative morbidity and mortality (1). Pain after liver resection can be intense and prolonged (2, 3). Inadequate pain management can lead to increased postoperative morbidity and delayed recovery (4). Epidural analgesia has been shown to provide excellent dynamic pain relief as well as improve postoperative pulmonary, cardiovascular, and gastrointestinal function (2, 5–9). Epidural analgesia can enhance rehabilitation and reduce hospital length of stay after major abdominal surgical procedures, presumably due to superior pain relief as well as reduced opioid use and reduced opioid-related adverse effects (10, 11). Recent studies have shown that the use of epidural analgesia as part of a fast track protocol–enhanced recovery can reduce hospital stay after liver resection (12, 13). However, the use of epidural analgesia in patients undergoing liver resection remains controversial (3), probably due to concerns for postoperative coagulation disturbances and subsequent catastrophic neurologic injuries resulting from epidural hematoma (14, 15). In addition, routine use of epidural analgesia is being increasingly questioned due to its several potential adverse effects (16–18). Current patterns of use of epidural analgesia for liver resection in the US are unknown. Furthermore, data on the benefits and incidence of complications related to the use of epidural analgesia for liver surgery are scant (2, 3). The purpose of this study was to examine the utilization and associated complications of epidural analgesia in patients undergoing open liver resection surgery in the US. We hypothesized that use of epidural analgesia would improve perioperative outcomes after major liver resection surgery. The Nationwide Inpatient Sample (NIS), the largest all-payer inpatient database in the US, was used for this purpose.

METHODS

The population for this study consisted of adult patients undergoing major liver resections (excluding liver transplants) in the US. Data were obtained from the 2001 to 2010 NIS datasets from the Healthcare Cost and Utilization Project of the Agency for Health Care Research and Quality (19). The NIS is a stratified probability sample representing 20% of the universe of US community nonrehabilitation hospitals. To ensure nationwide representativeness, the NIS sampling strategy stratifies hospitals according to five characteristics: geographic region, control (public vs private), urban or rural location, teaching status, and bed size. Once a hospital is selected for the NIS in a specific year, all of its discharge data are included in the survey in that year. Approximately 8 million hospital discharges from about 1000 hospitals are available in the database each year. The number of states contributing to the NIS has been increasing over time, with 33 states contributing in 2001 and 45 states contributing in 2010. Given the deidentified and publicly available nature of the NIS data, the study was determined to be exempt from review by the University of Texas Southwestern Medical Center institutional review board.

Hospital discharges with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)
procedure codes for open major liver resections, including partial hepatectomy (50.22) and total hepatic lobectomy (50.3), were identified from the NIS datasets. Records for patients younger than 18 years or with ICD-9-CM procedure codes for total hepatectomy (50.4), liver transplantation (50.5), liver donors (V59.6), and other nonmajor liver procedures (50.21, 50.23–50.29), as well as liver resections because of trauma (diagnosis ICD-9-CM codes 864–869) and records with codes for complications of transplanted liver (996.82), were excluded from the analyses. Laparoscopic liver resections (ICD-9-CM procedure code 50.25) were also excluded. Patients who received epidural analgesia for postoperative pain management were identified using the ICD-9-CM procedure codes 03.90 and 03.91.

The Agency for Health Care Research and Quality Comorbidity Software, a family of tools developed as part of the Healthcare Cost and Utilization Project, was used to create 26 comorbidity variables (including hepatitis, alcoholism, and coagulation disorders) from the up to 25 ICD-9-CM diagnosis codes available in each hospital discharge record (20). Furthermore, the Deyo adaptation of the Charlson comorbidity index was calculated for each patient based on ICD-9-CM diagnosis codes available from the database. The Charlson comorbidity index is a validated measure for use with administrative data that correlates with in-hospital morbidity and mortality after surgical procedures (21). Charlson scores were further collapsed into three categories: 0; 1 to 2; and ≥ 3. Geographic region was defined according to the hospital’s census region in Northeast, Midwest or North Central, South, and West. Hospital characteristics including teaching status of hospital (teaching vs nonteaching), location of hospital (urban vs rural), and bed size (small, medium, large) are provided as separate variables in the NIS. Based on ICD-9-CM codes assigned to the principal diagnosis, cases were categorized as primary malignant neoplasm of the liver or bile ducts (155.0–156.9), secondary malignant neoplasm of the liver (197.7), and other benign diseases of the liver (211.5, 572–576). Cirrhosis and other chronic liver diseases were identified by the codes 571.0–571.9 and chronic viral hepatitis B and C using codes 070.2, 070.3, and 070.7. Variables were created to adjust for the effect of the type of principal diagnosis on outcomes.

The outcomes of interest for the study included any complication related to the use of epidural analgesia (e.g., spinal hemorrhage/hematoma or abscess, spinal ischemia, spinal decompression, or procedures that may have been performed when a complication of epidural analgesia was suspected, such as spinal magnetic resonance imaging [MRI]/computed tomography [CT] scans and transfusion of coagulation factors), as well as the incidence of any postoperative adverse events including in-hospital death, respiratory failure, pneumonia, ileus, pulmonary embolism or deep vein thrombosis, urinary retention, myocardial infarction, and acute renal failure. In addition, hospital length of stay was compared between the groups. All the endpoints were selected a priori based on current literature on use of epidural analgesia for major abdominal surgery (5, 7, 22, 23). In-hospital death was determined directly from a variable present in the database. In-hospital postoperative adverse events were determined from the diagnostic and procedure ICD-9-CM codes.

Baseline characteristics of patients undergoing liver resections with and without epidural analgesia were described using univariate analyses of the weighted NIS data. Weighted analyses on the nonmatched sample were conducted using the SURVEY FREQ, SURVEY REG, and SURVEY MEANS procedures of the SAS software, to account for the NIS survey design. Continuous variables are summarized as means ± standard deviations, except for heavily skewed distributions, which are reported as medians and interquartile ranges. Discrete variables are presented as frequencies and group percentages. Trends in the use of epidural analgesia for liver resection across the study period were assessed with the Cochran-Armitage trend test.

A 1:1 matched cohort of patients receiving or not receiving epidural analgesia was created based on propensity scores derived from a logistic regression model (constructed to estimate the conditional probability for receiving epidural analgesia). The independent variables included in the regression model for propensity scores consisted of demographic characteristics, comorbidity score, type of principal diagnosis, comorbidities...
such as cirrhosis and chronic viral hepatitis, type of health care insurance, and hospital characteristics. Propensity matching was done using a greedy 8 to 1 digit-matching algorithm technique. Differences in the incidence of postoperative adverse events were assessed between the matched groups using McNemar’s tests. Relative risks with 95% confidence intervals were calculated for each outcome. Due to its positively skewed distribution, hospital length of stay was described as medians and interquartile ranges and compared between the matched groups using Wilcoxon signed-rank tests. All statistical tests were two-tailed, and a P value of 0.05 was considered statistically significant. SAS 9.2 software (Cary, NC) was used for all the analyses.

Table 1. Baseline characteristics of patients undergoing major liver resections with and without epidural analgesia, United States, 2001–2010, nonmatched sample

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No (n = 63,876)</th>
<th>Yes (n = 4044)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age categories (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to 39</td>
<td>7,708 (12.0%)</td>
<td>406 (10.0%)</td>
<td>0.337</td>
</tr>
<tr>
<td>40 to 64</td>
<td>33,456 (52.3%)</td>
<td>2097 (51.9%)</td>
<td></td>
</tr>
<tr>
<td>65 to 74</td>
<td>15,144 (23.7%)</td>
<td>1021 (25.2%)</td>
<td></td>
</tr>
<tr>
<td>75+</td>
<td>7,675 (12.0%)</td>
<td>520 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>32,865 (51.4%)</td>
<td>2068 (51.1%)</td>
<td>0.891</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7,878 (12.3%)</td>
<td>387 (9.6%)</td>
<td>0.031</td>
</tr>
<tr>
<td>1–2</td>
<td>10,548 (16.5%)</td>
<td>568 (14.0%)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>45,557 (71.2%)</td>
<td>3089 (76.4%)</td>
<td></td>
</tr>
<tr>
<td>Geographic region of hospital</td>
<td></td>
<td></td>
<td>0.075</td>
</tr>
<tr>
<td>Northeast</td>
<td>17,202 (26.9%)</td>
<td>791 (19.6%)</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>12,530 (19.6%)</td>
<td>1442 (35.7%)</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>19,342 (30.2%)</td>
<td>1114 (27.5%)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>14,909 (23.3%)</td>
<td>697 (17.2%)</td>
<td></td>
</tr>
<tr>
<td>Hospital bed size</td>
<td></td>
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<td>0.498</td>
</tr>
<tr>
<td>Small</td>
<td>3,548 (5.6%)</td>
<td>420 (10.4%)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>7,257 (11.4%)</td>
<td>505 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>53,077 (83.1%)</td>
<td>3119 (77.1%)</td>
<td></td>
</tr>
<tr>
<td>Urban location of hospital</td>
<td>62,709 (98.2%)</td>
<td>3924 (97.0%)</td>
<td>0.435</td>
</tr>
<tr>
<td>Procedure in teaching hospital</td>
<td>56,397 (88.3%)</td>
<td>3394 (83.9%)</td>
<td>0.339</td>
</tr>
<tr>
<td>Patient comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>24,934 (38.9%)</td>
<td>1576 (38.9%)</td>
<td>0.997</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>5,881 (9.2%)</td>
<td>396 (9.8%)</td>
<td>0.584</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1,352 (2.1%)</td>
<td>87 (2.2%)</td>
<td>0.938</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9,179 (14.3%)</td>
<td>572 (14.1%)</td>
<td>0.889</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>1,171 (1.8%)</td>
<td>76 (1.9%)</td>
<td>0.915</td>
</tr>
<tr>
<td>Obesity*</td>
<td>3,406 (5.3%)</td>
<td>199 (4.9%)</td>
<td>0.706</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>1,160 (1.8%)</td>
<td>77 (1.9%)</td>
<td>0.851</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>1,319 (2.1%)</td>
<td>63 (1.5%)</td>
<td>0.305</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>7,383 (11.5%)</td>
<td>324 (8.0%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Surgical diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary carcinoma of liver or bile ducts</td>
<td>11,634 (18.2%)</td>
<td>677 (16.7%)</td>
<td>0.354</td>
</tr>
<tr>
<td>Metastatic liver disease</td>
<td>32,830 (51.3%)</td>
<td>2438 (60.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other benign liver disease</td>
<td>21,577 (33.7%)</td>
<td>1218 (30.1%)</td>
<td>0.171</td>
</tr>
</tbody>
</table>

*Obesity was defined as body mass index >30 kg/m² using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 278.00 and 278.01.
RESULTS

We found 68,028 major liver resections recorded in NIS between 2001 and 2010. This may represent 340,140 such procedures having been performed in the US during that time. The number of liver resections increased from 3937 in 2001 to 9836 in 2010 (Figure 1a). Most liver resections were performed for treatment of cancer: 51.3% for metastatic liver disease and 18.2% for primary carcinomas of the liver or bile ducts. About one-third of liver resections (33.7%) were associated with a principal diagnosis of benign neoplasms or other benign diseases of the liver.

Figure 1b displays the percentage of patients receiving epidural analgesia for major liver resections in the US across the study period. Overall, epidural analgesia was administered in 5.9% (n = 4044) of the patients. In 2001, epidural analgesia was used in 7.2% of the cases, while in 2010 it was used in 6.7% of the cases. However, there was not a statistically significant linear trend towards decreasing use of epidural analgesia across the study period (P for trend = 0.108; Cochran-Armitage trend test).

Table 1 describes the baseline clinical, demographic, and hospital characteristics of patients undergoing major liver resections with and without the use of epidural analgesia in 2001 to 2010 in the nonmatched cohort. Although there were no significant differences in the age distributions, patients receiving epidural analgesia had higher comorbidity scores than those without epidural analgesia. Also, metastatic liver disease was more common among patients receiving epidural analgesia (60.3% vs 51.3%; P < 0.0001). In contrast, the prevalence of hepatic cirrhosis was lower among patients having epidural analgesia (8.0% vs 11.5%, P = 0.006). Hospital characteristics, such as teaching status, bed size, or urban/rural location of the hospital, were not associated with differences in the use of epidural analgesia for liver resection.

None of the patients in either group experienced any complication directly related to the use of epidural catheters (including spinal ischemia, abscess, or hematoma) or any event indicating that any of these complications was suspected or treated (including use of spinal MRIs or CT scans or procedures for decompression of the spinal cord). Univariate analyses of perioperative outcomes in the unmatched sample are displayed in Table 2. The unadjusted rate of perioperative blood transfusions and postoperative atelectasis was higher in the group receiving epidural analgesia. However, the incidence of other adverse events was not statistically different between the groups.

Table 3 describes the baseline characteristics of patients in the propensity-matched sample. A cohort of 802 patients not receiving epidural analgesia and 802 patients receiving epidural analgesia for liver resections, well balanced on baseline characteristics, was derived from the propensity-matching algorithm. The rate of in-hospital mortality was the same in both groups (2.1%). The matched analyses confirmed that patients receiving epidurals were significantly more likely to have transfusion of

<table>
<thead>
<tr>
<th>Postoperative outcome</th>
<th>No (n = 63,984)</th>
<th>Yes (n = 4044)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital death</td>
<td>1550 (2.4%)</td>
<td>88 (2.2%)</td>
<td>0.655</td>
</tr>
<tr>
<td>Hemorrhage/hematoma</td>
<td>2132 (3.3%)</td>
<td>115 (2.8%)</td>
<td>0.459</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>440 (0.7%)</td>
<td>13 (0.3%)</td>
<td>0.196</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2408 (3.8%)</td>
<td>186 (4.6%)</td>
<td>0.301</td>
</tr>
<tr>
<td>Pulmonary embolism or DVT</td>
<td>1090 (1.7%)</td>
<td>64 (1.6%)</td>
<td>0.805</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1434 (2.2%)</td>
<td>83 (2.0%)</td>
<td>0.715</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>11859 (18.5%)</td>
<td>977 (24.1%)</td>
<td>0.047</td>
</tr>
<tr>
<td>Transfusion of coagulation factors</td>
<td>4042 (6.3%)</td>
<td>249 (6.1%)</td>
<td>0.906</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>410 (0.6%)</td>
<td>42 (1.0%)</td>
<td>0.330</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>2243 (3.5%)</td>
<td>121 (2.9%)</td>
<td>0.555</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>1607 (2.5%)</td>
<td>98 (2.4%)</td>
<td>0.890</td>
</tr>
<tr>
<td>Ileus</td>
<td>5996 (9.4%)</td>
<td>480 (11.9%)</td>
<td>0.055</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>4839 (7.6%)</td>
<td>427 (10.6%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1390 (2.2%)</td>
<td>116 (2.9%)</td>
<td>0.226</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2147 (3.3%)</td>
<td>112 (2.8%)</td>
<td>0.302</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1136 (1.8%)</td>
<td>48 (1.2%)</td>
<td>0.247</td>
</tr>
<tr>
<td>Any infection</td>
<td>1882 (2.9%)</td>
<td>132 (3.2%)</td>
<td>0.550</td>
</tr>
<tr>
<td>LOS (days, median, IQR)</td>
<td>6 5–8</td>
<td>6 5–8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DVT indicates deep vein thrombosis; IQR, interquartile range; LOS, length of stay.
blood products during the hospitalization (24.3% vs 17.8%; relative risk = 1.36; 95% confidence interval = 1.12 to 1.65; $P = 0.001$). However, the use of transfusion of coagulation factors (6.2% vs 6.2%, $P = 1.000$) and the incidence of postoperative hemorrhage or hematomas (2.6% vs 3.4%, $P = 0.379$) was similar between the groups. In the propensity-matched cohort, the use of epidural analgesia was not associated with differences in the incidence of postoperative respiratory complications (respiratory failure, pneumonia, atelectasis), cardiac complications or myocardial infarction, thrombotic events, acute renal failure, ileus, sepsis, or urinary complications (Table 4). Finally, the length of hospital stay (median, [interquartile range]) was 6 [5–8] days vs 6 [4–8] days for patients with and without epidurals, respectively.

Table 3. Baseline characteristics of patients undergoing major liver resections with and without epidural analgesia, United States, 2001–2010, propensity-matched sample

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Epidural analgesia</th>
<th>$P$ value</th>
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</thead>
<tbody>
<tr>
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<tr>
<td>Age categories (years)</td>
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<tr>
<td>18 to 39</td>
<td>85 (10.6%)</td>
<td>81 (10.1%)</td>
</tr>
<tr>
<td>40 to 64</td>
<td>406 (50.6%)</td>
<td>415 (51.8%)</td>
</tr>
<tr>
<td>65 to 74</td>
<td>202 (25.2%)</td>
<td>203 (25.3%)</td>
</tr>
<tr>
<td>75+</td>
<td>109 (13.6%)</td>
<td>103 (12.8%)</td>
</tr>
<tr>
<td>Female sex</td>
<td>401 (50.0%)</td>
<td>411 (51.2%)</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>79 (9.9%)</td>
<td>77 (9.6%)</td>
</tr>
<tr>
<td>1–2</td>
<td>115 (14.3%)</td>
<td>114 (14.2%)</td>
</tr>
<tr>
<td>≥3</td>
<td>608 (75.8%)</td>
<td>611 (76.2%)</td>
</tr>
<tr>
<td>Geographic region of hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>136 (17.0%)</td>
<td>149 (18.6%)</td>
</tr>
<tr>
<td>Midwest</td>
<td>289 (36.0%)</td>
<td>283 (35.3%)</td>
</tr>
<tr>
<td>South</td>
<td>224 (27.9%)</td>
<td>230 (28.7%)</td>
</tr>
<tr>
<td>West</td>
<td>153 (19.1%)</td>
<td>140 (17.5%)</td>
</tr>
<tr>
<td>Hospital bed size</td>
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<tr>
<td>Small</td>
<td>95 (11.9%)</td>
<td>86 (10.7%)</td>
</tr>
<tr>
<td>Medium</td>
<td>104 (13.0%)</td>
<td>100 (12.5%)</td>
</tr>
<tr>
<td>Large</td>
<td>603 (75.2%)</td>
<td>616 (76.8%)</td>
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<tr>
<td>Urban location of hospital</td>
<td>783 (97.6%)</td>
<td>777 (96.9%)</td>
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<tr>
<td>Procedure in teaching hospital</td>
<td>665 (82.9%)</td>
<td>669 (83.4%)</td>
</tr>
<tr>
<td>Patient comorbidities</td>
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</tr>
<tr>
<td>Hypertension</td>
<td>327 (40.8%)</td>
<td>317 (39.5%)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>70 (8.7%)</td>
<td>77 (9.6%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>17 (2.1%)</td>
<td>18 (2.2%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>104 (13.0%)</td>
<td>115 (14.3%)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>25 (3.1%)</td>
<td>15 (1.9%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>48 (5.9%)</td>
<td>41 (5.1%)</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>18 (2.2%)</td>
<td>15 (1.9%)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>10 (1.2%)</td>
<td>13 (1.6%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>72 (8.9%)</td>
<td>64 (7.9%)</td>
</tr>
<tr>
<td>Surgical diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary carcinoma of liver or bile ducts</td>
<td>125 (15.6%)</td>
<td>132 (16.4%)</td>
</tr>
<tr>
<td>Metastatic liver disease</td>
<td>481 (60.0%)</td>
<td>484 (60.3%)</td>
</tr>
<tr>
<td>Other benign liver disease</td>
<td>247 (30.8%)</td>
<td>240 (29.9%)</td>
</tr>
</tbody>
</table>
**Table 4. Outcomes in patients undergoing major liver resections with and without epidural analgesia, United States, 2001–2010, propensity-matched sample**

<table>
<thead>
<tr>
<th>Postoperative outcome</th>
<th>No (n = 802)</th>
<th>Yes (n = 802)</th>
<th>Relative risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital death</td>
<td>17 (2.1%)</td>
<td>17 (2.1%)</td>
<td>1.00 (0.51–1.94)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hemorrhage/hematoma</td>
<td>27 (3.4%)</td>
<td>21 (2.6%)</td>
<td>0.77 (0.44–1.36)</td>
<td>0.379</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>7 (0.9%)</td>
<td>3 (0.4%)</td>
<td>0.43 (0.11–1.65)</td>
<td>0.204</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>32 (4.0%)</td>
<td>37 (4.6%)</td>
<td>1.15 (0.72–1.83)</td>
<td>0.538</td>
</tr>
<tr>
<td>Pulmonary embolism or DVT</td>
<td>16 (2.0%)</td>
<td>13 (1.6%)</td>
<td>0.81 (0.39–1.67)</td>
<td>0.574</td>
</tr>
<tr>
<td>Sepsis</td>
<td>19 (2.4%)</td>
<td>16 (2.0%)</td>
<td>0.84 (0.43–1.62)</td>
<td>0.608</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>143 (17.8%)</td>
<td>195 (24.3%)</td>
<td>1.36 (1.12–1.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>Transfusion of coagulation factors</td>
<td>50 (6.2%)</td>
<td>50 (6.2%)</td>
<td>1.00 (0.68–1.46)</td>
<td>1.000</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>4 (0.5%)</td>
<td>8 (1.0%)</td>
<td>2.00 (0.60–6.61)</td>
<td>0.246</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>23 (2.9%)</td>
<td>24 (3.0%)</td>
<td>1.04 (0.59–1.83)</td>
<td>0.882</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>20 (2.5%)</td>
<td>20 (2.5%)</td>
<td>1.00 (0.54–1.84)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ileus</td>
<td>84 (10.5%)</td>
<td>94 (11.7%)</td>
<td>1.11 (0.84–1.47)</td>
<td>0.426</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>72 (9.0%)</td>
<td>81 (10.1%)</td>
<td>1.12 (0.83–1.52)</td>
<td>0.444</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>19 (2.4%)</td>
<td>23 (2.9%)</td>
<td>1.21 (0.66–2.20)</td>
<td>0.531</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>21 (2.6%)</td>
<td>22 (2.7%)</td>
<td>1.05 (0.58–1.89)</td>
<td>0.877</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>17 (2.1%)</td>
<td>10 (1.2%)</td>
<td>0.58 (0.27–1.27)</td>
<td>0.174</td>
</tr>
<tr>
<td>Any infection</td>
<td>29 (3.6%)</td>
<td>26 (3.2%)</td>
<td>0.89 (0.53–1.50)</td>
<td>0.680</td>
</tr>
<tr>
<td>LOS (days, median, IQR)</td>
<td>6 4–8</td>
<td>6 5–8</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; DVT, deep vein thrombosis; IQR, interquartile range; LOS, length of stay.

**DISCUSSION**

This study of a large cohort of patients undergoing major liver resection shows that epidural analgesia is not widely used in this patient population. Despite the increase in the number of states contributing data to the NIS between 2001 and 2010, the sampling methodology of the database has not changed during that period of time. Therefore, our findings suggest that major liver resections are increasing in the US (Figure 1a). Although there was not a significant linear trend in the use of epidural analgesia for major liver resections during the study period, a notable decrease was observed in 2007 (Figure 1b). However, with the data available, we cannot determine if this dip is a true decrease in the use of epidural analgesia or the effect of undercoding the procedure.

The propensity-matching technique allowed for a more robust comparison between the patients who received epidural analgesia and those who did not, because all the observable variables such as demographics, comorbidities, type of facility, and type of surgical procedure were well balanced between the groups. Except for an increased incidence of blood transfusions in the epidural group, the propensity matching analyses revealed similar rates of postoperative complications despite the use of epidural analgesia.

One would assume that epidural analgesia would be used more often in teaching hospitals, particularly in larger hospitals with acute pain services. However, we found that hospital characteristics (e.g., teaching status, size, and location) did not influence the use of epidural analgesia. It is possible that the reports of lack of benefits of epidural analgesia (25, 26) combined with the concerns of potential complications may have resulted in the reduced use of epidural analgesia (27–29). In addition, the use of epidural analgesia may have been influenced by the reports of the high failure rate of epidural analgesia (30). Also, use of epidural analgesia may have been further reduced due to the reports of similar postoperative outcomes with the use of rational multimodal analgesia techniques (31).

There are several observations that are worth noting. The prevalence of hepatic cirrhosis was lower among the patients receiving epidural analgesia, probably due to concerns of coagulopathy and epidural hematoma in patients with cirrhosis. Patients receiving epidural analgesia had higher comorbidity scores and metastatic liver disease. This suggests a preferential use of epidural analgesia in sicker patients, indicating that epidural analgesia was considered an appropriate analgesic technique for pain management in the sicker patients undergoing liver resection. Despite the higher comorbidity burden in the patients receiving epidural analgesia, the incidence of complications, including mortality, was similar. This may suggest that epidural analgesia may offer some protection against postoperative complications in the high-risk population.

Patients receiving epidural analgesia were more likely to receive transfusion during their hospital stay. Although the reasons...
for this observation are not clear, it is possible that the patients in the epidural group received larger amounts of crystalloids (3), probably due to vasodilation caused by sympathetic blockade from epidural analgesia. The resulting hemodilution, therefore, may have triggered blood transfusion. Also, because the patients in the epidural group were sicker, higher hematocrit levels may have been maintained in this patient group. Of note, the use of coagulation factors and the incidence of hemorrhage and hematoma formation were similar with or without epidural analgesia.

Interestingly, we found that the patients receiving epidural analgesia had a longer hospital stay. Similar observations have been reported in patients undergoing colonic resection (24). It is possible that the delayed discharge was due to the higher comorbidities in the group that received epidural analgesia. Also, we can speculate that the longer hospital stay may be related to unplanned delays in epidural catheter removal because of concerns of epidural hematoma related to inadequate postoperative coagulation (32). However, we could not confirm this observation because the NIS datasets do not provide information on laboratory test results or timing of removal of the epidural catheters.

Although we studied a large nationwide sample, this study has several limitations related to the use of administrative datasets. Retrospective analysis prohibits examination and incorporation of factors other than those provided in the dataset. There is a lack of clinical information, including the details of analgesic regimens used in the nonepidural analgesia population as well as the details regarding the epidural analgesia regimens. In addition, there is no information on the degree of pain relief as well as some outcome measures such as time to ambulation. Unfortunately, the restricted use of epidural analgesia (i.e., limited sample size afforded from this database) limits our ability to assess differences in outcomes, particularly in complications with a very low incidence such as epidural hematoma or abscess formation.

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Case reports published by residents of Texas Tech University Health Sciences Center, Lubbock, 2008–2013

Dolores Buscemi, MD, Erwin Argueta, MD, and Kenneth Nugent, MD

Case report publications introduce new information into the current body of medical information and provide trainees with an opportunity to develop skills that enhance patient care. However, opportunities for publication are limited because journals often have other editorial priorities and some journals do not want to publish articles that might decrease their impact factors. Using PubMed and Google Scholar, we identified the case report articles published by our residents who completed training between 2008 and 2013. Sixty-one residents published 55 case reports and/or letters. Twenty-five of these publications had 87 citations in the years of publication and up 5 years after publication. Most of these citations occurred in other case reports (36) or in review articles (24). In conclusion, publishing case reports by residents has important benefits for the individual resident and the residency program and provides another resource for medical care.

Many prominent journals limit the number of case report publications because these articles have a low citation frequency and may lower the journals’ impact factors (1). Other reasons include the possibility that case reports “dilute” other medical publications and that they distract readers from “more important topics” (2). We think that writing and publishing case reports has value because case reports provide a resource for the medical community managing unusual cases, may provide a stimulus for additional research studies, and provide valuable academic experience for residents and fellows. We wanted to determine the level of success our residents had with their efforts: in particular, how many case reports they had published and whether these reports were cited in other journals.

METHODS

Our residency program at Texas Tech University Health Sciences Center in Lubbock, Texas, has 36 categorical residents and 2 preliminary residents. From 2008 through 2013, we graduated 61 residents. We compiled a list of all residents from 2008 to 2013 who had completed our program and searched for all case report publications by these residents using PubMed and Google Scholar. We determined the impact factors for all journals publishing these case reports using Journal Citations Reports. We then identified and classified all articles that had cited the case reports through 2013 using Google Scholar and Scopus.

RESULTS

The 61 residents who had graduated published 55 case reports and letters. Thirty-nine journals (69.6%) had impact factors; the median was 1.87 with an interquartile range (25%–75%) of 1.32 to 4.38. Twenty-five case reports had a total of 87 citations (mean 3.48 ± 2.57); the median number of citations for these 25 articles was 2.00, with an interquartile range of 1.00 to 4.25 and an overall range of 1 to 12. The types of articles citing the case reports included 36 case reports (41.4%), 24 review articles (27.6%), 11 letters (12.6%), nine clinical studies (10.3%), three research studies (3.4%), two book chapters (2.3%), one image (1.1%), and one editorial (1.1%). Fifty citing journals had impact factors, and the median was 1.97 with an interquartile range of 1.29 to 3.90. There was no difference in impact factors between the publishing journals and the citing journals using the Wilcoxon Mann-Whitney test (P = 0.40). The Table reports the number of publications, the number of publications with citations, and the time frame for citations.

DISCUSSION

The Residency Review Committee for Internal Medicine requires residents to do scholarly projects and to develop an understanding of scientific methods needed for medical science. Writing case reports provides valuable learning experiences for residents and fellows and can help meet these requirements. This activity requires review of prior publications, careful analysis of the case, and manuscript preparation with frequent revisions, requiring considerable time and effort. Given the time constraints and limitation of resources in residency training, these projects are more likely to be completed than a clinical research project. This activity allows programs to monitor scholarly activity in its faculty, organize clinical conferences

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about important patient care outcomes, and assess resources available for resident training. Programs need to know the attitudes of their residents toward this work to create the most constructive learning environment. Takahashi and colleagues (3) found a significant positive association between resident satisfaction with the program and scholarly activity.

Vandenbroucke argues that case reports have “their own role in the progress of medical science” and that they are often “the first line of evidence” (4). Case reports can describe new diseases, report new and important drug side effects, and, of course, promote medical education. He suggests that case reports that just list case after case without any discussion of previous publications are not useful, but case reports with thorough reviews and insightful discussions can contribute to clinical care. Medical publications, especially when using Internet resources, can often provide immediate solutions when managing a patient with an uncertain diagnosis or unclear therapeutic options, and in some situations an “obscure” case report may be the only available resource. Information about new diseases, including, for example, the recognition of the West Nile virus, and about new treatments, such as the first heart transplant, has been disseminated through case report publications (4, 5). Case reports frequently describe adverse reactions to drugs and may identify side effects missed in clinical trials. For example, Loke and associates (6) compared adverse reactions to amiodarone in three sources of information, namely meta-analyses, case reports, and reports sent to the World Health Organization. In that study, case reports reported respiratory complications at a higher frequency than the other two sources. Finally, case reports also lead to additional studies. Albrecht et al (7) reviewed articles published in Lancet between January 1996 and June 1997 and found that 64 case reports and 39 case series generated 24 follow-up trials, including 9 in the register of current controlled clinical trials. None of the case reports in our review generated a study, but 12 were cited in clinical or research studies.

Cirrhosis and operative trauma: determining when care is futile
Claire Isbell,* Mina Ghneim, Matthew Davis, Marc DeMoya, Terence O’Keefe, Kenji Inaba, and Stephen Cohn (e-mail: claire.r.larson@gmail.com)

The trauma patient with cirrhosis remains one of the most difficult to manage: mortality is high and tremendous resources are consumed, as no good metrics exist to determine futility. We sought to study cirrhotic trauma patients to establish accurate predictors of futile care. We conducted a multicenter chart review from 2001 to 2011 to identify patients with cirrhosis confirmed during trauma laparotomy. Demographic, vital sign, and laboratory data at the time of admission and operation and at 6, 24, and 48 hours postoperatively were recorded. Five centers contributed a total of 65 patients to our exploratory analysis. The median age was 49 (interquartile range [IQR] 44–56) with 94% (61/66) being male. Mortality was 47% (31/66), with a median survival of 5 days (IQR 0–26 days). In conclusion, admission vital signs cannot be used to determine futility in a cirrhotic trauma patient who needs laparotomy. However, transfusion of >17 units of blood in the first 6 hours appears to be highly predictive of mortality in these patients.

A comparison of the Injury Severity Score and the Trauma Mortality Prediction Model
Jo Weddle,* Alan Cook, Susan Baker, David Hauser, Laurent Glance, Lee Friedman, and Turner Oiler (e-mail: Rebecca.Weddle@BaylorHealth.edu)

Performance benchmarking requires accurate measurement of injury severity. Despite its shortcomings, the Injury Severity Score (ISS) remains the industry standard 40 years after its creation. A new severity measure, the Trauma Mortality Prediction Model (TMPM), uses either the Abbreviated Injury Scale (AIS) or International Classification of Diseases (ICD)-9 lexicons and may quantify injury severity better than ISS. We compared the performance of TMPM to ISS and other measures of injury severity in a single cohort of patients. We included 337,359 patient records with injuries reliably described in both the AIS and ICD-9 lexicons from the National Trauma Data Bank. Five injury severity measures (ISS, Max AIS, New Injury Severity Score [NISS], ICD-derived Injury Severity Score [ICISS], and TMPM) were computed using either the AIS or ICD-9 codes. These measures were compared for discrimination (area under the receiver operator characteristic curve [ROC]), an estimate of proximity to a model that perfectly predicts the outcome (Akaike information criterion [AIC]), and model calibration curves. TMPM demonstrated superior ROC, AIC, and calibration using either the AIS or ICD-9 lexicons. Calibration plots demonstrated the monotonic characteristics of the TMPM models contrasted by the nonmonotonic features of the other prediction models. Severity measures were more accurate with the AIS than with the ICD-9 lexicon. NISS proved superior to ISS in either lexicon. Since NISS is simpler to compute, it should replace ISS when a quick estimate of injury severity is required for AIS-coded injuries. Calibration curves suggest that the nonmonotonic nature of ISS may undermine its performance. TMPM demonstrated superior overall mortality prediction compared to all other models, including ISS, whether the AIS or ICD-9 lexicons were used. Because TMPM provides an absolute probability of death, it may allow clinicians to communicate more precisely with one another and with patients and families.

Prevalence of brachial plexus injuries in patients with scapular fractures: a National Trauma Data Bank review
Edward Chamata,* Raman Mahabir, and Robert Weber (e-mail: chamata@medicine.tamhsc.edu)

Literature investigating the prevalence of brachial plexus injuries associated with scapular fractures is sparse, frequently limited by small sample sizes and often restricted to one center’s experience. The purposes of this study were to find the prevalence of brachial plexus injuries associated with scapular fractures, to determine how the
prevalence varies with the region of the scapula injured, and to assess which specific nerves of the brachial plexus were involved. The data set of the National Trauma Data Bank was retrospectively reviewed for the 5-year period of 2007 to 2011. Of 68,118 patients with scapular fractures identified during this period, brachial plexus injury was present in 1173, or 1.72%. In patients with multiple scapular fractures, the prevalence of brachial plexus injury was 3.12%, and the prevalence ranged from 1.52% to 2.22% in patients with single scapular fractures, depending on the specific anatomic location of the fracture. Of the 426 injuries with detailed information on the nerve injury, there were 208 (49%) radial nerve injuries, 113 (26.5%) ulnar nerve injuries, 65 (15%) median nerve injuries, 36 (8.5%) axillary nerve injuries, and 4 (1%) musculocutaneous nerve injuries. In conclusion, the prevalence of brachial plexus injuries in patients with scapular fractures was 1.72%. The prevalence was similar across anatomical regions for single scapular fracture and was higher with multiple fractures. The radial nerve accounted for the largest percentage of nerve injuries.

Accuracy of clinical evaluation of orbital floor defects

James Goggin,* Marecin Czewinski, and Daniel Jupiter (e-mail: jgoggin@sw.org)

Orbital floor (OF) fractures are common in facial trauma. Repair of traumatic OF defects ≥2 cm² is critical to prevent significant enophthalmos. A formula to precisely calculate OF defect size has been reported but is cumbersome for routine clinical use. Thus, surgeons may inaccurately rely on estimated calculations or clinical impressions to determine if repair is necessary. This study’s objective was to evaluate the accuracy of simple, rapid methods of defect size estimation and determine if any are suitable for clinical use. Following power analysis, 99 patients with OF fractures in a single regional level I trauma center were identified. True OF defect sizes were calculated using a previously validated formula, based on measurements obtained from coronally reformatted thin (<3 mm) axial computed tomography (CT) images. Estimated OF defect sizes were calculated using geometric area formulae, assuming the defect approximated the shape of an ellipse, circle, square, or rectangle, based on measurements from coronal and sagittal CT images. For each method, we determined its accuracy, sensitivity, specificity, and negative and positive predictive values in declaring the defect critical. Of the 99 patients identified, 55 had true OF defects of critical (≥2 cm²) or greater size. The geometric formulae showed an accuracy of 0.76 to 0.93, a sensitivity of 0.62 to 1.0, and a specificity of 0.63 to 0.91. The accuracy of defect size approximation using the area of an ellipse was highest. Geometric formulae showed an accuracy of 0.76 to 0.93, a sensitivity of 0.62 to 1.0, and a specificity of 0.63 to 0.91. The accuracy of defect size approximation using the area of an ellipse was highest. Geometric formulae showed an accuracy of 0.76 to 0.93, a sensitivity of 0.62 to 1.0, and a specificity of 0.63 to 0.91.

Cost containment in a rapidly expanding elderly population: a predictive model to guide rib fracture management

Katherine Schnell,* Mira Ghneim, Daniel Jupiter, Francis Chan, Matthew L. Davis, and Justin L. Regner (e-mail: katherine.schnell@gmail.com)

The Census Bureau predicts that the elderly population (age ≥65 years) will increase from 40 million to 81 million between 2010 and 2040, becoming the fastest-growing cohort in the US. The most prevalent injury sustained by the elderly is rib fracture. Prior studies have assessed rib fractures alone as predictors of morbidity, but none have accounted for baseline comorbidities or the injury’s financial impact. We predicted that triage of the elderly trauma patient sustaining rib fractures would be more accurate using a scoring system that incorporates both preexisting comorbidities and new trauma burden. A retrospective
cohort study evaluated 400 patients 55 years or older (229 [57%] of whom were elderly) with rib fractures admitted to a Level I trauma center from 2007 to 2012. Comorbidities included chronic obstructive pulmonary disease, heart failure, coronary artery disease, tobacco use, obesity, and functional status. Trauma data points included number of rib fractures, tube thoracostomy, pulmonary contusions, spinal injury, and lower body fractures. Exclusion criteria included a Glasgow Coma Score <13, emergent thoracoabdominal surgery, or deaths not due to rib fractures. Bivariate and logistic regression analysis determined the contribution of these factors to the combined outcome of intubation or pneumonia. Based on initial bivariate and multivariate analysis, significant variables were then used in a logistic regression analysis to create a scoring system to predict morbidity. The scoring system was cross-validated and assessed for accuracy in predicting intubation or pneumonia as markers for intensive care unit (ICU) admission. Six variables increased the risk of intubation or pneumonia: chronic obstructive pulmonary disease (odds ratio [OR] 3.9), low albumin <3.5 g/dL (OR 3.0), assisted living status (OR 2.9), tube thoracostomy (OR 2.4), Injury Severity Score (ISS) (OR 1.09 per unit increase in score), and total rib fracture (OR 1.13 per rib fracture) (P < 0.05). These six variables and heart failure (OR 1.9, P = 0.06) were used to create a predictive model for risk of intubation or pneumonia. This model assigns to each variable the scores 1.4, 1.1, 1, 0.9, 0.1(n), 0.1(n), and 0.6, respectively. A total score of >3.7 had a sensitivity and specificity of 78.5% and 78.9% for intubation or pneumonia but had a negative predictive value of 94.5%, suggesting that patients with scores <3.7 were at minimal risk of requiring ICU admission. When applied to our cohort, 92 patients (40% of ICU admits) had <3.7 for a predictive score. Eleven (12%) of these patients had intubation or pneumonia; however, only five were due to rib fractures. Of the remaining 81 patients with a score <3.7 admitted to the ICU, none developed pneumonia or were intubated. Forty had no other indication for ICU admission aside from the rib fracture and could have been managed on the floor. These 40 patients had a 1.7-day average length of stay in the ICU at an increased cost of $2200 per patient. Based on the scoring system we identified, which has a strong negative predictive value for intubation and pneumonia, patients with a score <3.7 should be stable on the floor and able to avoid ICU admission. This scoring system should be assessed prospectively to minimize morbidity and cost in the elderly.

Apples to apples? Redundancy and variability in quality and outcome reporting for cardiac and thoracic surgery

Jennifer Dixon,* Harry T. Papaconstantinou, Bonnie Hodges, Robyn S. Korsho, Dan Jupiter, Jay Shake, Basar Sareyyupoglu, and Scott I. Reznik (e-mail: jdxion@sw.org)

Health care is evolving into a value-based reimbursement system focused on quality and outcomes. Reported outcomes from national databases are used for quality improvement projects and public reporting. Each database has specific criteria and definitions for reporting performance and may overlap specialties. This leads to duplication of work and possible reporting inconsistencies. This study compared reported outcomes in cardiac and thoracic surgery from two validated reporting databases. Our institution is a tertiary care academic medical center that has an active quality improvement program that participates in both the Society of Thoracic Surgeons (STS) database and National Surgical Quality Improvement Program (NSQIP). Reported data were compared between the two databases from January 2011 to June 2012. Quality metrics and outcomes included mortality, wound infection, prolonged ventilation, pneumonia, renal failure, stroke, and cardiac arrest. The rates were compared by chi-square analysis. A total of 737 and 177 cardiac surgery cases and 451 and 105 thoracic cases were captured by the STS database and NSQIP, respectively. Within cardiac surgery, there was a statistically significant difference in the reported rates of superficial wound infection, prolonged ventilation, renal failure, and mortality. No differences were found in the variables for thoracic surgery. Our data indicate a significant discordance in quality reporting for cardiac surgery between the NSQIP and STS databases. The disparity between databases and duplication of database participation strongly indicate that a unified national quality reporting program is required. Consolidation of reporting databases and standardization of morbidity definitions across all databases may improve participation and reduce hospital cost.

Outcomes of corticosteroid treatment for trigger finger by stage

Janae Maher,* Daniel Jupiter, Wendy Parker, and Robert Weber (e-mail: janaemaher@gmail.com)

Trigger finger is one of the most common hand ailments, with an incidence of 2% to 3% in the general population and up to 10% in diabetics. Currently, there are multiple accepted management options; however, none have been linked to a clinical classification of the disease state. Our goal was to develop a classification system, stratify patients into the derived disease stages, and determine whether there is a difference in the response rate to corticosteroid injection based on stage of disease in the affected digit. This prospective longitudinal study involved four cohorts distinguished by stage of disease: 0) pain and tenderness over A1 pulley, no clicking, popping, or locking; 1) pain with clicking, popping, palpable nodule, but without locking; 2) locking overcome with affected hand; 3) locking overcome with opposite hand; and 4) inability to flex or extend affected digit. Patient cohorts underwent corticosteroid injection and scheduled follow-up at 1, 3, 6, 9, and 12 months. Michigan Hand Outcome Questionnaire results were obtained at the initial visit and 1-year follow-up. A total of 87 patients were enrolled, with 26 in Stage 1, 32 in Stage 2, 22 in Stage 3, and 7 in Stage 4. Patients with trigger finger reported significantly worse overall hand function, difficulties with activities of daily living, severity of pain, and overall satisfaction of function with the affected hand compared with the nonaffected hand (P < 0.001). After corticosteroid injection, overall success rates at 1-month follow-up were 88%, 79%, 45%, and 57% for Stage 1 through 4, respectively. Combined resolution rates for Stage 1 and 2 at 1-month follow-up were significantly higher than those for Stage 3 and 4 (P = 0.01). In conclusion, early data suggest that our classification system for trigger finger has prognostic significance, which can have a significant impact on patient care, treatment algorithms, interpractitioner communication, medical costs, future research, and most importantly treatment success.

Maternal preeclampsia increases risk of neonatal necrotizing enterocolitis

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Similar immunologic mechanisms underlie development of preeclampsia and necrotizing enterocolitis. Although preeclampsia is a known risk factor for prematurity and intrauterine growth restriction, our hypothesis

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was that maternal preeclampsia independently increases necrotizing enterocolitis (NEC) risk in newborns. The database of all births at our institution from 2008 to 2011 (n = 9993) was retrospectively reviewed after institutional review board approval. Multiple mother and baby variables, including maternal age, race, parity, mode of delivery, gestational age, birth weight, sex, and Apgar score, were included in the analysis. Babies born to mothers with preeclampsia (n = 1368) were compared with the control group of non-preeclamptic mothers (n = 8625). Babies with birth weights <10th percentile for gestational age were classified as small-for-gestational-age (SGA). Statistics were performed using Pearson’s chi-square test. The incidence of NEC was 1.5% in the control group (n = 126) and 4.6% in the preeclampsia group (n = 63) (P < 0.001). A higher percentage of babies in the preeclampsia group were preterm (<37 weeks gestational age (14.5% in control vs 41.4% in preeclampsia, P < 0.001) and SGA (6.3% in control vs 10.2% in preeclampsia, P < 0.001). Within the preterm population, 9.0% of the control babies and 10.8% of the preeclampsia babies developed NEC (P = 0.25). The effect of preeclampsia was dramatic in the SGA group, where 1.5% of controls developed NEC compared with 13.6% of preeclampsia babies (P < 0.001). We conclude that preeclampsia is an independent risk factor for development of NEC in babies with intrauterine growth restriction, given the observed 10-fold odds increase. Abnormal placentation results in the proinflammatory condition that characterizes maternal preeclampsia and often leads to fetal hypoxia, which manifests as growth restriction. This combination of maternal systemic inflammatory response and fetal hypoxia can prime the fetal immune system in favor of the proinflammatory phenotype and reduced immune regulation in utero. Affected newborns are thus predisposed to development of systemic inflammatory diseases such as NEC at birth.

**Effects of native nephrectomy on blood pressure in patients with autosomal dominant polycystic kidney disease after renal transplantation**

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(e-mail: lchiles@sw.org)

This study evaluated how removal of polycystic kidneys affected blood pressure and use of antihypertensive medications in renal transplant patients with adult polycystic kidney disease. A retrospective review was conducted of cases of native nephrectomies on renal transplant recipients performed by a single urologic surgeon at our institution between December 2003 and January 2012. Preoperative and postoperative values for systolic and diastolic blood pressure, creatinine, and hematocrit were reviewed using the average values the year prior to surgery and over the year following surgery. A paired t test was then used to evaluate if these markers changed from pre- to postoperative. Statistical analysis of the use of antihypertensive medications required pre- and postoperatively was also performed. A total of 18 nephrectomies were performed on 13 patients. Systolic blood pressure dropped an average of 1.91 mm Hg (11.88), diastolic blood pressure dropped 2.52 mm Hg (8.68), creatinine increased 0.13 mg/dL (0.30), and hematocrit dropped 3.63 percentage points (2.60). Only the change in hematocrit was statistically significant (P < 0.001). The mean and median numbers of drugs patients were on before and after surgery were 1.94 and 1.5 presurgery, and 1.5 and 1 post surgery, respectively. After nephrectomy, 14 (77.8%) cases saw their number of drugs either remain the same or decrease. This is a statistically significantly higher proportion than 50%. Eight of these 14 cases (44.4%) saw their number of drugs drop. This is not a statistically significant different proportion than 50%; however, it had significant clinical benefits for at least two patients. One was a young hypertensive patient who went from three to zero medications. Another was a patient with renal artery stenosis who went from four to one medication, which was reduced in dose. In conclusion, select renal transplant patients experience improvement in blood pressure control after removal of polycystic kidneys, as measured by reduction in blood pressure and/or antihypertensive medication requirements. It is hoped that this study will prompt further evaluation into identifying patients in whom nephrectomy would be beneficial in improving blood pressure control.

**Necrotic versus perforated appendix: Can CT scan differentiate the difference? Does it matter?**

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Historically, the progression from simple to complicated appendicitis is thought to occur as a result of full-thickness appendiceal wall necrosis leading to perforation. Currently, in order to minimize postoperative infections, surgeons attempt to perform appendectomy prior to perforation. However, infections still occur. Our goal was to evaluate whether computed tomography (CT) scan findings could predict risk of necrosis or perforation. The secondary aim was to determine if these two endpoints affected clinical outcomes. Retrospective cohorts from 2007 to 2012 at an academic tertiary referral center were evaluated. Patients with nonperforated appendicitis by CT scan were stratified based on the operative finding of perforation and pathologic assessment of appendical wall necrosis. Demographics, CT findings, operative and pathologic data, time sequence, and postoperative outcomes were studied. Of the 402 patients reviewed, 281 (70%), aged 39.7 ± 16.25 years (47.5% male) had uncomplicated appendicitis (no evidence of perforation or necrosis); 121 (30%) had either necrosis of the appendix (42, 10.3%), perforation (48, 12%), or both (31, 7.7%) (P < 0.001). CT scan findings of fecalith (odds ratio [OR] 2.31, P = 0.01), pericolic fluid (OR 2.47, P = 0.012), and appendiceal wall thickening (OR 2.41, P = 0.02) were risk factors for perforation, but no CT scan findings could significantly predict necrosis. Superficial surgical site infections occurred in 5 of 281 patients (1.8%) with uncomplicated appendicitis versus 8 patients (6.6%, P = 0.017) with perforation or necrosis. Intraabdominal abscesses did not occur in simple appendicitis, but occurred in 9 of 121 (7.4%, P = 0.0001) patients with perforation or necrosis. While CT scan findings can predict patients at risk for perforation, no specific findings could detect or predict patients at risk of necrosis. Since both necrosis and perforation significantly increase the risk of postoperative infections, all patients with appendicitis should benefit from prompt surgical intervention.

Complications associated with inferior vena cava filters: a large, single-institution review

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To quantify and evaluate complications arising from indwelling inferior vena cava (IVC) filters through the examination of incidentally performed computed tomography (CT) scans, a retrospective review was conducted of all patients who had an IVC filter placed at our institution from January 1, 2000, to December 31, 2011. All incidental CT studies performed at least 6 months after IVC placement and showing the IVC filter were evaluated using the average values the year prior to surgery and over the year following surgery. A paired t test was then used to evaluate if these two endpoints affected clinical outcomes. Retrospective cohorts from 2007 to 2012 at an academic tertiary referral center were evaluated. Patients with nonperforated appendicitis by CT scan were stratified based on the operative finding of perforation and pathologic assessment of appendical wall necrosis. Demographics, CT findings, operative and pathologic data, time sequence, and postoperative outcomes were studied. Of the 402 patients reviewed, 281 (70%), aged 39.7 ± 16.25 years (47.5% male) had uncomplicated appendicitis (no evidence of perforation or necrosis); 121 (30%) had either necrosis of the appendix (42, 10.3%), perforation (48, 12%), or both (31, 7.7%) (P < 0.001). CT scan findings of fecalith (odds ratio [OR] 2.31, P = 0.01), pericolic fluid (OR 2.47, P = 0.012), and appendiceal wall thickening (OR 2.41, P = 0.02) were risk factors for perforation, but no CT scan findings could significantly predict necrosis. Superficial surgical site infections occurred in 5 of 281 patients (1.8%) with uncomplicated appendicitis versus 8 patients (6.6%, P = 0.017) with perforation or necrosis. Intraabdominal abscesses did not occur in simple appendicitis, but occurred in 9 of 121 (7.4%, P = 0.0001) patients with perforation or necrosis. While CT scan findings can predict patients at risk for perforation, no specific findings could detect or predict patients at risk of necrosis. Since both necrosis and perforation significantly increase the risk of postoperative infections, all patients with appendicitis should benefit from prompt surgical intervention.
included. Two observers independently evaluated the CT scans. Filter model as well as IVC penetration, erosion, migration, filter fracture, and other complications were recorded. Penetration of the IVC was defined by at least one strut of the device being >4 mm outside of the IVC wall. A total of 1470 filters of 8 different models were inserted in the specified time period. Of these, 66% were retrievable, 6.9% were removed, and 0.8% failed removal. The number of these patients who had incidental CT studies performed in which the IVC filters were visible was 335 (22.7%). Filter penetration of the IVC was observed in 129 (38.5%) of the filters seen on subsequent CT scans, which further calculates to a known overall perforation rate of 9% for the entire series. IVC penetration was observed in 42 of 163 Optease filters (26%), 41 of 107 TrapEase filters (38%), 25 of 29 G2/G2X filters (86%), 9 of 14 Greenfield filters (64%), 1 of 9 Vena-Tech filters (11%), 6 of 8 Celect filters (75%), 3 of 3 Eclipse filters, (100%), and 2 of 2 Tulip filters (100%). Thus, IVC filters were found to have a high rate of IVC penetration when observed through incidental CT scans. Further prospective studies and programs are needed to increase IVC filter retrieval rate.

Interleukin-1β induces brain microvascular endothelial cell hyperpermeability through matrix metalloproteinase-9

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Brain microvascular hyperpermeability is a major contributor of vasogenic brain edema that occurs following traumatic and ischemic injuries and involves upregulation of interleukin-1 beta (IL-1β). Our objective was to determine if IL-1β mediates blood-brain barrier hyperpermeability via matrix metalloproteinases (MMPs)-induced tight junction (TJ) disruption. Rat brain microvascular endothelial cell (RBMEC) monolayers were exposed to various concentrations of IL-1β, and the optimal concentration and time to induce permeability were determined. RBMEC monolayers were exposed to IL-1β alone or following an MMP inhibitor (GM6001; 1 hour), MMP9 inhibitor-1, and MMP-9 siRNA. MMP-9 activity was measured following IL-1β exposure. TJ integrity and cytoskeletal assembly were studied using zonula occludens-1 immunofluorescence and rhodamine phalloidin staining for F-actin, respectively. Results showed that IL-1β increased monolayer permeability and MMP-9 activity significantly (P < 0.05) and induced TJ disruption and actin stress fiber formation. GM6001, MMP9 inhibitor-1, and MMP-9 siRNA attenuated IL-1β–induced hyperpermeability significantly (P < 0.05). An MMP-9 specific inhibitor (MMP9 inhibitor-1) protected both TJ integrity and actin cytoskeletal assembly. These findings suggest that up-regulation of IL-1β promotes activation of MMP-9, leading to blood-brain barrier breakdown and microvascular hyperpermeability.

Melatonin inhibits thermal injury–induced hyperpermeability in microvascular endothelial cells

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Burns are known to induce intense systemic inflammatory reactions and hyperpermeability. The mechanisms that regulate this process are unclear, but it is known that the breakdown of endothelial cell adherens junctions is integral and that reactive oxygen species play a large role in initiating this process. We hypothesized that burn-induced junctional damage and hyperpermeability could be attenuated with the use of the antioxidant melatonin. After Institutional Animal Care and Use Committee approval, Sprague Dawley rats were assigned to either sham or burn groups (30% total body surface area). Fluorescein isothiocyanate–albumin was administered intravenously. Mesenteric postcapillary venules were examined with intravital microscopy to analyze and determine the flux of the albumin from the intravascular space to the interstitium. Fluorescence intensities were measured and serum was collected. Rat lung microvascular endothelial cells were then grown as monolayers on Transwell inserts. Wells were divided into four groups, and sham serum, burn serum, melatonin plus sham serum, and melatonin plus burn serum were applied. Fluorescein isothiocyanate–albumin flux across the monolayer was obtained as an indicator of permeability. Wells were again divided into four groups. Immunofluorescence staining for the adherens junction proteins β-catenin and vascular endothelial-cadherin, and rhodamine phalloidin staining for F-actin were performed. Images were obtained. Statistical analysis was conducted using Student's t test. Data from intravital microscopy revealed a significant increase in vascular hyperpermeability following burn trauma. Monolayer permeability was increased with burn serum when compared with sham. However, this increase in permeability was attenuated with melatonin treatment. Immunofluorescence showed that damage of rat lung microvascular endothelial cell adherens
junctions occurred with exposure to burn serum and melatonin restored integrity. Rhodamine phalloidin staining showed an increase in F-actin stress fiber formation following exposure to burn serum, and melatonin decreased this. This insight into the mechanisms of burn-induced fluid leak confirms the role of reactive oxygen species but more importantly hints at the possibility of exciting new treatments to combat vascular hyperpermeability in burn.

The level of evidence of research presented at the Department Surgery Research Day

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Evidence-based medicine (EBM) provides an objective assessment of clinical practices. Since its popularization in the 1980s, EBM has improved the quality of medicine, discredited some antiquated practices, and shown that impressive results seen at the cellular and animal model levels do not necessarily produce the same effects when tested in clinical practice. The purpose of the study was to evaluate the level of evidence (LOE) of research presented at the annual Department of Surgery Research Day. Two independent reviewers evaluated all abstracts presented since the inception of the Department of Surgery’s Research Day and scored each abstract for LOE according to criteria from the Centre for Evidence-Based Medicine. The senior author randomly reviewed one out of 10 articles to provide interobserver reliability. No inconsistencies were found in the reviewed articles. Reviewers were blinded to the authors of individual abstracts. A total of 101 abstracts were presented over the 7-year period. Thirty-six were excluded because they were basic science or educational/teaching abstracts, opinion polls, or editorials. There were only six (9%) Level I or II studies over that time period. The average LOE was 3.43 and remained stable. The nature of surgical practice makes it unlikely that EBM will ever gain as much popularity as it currently enjoys within the medical specialties. Limitations of randomized controlled trials in surgery, including technical, practical, funding, and ethical issues, are intrinsic to the field. An increased emphasis and reward for research of a higher level of evidence rather than a higher volume may be beneficial to improve the quality of evidence presented.
Measuring testosterone levels became easier in the 1970s, and it wasn’t long before levels were being checked in men across all age groups. At that time, several authors reported an age-associated decline of serum testosterone levels beginning in the fourth or fifth decades of life. Other studies found that the decline in testosterone with age might be more related to comorbidities that develop in many aging men. Aggressive marketing campaigns by pharmaceutical companies have led to increased awareness of this topic, and primary care physicians are seeing more patients who are concerned about “low T.” Unfortunately, testosterone replacement therapy has not been straightforward. Many men with low testosterone levels have no symptoms, and many men with symptoms who receive treatment and reach goal testosterone levels have no improvement in their symptoms. The actual prevalence of hypogonadism has been estimated to be 39% in men aged 45 years or older presenting to primary care offices in the United States. As the US population ages, this number is likely to increase. This article, targeted to primary care physicians, reviews the concept of late-onset hypogonadism, describes how to determine the patients who might benefit from therapy, and offers recommendations regarding the workup and initiation of treatment.

A 56-year-old overweight man with symptoms of low energy, daytime sleepiness, and decreased libido happens to be watching a golf tournament on TV from his favorite recliner and suddenly a commercial appears. This patient is in your office the following Monday and asks you, “Is it low T?”

Aggressive marketing campaigns by pharmaceutical companies have led to increased awareness of hypogonadism among men, who may then present to the clinic requesting testing or treatment (1). As a result, primary care physicians are seeing more patients like the one described above. The physiological age-related decrease in testosterone production should be differentiated from late-onset hypogonadism (LOH), defined as the presence of three sexual symptoms and low testosterone (low T) in aging men (2). This definition was proposed to help clinicians identify aging men with low testosterone who could potentially benefit from hormonal replacement therapy. The purpose of this article is to review the data on LOH, also known as low T, and present the most recent evidence and recommendations regarding the approach to the patient from our case scenario.

Physiology and Definitions

Male reproductive endocrine physiology involves the hypothalamic-pituitary-target organ and feedback model. Disruptions at different levels of this pathway can lead to disturbed androgenic effects: primary disorders of the testes (primary hypogonadism), disorders of the pituitary or hypothalamus (secondary hypogonadism), and disorders of androgen action on target tissue or androgen resistance. Other less common entities that manifest as androgen deficiency include chronic stress (by suppressing gonadotropin-releasing hormone secretion) and exogenous glucocorticoids, which can theoretically block the effects of testosterone on its target tissues (3).

In men, testosterone levels increase from puberty to adulthood and then progressively decline starting by the fourth or fifth decade of life (4). Multiple studies have raised the question of whether or not the declining T level seen in aging men is a natural age-related process or is caused by the accumulation of multiple chronic medical illnesses that virtually all aging men experience. One small study investigated this question by looking at groups of men across different age groups who were in “very good or excellent health” (5). The authors found no statistically significant difference in serum total testosterone levels across the cohorts grouped by decades of age. Their data support the idea that “the decline in serum T with male ageing is a non-specific effect of the common co-morbidities that accumulate during ageing” (5). Despite this novel study’s results, the fact remains that most aging men seen in primary care offices are very likely to have at least two chronic medical illnesses (6) and are dissimilar from the study population. It would be helpful if health care professionals could identify men with low serum testosterone levels who are likely experiencing symptoms purely from androgen deficiency and would therefore benefit from treatment.

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LATE-ONSET HYPOGONADISM

Symptoms of hypogonadism are highly nonspecific and include decreased libido, erectile dysfunction, decreased volume of ejaculate, loss of body and facial hair, decreased bone density, decreased lean body mass, increased body fat, fatigue, weakness, increased anxiety, profuse sweating, and anemia (7). It is challenging to differentiate these symptoms from those that result from aging per se, and this was one of the reasons why the concept of LOH was introduced.

LOH is defined as a total testosterone level \(<300\) ng/dL combined with the presence of three sexual symptoms:

- Decreased frequency of morning erection
- Erectile dysfunction
- Decreased frequency of sexual thoughts

Sexual symptoms have been found to be more strongly associated with androgen deficiency and are therefore specified in the definition of LOH (8). This syndromic approach involving clinical and biochemical criteria allows physicians to identify patients who are symptomatic from androgen deficiency and separate them from those with isolated biochemical hypogonadism and nonspecific symptoms from aging. Further research by the European Male Aging Study has found an association between LOH and end-organ deficits compatible with androgen deficiency, specifically low hemoglobin, reduced bone mineral density, and reduced muscle mass (2).

Data on the prevalence of low T are highly variable due to the different cutoffs used to define low testosterone and the clinical syndrome of LOH (3, 9, 10). The Massachusetts Male Aging Study (10), an observational cohort study conducted on healthy men aged 40 to 70 years from the Boston area, estimated that the prevalence of androgen deficiency (total testosterone \(<400\) ng/dL) in men in this age group was 25.3% to 39.3%, but when considering the presence of at least three signs or symptoms of low T (the definition of LOH), the prevalence dropped to 6% to 12%.

DIAGNOSIS

Guidelines, including the most recent guidelines published by the Endocrine Society in 2010, recommend against screening asymptomatic patients and against case finding with tools such as the ADAM (Androgen Deficiency in the Aging Male) questionnaire. Guidelines do recommend considering case detection, which involves testing specific groups of patients that may be at higher risk of androgen deficiency due to certain comorbid diseases (type 2 diabetes mellitus, moderate to severe chronic obstructive pulmonary disease, obesity, etc.) (11).

Symptoms are mostly nonspecific. Even the sexual symptoms can be due to many other conditions, including vascular disease, chronic alcohol use, and depressive disorders. Thus, many men are seeking solutions for these bothersome symptoms, which may involve indiscriminant testing and possible overtreatment.

The physical exam also is generally nonspecific. Typical exam or diagnostic findings include obesity, loss of body hair, gynecomastia, mild anemia, and osteoporosis. Testicular volume may be decreased (normal volume 15 to 30 mL, equivalent to the size of a quarter dollar coin). In addition to size determination, the testes should be palpated to rule out the presence of a mass, which may represent a benign or malignant tumor. A pituitary mass may cause visual field deficits, and prolactinomas specifically can cause galactorrhea (11, 12).

The diagnostic approach to hypogonadism is illustrated in Figure 1. Normal values for testosterone levels vary among different sources (2, 11, 12). The most common cutoff transitioning from normal to low ranges from 280 ng/dL to 320 ng/dL; the guidelines recommend using 300 ng/dL as the cutoff (11). Serum testosterone levels exhibit ultradian and circadian variation, providing physiologic sources of biologic variability. Ultradian fluctuations (rhythmic fluctuations of less than a 24-hour period but more than 1 hour) are more pronounced in older men, while circadian variation in testosterone is blunted, but still present, in older men (12). Therefore, except in older men, a morning (7 to 11 AM) serum total testosterone should be checked initially, if testing is necessary. There is some evidence that a glucose load can significantly decrease testosterone levels for a short time, so conducting this test in the fasting state may result in improved accuracy (13). If initial test results are low, repeat measurements are recommended in 2 to 3 weeks, since repeat levels may be within the normal range in up to 30% of cases. Additionally, at this point it is prudent to consider outside influences on sex hormone production and address these issues first if appropriate. Such issues include use of corticosteroids or opiates, malnutrition, acute illness, alcoholism, and cirrhosis.

![Figure 1](image-url). Diagnostic approach for patients suspected of having hypogonadism.
If the testosterone levels are equivocal, consider checking a free or bioavailable testosterone level. It is important to note that there is an age-associated increase of sex hormone binding globulin levels by about 1.2% per year, so the decrease of free testosterone is larger than that of total serum testosterone in older patients.

If testosterone is confirmed to be low, it is recommended to categorize the hypogonadism as primary or secondary by checking levels of luteinizing hormone and follicle-stimulating hormone. Elevated levels of these hormones would indicate primary testicular failure. Causes include LOH, Klinefelter syndrome, and infectious diseases such as chlamydia- and gonorrhea-associated epididymo-orchitis and mumps. If luteinizing hormone and follicle-stimulating hormone levels are low (or inappropriately normal), secondary hypogonadism is diagnosed and hypothalamic/pituitary pathologies should be considered (11, 12) depending on the patient’s presentation.

TREATMENT

Once the diagnosis of LOH is confirmed, testosterone replacement therapy (TRT) should be considered with the goals of improving secondary sexual characteristics, sexual function, sense of well-being, and bone mineral density. During the initial workup, if a clear treatable condition that explains androgen deficiency is diagnosed, it should be addressed first (11, 14).

In obese individuals, several studies have demonstrated that intense lifestyle intervention and weight loss are associated with a rise in testosterone levels. Androgen rise has been found to be greater in those patients who lose more weight (14, 15). It is therefore important to recommend weight loss either prior to or concomitant with TRT in obese patients. Obese patients should also be assessed for obstructive sleep apnea, which is also an important cause of low T (16).

TRT in older men with low testosterone concentrations has been associated with improved libido, sexual function, mood, and possibly muscle strength (12, 17). Improvement in bone mineral density has been reported, but no studies exist that determine whether the risk of fractures in these patients decreases when receiving TRT (11, 12, 18).

Controversy exists about the long-term safety of TRT. Although several studies have reported a significant reduction of carotid intima media thickness; decreases in fat mass, blood pressure, fasting glucose, and insulin resistance; and increases in high-density lipoprotein cholesterol (12, 19), the effect of TRT on cardiovascular risk is still uncertain. One study in men older than 65 years of age with limitations in mobility and a high prevalence of chronic disease concluded that the application of a testosterone gel was associated with an increased risk of cardiovascular adverse events (20). Many argue that the investigators used higher dosages of testosterone than recommended by the guidelines or that the results might have been associated with increased hematocrit in the treatment group. In contrast, other studies have found increased cardiovascular mortality in patients with testosterone deficiency (19). Further studies are needed to determine the exact role of testosterone and TRT in cardiovascular risk. This is an issue patients should be aware of when considering TRT. Debate also surrounds to what extent metastatic prostate cancer and breast cancer may be stimulated during testosterone treatment. For this reason, all men should be assessed for risk of breast and prostate cancer prior to treatment. Other potential side effects of TRT include fluid retention, acne, sleep apnea, gynecomastia, and infertility (11). The 2010 guidelines list the following contraindications to TRT: breast cancer, severe lower urinary tract symptoms, and poorly controlled heart failure.

The different testosterone preparations available include intramuscular injections, topical gels, solutions, and skin patches. Tablets and implanted subcutaneous pellet formulations are less commonly used options. Each preparation has advantages and disadvantages and should be presented as an option to the patient (Table 1). Intramuscular injections are administered every 2 to 3 weeks and trade the inconvenience of bimonthly injection visits with the avoidance of possible medication contact.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Route</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone cypionate,</td>
<td>Intramuscular</td>
<td>Effective, avoids daily administration</td>
<td>Requires intramuscular injection of oily solution</td>
</tr>
<tr>
<td>Testosterone enanthate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patch</td>
<td>Transdermal</td>
<td>Relatively convenient, stable serum concentrations</td>
<td>Daily application, rash in up to 30%, unavailable in some countries</td>
</tr>
<tr>
<td>Gels</td>
<td>Transdermal</td>
<td>Consistent serum levels</td>
<td>Daily application, theoretical transfer to others upon skin contact</td>
</tr>
<tr>
<td>Injection (pellets)</td>
<td>Subcutaneous fat implants</td>
<td>Only needed every 3–6 months</td>
<td>Requires surgical implantation</td>
</tr>
<tr>
<td>Fluoxymesterone, Methyltestosterone</td>
<td>Oral</td>
<td>Convenience</td>
<td>Up to 4 daily doses may be needed, potentially significant hepatic effects and first-pass metabolism leading to ineffective therapy</td>
</tr>
<tr>
<td>Testosterone undecanoate</td>
<td>Oral</td>
<td>Convenience</td>
<td>Same as other orals but possibly fewer hepatic effects; available in Canada and Europe, not USA</td>
</tr>
<tr>
<td>Buccal testosterone</td>
<td>Oral (patch that adheres to buccal mucosa)</td>
<td>Convenience</td>
<td>Some dropout in trials due to discomfort due to patch</td>
</tr>
</tbody>
</table>

Table 1. Therapeutic options for testosterone replacement therapy
with other household members. A disadvantage of the injections is the fluctuation in serum testosterone concentration that can cause fluctuating libido, energy level, and mood. Transdermal forms offer more stable concentrations (13), but they can cause rash in the applied area.

**MONITORING AND FOLLOW-UP**

The general target level for testosterone ranges from 350 to 750 ng/dL, which is roughly the range for healthy, androgen-sufficient adult men. Testosterone levels should be monitored 3 to 6 months after initiation of treatment. Patients receiving the intramuscular testosterone enanthate or cypionate should have levels checked midway between injections, and levels should be checked 3 to 12 hours after application in the case of transdermal patches (11, 13).

The recommended duration of testosterone administration is uncertain. A hematocrit test is recommended prior to therapy initiation to establish a baseline for future monitoring. Hematocrit and prostate-specific antigen (PSA) levels should be measured 3 to 6 months after treatment initiation and then annually. TRT should be reconsidered in patients with a hematocrit >50%. An increase in PSA of more than 1.4 ng/mL within a 12-month period of testosterone treatment or an International Prostate Symptom Score above 19 should prompt urological evaluation. On the other hand, what should a clinician do with a PSA value that increases to a lesser degree per year but is steadily increasing every time it is checked? This can be managed using the concept of PSA velocity. Any PSA velocity >0.4 ng/mL per year should also prompt urological evaluation (at least 2 years after initiating therapy). For example, PSA levels of 1.5 ng/mL, 2.3 ng/mL, and 3.3 ng/mL over 3 years do not meet the first indication for urology referral (more than 1.4 ng/mL over a year’s time) but show an average PSA velocity of 0.9 ng/mL and require referral based on that criterion (11).

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Donepezil, an acetylcholinesterase inhibitor, is approved for the treatment of mild to moderate dementia secondary to Alzheimer’s disease. Although most prescribers are aware of the common gastrointestinal side effects of donepezil, cardiovascular side effects are rarely observed. Cardiovascular side effects of donepezil have almost always been observed in patients with a history of conduction defects or sick sinus syndrome. We report a case of a woman with early onset Alzheimer’s disease and no history of cardiac disease who developed second-degree heart block after a few weeks of therapy with donepezil. Withdrawal of donepezil led to resolution of the atrioventricular block.

Donepezil, along with galantamine and rivastigmine, has been commonly prescribed for treatment of Alzheimer’s disease. Although cardiovascular adverse events have been reported, they are rarely experienced. This case highlights atrioventricular block as a potential adverse effect of donepezil.

**CASE PRESENTATION**

A 50-year-old woman who had developed early onset Alzheimer’s dementia at the age of 45 was brought to the hospital after she experienced a witnessed syncopal event. According to her husband, she lost consciousness for about a minute with no signs of seizure activity. Her husband reported that she had been “slow” for a few days. She was not on any prescription medication other than donepezil, which was started a few days prior to presentation. Her family indicated that she had been taking donepezil regularly and did not take more than the prescribed dosage. The family history was significant for Alzheimer’s disease. On physical exam, there were signs of advanced dementia. Thyroid function, syphilis serology, and vitamin B12 were normal or negative. The electrocardiogram (ECG) obtained by paramedics showed second-degree atrioventricular block (AVB) (Figure 1) with a heart rate of 30 beats per minute. No previous ECG was available for comparison. An echocardiogram showed a normal left ventricular ejection fraction and no structural abnormalities.

The patient was admitted to the hospital and donepezil was stopped. Her heart rate gradually rose, and no new syncopal events occurred. A later ECG showed sinus rhythm, with only a first-degree AVB (Figure 2). The patient remained asymptomatic during the rest of her hospital stay and was subsequently discharged. At 1-month follow-up, her ECG showed no AVB.

**DISCUSSION**

Cholinesterase inhibitors are a class of drugs that include donepezil, rivastigmine, and galantamine. They inhibit acetylcholinesterase enzyme in the central nervous system and increase acetylcholine, which is deficient in Alzheimer’s disease (1). Donepezil is highly selective for the central nervous system and is widely used in Alzheimer’s disease. Common side effects include nausea, diarrhea, malaise, and dizziness. In theory, the cholinergic effect of donepezil can cause sinus bradycardia and AVB. Donepezil, being a cholinesterase inhibitor, leads to increased levels of acetylcholine, which stimulates glycnergic and GABAergic inhibitory receptors by vagal neurotransmission, which in turn act to slow the heart rate (2). Theoretically, donepezil and other acetylcholinesterase inhibitors can aggravate preexisting nodal disease and lead to AVB (2). Heart rhythm disturbances, however, are rare (3). In a study of 1762 patients with Alzheimer’s disease on donepezil, Dunn et al reported nausea, diarrhea, malaise, dizziness, and insomnia as common side effects, with no reported cardiac rhythm disturbances (4).

Bordier et al reviewed 16 patients with Alzheimer’s disease who presented with syncope. AVB was present in 2 of the 16 cases (5). Suleyman et al (3) reported complete AVB and ventricular arrhythmia associated with donepezil use.

Rowland et al have suggested guidelines for managing cardiovascular risks prior to and during treatment with acetylcholinesterase inhibitors. A heart rate check is recommended at baseline, and if the rate is <50 beats per minute, the cause of bradycardia needs to be investigated before starting the medication. Monthly follow-up is recommended after drug initiation or dosage change, and 6-month follow-up is recommended during the drug maintenance phase (2).
We describe herein a 61-year-old African American woman who presented with takotsubo cardiomyopathy preceded by lupus myopericarditis. The case highlights the importance of the association between pericarditis and takotsubo cardiomyopathy. This new stressor adds to the existing evidence that these two entities may coexist and do not have to be mutually exclusive.

Takotsubo cardiomyopathy (TC), also known as stress-induced cardiomyopathy or apical ballooning syndrome or broken heart syndrome, produces transient systolic dysfunction of the left ventricular apical and/or mid segments in the absence of significant coronary artery disease (1–4). Common triggering factors are acute medical illness and severe emotional or physical stress, such as domestic violence, arguments, the unexpected death of relatives, catastrophic medical diagnoses, devastating financial or gambling losses, and natural disasters (1–4). We herewith report a case of TC where the likely preceding stressor was chest discomfort from a preceding lupus myopericarditis, highlighting the association of these two syndromes.

CASE REPORT

A 61-year-old African American woman with systemic hypertension and systemic lupus erythematosus presented to the hospital with the chief complaint of moderate to severe pleuritic chest discomfort. Chest pain had been present for 1 week and had worsened a day before presentation to the hospital. The pain was stronger when lying flat and improved when sitting upright or leaning forward. She also reported mild arthralgias and fatigue. Prior to arrival, she presented to an outside hospital where an electrocardiogram demonstrated diffuse ST-segment elevation and an elevated serum cardiac troponin level (0.8 ng/mL). She was treated with aspirin, clopidogrel, and heparin and referred to our facility for cardiac catheterization. Upon arrival, her vital signs were within normal limits, and an electrocardiogram demonstrated diffuse ST-segment elevations. Cardiac angiography revealed a 50% to 60% narrowing (diameter reduction) of the left anterior descending coronary artery, and a ventriculogram revealed severe apical ballooning/hypokinesis and basal hyperkinesis with an estimated left ventricular ejection fraction of 25%, consistent with a takotsubo pattern (Figure 1). Physical examination disclosed a facial rash and a pericardial rub. A detailed review of systems revealed no preceding emotional stressor. Preceding the pleuritic chest pain, however, the patient’s lupus had flared, which she found annoying and stressful.

The troponin I level was 2.24 ng/mL (normal: 0.00–0.03 ng/mL); creatine kinase MB index, 10.3% (0.0–2.5%); and creatine kinase MB, 15.6 U/L (0.0–5.0 ng/mL). Brain natriuretic peptide was 173 pg/mL (0–99 pg/mL), and her thyroid function profile was within reference range. A chest radiograph revealed mild enlargement of the cardiac silhouette. The initial 12-lead electrocardiogram demonstrated diffuse ST elevation and PR depression (except aVR and V1, where it showed PR elevation) (Figure 2). Subsequent tracings obtained after 12 hours and 18 hours revealed PR segment normalization (Figure 3), and after 30 hours, diffuse T wave inversions (Figure 4) (5, 6).

The patient was hemodynamically stable and was placed on aspirin 325 mg 3 times a day, colchicine 0.6 mg twice a day, atorvastatin, carvedilol, and lisinopril. Her home dose of prednisone (10 mg daily) was continued for underlying lupus (7). The patient was discharged 3 days later with complete resolution of her symptoms. A transthoracic echocardiogram performed prior to discharge (2 days after cardiac catheterization) demonstrated significant improvement in the left ventricular ejection fraction (now 50%–55%) and only mild apical ballooning in ventricular systole, with hypokinesis of the apex and the distal third of the anterior wall.

DISCUSSION

There have been at least seven reports of patients with TC associated with pericarditis. Of these, at least three cases reported pericarditis preceding the development of TC, while three other reports suggested the possible occurrence of pericarditis in the resolution phase of TC and one report did not specify the onset of pericarditis with respect to TC (8–15). We believe that our

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The patient had pericarditis before the development of TC. TC was likely due to an intense sympathetic stimulation resulting from pericarditis-induced severe chest discomfort. In cases where TC is the primary pathology, pericarditis may result secondary to the extension of the myocardial inflammation to the overlying pericardium, considering the inflammatory hypothesis for TC. One may also argue that such a coexistent association may actually represent a perimyocarditis variant manifesting as transient ST elevation on electrocardiogram and elevated cardiac biomarkers (16, 17).

The coexistence or association between TC and acute pericarditis or myopericarditis can have several diagnostic and therapeutic implications. First, this association challenges the current existing Mayo Clinic criteria for the diagnosis of TC and suggests a call for their revision (18). Given now several reported cases of TC pericarditis, it is important that one should not completely exclude the diagnosis of TC if pericarditis or myopericarditis coexist, as advocated by the current diagnostic criteria. These two conditions do not need to be mutually exclusive and in fact can be present simultaneously. Additionally, two important

Figure 1. (a) End-diastolic and (b) end-systolic ventriculogram tracings reveal apical ballooning and preserved basal contractility, consistent with takotsubo cardiomyopathy. (c) Angiogram reveals a 50% to 60% stenosis of the mid left anterior descending (LAD) coronary artery just after the takeoff of the diagonal branch. Coronary intravascular ultrasound demonstrated positive remodeling in the mid-LAD with significant plaque burden and a minimal lumen area of 4.1 mm². There was no evidence of plaque rupture, intramural hematoma, or thrombus.

Figure 2. Initial 12-lead electrocardiogram demonstrated diffuse ST elevation and PR depression (except aVR and V1, where it showed PR elevation), likely consistent with changes of stage 1 acute pericarditis.
management considerations should be made because the electrocardiographic presentation in some cases may masquerade as ST-segment–elevation myocardial infarction (STEMI). Such patients (TC with coexistent pericarditis), if treated with thrombolytic therapy for suspected STEMI at centers unable to perform primary percutaneous coronary intervention, may be exposed to a potential hazard of hemorrhagic tamponade. This may be an even bigger problem in developing countries where thrombolytic therapy is employed routinely for management of suspected STEMI. Also, the TC-pericarditis association emphasizes that a careful clinical history and ventriculography during cardiac catheterization should be routinely employed in such patients presenting with ST-segment elevation, especially if the electrocardiogram and echocardiographic features are more suggestive of TC, to avert the need for unnecessary thrombolytic therapy and to avoid missing a more serious diagnosis of STEMI. The association also calls for a cautionary use of anticoagulants and glycoprotein IIb/IIIa inhibitors in cases of TC when coexistent pericarditis is present (15).

Acute pericarditis and Dressler syndrome have been reported as possible complications of TC (9, 10). Conversely, acute pericarditis complicated by TC has been reported on at least three occasions (11–13), where pericarditis was the primary pathology. Systemic lupus erythematosus presenting with myopericarditis and associated with TC as a complication is the first such case reported, to the best of our knowledge.


Nontraumatic intracerebral hemorrhage unassociated with arterial aneurysmal rupture as a cause of sudden unexpected death

Carey Camille Roberts, BS, George J. Snipes, MD, Jong Mi Ko, BS, William Clifford Roberts, MD, and Joseph M. Guileyardo, MD

Sudden death from intracerebral hemorrhage was observed in two patients admitted to Baylor University Medical Center at Dallas in a single month. Each had been drinking alcohol at the time of onset of first symptoms. Intracerebral hemorrhage was diagnosed in one patient by computed tomography, but not in the second patient who clinically was diagnosed as having acute coronary syndrome. Both died within 24 hours of onset of symptoms, and autopsy in both disclosed intracerebral hemorrhage, an infrequent cause of sudden death. This report calls attention to intracerebral hemorrhage as a cause of sudden death.

This report describes two patients who collapsed while drinking alcohol and died within 24 hours (sudden death [SD]). Necropsy in each case disclosed intracerebral hemorrhage (ICH) as the cause, an infrequent cause of SD.

PATIENT DESCRIPTIONS

Pertinent clinical and morphologic findings in the two patients are tabulated in Table 1. The first patient suddenly became lethargic with slurred speech at a party and was taken to the emergency department. Shortly after arriving, she became unconscious. Computed tomography (CT) of the brain disclosed a large frontal hemorrhage centered within the right thalamus (Figure 1). The second patient was found unconscious by coworkers and was brought to the emergency department; a diagnosis of acute coronary syndrome with cardiogenic shock was made. He never regained consciousness. Both patients had been drinking alcohol just before the symptoms appeared. Both patients had had untreated systemic hypertension. Both patients had ICH, which bled into the ventricular cavities. The first patient had no coronary artery disease, and the second patient had focal but diffuse coronary artery disease. Neither had dilated ventricular cavities or significant myocardial scarring.

DISCUSSION

There are many causes of SD, with cardiac disease by far being the most prevalent in the Western world (1) (Figure 2). ICH is an infrequent cause of SD but is illustrated by our two patients who were seen in the same hospital in a single month in 2014. Although CT in case 1 indicated clinically that an acute intracerebral problem was the cause, in case 2, the central nervous system cause of sudden unconsciousness would not have been appreciated had not an autopsy been performed (Figures 3 and 4). Thomas and colleagues (2) studied 322 patients at necropsy who died from a nontraumatic condition within 6 hours.

Table 1. Clinical and morphologic findings in two patients with sudden death from intracerebral hemorrhage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52</td>
<td>53</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>African American</td>
<td>Latin American</td>
</tr>
<tr>
<td>Interval: collapse to death (hours)</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Diagnosis in emergency department</td>
<td>Stroke</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>19.7</td>
<td>31.2</td>
</tr>
<tr>
<td>Past chronic headaches</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Previous serious illnesses</td>
<td>COPD</td>
<td>0</td>
</tr>
<tr>
<td>Habitual alcoholism</td>
<td>+</td>
<td>?+</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation (therapy)</td>
<td>0</td>
<td>(+)</td>
</tr>
<tr>
<td>Heart weight (g)</td>
<td>260</td>
<td>625</td>
</tr>
<tr>
<td>Atherosclerotic coronary disease</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Blood alcohol level (g/dL)</td>
<td>0.039</td>
<td>0.031</td>
</tr>
<tr>
<td>Location of intracerebral hemorrhage</td>
<td>Thalamus</td>
<td>Cerebral white matter (parieto-occipital)</td>
</tr>
</tbody>
</table>

COPD indicates chronic obstructive pulmonary disease.
of onset of symptoms, and in 14 patients (4%), ICH or rupture of a berry aneurysm was the cause of SD. Most of the 322 SDs (59%) were caused by coronary heart disease. In Asian countries, ICH appears to be a more common cause of SD than in the Western world. Omae and colleagues (3) in Japan, for example, studied 73 patients (autopsies in 62) who died within 24 hours of the first onset of symptoms, and intracranial hemorrhage, comprising both subarachnoid and ICH, was the cause in 38 (53%). ICH also appears to be a more common cause of SD in younger as compared to older patients. Gallerani and colleagues (4) in Italy, for example, studied at necropsy 610 patients who died within 24 hours of the first onset of symptoms: of the 225 <65 years of age, ICH was the cause of death in 12 patients (5%); of the 385 patients ≥65 years of age, ICH was the cause of death in 3 patients (0.8%).

Among patients presenting clinically with stroke, the frequency of ICH of course is much higher than is the frequency of ICH among patients presenting with SD. Phillips and colleagues (5) studied 993 patients presenting with stroke, and 52 (5%) died within 24 hours of the first onset of symptoms: of them, 26 (50%) had ICH, 23 with previous systemic hypertension. Both of our patients had untreated systemic hypertension.

The location of ICH in patients with and without SD is variable. Freytag (6) studied 393 hypertensive patients who died from ICH. The hemorrhage occurred in the striate body in 165 patients (42%), in the pons in 63 patients (16%), in the

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**Figure 1.** Axial noncontrast computed tomography image demonstrates a large, 3.9 cm hemorrhage within the right thalamus with intraventricular extension and casting of the right lateral ventricle.

**Figure 2.** Diagram illustrating the various causes of SD. HD indicates heart disease. Reproduced from reference 1 with permission from author (Roberts WC) and publisher (Elsevier).
thalamus in 60 patients (15%), in the cerebral white matter in 38 patients (10%) (parieto-occipital = 18, temporal = 16, and frontal = 4), and other or multiple sites in 20 patients (5%). Of the 393 patients, 294 (75%) had bleeds into the ventricular space and 58 patients (15%), into the subarachnoid space.

Habitual alcohol use appears to increase the frequency of ICH. Both of our patients probably were alcoholics. Casolla and colleagues (7) of France studied 540 patients with ICH and found that 137 patients (25%) were habitual alcoholics and that they were younger than the nonalcoholics (median 60 years vs. 74 years).

Nontraumatic intracranial hemorrhage appears to occur equally in patients with chronic episodic headaches and in patients without frequent headaches. Case 1 had a known history of chronic headaches while case 2 did not. Inamasu and colleagues (8) in Japan studied by intracranial CT 124 patients who had witnessed out-of-hospital cardiac arrest: 12 (10%) had fatal intracranial hemorrhage, 2 of whom had ICH. Of the 2 patients with fatal ICH, one had a known history of chronic periodic headaches and the other did not.

A 53-year-old man with the Marfan syndrome had undergone aortic valve replacement with a Bjork-Shiley prosthesis for aortic regurgitation at another hospital 15 years earlier. At the same operation he had a Kay-type suture plication tricuspid annuloplasty of the posterior-septal commissure. He came to the cardiology clinic for preoperative clearance for inguinal hernia repair. An aortic regurgitation murmur was noted, and he admitted to exertional dyspnea. An electrocardiogram showed sinus rhythm, a normal P-R interval, and right bundle branch block. An echocardiogram revealed a dilated ascending aorta, severe aortic regurgitation due to a perivalvular leak, normal left ventricular systolic function, and pulmonary arterial hypertension with tricuspid regurgitation and a large right ventricle. Because of these findings he underwent a Cabrol procedure, i.e., a composite aortic valve and root replacement with reimplantation of the coronary arteries, and tricuspid valve replacement. Mechanical valves were used in both the aortic and tricuspid positions.

A postoperative electrocardiogram showed sinus arrhythmia, at a rate of 88 beats/minute, that was completely dissociated from a regular, accelerated junctional rhythm, at a rate of 67 beats/minute, with right bundle branch block and left anterior fascicular block (Figure). Alternatively, the subsidiary pacemaker could have been in the left posterior fascicle. Many of the P waves were positioned where they would be expected to be conducted to the ventricles, but the perfectly regular ventricular

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rhythm indicated that none were. Thus, there was some degree of atrioventricular block. The relatively rapid subsidiary pacemaker may have contributed to the complete atrioventricular dissociation, and the atrioventricular block may have not been complete. Marriott has referred to this as “block-acceleration dissociation” (1).

Aortic valve replacement requires the surgeon to operate in close proximity to the atrioventricular conduction tissue (2). As a consequence, atrioventricular block and/or an accelerated junctional rhythm may develop, and the chances of this are greater if, as in this patient, the anatomy has been distorted by a prior operation. The rhythm disturbance in this patient is a combination of the two, i.e., a conduction disturbance in combination with increased automaticity. Other conditions, such as inferior myocardial infarction or digitalis toxicity, also may produce block-acceleration atrioventricular dissociation (1).

Complete atrioventricular block is virtually never persistent in patients with inferior myocardial infarction or digitalis toxicity, and consequently these patients do not require permanent electronic pacing. In contrast, complete atrioventricular block developing after aortic valve surgery may be persistent, and those patients require permanent pacing (3, 4).

A patient with multiple erythematous nodules on her posterior scalp presented to our dermatology clinic. Biopsy confirmed the diagnosis of angiolymphoid hyperplasia with eosinophilia. The etiology of this disorder is unclear. Several cases have been treated in the past with complete surgical excision, although the recurrence rate remains relatively high.

CASE REPORT

A 64-year-old Caucasian woman with previous osteoarthritis, anemia, hypertension, and hyperlipidemia presented to the clinic with a 2-year history of recurrent painful nodules on her occipital scalp. She described them as painful lesions with a tendency to bleed spontaneously; she frequently awakened to find blood on her pillow. She denied pruritus, scaling, nonbloody discharge, or any trauma or episodes of infection. Her only medications were enalapril and verapamil. She reported allergies to adhesive tape, sulfa drugs, and penicillin. She denied any family history of cutaneous disorders. A prior excisional biopsy of one of the nodules in March 2012 was reported as angiolymphoid hyperplasia with eosinophilia (ALHE). Her other lesions were subsequently treated with excision as well.

During her current presentation, the patient had multiple coalescing nodules on the medial aspect of her occipital scalp: a 4 mm pink nodule, a 0.5 to 1.0 cm reddish brown nodule, and a confluent plaque resulting from 1.5 cm coalescing nodules (Figure 1). These areas were surrounded by secondary lichenification due to constant scratching or picking. She underwent punch biopsy of two of the nodules, and histologic examination confirmed the initial diagnosis of ALHE. The biopsy showed proliferation of thick-walled vessels in the dermis with prominent, protuberant endothelial cells and nodular infiltrate of lymphocytes and eosinophils in the stroma (Figure 2).

DISCUSSION

ALHE is a benign, locally proliferating lesion, which usually affects middle-aged Caucasian women and tends to have a predilection for the periauricular area and scalp (1). Other common areas of involvement include oral mucous membranes, pharynx, and orbit. The lesions tend to be persistent and recurrent erythematous or hyperpigmented dome-shaped dermal papules. The nodules can be pruritic or painful and do not tend to resolve spontaneously (1, 2). The nodules are normally 2 to 3 cm in diameter, with rare cases of larger and deeper neoplasms (1, 2). It is unclear whether ALHE is a reactive or neoplastic disease (3). In its active phase, it can be misdiagnosed as an angiosarcoma; however, eosinophilia is not a usual feature of malignant angiosarcoma (4).

Histologically, there is both a vascular and inflammatory component. The lesions consist of small blood vessels surrounded by enlarged endothelial cells as well as aggregates of noncanalized, plump endothelial cells (1). There is a dense perivascular and interstitial infiltrate of lymphocytes, plasma cells, and eosinophils. There is some evidence for the existence of arterial structures among venules, which may suggest the presence of arteriovenous shunts (3).

The main differential diagnosis of ALHE is Kimura’s disease, which was originally considered the same entity but is now considered a separate disease process (4). These two conditions are histologically described as lymphoid infiltration, vascular proliferation, and tissue eosinophilia. However, the clinical appearance of Kimura’s disease is consistent with subcutaneous
swelling and may not involve erythematous papules or nodules (4, 5). Some evidence suggests that Kimura’s disease is recognized as a chronic, allergic, inflammatory disease with unknown etiology, whereas ALHE is considered a benign vascular proliferative disorder of unknown origin (4). However, theories about ALHE occurring due to an antigenic response have also been proposed, which overlap the descriptions of Kimura’s disease.

ALHE may also be confused with lymphomatoid papulosis, which is a form of primary cutaneous CD30+ T-cell lymphoproliferative disorder (6). The clinical manifestations of lymphomatoid papulosis include recurrent papulonecrotic eruption on the extremities or trunk with hypo- or hyperpigmented scars. Many cases of ALHE have also occurred in the setting of high levels of interleukin-5 and related to peripheral T-cell lymphoma.

Although the etiology of ALHE is unclear, the two main theories suggest a benign vascular neoplasm or an allergic reaction to a variety of agents (7). A curious immunoglobulin E reticulated pattern is observed with ALHE, consistent with an atopic reaction (7). It is postulated that ALHE can occur due to antigenic stimulation following insect bites, injury, or even administration of tetanus toxoid vaccines; however, no specific agent has been solely identified (7). An association with cryoglobulins in the patients’ serum, nonspecific renal diseases, and unclassified systemic connective tissue diseases has been shown to relate this entity to an abnormal immunological response (7).

No definitive treatment is reported for this condition. Complete excision can be curative, but recurrences are common. Moh’s micrographic surgery with excision of abnormal vessels at the base of the lesion may be more effective in reducing recurrences (2). Intrallesional injections of corticosteroids, interferon alfa-2a, and cytotoxic agents have been shown to be effective (1). Other options include cryotherapy, radiotherapy, and laser treatments with pulsed dye or carbon dioxide (1). The laser treatments are designed to target the vasculoproliferative component of this disorder. There have been rare cases of successful treatment without recurrences in patients with coexisting ALHE and Kimura’s disease with extended surgical resection followed by full-thickness skin graft (8). In our case, after presentation at our biweekly multispecialty skin tumor conference, magnetic resonance imaging was recommended to fully assess the depth of the tumor with subsequent microscopically controlled full excision.

Clear cell carcinoma of the ovary (CCCO) is an uncommon, clinically aggressive neoplasm that has a propensity for the development of venous thrombosis and embolization, especially when compared to other subtypes of ovarian malignancies. We present a fatal case of a 59-year-old woman with a clinical course complicated by venous thrombosis and pulmonary thromboembolism that was attributed to CCCO discovered initially at autopsy.

Clear cell carcinoma of the ovary (CCCO) is a distinct histopathologic subtype of epithelial ovarian tumors and accounts for <5% of all ovarian malignancies (1). Most cases of CCCO occur in women in the fourth and fifth decades of life, and clinical presentation includes a mass usually detected on physical examination or by imaging. Relative to other ovarian neoplasms, CCCO has been more commonly associated with earlier stages and increased risk of venous thrombosis (2). We present the clinical, pathologic, and autopsy findings of a fatal case of a clinically undiagnosed CCCO discovered at autopsy associated with deep vein thrombosis and pulmonary thromboemboli.

CASE PRESENTATION

A 59-year-old white woman with prior hypertension, hyperlipidemia, and depression developed bilateral deep vein thrombosis (DVT) and bilateral pulmonary thromboembolism. An inferior vena cava filter was placed and warfarin therapy begun. Several weeks later, she presented to the emergency department at Baylor Regional Medical Center at Grapevine with pain, swelling, and a markedly swollen and discolored left lower extremity with mottling at the lateral aspect. On admission, her hemoglobin was 7.6 g/dL; hematocrit, 26%; white blood cell count, 9.8 K/uL; blood urea nitrogen, 40 mg/dL; creatinine, 1.6 mg/dL; prothrombin time, 37.2 seconds (reference range 9.0–12.0 seconds); and international normalized ratio, 3.6. Computed tomography disclosed a 19.2 × 12.3 × 10.8 cm mass in the pelvis consistent with multiple large uterine fibroids with areas of heterogeneity and cystic degeneration. She developed acute respiratory failure and hypotension. An echocardiogram found an ejection fraction of 25%. Despite adequate anticoagulation, her DVT persisted, and she eventually developed DVT in her peripherally inserted central catheter. She progressed to multisystem organ dysfunction and died 2 days later.

Autopsy disclosed a 38.0 × 19.5 cm area of red-purple discoloration with epidermal sloughing that extended from the left leg to the medial aspect of the left thigh. The distal portion of the left foot had an area of sloughing and purple discoloration of all digits. There were bilateral ovarian masses measuring 9.5 cm and 15.0 cm on the right and left sides, respectively (Figure 1). The cut surface of both masses showed white-tan solid nodules with occasional cystic spaces containing brown-yellow fluid. There were multiple intramural, tan-white, brown-yellow cystic areas.
whorled, well-circumscribed nodules, ranging up to 2.0 cm in diameter within the myometrium of the uterus. Multiple intravascular thromboemboli were found in the left lung hilum and in the right and left lower lobes. The left lower lobe had two well-demarcated areas of dark red, hemorrhagic induration in the periphery (5.0–7.0 cm). Leg dissection revealed thrombi in the deep leg veins bilaterally. Thrombotic material was adherent to the inferior vena cava filter.

Microscopically, the ovaries were composed of nests and sheets of tumor cells with eccentrically located angulated nuclei, clear cytoplasm, and focal hobnail patterns (Figure 2). Also present were areas of necrosis and hemorrhage. Sections from bilateral deep leg veins showed laminated thromboemboli with organization into the endothelial wall. Organizing intravascular thromboemboli with surrounding areas of parenchymal hemorrhagic necrosis were found in both lungs.

**DISCUSSION**

In 2003, the World Health Organization described CCCO as being composed of clear cells, growing in a solid, tubulocystic, or papillary pattern, with hobnail cells lining tubules and cysts (3). Patients usually present in their fourth to fifth decade of life with a pelvic mass ranging in size from 3.0 to 20.0 cm, and most cases are detected preoperatively either by physical examination or radiographic imaging (4). Women with CCCO present at a younger age and an earlier stage relative to other epithelial ovarian carcinomas (5). Treatment includes surgery and chemotherapy, but prognosis in advanced stages is generally dismal, especially when compared with other subtypes of epithelial ovarian neoplasms (6). CCCO has been associated with hypercalcemia (2) and endometriosis, and some authors suggest that atypical endometriosis may be a precursor lesion (7, 8).

CCCO is more commonly associated with development of venous thromboembolic events when compared to other subtypes of epithelial ovarian tumors (9, 10). In a study performed by Duska et al, venous thromboembolic events occurred in 42% of patients with CCCO, which was two times the rate found in matched non-CCCO controls with epithelial ovarian carcinomas of other histologies (9).

In 1865, Troussseau first described the association between malignant diseases and thromboembolic events (11). Hypercoagulability is often seen in concurrence with malignancy, and the overall incidence varies from 1% to 11% (12, 13). DVT as a postoperative complication of gynecologic surgeries has also been chronicled (14, 15).

The development of venous thrombosis is caused by alterations to one or more components of Virchow's triad, which consists of stasis, damage to the vascular endothelium, and hypercoagulable states. Stasis is often due to various causes of immobility (16, 17). Hypercoagulable states include a myriad of acquired and inherited conditions such as protein C and S deficiencies, antithrombin III deficiency, factor V Leiden, pregnancy, oral contraceptive use, and malignancy (16, 18, 19). Endothelial damage often occurs because of recent trauma or surgery (16, 18). Anatomically, it is reasonable to deduce that the large, bilateral pelvic masses compressed the pelvic veins, which resulted in blood stasis and thrombosis leading to DVT and pulmonary embolism; however, a hypercoagulable state due to this tumor may have also contributed to the death of this patient.

It is important to recognize the association between CCCO and the development of venous thromboemboli, as it has been suggested that these patients receive anticoagulation therapy indefinitely after surgery since there is a high rate of venous thromboembolism after surgery (9).

Although venous thrombosis and pulmonary thromboembolism may be present at the time of ovarian cancer diagnosis, this case is unusual, in our experience, since the patient died before a cancer diagnosis was established.


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**Avocations**

Old Glory reflection. This image shows reflections of the American flag on glycerin droplets. The main subject was a full-sized flag hung upside down about 2 meters away from the droplets. This was highlighted by fluorescent spot lighting. Ambient light was utilized for the droplets. (Camera, Nikon FX D610; lens, Nikon AF Micro Nikkor 200 mm; aperture, f 14.0; shutter speed, 1/40; ISO speed, 4000; focal length, 200; manual exposure; manual focusing.) Photo copyright © Rolando Solis, MD. Dr. Solis is an interventional cardiologist practicing at Baylor Medical Center at Garland and the Heart Hospital Baylor Plano (e-mail: rmsolis@me.com).
Intravascular large B-cell lymphoma (IVL) is rare and characterized by selective growth of neoplastic cells within the lumina of small blood vessels. We present the case of a 69-year-old woman who died of a widespread IVL with extravascular involvement of the lymph nodes, liver, bladder, and adrenal gland. This report discusses the unique features of IVL with concurrent extravascular components.

Intravascular large B-cell lymphoma (IVL), also known as angiotrophic lymphoma, was first described in 1959 as an endothelial neoplasm with vascular propagation (1). Only within the last 15 years has IVL been considered distinctive enough for World Health Organization (WHO) classification (2). The 2008 WHO definition states that IVL is a type of extranodal large B-cell lymphoma that selectively grows within the lumina of vessels, particularly capillaries, with the exception of larger arteries and veins. The WHO classification also states that this lymphoma is often widely disseminated in extranodal sites, and lymph nodes are usually spared (3). It is also important to note that extravascular infiltration by tumor cells is observed in only 11% of IVL cases, and patients presenting with classic features of IVL have later developed a nodal diffuse large B-cell lymphoma with shared immunophenotypic markers (1). There are also reports of nodal B-cell lymphoma recurring as IVL (4, 5) and IVL presenting concurrently with a lymphomatous mass in the central nervous system (6). We report the autopsy findings of a widely disseminated IVL with extensive extravascular involvement by tumor of the lymph nodes, bladder, liver, and adrenal gland.

CASE REPORT

A 69-year-old woman was admitted to Baylor University Medical Center at Dallas with symptoms of fatigue and generalized weakness for the past year, as well as night sweats and fever of 2 weeks’ duration. On admission she had a blood pressure of 91/42 mm Hg, a pulse of 140 beats per minute, a temperature of 100.5°F, and oxygen saturation of 95% on room air. The clinical diagnosis was probable sepsis. Laboratory studies revealed the following: white blood cell count of 8200/uL (82% segmented neutrophils, 6% normal lymphocytes, 7% monocytes, 4% bands, and 1% metamyelocytes), hemoglobin of 11.4 g/dL, hematocrit of 34.5%, platelet count of 128,000/uL, sodium of 125 mEq/L, potassium of 4.8 mEq/L, bicarbonate of 17 mEq/L, creatinine of 0.9 mg/dL, glucose of 98 mg/dL, calcium of 7.4 mg/dL, lactate dehydrogenase of 2070 U/L (normal level: 100–190 U/L), erythrocyte sedimentation rate of 58 mm/h (normal level: 0–30 mm/h), and C-reactive protein of 19.8 mg/dL (normal level: 0–0.3 mg/dL). A chest computed tomography (CT) scan revealed a paratracheal mass, raising clinical suspicion for paraneoplastic syndrome due to lung cancer, and an abdominal CT scan revealed only diverticulosis and abdominopelvic ascites. Despite therapy, she continued with fevers and hypovolemia and developed severe metabolic acidosis (pH 7.12) and acute respiratory failure. She died on the third day after admission.

At necropsy the paratracheal mass seen on imaging proved to be a hematoma contiguous with a central catheter insertion site at the right jugular vein. There was a focal thrombus in the left brachiocephalic vein associated with central catheter placement through the left jugular vein. Grossly within the liver there were numerous tan nodules ranging from 0.2 to 1.8 cm in diameter. Also present was a 1.6 cm tan, firm mucosal nodule in the urinary bladder, nodular expansion of the left adrenal gland, and two enlarged periaortic and perinephric lymph nodes. Both lymph nodes were approximately 1.5 cm and firm.

Microscopic examination demonstrated atypical lymphoid cells within the lumina of small vessels in most organs and tissues throughout the body, most prominent in the lungs (Figure 1a). These intravascular lymphoid cells were enlarged with pleomorphic, vesicular nuclei, prominent nucleoli, and multiple mitotic figures. The thrombus from the left brachiocephalic vein also contained these atypical cells but the paratracheal hematoma did not.
While most of the tumor was intravascular, there was also significant extravascular tumor infiltration. The bladder, liver, and adrenal gland nodules were dense populations of lymphoma cells (Figure 1b). The enlarged lymph nodes were sclerotic and diffusely involved by intravascular and extravascular lymphoma. The bone marrow was 60% to 70% cellular with scattered atypical lymphoid cells present within vascular spaces, but no lymphomatous infiltration was identified. Immunohistochemical staining revealed that both the intra- and extravascular lymphoma cells of an involved node were CD20 and MUM-1 positive and CD3, CD30, CD15, CD10, BCL6, and Alk-1 negative (Figure 1c). The MUM-1 positivity and the CD10 and BCL6 negativity indicate that this lymphoma was of postgerminal center origin (activated B-cell type). A Ki-67 proliferation index revealed approximately 50% of the tumor cells to be positive.

DISCUSSION

Although 55 years have passed since IVL was first described, our understanding of this entity is still incomplete. Presenting clinical features are usually nonspecific and quite variable due to the widespread nature of the disease. There is no laboratory, radiologic, or cytogenetic study specific for this diagnosis, and despite being intravascular, peripheral blood involvement is only demonstrated in 5% to 9% of patients (7). All of these factors commonly delay or prevent antemortem diagnosis. The neoplastic cells tend to remain confined to small- and intermediate-sized blood vessels with no particular organ preference. Defects in adhesion molecules CD29 (beta 1 integrin), which is essential for leukocyte extravasation, and CD54 (ICAM-1), which is involved in transvascular lymphocyte migration, have been suggested as an explanation for the intravascular localization (8); however, the mechanism is likely multifactorial and more studies are needed.

The current case of IVL is unusual because this patient had a prominent, diffuse intravascular component of tumor cells associated with a significant extravascular component. The morphologic and immunohistochemical characteristics of both components were identical. We believe this aggressive IVL extravasated into the lymph nodes, liver, bladder, and adrenal parenchyma as a diffuse large B-cell lymphoma. Nodal lymphoma transformation into intravascular lymphoma (4, 5) is less likely due to the overwhelming intravascular component of lymphoma cells. However, it is not possible to prove the actual temporal sequence without previous biopsies exhibiting the pattern of disease progression. Nevertheless, the distinction can be important since most patients diagnosed with IVL are treated with regimens used for advanced diffuse large B-cell lymphoma (7).
IVL continues to present diagnostic challenges due to its elusive and diverse pathologic and clinical findings, and according to Ponzoni and colleagues (9), a comprehensive analysis is needed to find analogies and differences between the intravascular and extravascular components of large B-cell lymphomas to further characterize them and potentially formulate more focused treatment depending on each patient’s unique presentation.

Primary splenic sarcoidosis

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Here we report a case of primary splenic sarcoidosis presenting with isolated splenomegaly with multiple splenic nodules. The sarcoidosis was diagnosed and treated by splenectomy.

Sarcoidosis is a systemic granulomatosis disease of unknown origin, characterized by the presence of non-caseating granulomatous lesions (1). The primary site of involvement is the pulmonary system in more than 90% of cases (2). Extrapulmonary involvement usually occurs in the presence of lung involvement; isolated extrapulmonary manifestations of sarcoidosis are rare, occurring in only 10% of cases (3). Here we report the case of a 50-year-old woman who presented with a significant weight loss and isolated splenomegaly with multiple splenic nodules and was diagnosed and treated by splenectomy.

CASE PRESENTATION

A 50-year-old South Indian housewife presented with a 6-month history of loss of appetite and weight loss, associated with upper abdominal discomfort and early satiety. Her past surgical history included vaginal hysterectomy for uterine fibroids 6 years previously. Examination revealed splenomegaly, palpable 2 cm from the left costal margin. No other masses were palpable.

She had no history of any leprosy contact, and no rashes were found on physical examination. Her respiratory system, cardiovascular system, and neurological systems were normal. Baseline investigations were within normal range, including a complete blood count; serum calcium level; tests for tuberculosis, thyrotoxicosis, and immunodeficiency; renal function, liver function, blood sugar, and electrolyte testing; bone marrow aspiration; and a tumor marker profile with CA125, CA19-9, and carcinoembryonic antigen (CEA). Her erythrocyte sedimentation rate was 32 mm at 1 hour. Preliminary chest imaging showed a normal radiograph. Ultrasonography of the abdomen showed splenomegaly with multiple hypoechoic lesions in the spleen. A computed tomography (CT) scan of the abdomen and pelvis with contrast showed multiple hypodense lesions in the spleen (Figure 1a). The CT scan of the thorax was normal.

A diagnostic splenectomy was performed. The spleen was grossly enlarged, weighing 210 g, with multiple nodules throughout its surface and inside.

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Figure 1. (a) CT scan of the abdomen and pelvis with contrast showing multiple hypodense lesions in the spleen. (b) Gross specimen after splenectomy showing a grossly enlarged spleen with multiple nodules throughout its surface and inside.
throughout its surface (Figure 1b). Histopathological examination showed splenic parenchyma with discrete, round to oval non-caseating granuloma composed of epithelioid histiocytosis and multinucleated giant cells, and (b) an asteroid inclusion body. Reticulin stains showed an extensive reticulin network.

Postoperatively, the patient didn’t receive any form of systemic treatment. She has regained her appetite and weight and remained asymptomatic 3 years after diagnosis.

DISCUSSION

In India, the exact prevalence of sarcoidosis is not known. It has been variously estimated as 61 and 150 cases per 100,000 outpatients in Delhi and Kolkata hospitals, respectively. The frequency of splenic involvement in sarcoidosis has been reported to be 10% to 50%, depending on whether it is detected on physical examination (5% to 14%), a radiological test (33% to 53%), or a tissue biopsy (24% to 59%) (4). Splenic involvement is usually asymptomatic, although left upper quadrant pain is occasionally present. Constitutional symptoms such as night sweats, fever, and malaise may occur. Massive splenomegaly is found in 3% of patients with splenic involvement. Splenic sarcoidosis may cause hypersplenism resulting in anemia, leukopenia, thrombocytopenia, or any combination including pancytopenia. Radiologically, splenic sarcoidosis manifests as multiple nodular lesions throughout the splenic parenchyma (5).

Isolated involvement of the spleen in sarcoidosis is extremely rare. Very few cases have been reported in the literature (6). Most patients with splenic sarcoidosis do not require any treatment. In our case, we performed a splenectomy because we had a strong clinical suspicion of lymphoma. The indications for splenectomy include symptomatic abdominal pain from splenomegaly, hypersplenism, functional asplenia, splenic rupture, or a strong suspicion of an alternative diagnosis.

Figure 2. Histopathology showing (a) splenic parenchyma with a discrete, round to oval noncaseating granuloma composed of epithelioid histiocytosis and multinucleated giant cells, and (b) an asteroid inclusion body.

Posttransplant lymphoproliferative disorder is a well-known complication associated with the transplant recipient. We chronicle a case of PTLD in a failed graft presenting as a small bowel obstruction in a pancreas-only transplant patient. While typical symptoms may be elusive in the complex immunosuppressed patient, graft pain along with persistent graft pancreatitis and a positive Epstein-Barr viremia should raise suspicion for an underlying PTLD.

Solid organ transplant recipients are at an increased risk for developing malignant neoplasms. More specific to the transplant population is the collection of lymphoid malignancies known as posttransplant lymphoproliferative disorder (PTLD). PTLD differs from lymphomas in immunocompetent patients in that it may present outside of nodal tissue and is frequently Epstein-Barr virus (EBV) driven (1, 2). Although PTLD in simultaneous pancreas-kidney (SPK) transplantation has been reported, little information is available on the isolated involvement of the pancreas allograft after pancreas transplantation alone (PTA). We report a case of PTLD presenting as a small bowel obstruction in a patient who underwent PTA.

CASE REPORT

A 37-year-old woman who underwent a laparoscopic Roux-en-Y gastric bypass in January 2007 developed debilitating hypoglycemia requiring in-hospital management. A thorough workup did not reveal an insulinoma but a hyperinsulin-secreting pancreatic head and tail by selective mesenteric angiogram with calcium gluconate injection. Thus, she underwent a subtotal pancreatectomy with splenectomy in September 2009. The hypoglycemia resolved temporarily. She underwent a completion Whipple procedure in December of the same year. Pathology from both specimens revealed islet cell hyperplasia.

As expected, the patient developed insulin-dependent diabetes and was approved for a PTA. She received a pancreas allograft (six-antigen mismatch) from a 24-year-old male donor in August 2011. The graft was implanted in the right retroperitoneal space with systemic venous and enteric exocrine drainage. Donor serologies were positive for cytomegalovirus (CMV) and EBV IgG. The recipient was CMV positive. Immunosuppression consisted of antithymocyte globulin induction, followed by a regimen of tacrolimus, mycophenolate mofetil, and corticosteroids. The patient had an uneventful recovery and was discharged 6 days after transplantation.

Two weeks posttransplant, she was admitted with abdominal pain, nausea, and vomiting. Additionally, she was having sporadic hyperglycemia. Serum pancreatic enzyme levels were normal, and a Doppler ultrasound of the transplanted pancreas noted venous and arterial flow. A percutaneous graft biopsy showed no rejection. Her primary immunosuppressant was changed from tacrolimus to cyclosporine, which resolved the intermittent hypoglycemia. An upper endoscopy revealed a normal gastric pouch and unremarkable Roux-Y reconstruction. Her nausea was felt to be medication related. Her symptoms resolved and she was discharged without pain or gastrointestinal complaint.

Five months later, she presented with fever and anemia. She was diagnosed with CMV viremia (3670 copies), and intravenous ganciclovir therapy was initiated. She was discharged on continued outpatient antiviral therapy and eventually returned to her clinical baseline. Seven weeks later, she was hospitalized with fever, anemia, and pain over the right lower quadrant. A repeat CMV polymerase chain reaction (PCR) test was negative, but an EBV PCR test returned positive (331 copies, IgM negative). No further antiviral treatment was given.

Eight months after transplant, she was readmitted again with right lower quadrant pain. Her serum lipase level was moderately elevated at 542 U/L, and an ultrasound once again noted patent vasculature. A computed tomography (CT) scan noted minimal edema around the graft without evidence of a fluid collection. Another allograft biopsy showed no evidence of rejection, but did note changes consistent with chronic graft pancreatitis. After empiric treatment with antibiotics, her symptoms resolved and her pancreatic enzymes normalized.

Over the next few months, she required multiple admissions for persistent graft pain. Repeat CT scans demonstrated peripancreatic

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inflammation consistent with graft pancreatitis, followed by the development of peripancreatic fluid suggesting an abscess. As a result, she started treatment with intravenous antibiotics. She also developed mild hyperglycemia, at first believed to be secondary to the inflammatory response. However, in the outpatient setting, the hyperglycemia progressed and she was started on sliding-scale insulin therapy, indicating failure of the allograft.

A few days before her 1-year anniversary of transplant, the patient returned to the emergency department with abdominal pain, emesis, and a 7 kg weight loss over the previous 6 weeks. CT findings were consistent with a high-grade small bowel obstruction at the level of the pancreas transplant and a definitive peripancreatic abscess (Figure 1). Findings on surgical exploration were a thrombosed arterial conduit and portal vein (outflow) in addition to necrotic graft duodenum and pancreatic tail forming an abscess. The graft was removed, and immunosuppressive therapy was suspended. On pathology, the explant revealed a nonviable graft with areas containing an atypical lymphoid infiltrate consistent with PTLD, diffuse large B-cell type (CD 20+ and CD79a+). Margins were negative and the EBER (EBV-encoded small RNA) in situ hybridization test was positive, confirming an EBV-driven process (Figure 2). After a prolonged recovery, she was discharged home in improved condition.

On follow-up studies, a bone marrow biopsy was negative and positron emission tomography showed no residual disease. No chemotherapy was recommended as she was considered treated. She remains disease free by imaging study 18 months after graft pancreatectomy.

DISCUSSION

PTLD is a spectrum of neoplastic diseases ranging from a benign polyclonal lymphoid proliferation resembling infectious mononucleosis to a highly aggressive monoclonal process, such as diffuse large B-cell lymphoma. The exact pathophysiology of PTLD is not completely understood, but most cases (80%–90%) are of B-cell origin and are associated with an EBV infection (1). Additionally, at least 90% of PTLD cases in solid organ transplants arise from recipient cells, in contrast to the PTLD seen after bone marrow transplantation (2). The intensity of immunosuppression, including the use of muromonab-CD3...
(OKT3) or antithymocyte globulin induction therapy, plays a paramount role in triggering PTLD (3).

EBV is an endemic, oncogenic virus with potential to cause systemic lymphoproliferation if host immune surveillance fails. Unfortunately, a positive EBV DNA result has no prognostic value. An elevated level may be interpreted as suspicious for PTLD, but no viral load threshold has been clearly identified (1, 4). Nonetheless, viral load monitoring may be used to guide immunosuppression or track the response to treatment.

The incidence of PTLD typically peaks in the first year after transplantation, occurring more frequently in intestinal, multivisceral, and lung transplant recipients (3). Graft, central nervous system, and multiple site involvement are poor prognostic factors. Presenting symptoms of PTLD may be mild, resembling a mononucleosis-like syndrome (malaise, sweats, and fever). Although uncommon, palpable or identifiable lymphadenopathy should prompt a biopsy, as histologic analysis is key to establishing the correct diagnosis. Early stages of PTLD may be effectively treated by immunosuppression reduction or discontinuation. However, other types or advanced stages of PTLD may require chemotherapy, radiation therapy, B-cell–directed antibodies (i.e., rituximab), or surgery.

Data regarding PTLD and pancreas transplantation are sparse. However, a recent analysis by Jackson et al. using the United Network for Organ Sharing database identified several factors associated with the development of PTLD: recipient EBV seronegativity, younger recipient age, white ethnicity, closer HLA matching, and an agent other than tacrolimus as the main immunosuppressive agent, the latter perhaps a contributing factor in our case. The incidence of PTLD over the 10-year review period was 1%, and patients with PTLD had a significantly lower 5-year survival rate than those without (70% vs 88%, P < 0.001). The type of the pancreas transplant (pancreas alone, simultaneous with kidney, or after kidney) had no association with PTLD (5).

In the largest reported single-center experience, Paraskevas et al compared the outcomes of PTLD in their pancreas transplant recipients (N = 1357) against liver and kidney transplant recipients. Compared with the other two groups, pancreas transplant recipients with PTLD had a significantly shorter overall survival (P = 0.001), with a greater mean number of organs involved at the time of presentation (3.7 vs 2.0, P = 0.007) (6).

PTLD in PTA has been described in three single-center experiences with all three types of pancreas transplantation (6–8). In these studies, involving 11 total PTA cases, the reported incidence of PTLD ranged from 1.0% to 8.9%. Due to low overall power, no further generalizations can be made about this subset of pancreas recipients.

PTLD in the pancreatic graft itself is not common; when present, other sites are also usually involved. As demonstrated across other solid organ transplants, disseminated disease carries a poorer prognosis than lymph node disease alone (3). Two case studies reported PTLD limited to the pancreatic allograft after SPK transplant (9, 10). In each case, the recipient had multiple admissions and a presentation that was initially thought to be graft pancreatitis. One presented with signs of intestinal obstruction. Due to continued complications, graft pancreatectomies were performed despite functioning grafts. Both patients survived, highlighting a favorable outcome for single-site PTLD.

Only one center experience clearly described PTLD in the allograft after PTA. Of 13 total cases reported, six cases were in PTA recipients, one of whom had graft and colon involvement. This multisite patient died early from lymphoma progression (7).

Our case report describes a patient who developed CMV viremia 6 months after transplant, followed by a positive, low-viral-load EBV count. Unfortunately, the EBV viremia was not followed, and it may have been used to gauge the possibility of a forthcoming PTLD. A subsequent graft biopsy demonstrated pancreatitis, which may have masked the underlying malignancy. CT scans also revealed graft pancreatitis—as has been described in patients ultimately diagnosed with PTLD (8, 10)—rather than an overt focal mass. Persistent pancreatitis likely resulted in chronic ischemia, abscess formation, and graft failure. In our patient, PTLD was an unexpected finding on explant. As the disease was limited to the graft itself, pancreatitis was curative without the need for further adjuvant therapy.

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Painful periostitis in the setting of chronic voriconazole therapy

Margaret Skaug, MD, Cedric Spak, MD, MPH, and Umesh Oza, MD

A 72-year-old woman on chronic voriconazole therapy for recurrent histoplasmosis developed a painful forearm mass. Laboratory and imaging findings were consistent with a diffuse periostitis. Her symptoms resolved after discontinuation of voriconazole. To our knowledge, this is the first case of voriconazole-induced periostitis to be reported in a patient with chronic histoplasmosis.

Chronic voriconazole therapy can produce a syndrome of painful periostitis, the etiology of which is a subacute fluoride toxicity. Knowledge and recognition of this entity allows for discontinuation of voriconazole, which results in prompt symptom resolution.

CASE DESCRIPTION

A 72-year-old African American woman with past mixed connective tissue disease (MCTD) with scleroderma-type features and recurrent histoplasmosis presented with left forearm pain and mass. She previously had developed extrapulmonary histoplasmosis with colonic perforation while being treated with high-dose oral prednisone for her rheumatologic illness. After successful induction with amphotericin B, she was placed on maintenance voriconazole therapy at 4 mg/kg twice a day for 4 years. She was then lost to follow-up and discontinued voriconazole. Fifteen months later, she presented with a nontender breast mass, and biopsy showed it to be recurrence of histoplasmosis, confirmed by culture and positive antigenemia. Due to mild renal insufficiency, amphotericin was deferred, and she was treated with voriconazole at 4 mg/kg twice daily. In addition, low-dose prednisone was continued for MCTD. The breast mass resolved, and she had been maintained on voriconazole 4 mg/kg twice daily for 3 years. Examination on a routine follow-up disclosed a painful palpable mass on the distal left forearm. The alkaline phosphatase was 585 U/L (normal range 35–104 U/L), having increased from 173 U/L 3 months before and a remote value of 71 U/L.

Radiographs of her forearm demonstrated two irregular calcific deposits between the radius and ulna along the distribution of the interosseous membrane (Figure 1). Nuclear bone scan images showed nonspecific multifocal increased radiotracer uptake involving the scapulae, left forearm, hips, and femoral diaphyses (Figure 2). A background of degenerative uptake was present at the shoulders, spine, knees, and ankles. Single photon emission computed tomography/computed tomography (SPECT/CT) imaging of the chest localized the radiotracer uptake to sites of periosteal calcification, including exostoses, along ribs and the scapulae bilaterally (Figure 3). Both voriconazole and prednisone were discontinued, and her symptoms improved. Her alkaline

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phosphatase level fell to 73 U/L within 3 months of discontinuing voriconazole. Since that time, her MCTD has been quiescent.

DISCUSSION

Voriconazole is a second-generationazole antifungal agent. It is generally well tolerated and has a broadened antifungal spectrum as compared to first-generation azoles (1). Since voriconazole’s approval in 2002, an iatrogenic painful periostitis has been reported in patients on voriconazole long term. Many are lung transplant patients taking voriconazole for treatment of or prophylaxis for aspergillosis (2–5). Cases have also been seen in immunosuppressed patients with other solid organ transplants (6) and in patients with hematologic malignancies (7). A case report of a patient who developed periostitis while on voriconazole for fungal endophthalmitis did not remark on whether the patient was immunocompromised (8). Common to the cases are a history of long-term voriconazole use and prompt resolution of musculoskeletal symptoms within days to weeks of discontinuation of the medication.

In these cases, periostitis was evidenced by musculoskeletal pain, elevated alkaline phosphatase, radiographic abnormalities, and/or multifocal radiotracer uptake on nuclear medicine bone scan. In the case series presented by Wang and colleagues (2) reviewing radiologic findings in five patients, the plain film and CT findings were described as irregular, dense, and undulating or feathery. Bone scans show multifocal intense radiotracer uptake. Distribution of radiographic and bone scan abnormalities were diffuse, involving both the axial and appendicular skeleton with involvement most commonly of the rib, clavicle, and proximal medial humerus; other common sites included the hands, scapulae, proximal femurs, acetabulae, and pubic

Figure 2. Whole-body bone scan images in the anterior and posterior projection show multiple foci of abnormal radiotracer uptake involving the scapulae, left forearm, hips, and femoral diaphyses (arrows). Ultimately, these findings are nonspecific, requiring correlation with radiographs or CT and clinical history. The bone scan provides a skeletal survey of the osseous abnormalities and can serve as a baseline study prior to voriconazole therapy being withheld and subsequent follow-up. A background of degenerative uptake is present at the shoulders, spine, knees, and ankles. Tracer overlying the right elbow is related to injection of tracer in a right antecubital vein.

Figure 3. (a) Transversal SPECT, (b) low-dose CT, and (c) fusion images from SPECT/CT through the chest at the level of the scapulae demonstrate areas of increased tracer activity corresponding to osseous projections, or exostoses, off the scapulae (arrows) in this patient with voriconazole-induced periostitis.
bones. Imaging follow-up has been infrequently reported. In the study by Wang et al, follow-up bone scans were obtained in two patients after discontinuation of voriconazole; one was performed 2 months after and the other, 6 months after. These examinations showed marked improvement of the abnormal multifocal radiotracer uptake (2). Partial resolution of imaging findings on follow-up imaging has been described in two case reports (3, 8).

Although the process remains to be fully characterized, the radiographic appearance and developing laboratory evidence support a subacute fluoride toxicity from chronic therapy with voriconazole, a fluoride-containing compound. Fluoride toxicity has been recognized as a cause of a bone disease called periostitis deformans since the mid 20th century (9). First described in those who drank wine with a fluoride preservative, it has since been described in a number of other scenarios, including fluorinated medications. Serum fluoride is distributed throughout the body, with the greatest amount retained in calcium-rich bone and teeth (10). Fluoride acts on bone by stimulating osteoblasts, with a corresponding increase in serum alkaline phosphatase (11). Fluorosis results in osteosclerosis followed later by osteoporosis, periosteal changes including pathognomonic tumor-like zones of periosteal hyperostosis, and osteophytes at tendon, fascial, and muscle insertions (12).

Voriconazole contains three fluoride molecules, and 5% of voriconazole is metabolized to free fluoride (13), which is primarily excreted by the kidneys (10). A small study comparing post-lung transplant patients on voriconazole for 6 months versus controls not on voriconazole found that all patients on voriconazole had elevated plasma fluoride levels, while none of the patients in the control group did (14). In a small retrospective study comparing voriconazole to other azoles (itraconazole and posaconazole), elevated fluoride levels were present only with voriconazole; additionally, the presence of an elevated fluoride level with voriconazole was independent of treatment duration (15). Although both studies show elevated fluoride levels in patients on voriconazole, it remains to be demonstrated why some patients develop symptomatic periostitis and others do not. The role of renal insufficiency remains unclear, with one study finding it significant (15), while the other found that it was not predictive of fluoride levels (14).

This case report describes the early use of functional electrical stimulation on an individual with an incomplete spinal cord injury to assist with motor recovery and a return to ambulation. A 32-year-old woman sustained a C7 burst fracture after a fall, requiring anterior cervical fixation from C6 to T1 prior to transfer to acute rehabilitation. She presented as a C8 AIS B spinal cord injury, meaning she had some sensory function spared below the level of injury but not motor function. At discharge from acute inpatient rehabilitation, she was able to ambulate household distances with supervision using a rolling walker and required a manual wheelchair for community mobility. Four months after discharge, she was ambulating in the community using a standard cane.

Functional electrical stimulation (FES) cycle ergometry uses electrical current to stimulate peripheral motor units during a functional task such as cycling. Although FES cannot reverse denervation, it can assist with the conversion of type II fast-twitch muscle fibers back to type I slow-twitch muscle fibers (1). FES reverses the order in which muscle fibers are recruited from that of a volitional muscle contraction. Fast-twitch, fatigable muscle fibers are recruited first, followed by fast-twitch, fatigue-resistant units and then slow-twitch, fatigue-resistant units (2). This is clinically significant because after spinal cord injury (SCI), individuals are less active due to decreased motor and sensory function below the level of injury, resulting in the loss of type I fibers. Repeated use of FES can lead to sensorimotor improvements as well as cortical reorganization, changes that cannot be accomplished with passive range of motion alone (1) due to lack of sensory or motor input or activation of motor units, which is essential for motor relearning and neuromuscular reeducation. When movement is generated in paralyzed musculature, cortical reorganization begins to take place and may lead to long-term effects, such as ultimately assisting with return to ambulation. This case study describes the use and response of FES in an individual with incomplete SCI.

CASE DESCRIPTION

A 32-year-old woman fell from a second-story balcony and sustained a C7 burst fracture with retropulsion requiring anterior cervical fixation from C6 to T1 and sutures to the left knee. Her goal at initial evaluation was to ambulate, but the goal evolved to improving all areas of function that were spared. Before the accident, the patient was healthy and physically active, and she was highly motivated to focus on her rehabilitation. She was also able to continue working during rehabilitation.

The patient was a good candidate for FES since she had sensory function below the level of her injury and positive rectal tone. Based on assessment with the American Spinal Injury Association Impairment Scale (AIS) (3) during her initial examination, the last fully innervated spinal level for both sensory and motor function was C8 AIS B, indicating absent motor function but intact sensation below the level of injury; however, this result was questionable initially due to inconsistent responses during the exam. Passive range of motion of upper and lower extremities was determined to be within functional limits, and ankle clonus was noted bilaterally. Intermittent physical assistance was required for her to maintain static sitting balance at the edge of the bed, and minimal assistance was required during dynamic sitting balance activities such as reaching within 2 inches of her base of support.

The patient participated in a comprehensive SCI inpatient rehabilitation program for 8 weeks. After she provided informed consent, FES was added to the interventions. Initially, FES resulted in sensory stimulation but did not produce any visible muscle tetany. The setup included two sets of two electrodes placed over the quadriceps, hamstrings, tibialis anterior, and gastrocnemius muscles bilaterally in a cephalad and caudal pattern, for a total of 16 electrodes. The goal was to have 20 minutes of stimulation and a 5-minute warm-up/cool-down period with no stimulation during each FES session. As shown in Figure 1, stimulation time was less than 20 minutes due to unexpected factors, such as late arrival to the therapy session, wound care issues, and fatigue, and the warm-up/cool-down period was often skipped. At times, the patient could not tolerate FES stimulation on her left leg due to her knee wound. The intensity of the current was adjusted and sometimes stopped to allow continued comfort.

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Initially, the patient could feel the electrical current, but muscle tetany was not achieved. With continued use of FES 3 to 5 days a week, she began to demonstrate muscle tetany and observable motor changes, beginning with trace movement in the adductor muscles, followed by the right quadriceps muscle without FES use and progressing to movement against gravity and finally support of her own body weight with use of an assistive device. Body weight–supported treadmill training was initiated and utilized in addition to FES to assist with neuromuscular reeducation. Once the patient was able to ambulate over ground, we began to utilize bilateral double-adjustable ankle-foot orthoses to control anterior tibial translation over the talus for increased knee control and stability, prevention of knee hyperextension in the stance phase of gait, and assistance with toe clearance during the swing phase of gait due to weakness in the anterior tibialis muscle. A platform rolling walker was initially used to assist with proximal hip weakness. The patient progressed to the use of a rolling walker after she demonstrated improved strength and control in her gluteal muscles.

The patient had increased difficulty maintaining a neutral pelvis, evidenced by a significant anterior pelvic tilt with increased lumbar lordosis and knee hyperextension. Therefore, FES was utilized for core strengthening. The setup included stimulation to the transversus abdominis and oblique muscles to assist with stabilization and to reduce anterior pelvic tilt along with manual facilitation. Good results were observed while the patient performed standing balance exercises or core strengthening exercises in both seated and supine positions. The wound over her left knee prevented weight-bearing activities in quadruped and tall kneeling, which are typically used to facilitate core and gluteal strengthening.

Progress continued on a weekly basis during her 8-week inpatient rehabilitation stay. Initially, she had no active movement in bilateral lower extremities, but with continued FES treatment she began to demonstrate motor return in bilateral lower extremities and was able to return to ambulation after 11 FES treatments, with decreased amounts of electrical stimulation required to achieve muscle tetany and produce an active muscle contraction (Figure 2) for all muscles with the exception of the left anterior tibialis muscle. At discharge, she ambulated in her home with supervision using a rolling walker and used a manual wheelchair for community mobility.

**DISCUSSION**

The many proposed benefits of FES during acute rehabilitation include prevention of disuse muscle atrophy, maintenance of bone mineral density, neuromuscular reeducation, improvement of functional mobility, and strengthening (4–8). Long-term effects of FES are still undetermined, and more research is needed in this area.

At present, minimal research describes the use of early FES during acute inpatient rehabilitation to assist with return to ambulation for individuals with incomplete SCI. Results from this case report indicate that early FES cycling following SCI may facilitate conversion from sensory incomplete to motor incomplete, thus increasing the probability of returning to ambulation. However, for patients to benefit from FES, they must be able to feel the electrical stimulation, and/or muscle tetany should be achieved. If neither of these factors is produced, then the likelihood of the individual’s developing any motor changes is significantly decreased. With continued FES use, this patient was able to develop volitional muscle contractions and move against gravity in bilateral quadriceps muscles and hamstrings. She also progressed to supporting her own body weight and ultimately returned to ambulation at home. Four months after discharge, she was ambulating in the community using a standard cane. The success of the FES intervention presented in this case study indicates that further research is needed to develop standardized treatment protocols and recommended practices for acute motor relearning in the incomplete SCI patient population.
Limitations of this case study include the inability to examine how manual muscle testing scores changed from week to week with continued use of FES and the absence of standardized outcome measures such as Timed Up and Go, five-time sit-stand test, Berg Balance Scale assessment, and 6-minute walk test. It would have been beneficial to look at the results of outcome measures, manual muscle testing scores, and modified Ashworth scores in addition to functional independence measure scores to see how continued use of FES affected this patient’s functional mobility and to gain a better understanding of how she responded to stimulation.

Acknowledgments

The author wishes to thank Kelli R. Trungale, MLS, ELS, for editorial assistance as well as Stephen Thomason, DO, Lauren Rachal, PT, DPT, NCS, and Simon Driver, PhD.


Binasal hemianopia is a rarely encountered visual field defect. We examined two asymptomatic female patients, aged 17 and 83, with complete binasal hemianopia. Both patients had unremarkable eye exams except for the visual field deficits and minimally reduced visual acuity and color vision. Both patients had normal neuroimaging. These are the first reported cases of complete binasal visual field defects without an identifiable ocular or neurologic cause.

Neuro-ophthalmologists rarely encounter patients with binasal (heteronymous) hemianopia. Several reports of incomplete binasal visual field defects have appeared (1–5). We found no reports, however, of complete binasal hemianopia. Here we present two cases of asymptomatic complete binasal hemianopia associated with minimally reduced visual acuity and color vision, but with otherwise unremarkable eye exams and neuroimaging.

**CASE 1**

A 17-year-old white female presented to the neuro-ophthalmology clinic for abnormal visual fields first detected by an outside optometrist at a regular vision check. She had no specific visual complaints and had noticed no recent changes in her vision. The provider performed a screening visual field exam, which demonstrated dense binasal hemianopia respecting the vertical meridian. She was referred to an ophthalmologist who repeated the visual field exam on multiple occasions. By the time she arrived for consultation in the neuro-ophthalmology clinic, she had undergone visual field testing 17 times. Every visual field test revealed the same pattern. Throughout this entire course she denied any visual problems. Her past medical and family history were only significant for obesity. Her best corrected visual acuity was 20/20 in the right eye and 20/25 in the left eye with a mild myopic astigmatism. Intraocular pressure was normal at 19 mm Hg OU. Hardy-Rand-Rittler color plate testing was subnormal, with 7 of 10 correct in the right eye and 7.5 of 10 correct in the left eye. Her pupils were normal without a relative afferent pupillary defect. Confrontation testing revealed a complete binasal hemianopia respecting the vertical midline. Repeat Humphrey 24-2 perimetry (Humphrey Field Analyzer, Carl Zeiss Meditec, Dublin, CA) again revealed a dense, complete binasal hemianopia that perfectly respected the vertical meridian (Figure 1a, 1b). Her anterior segment and funduscopic exams were completely normal except for a mild blurring of the superior margin of the left optic nerve without any other signs of active swelling. Spontaneous venous pulsations were readily visible. Red free photography revealed an intact nerve fiber layer verified by optical coherence tomography of the optic nerve head and retinal nerve fiber layer (OCT, Figure 1).
ONH, and RNFL Analysis, Carl Zeiss Meditec, Dublin, CA). Subsequent magnetic resonance (MR) imaging of the brain, with and without contrast, performed with attention directed toward the chiasm was normal.

**CASE 2**

An 83-year-old white woman presented to the neuro-ophthalmology clinic after an outside ophthalmologist noted binasal visual field defects on confrontation testing. Humphrey 30-2 visual field testing documented a complete binasal hemianopia. The patient had a history of hypertension, but was otherwise healthy with a noncontributory family history. She had no visual complaints and specifically denied difficulty with her peripheral vision. Examination by the neuro-ophthalmologist revealed a best corrected visual acuity of 20/25 in each eye. Her pupillary exam was normal. Her intraocular pressures measured 18 and 15 mm Hg. Color vision testing was markedly abnormal. Her anterior segment exam was normal except for mild cataracts. Fundus examination revealed no optic atrophy or other optic disc abnormalities and was otherwise unremarkable except for scattered peripheral drusen in both eyes. Repeat Humphrey 24-2 perimetry confirmed the same binasal defect (Figure 1c, 1d). Optical coherence tomography of the optic nerve head was entirely normal for her age.

**DISCUSSION**

In 1912 Harvey Cushing and C. B. Walker (1) reported “binasal hemianopia” in a patient with a brain tumor. Ashwin and Quinlan (2) reported a single case due to keraotconus. Other reports of ocular or intracranial etiologies for binasal field defects include bilateral internal carotid artery aneurysms, hydrocephalus, intracranial mass lesions, and elevated intracranial pressure (2, 3). Pringle and colleagues (4) reported binasal hemianopia in a patient with neurosyphilis (tabes dorsalis). Salinas-Garcia and Smith reported 8 patients with incomplete binasal hemianopia in 1978. All eight patients had incomplete binasal visual field defects measured with Goldmann perimetry. All of their patients had identifiable causes, with most due to ocular or optic nerve etiologies including ischemic optic neuropathy, optic nerve head drusen, glaucoma, bilateral optic nerve pits, and retinitis pigmentosa sine pigmento (5).

Herein we present two patients, one in youth and one in older age, with complete binasal hemianopia without an identifiable ocular or intracranial etiology. Our patients were both visually asymptomatic. They were completely unaware of their visual field defects until the deficits were identified during routine eye exams. To our knowledge, these are the first reported cases of complete binasal hemianopia. Our examinations differ from prior reports in that automated perimetry was used rather than manual perimetry, as in prior series. We also recognize that our characterization of these visual field defects as “complete” is somewhat artificial. The defects appear to be complete on automated perimetry and with confrontation testing. Although both patients could have had some vision in their nasal hemifields, these testing methods identified no visual responses in those areas, whereas the temporal fields were completely intact.

We considered the possibility of a functional (nonorganic) etiology for the field defects in our patients. However, neither patient complained of visual problems. These deficits were identified on routine eye exams. Neither patient appeared to have any secondary gain from the visual field defects. The younger patient (case 1) was actually quite annoyed that she had to endure so many eye exams and visual field tests. All she wanted was a new pair of glasses. She was greatly relieved when we recommended no further testing.

We do not believe these patients had retinal pathology that could explain their field defects. Other than scattered drusen in the peripheral retina of one patient, our cases had completely normal funduscopic examinations. We cannot conceive of a retinal problem that would cause such a profound bilateral nasal field defect with perfect respect of the vertical meridian and a completely normal funduscopic exam. Likewise, an optic neuropathy of any form is an unlikely explanation given the absence of visible optic atrophy and the intact nerve fiber layer in these patients. Both patients had subnormal visual acuity, although the older patient (case 2) had cataracts that easily explained her minimally reduced acuity. However, both patients also had subnormal color vision. This may have been an artifact of testing. Patients with homonymous hemianopia will often have subnormal color vision with standard testing methodologies. Our patients may have performed poorly simply as a result of the visual field deficit, not because of any true color vision abnormality. Neither patient had definitive evidence of optic neuropathy.

We propose a congenital etiology for these binasal visual field defects. Although we cannot prove that the field defects in our patients had been present from birth, the complete absence of symptoms strongly suggests a very longstanding problem. Patients with congenital homonymous hemianopia are often asymptomatic (6). Likewise, patients with other congenital field defects, such as the monococular altitudinal defects seen in patients with “toples disc syndrome,” are typically asymptomatic (7). Neuroimaging studies on our two patients revealed no identifiable abnormalities of the optic nerves, chiasm, postchiasmal visual pathways, or occipital cortex. The binasal field defects could be due to a defect in the normal sorting and segregation of retinal ganglion axon populations that decussate and those that remain ipsilateral upon entering the optic chiasm from the optic nerves. Such sorting defects have been described in albinism, in which ipsilaterally destined temporal retinal fibers erroneously decussate and project contralaterally at the optic chiasm. But, this does not result in binasal hemianopia in human albinos. In achiasmatic syndrome, nasal retinal fibers fail to decussate adequately at the chiasm, projecting instead ipsilaterally towards the lateral geniculate nuclei together with temporal retinal fibers (8). Pomeranz and Lessell described a family in which there was a hereditary, probably autosomal recessive, chiasmal optic neuropathy in which all of the siblings had bitemporal visual field defects (9). Our patients may represent examples of a congenital temporal retinal axon missorting syndrome. However,
the absence of optic atrophy suggests that the pathology likely resides along the postgeniculate visual pathways. The congenital defect seems to have resulted in a lack of cortical representation of the retinal ganglion cells from the temporal half of each retina. Whatever the neuroanatomic correlate may be, it results in isolated binasal visual field defects without identifiable structural abnormality of the optic chiasm, optic nerve, or postchiasmal visual pathways.

Liposarcomas are the most common soft tissue sarcomas in adulthood, comprising approximately 20% of all sarcomas; most present in the extremities and retroperitoneum (1). Despite the large amount of adipose tissue in the orbit, orbital liposarcomas are rare. Diagnosis can be challenging due to the rarity of the entity and the pathological similarity to benign adipose tumors (2, 3). Fortunately, the advent of immunohistochemical staining has aided in diagnosis. Management of orbital liposarcoma also can be challenging, as illustrated by the case described herein (4).

CASE REPORT

A 67-year-old man reported proptosis, pain, diplopia, and tearing in his right eye for 1 year. Brain imaging with computed tomography (CT) and magnetic resonance imaging (MRI) revealed a well-defined, somewhat oval-shaped mass in the intraconal space of the right orbit measuring 2.7 cm in anterior-posterior, 2.7 cm in transverse, and 2.1 cm in craniocaudal dimension (Figure 1). The patient had 20/20 visual acuity bilaterally, with motility limited in abduction and infraction and 4 mm of proptosis. Anterior segment examination disclosed superficial punctate keratopathy and 2+ conjunctival injection; fundus examination demonstrated a sharp disk with normal vasculature and normal macula.

The mass was removed using Stryker navigation. A Krönlein lateral orbitotomy with bone flap was performed with subsequent reconstruction of the lateral orbital wall with osteoplasty. The tumor appeared to be encapsulated but adherent to the inferior rectus muscle at surgery. The tumor and pseudocapsule were removed entirely, but because of the adherence to the inferior rectus muscle, it was not believed that complete excision was possible. The specimen was excised in two parts: one measured 2.9 × 2.4 × 2.3 cm and one 1.1 × 0.6 × 0.3 cm. Histologically, the cells were loosely arranged without a prominent plexiform vascular pattern. The nuclei were mostly bland. The tumor infiltrated the extraocular muscle fibers. Staining and immunohistochemistry revealed a Ki-67 index of <3%. The specimen was desmin positive, smooth muscle actin negative, MDM2 positive (Figure 2), and S-100 positive. Interphase fluorescence in situ hybridization was performed with probes for MDM2 and intrachromosomal comparison for the chromosome 12 centromere regions. Gains of MDM2, compared to the centromere region, were seen in 58% of cells; 16% of cells contained a high-level increase in MDM2. One year after excision no residual orbital mass was evident.

DISCUSSION

Orbital liposarcomas are typically classified along cytogenetic, morphologic, and clinical lines as either well differentiated (including adipocytic, sclerosing, inflammatory, spindle cell, and dedifferentiated subtypes [5]), myxoid/round cell, and pleomorphic types (6). The well-differentiated category is also referred to as the atypical lipomatous tumor/well-differentiated liposarcoma/dedifferentiated liposarcoma.
category (ALT-WDLPS/DDLPS). In the orbit, the myxoid type is most common, representing 60% of cases; well-differentiated types account for 30%, and pleomorphic lesions make up the remaining 10% (7).

The classification scheme reflects distinct chromosomal aberrations in each category. Well-differentiated (ALT-WDLPS) lesions have ring or giant marker chromosomes composed of material from chromosome 12q13-15 with amplification of MDM2 and often CDK4 (3). Myxoid/round cell liposarcomas contain a reciprocal translocation involving chromosomes 12 and 16 resulting in production of the TLS/FUS-CHOP fusion transcript. The pleomorphic type has a complex karyotype, as one might expect, with numerous genetic imbalances described; however, 12q13-15 amplification is rarely present (3). The lesion in question had high levels of expression of MDM2, placing it in the well-differentiated category of orbital liposarcomas.

Once the diagnosis has been made, local control and full excision represent the best approach to enable a cure. Unfortunately, this tumor often invades surrounding structures, as it did in our case. The mass invaded the extraocular muscles, and complete excision would have led to irreparable deficits.

Neoadjuvant and adjuvant radiation therapy has led to decreased recurrence rates in liposarcomas in general; however, data for its use in orbital liposarcoma are scarce (8, 9).

Sickle cell intrahepatic cholestasis (SCIC) is a rare but fatal complication of sickle cell disease. It is found mainly in homozygous sickle cell disease. To date, there are no standard diagnostic criteria or well-established therapeutic approaches to this condition. Herein, we report this case of a 48-year-old man with sickle cell anemia and a total bilirubin of 78.5 mg/dL without evidence of extrahepatic biliary obstruction or viral hepatitis. The patient had a hemoglobin S level of 87.9%, acute renal failure, and mild coagulopathy. Despite the disease severity, he refused exchange transfusion (ET) with packed red blood cells. He was transfused with 2 units of blood and treated mainly with supportive measures. His total bilirubin levels trended down to normal days after discharge. Multiple studies have shown a significant decrease in the mortality rate in SCIC after ET. To date, only two reported adult cases have survived SCIC without aggressive treatment. Our case is the third case that demonstrates recovery of severe SCIC without ET.

CASE REPORT

A 48-year-old man with sickle cell anemia presented with jaundice and mild abdominal pain that had lasted for 1 week. He denied fever, shortness of breath, chest pain, and any change in urine or stool color. His physical exam was unremarkable except for icteric sclerae. Blood analysis was significant for a total bilirubin level of 48.9 mg/dL. His hemoglobin at baseline was 7 g/dL, and hepatitis serology was nonreactive. An ultrasound revealed cholelithiasis without evidence of cholecystitis and choledocholithiasis. Because the patient had taken doxycycline as malaria prophylaxis for a trip to China 2 months earlier, he was initially diagnosed with doxycycline-induced hyperbilirubinemia. His bilirubin level prior to hospital discharge was 50 mg/dL; follow-up in the clinic showed a stable bilirubin level of 50.3 mg/dL.

He was seen 1 week later with increased abdominal pain, fatigue, and fever. Physical examination now revealed mild epigastric and right upper quadrant tenderness and a palpable liver. Blood analysis was significant for a total bilirubin level of 77.5 mg/dL; aspartate aminotransferase, 91 IU/dL; alanine aminotransferase, 31 IU/dL; creatinine, 1.4 mg/dL (an increase from a baseline of 0.8 mg/dL); hemoglobin, 6.5 g/dL; white blood cell count, 13.6 K/µL, with predominant neutrophils; platelets, 400 K/µL; a normal albumin and coagulation panel; alkaline phosphatase, 179 IU/L; and lactate dehydrogenase, 702 U/L. Hemoglobin electrophoresis showed a hemoglobin S of 88.6%. A computed tomography scan of the abdomen confirmed the findings from the previous ultrasound. Magnetic resonance cholangiopancreatography ruled out an obstruction. The patient was diagnosed with intrahepatic cholestasis.

The patient refused ET and liver biopsy but accepted intermittent transfusions. He received 2 units of packed red blood cells. His bilirubin level then rose to a maximum level of 78.9 on day 6 of readmission, and his serum creatinine increased to 3.3 mg/dL. The next day, the patient developed a myoclonic jerk with normal mental status, which was relieved with clonazepam. His ammonia level and results of magnetic resonance imaging of his brain were normal. Electroencephalography completed while the patient was sleeping showed a slow wave form pattern. His kidney function improved with fluids and returned to normal.
baseline. Broad-spectrum intravenous antibiotics were initiated early in the hospital stay and were subsequently deescalated to oral moxifloxacin. Cultures came back as negative, as did HIV, syphilis, and leptospirosis serology results, but IgG results for Q fever were positive in both phase I and II. Bilirubin trends down to a range of 50 to 60 mg/dL before discharge from the current hospital admission (Table 1). Outpatient follow-up showed a normal bilirubin level in a 2-month period (Figure 1). After being discharged from the hospital, the patient remained asymptomatic and now continues with his regular clinic visits.

DISSCUSION

Sheehy first categorized sickle cell hepatopathy in 1977 into five clinical syndromes: viral hepatitis, hepatitis crisis, cirrhosis, cholelithiasis with cholecystitis, and intrahepatic cholestasis (SCIC). The clinical manifestations of each entity are similar, including fever, right upper quadrant pain, and jaundice. There was no suggested guideline for diagnosis and treatment of SCIC. When a patient presents with extreme hyperbilirubinemia (defined as >13 mg/dL) (3), a careful physical examination and appropriate laboratory and radiologic studies should be conducted (7, 9). Liver biopsy was not strongly indicated to establish the diagnosis, since histological findings do not differ from findings of other sickle cell disease liver involvement (3). In our patient, viral hepatitis and cholelithiasis with cholecystitis were ruled out by negative serology and lack of evidence to suggest extrahepatic obstruction in imaging studies. Hepatic crisis is another common complication of sickle cell disease, characterized by short disease duration (2–3 weeks) with a serum bilirubin level that seldom exceeds 15 mg/dL (1). The development of myoclonic jerks was related to an abnormally high bilirubin level. Normal ammonia levels and lack of altered mentation in this clinical setting made hepatic encephalopathy unlikely. Q fever may have also contributed to hyperbilirubinemia through two mechanisms. First, infection can trigger the development of SCIC (1). Second, the disease itself can cause an increase in bilirubin levels. However, studies have shown that only one-third of Q fever patients develop hyperbilirubinemia, and the highest serum bilirubin level reported was 18.7 mg/dL (10). Therefore, Q fever itself was not the major cause of extreme hyperbilirubinemia in this case.

SCIC has an overall mortality rate of over 50% (3, 11). The only known effective management is ET to lower hemoglobin S levels to <30% (8). Ahn et al (3) conducted a literature review that compared two groups of 44 patients from 1953 to 2002 according to the degree of hepatic dysfunction. There were 16 adult cases in the study (those >18 years), 15 of whom were in the severe group, with a mean maximum bilirubin level of 76.8 mg/dL (opposed to 36.2 mg/dL in the mild
group). The mortality rate in the two groups was 4% and 64%, respectively. One death was reported among five patients who received ET, while 9 deaths were reported among 10 patients who underwent supportive treatment. This finding supports the evidence that ET can significantly reduce the mortality rate of SCIC.

Recent case reports have confirmed the successful outcome with ET. Eight adult cases (5, 11–16) have been reported since Ahn et al published their review in 2002 (Table 2). Seven out of the eight patients received ET, and two of them progressed to hepatic failure and death (5, 13). Two of the patients continued to receive regular ET to maintain their hemoglobin S level (14, 16). Overall, there are 24 case reports in the adult population. The mortality rate among those who received ET was 25% (3 deaths among 12 patients), compared with 83% in the supportive group (10 deaths among 12 patients). Only two reported cases (17, 18) survived SCIC without ET. One case presented as mild, self-limited hyperbilirubinemia (17). The other presented with severe anemia, with a hemoglobin of 2.8 g/dL and hepatic and renal failure (18). The patient was treated with packed red blood cells and plasma transfusions to correct anemia and coagulopathy. He then had reversal of organ failure within 48 hours of admission. Our case represents a third known case report of SCIC in an adult who had a favorable outcome with supportive treatment.


Table 2. Patients over 18 years of age with sickle cell intrahepatic cholestasis, 2003 to 2014

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>First author</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Type of sickle cell</th>
<th>Clinical feature</th>
<th>Max. total bilirubin (mg/dL)</th>
<th>Hemoglobin S (%)</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Tiftik</td>
<td>21</td>
<td>F</td>
<td>HbSS</td>
<td>A, H, J</td>
<td>48</td>
<td>79</td>
<td>Long-term ET</td>
<td>Survived</td>
</tr>
<tr>
<td>2004</td>
<td>Tiftik</td>
<td>40</td>
<td>M</td>
<td>HbS–beta</td>
<td>C, F, H, J, U</td>
<td>54.6</td>
<td>–</td>
<td>ET</td>
<td>Survived</td>
</tr>
<tr>
<td>2005</td>
<td>Baichi</td>
<td>27</td>
<td>F</td>
<td>HbSS</td>
<td>AHF</td>
<td>80</td>
<td>–</td>
<td>ET, transplant</td>
<td>Died</td>
</tr>
<tr>
<td>2005</td>
<td>Baichi</td>
<td>26</td>
<td>F</td>
<td>HbSS</td>
<td>AHF</td>
<td>58.5</td>
<td>15.1</td>
<td>ST, transplant</td>
<td>Died</td>
</tr>
<tr>
<td>2006</td>
<td>Costa</td>
<td>48</td>
<td>M</td>
<td>HbS–beta</td>
<td>A, C, H, J, ARF</td>
<td>59.7</td>
<td>58</td>
<td>ET</td>
<td>Died</td>
</tr>
<tr>
<td>2010</td>
<td>Brunetta</td>
<td>41</td>
<td>M</td>
<td>HbSS</td>
<td>A, H, J</td>
<td>58.9</td>
<td>88.4</td>
<td>ET</td>
<td>Survived</td>
</tr>
<tr>
<td>2014</td>
<td>Vlachaki</td>
<td>37</td>
<td>M</td>
<td>HbS–beta</td>
<td>H, J</td>
<td>46.8</td>
<td>74.5</td>
<td>Long-term ET</td>
<td>Survived</td>
</tr>
</tbody>
</table>

A, abdominal pain; AHF, acute hepatic failure; ARF, acute renal failure; C, coagulopathy; ET, exchange transfusion; F, female; F, fever; H, hematomegaly; HbSS, hemoglobin SS disease; HbS–beta, hemoglobin S–beta thalassemia; J, jaundice; M, male; ST, simple transfusion; U, dark urine.
Mach band sign: an optical illusion

Ragesh Panikkath, MD, DM, and Deepa Panikkath, MD

The chest radiograph of a 63-year-old woman who was found unresponsive was concerning for pneumopericardium, but lacked the other corroborative features suggestive of pneumopericardium. None of the follow-up chest radiographs showed evidence of air around the heart. The radiolucent shadow that mimicked pneumopericardium in this case was due to an artifact known as Mach band sign, an illusion created by lateral inhibition in the light receptors in the retina.

Physicians rely on radiographs and computed tomography for diagnosis. However, they must realize that radiographs provide shadows of objects, and several artifacts arising from our visual perception can mimic pathologic lesions. This case report illustrates the importance of recognizing one of the most common and important illusions, the Mach band effect.

CASE DESCRIPTION

A 63-year-old woman was found unresponsive by her husband. She was intubated on the scene by paramedics and transferred to the intensive care unit. The chest radiograph showed opacities in the mid and lower zones of the right lung (Figure). A linear hypodensity at the lateral margin of the right atrium was suspicious for pneumopericardium. No radiolucent line was visible on the left side of the heart or around the great vessels. The patient was treated with broad-spectrum antibiotics for possible aspiration pneumonia. She later improved and was extubated. No chest radiographs during her subsequent hospital course showed pneumopericardium. The radiolucent shadow seen lateral to the right atrium was due to the Mach band sign.

DISCUSSION

While interpreting chest radiographs, we believe that we are seeing true shadows of structures in the chest. However, several artifacts can arise due to our visual perception, which can lead to errors in diagnosis. One of them is the Mach band effect. This optical illusion is named after Ernst Mach, a physicist who described the sign in 1865. It occurs due to spatial high-boost filtering by the human visual system on the image captured by the light receptors in the retina, where a phenomenon called lateral inhibition occurs (1). This is an edge enhancement method to facilitate the detection of edges of an object. It is more prominent with objects that have a curved border than in those with an angled border. The eye enhances the edges of the object by making the edge of a dark object lighter and the edge of a lighter object darker. This phenomenon can cause a physician to see a dark shadow when in fact there is none. This effect created the translucency at the cardiac borders mimicking a pneumopericardium in our case (2). Mach band sign can also simulate pneumothorax or fractures. Alternatively, the knowledge of this phenomenon might lead a radiologist to misinterpret a true shadow as a Mach band effect and ignore it.

In patients with pneumomediastinum, usually several other findings substantiate the presence of air in the mediastinum. The “continuous diaphragm sign” is due to air tracking on the inferior surface of the heart, giving the appearance of the diaphragm as a continuous line below the heart. Radioluencies may be seen surrounding great vessels due to the air tracking alongside them. Moreover, a bright white line (of parietal pericardium) bordering the free margin of the radiolucent shadow of air is also seen in true cases of pneumopericardium. These findings were not present in our patient. Apart from the phenomenon of optical illusion, the presence of radiolucent lung between the cardiac border and the descending branch of the right pulmonary artery is also believed to be responsible for this appearance.

A similar illusion, again caused by lateral inhibition in the retina, is the background contrast effect (3). The radiographic density of an image gets altered in comparison with its surrounding structures. This is similar to the Mach band effect, but it covers a larger area than the Mach effect, which creates only a narrow bandlike effect. Cornsweet illusion is a similar optical illusion, where an object of uniform intensity might
appear to have different intensities if separated by a line. This effect is similar to the background contrast effect, in that large areas can be affected, but unlike the Mach effect, here the region adjacent to lighter structures will appear lighter and the region near darker areas will appear darker.

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**U.S. News & World Report ranks two Baylor Scott & White Health hospitals in Texas’ top 10**

Seven Baylor Scott & White Health (BSWH) hospitals have been ranked some of the best in Texas for 2014–2015 by *U.S. News & World Report* in its annual Best Hospitals rankings. Two BSWH hospitals have ranked in the top 10 in the state of Texas. Baylor University Medical Center at Dallas is ranked No. 1 in the Dallas metro area and No. 2 in Texas. Scott & White Memorial Hospital is ranked No. 10 in Texas, moving up eight spots from the previous year.

“We are so proud to see the two flagship hospitals of the new Baylor Scott & White Health both rank in the top 10 in the state,” said Joel Allison, CEO, BSWH. “When we merged Baylor Health Care System and Scott & White Healthcare in 2013, we knew we were combining two exemplary systems known for high-quality care. These 2014–2015 U.S. News rankings are proof, as our new system now includes a total seven ranked hospitals throughout North and Central Texas.”

Baylor University Medical Center at Dallas, which has been included in the *U.S. News & World Report* rankings for more than 20 years, was ranked nationally in 2014 for six medical specialties: gastroenterology and GI surgery (no. 15 in the nation), diabetes and endocrinology (no. 30 in the nation), pulmonology (no. 35 in the nation), nephrology (no. 38 in the nation), neurology and neurosurgery (no. 40 in the nation), and orthopedics (no. 41 in the nation). The hospital is also high performing in cancer, cardiology and heart surgery, geriatrics, gynecology, urology, and ear, nose, and throat.

For 2014–2015, *U.S. News* evaluated hospitals in 16 adult specialties and ranked the top 50 in most of the specialties. Just 3% of the nearly 5000 hospitals that were analyzed for Best Hospitals 2014–2015 earned national ranking in even one specialty.

In its metro-area rankings, *U.S. News and World Report* gives consumers information about high-performing hospitals in their backyard. This year, *U.S. News and World Report* ranked six BSWH hospitals in the Dallas metro area:

- Baylor University Medical Center at Dallas: no. 1
- Baylor Regional Medical Center at Plano: no. 6
- Baylor Medical Center at Irving: no. 7
- Baylor All Saints Medical Center at Fort Worth: no. 8
- Baylor Regional Medical Center at Grapevine: no. 8
- Baylor Institute for Rehabilitation: no. 12

**Baylor Scott and White Health, eight other systems form Texas Care Alliance**

BSWH, the largest nonprofit health system in Texas, is one of nine Texas health systems joining forces to share clinical and administrative data to improve quality and efficiency, lower health care costs, and accelerate medical innovation in patient care. The Texas Care Alliance (TCA) was founded by BSWH and Trinity Mother Frances Hospitals and Clinics of Tyler in March 2013 to facilitate the coordination and delivery of health care services that are people centered and physician driven to improve the overall health of a defined population. TCA also includes Community Hospital Corporation, Plano; Good Shepherd Health System, Longview; Hendrick Health System, Abilene; Medical Center Health System, Odessa; Midland Memorial Hospital, Midland; Shannon Health System, San Angelo; and United Regional Health Care System, Wichita Falls. The systems’ service areas cover 193 Texas counties. TCA members have 20% of the state’s hospital beds with more than 6800 employed or affiliated physicians.

“Now more than ever, it is critical for community-based health care providers to collaborate and accelerate change,” said Joel Allison, BSWH CEO and TCA chairman of the board. “The TCA exists to support providers who are stepping up to the challenges of health care now and in the future. We are going to demonstrate innovative, value-based methods for reducing costs and improving quality in a post–health care reform world.”

To qualify for payment based on quality of care—which will account for two-thirds of health care revenue in 5 years—providers are employing powerful analytical tools for population health and risk management. TCA will be using Explorys, a data platform that is a spinoff of the Cleveland Clinic. The Explorys network includes more than 310 hospitals and 220,000 practitioners. Explorys will facilitate data sharing between practitioners, payers, and health systems. The data will allow health care providers to build a composite view of a population’s health to meet care needs, improve quality, and assess risk of disease. TCA will be able to harness the data from tens of millions of patient encounters from these health systems and compare them to the TCA experience as a whole as well as at the individual hospital and practitioner level to minimize uncertainty and potential study bias as better care and improved health at a lower cost is achieved.

**Baylor Carrollton receives game-changing imaging technology**

Installation of the AiroMobile Intraoperative computed tomography (CT) system—only the second in the world—delivers game-changing technology to Baylor Medical Center at Carrollton patients. Baylor Carrollton’s new imaging technology introduces mobile CT capabilities during surgery with real-time, high-quality patient images to aid operating room (OR) decision-making.

This imaging system offers a combination of mobility and speed previously unachievable in the OR setting. The CT scanner isn’t limited to one OR like many systems currently employed in the industry. It can be easily transported to any of the nine ORs and other patient care locations in the hospital. The equipment is extremely versatile—adapting to a variety of surgical setups and eliminating the need to move the patient in order to get images. CT images can be taken and developed in less than a minute or two in most cases. Alternative options use either two-dimensional x-rays or magnetic resonance scans, which can sometimes take 30 to 40 minutes to develop.

“This combination is a game changer. In the past, only one or maybe two of these capabilities were available to use along with image-guided surgery systems in an OR. The advantages of combining all of these in one allows the surgical team to be extremely precise, which is critically important when you are talking about complicated spine and brain surgeries,” said Michael Turner, MD, medical director of neurosurgery at Baylor Carrollton.

“We are excited to be one of the first hospitals not only in the country, but in the world, to use this new technology in our operating rooms at Baylor Carrollton. We hope this innovative imaging system will further enhance the quality care we are able to offer our patients,” said Michael Sanborn, hospital president.
Hospital equipment finds second life in Liberia, thanks to Faith in Action Initiatives

Phebe Hospital in Liberia, Africa, has been struggling to find the resources to care for the 350,000 people who rely on the 500-bed hospital for their medical care. Now, thanks to a delivery of hospital beds, equipment, and other supplies from Faith in Action Initiatives (FIAI), the hospital is making a dent in the need.

FIAI, a BSWH-based program, relies on connections and collaboration to accomplish its mission of strengthening the spiritual lives of staff and empowering medical mission work. As an offshoot of its primary mission, FIAI also provides “second-life resources”—retired medical equipment and supplies that are recycled and put to use in hospitals, clinics, and other nonprofit agencies. By using the synergy of volunteers, churches, and other faith-based agencies, FIAI has a global reach far beyond its size.

ACCOLADES

The nation’s oldest and most prestigious surgical organization, the American Surgical Association, has voted to approve Marion Levy, MD, FACS, for membership. This is an esteemed honor, not only because of the ASA’s premier reputation, but also because the ASA caps membership at 400.

David J. Ballard, MD, PhD, chief quality officer for BSWH, has been appointed to the National Advisory Council for Healthcare Research and Quality. The 21-member panel provides advice and recommendations to the secretary of the US Department of Health and Human Services and the director of the Agency for Healthcare Research and Quality on priorities for national health services research.

The cancer programs at Baylor Regional Medical Center at Plano and the Cancer Institute at Scott and White Memorial Hospital Temple—Central Texas were one of the top 74 programs in the US, according to the American College of Surgeons Commission on Cancer. These programs received a 2013 Outstanding Achievement award from the cancer commission, signifying that they are among “the best of the best,” according to Daniel P. McKellar, MD, FACS, chair of the commission.

In an effort to help patients make informed choices, Consumer Reports has begun rating hospitals based on outcomes of heart surgery. The Heart Hospital Baylor Plano scored in the top 15. Based on data from the Society of Thoracic Surgeons, Consumer Reports rates more than 400 hospitals in 45 states, plus Washington, DC, and Puerto Rico. Although more than 1000 hospitals report data to the Society of Thoracic Surgeons, only about 400 elected to share their information with Consumer Reports.

The Joint Commission, in conjunction with The American Heart Association/American Stroke Association, recently recognized Baylor All Saints Medical Center at Fort Worth with Advanced Certification for Primary Stroke Centers. Achievement of Primary Stroke Center Certification signifies an organization’s dedication to fostering better outcomes for patients.

Baylor Health Care System’s Supportive and Palliative Care Program was one of three in the United States to win the American Hospital Association’s 2014 Circle of Life Award: Celebrating Innovation in Palliative and End-of-Life Care. Baylor was chosen by a selection committee made up of leaders from medicine, nursing, social work, ethics, and health administration. The judges cited the success of the Baylor’s Supportive and Palliative Care Program in promoting the culture of palliative care for patients and families facing the most serious illness throughout the system. Robert L. Fine, MD, and Martha Philastre, MBA, direct the programs at Baylor Health Care System, now part of BSWH.

UPCOMING CME PROGRAMS

The A. Webb Roberts Center for Continuing Education of Baylor Health Care System is offering the following programs:

North Texas Regional Cardiovascular Conference, November 15, 2014, at the Gaylord Texan Resort and Convention Center, Grapevine, Texas

41st Annual Williamsburg Conference on Heart Disease, December 7–9, 2014, in Williamsburg, Virginia

18th Annual Tyler Breast Cancer Conference, March 27–28, 2015, at the Harvey Convention Center, Tyler, Texas

6th Annual Latest Advances in Ischemic and Hemorrhagic Stroke Therapy, May 16, 2015, at the Dallas Marriott City Center, Dallas, Texas

For more information, call 214.820.2317 or visit www.cmebaylor.org.

RECENT GRANTS

• Mechanisms of B cell responses in autoimmune disease; M12-ALG05-BRI
  Principal investigator: Virginia Pascual, MD
  Sponsor: Duke University/National Institutes of Health
  Funding: $334,737
  Award period: 5/1/2014–4/30/2015

• JC virus and human colorectal neoplasia
  Principal investigator: C. Richard Boland, MD
  Sponsor: National Institutes of Health
  Funding: $259,352
  Award period: 2/1/2014–1/30/2015

• Methylation biomarker development for noninvasive detection of colorectal cancer
  Principal investigator: Ajay Goel, PhD
  Sponsor: National Institutes of Health
  Funding: $327,289
  Award period: 5/21/2014–4/30/2015

• Pain management after thoracostomy: is EXPAREL better than lidocaine
  Principal investigator: Laura Petrey, MD
  Sponsor: Pacira Pharmaceutical Inc.
  Funding: $23,605
  Award period: 2/27/2014–2/26/2015
PHILANTHROPY NOTES

$1 million gift from Hal and Diane Brierley is far-reaching

Long-time supporters Diane and Hal Brierley have made a generous $1 million gift through the Hal and Diane Brierley Foundation. The gift will benefit diverse areas of need across Baylor Health Care System. This latest gift will support the Memory Center at Baylor University Medical Center at Dallas, Baylor’s service animal training program, and multiple myeloma research, for which the Brierleys have a personal connection.

Ryan Anthony, a world-renowned trumpet musician, has held the Principal/Diane and Hal Brierley Chair at the Dallas Symphony Orchestra since 2008. In 2013, Ryan was diagnosed with multiple myeloma. After researching treatment centers across the country, Ryan elected to have his bone marrow transplant and treatment at Baylor Health Care System, where he felt he would receive the best care and outcome. Ryan is currently in remission but remains passionate about the need to find a cure. He is helping to organize a fundraiser to support multiple myeloma research. The event will include performances by world-class trumpet players and be held at the Meyerson Symphony Center in March 2015.

Good Morning America co-host and breast cancer survivor, Amy Robach, to speak at 15th annual Celebrating Women luncheon

Breast cancer survivor, ABC News correspondent, and “Good Morning America” co-host Amy Robach will be the featured speaker at the 15th annual Baylor Health Care System Foundation Celebrating Women luncheon on Friday, October 24, at the Hilton Anatole Hotel in Dallas. As part of “Good Morning America Goes Pink Day” in honor of Breast Cancer Awareness Month last October, Amy had her first mammogram at age 40 and agreed to participate in the first-ever on-air mammogram. Following the mammogram, Amy received life-altering news that she had been diagnosed with breast cancer. In the weeks that followed, she underwent a double mastectomy and recently completed treatment for the disease.

Since the first Celebrating Women luncheon in 2000, more than $21 million has been raised to support Baylor Health Care System’s 50+ year fight against breast cancer. Donations to Celebrating Women have supported advanced diagnostic equipment, innovative clinical research, and safe, quality, compassionate care for Baylor Health Care System patients and families. Approximately 1200 passionate men and women attend the Celebrating Women luncheon each year in a show of support for Baylor Health Care System efforts to fight the disease.

For information about underwriting opportunities and tickets to Celebrating Women, call 214.820.4500 or e-mail CelebratingWomen@BaylorHealth.edu. Sponsorship and underwriting opportunities are still available; individual tickets start at $250 and table prices start at $2500.

Gift from Alon USA bears fruit

Thanks to a generous $100,000 gift from Alon USA in support of the Diabetes Health and Wellness Institute (DHWI), residents in the Frazier community in South Dallas will continue to enjoy access to fresh fruits and vegetables at the Friday Farm Stand. The Farm Stand, located inside DHWI’s facility, offers healthy produce options at a discounted price.

The USDA considers the Frazier community a “food desert” due to limited access to commercial grocery stores in the area. Frazier is one of the city’s oldest historic neighborhoods; it also has the highest rate of diabetes and diabetes-related complications and hospitalizations of any neighborhood in Dallas. DHWI relies heavily on philanthropic support to provide services to this underserved community. The fifth annual DHWI Healthy Harvest Fun Walk/5K Run and Diabetes Expo, an awareness and fundraising initiative benefiting the Institute, is scheduled for Saturday, October 25.

For more information about DHWI, please contact Amy Monday at 214.820.4771 or Amy.Monday@BaylorHealth.edu. For more information about sponsorship opportunities for the DHWI Healthy Harvest event, please contact Courtney Brown at 214.820.7410 or Courtney.Brown@BaylorHealth.edu.

$500,000 Fetal Care Challenge grant will help Baylor’s tiniest patients

Thanks to a $500,000 gift from an anonymous donor, Baylor Health Care System Foundation has been challenged to raise an additional $500,000 to support the work of the Fetal Care Center at Baylor University Medical Center at Dallas, under the medical direction of Kevin Magee, MD.

Known as the Fetal Care Challenge, the Foundation has a goal of raising an additional $500,000 to make the Fetal Care Center at Baylor Dallas the first center in North Texas to provide correction of spina bifida while the baby is still in the mother’s womb. In addition, gifts to the Fetal Care Challenge will support research to develop procedures to correct other significant medical issues faced by the unborn. This Fetal Care Challenge will also provide technologically advanced imaging and monitoring capability for the 30-bed maternal fetal care unit.

For information on how you can support these or other initiatives at Baylor, please contact the Foundation at 214.820.3136.
Dr. Joe Guileyardo is presently the chief of the autopsy service at Baylor University Medical Center at Dallas (BUMC). He was born on April 15, 1952, in Bogalusa, Louisiana, and grew up there. At age 18, he and his family moved to Hammond, Louisiana, where he attended Southeastern Louisiana University. In 1973, he entered Louisiana State University (LSU) Medical School in New Orleans, graduating in December 1976. His residency in anatomic and clinical pathology was at the Charity Hospital of Louisiana, LSU Division, from January 1977 until December 1980. He joined the LSU pathology faculty upon completion of his residency training, and then in 1982 he moved back to Hammond as pathologist for Seventh Ward General Hospital. Also during this time he served as coroner's pathologist for Tangipahoa Parish. In 1989, he moved to Dallas for his fellowship in forensic pathology at the Southwestern Institute of Forensic Sciences. He then entered active duty with the Army, serving as an Armed Forces medical examiner during the Gulf War before returning to Dallas as deputy chief medical examiner for Dallas County, a position that he held for the next 10 years. In 2001, he established his private forensic consulting firm in Dallas and remains its director.

In 2004, he joined the pathology department of BUMC and has been here ever since, and in 2010 he became the director of autopsy services. As such, Dr. Guileyardo plays a very important teaching and research role at BUMC. He interacts with physicians in all Baylor departments in a most pleasant fashion, and the morbidity and mortality conferences in this medical center have been enlightened considerably by his intellectual participation. Joe is a lovely guy, has a great sense of humor, and he and his wife, Sara, are a pleasure to be around. Professionally, Joe Guileyardo is a rarity in American and international medicine, and BUMC is fortunate to have him in our presence.

William Clifford Roberts, MD (hereafter, Roberts):
Dr. Guileyardo, I appreciate your willingness to come to my house to have this interview. It is June 10, 2014. To start, could you talk about your early life, where you grew up, your parents, and your siblings?

Joseph Manuel Guileyardo, MD (hereafter, Guileyardo):
Thanks for having me here. I was born in Bogalusa, Louisiana (Figure 1). My father’s parents had emigrated from Sicily to New York and subsequently came through New Orleans and settled in this small town north of Lake Pontchartrain. My mother’s parents were cotton farmers in north Louisiana. Bogalusa was on the border of Mississippi, close to the Pearl River. My paternal grandfather worked at the Great Southern Lumber Company, which was there because of the huge pine forests in that area. I was born on April 15, 1952—Tax Day. I was “my daddy’s little deduction.”

Figure 1. Joseph M. Guileyardo, about age 3, in Bogalusa, Louisiana.
I attended grammar school at Annunciation Catholic School in Bogalusa and public school for junior high and high school. My family then moved to Hammond, Louisiana, in 1970, where I attended Southeastern Louisiana University, whose main goal was to turn out teachers and educators for Louisiana. I had decided to become a professional photographer, got a job in Hammond as a newspaper photographer, and began my studies for a degree in photography. I was enrolled in Brooks Institute of Photography in Santa Barbara, California, and they required 1 year of specific college credits prior to transfer there. After my first semester in college, I switched my major to premed, completed 2 more years of college, and entered Louisiana State University School of Medicine in New Orleans in 1973.

I completed my freshman year of medical school not knowing anything about pathology or even what it was, and that summer I completed an American Heart Association research fellowship, working on an animal model for renal ischemia. During my sophomore year, the pathology course was an intense experience, and we were saturated in pathology from morning to night for most of the year. Jack Strong was chairman of the Department of Pathology, and his research interest was cardiovascular pathology. Before lectures, the pathology residents would bring over fresh specimens from the previous day’s autopsies. They presented the cases, and the staff pathologists would explain what we were looking at. This was the first time I had seen real pathology specimens. Listening to the discussions, I became fascinated with pathology, particularly with autopsy pathology, and that feeling has remained ever since. From then on, there was no doubt in my mind that I wanted to study pathology.

After completing several electives in the pathology department during medical school, I went to Dr. Strong and told him I would like to become a pathology resident. He said, “See you July 1.” (There wasn’t any kind of formal selection or matching process as there is today.) I didn’t apply anywhere else. Since I had completed my college program in 3 years and entered the accelerated medical school program, I finished both college and medical school in 6 years, and I was only 24 years old when I graduated from medical school (Figure 2). I then did 4 years of anatomic and clinical pathology residency and enjoyed every minute.

Towards the end of my residency, Dr. Strong was elected president of the International Academy of Pathology, and the meeting that year was in San Francisco. Dr. Strong wanted his department well represented, so he told us that anyone who had a manuscript accepted for presentation would receive an all-expense-paid trip to San Francisco. I had never even been on an airplane. There was an LSU professor, Pelayo Correa, MD, who had written a pathology textbook in Spanish and was well known in South America, and he was doing cancer and gastrointestinal research at LSU. The department had also collaborated with a researcher in Japan, Dr. Akazaki, on a prostate cancer project in which 500 prostate glands had been collected for study. The specimens went to Japan and were processed by Dr. Akazaki. They were made into whole mounts—full-size cross-sections on glass slides. The entire glands were subsectioned, and he had drawn maps of latent tumors within the prostate. The concept was evolving that there were probably two types of cancers in the prostate: some were latent and not destined to become a clinical problem, and others were more aggressive. I went to Dr. Correa and told him what Dr. Strong had offered for San Francisco and asked if he had anything that I could work on. He said that he had a whole room full of prostate slides that no one had done anything with, and there were maps of the prostates. I suggested measuring the tumor sizes in three dimensions and then classifying them histologically. We did this and reported the results in the Journal of the National Cancer Institute. Thus, I went to San Francisco in 1980.

I decided to focus on autopsy pathology so I applied for a fellowship in forensic pathology in Dallas in 1980 with the chief medical examiner, Dr. Charles Petty (Figure 3). I was accepted and was scheduled to come to Dallas when my first wife became...
seriously ill and was not able to leave New Orleans; therefore, I could not accept the fellowship. Dr. Strong offered to keep me on the faculty at LSU in the pathology department, primarily doing surgical pathology, where I stayed for 2 years. Then I got a call from a private pathology group in New Orleans. One of their satellite hospitals, Seventh Ward General Hospital in Hammond, Louisiana, was growing and demanding to have a full-time pathologist on site. They offered me this position, and I accepted. Therefore, in 1982, I left academic pathology, moved back to my hometown of Hammond, and began general hospital pathology. They also needed a coroner's pathologist to perform the forensic autopsies, and I volunteered to do that as well for Tangiaphoa Parish (Figure 4).

After a few years in Hammond, I decided to expand my horizons a little, and I called the Army to inquire about opportunities in the military. They didn’t need any active-duty pathologists at that time, but suggested I join a reserve unit to improve my chances for an appointment. Therefore, I joined the 4010th US Army Reserve Hospital out of New Orleans in 1986. Around 1988, I decided general pathology was becoming too broad for me, and I decided to subspecialize in autopsy and forensic pathology. Therefore, I called the Dallas Medical Examiner’s office again and told them I would like to reapply for a fellowship. The administrator apologized and said the fellows for next year were being decided on as we spoke. About a month later I got a phone call from Dr. Petty and he said, “Mildred remembered you and pulled your old application and put it on the pile to be considered. You got picked again!” So, I moved to Dallas and began the forensic fellowship in July 1989, and during my fellowship, Dr. Petty offered me a full-time faculty position to stay at the Dallas Medical Examiner’s Office (Figures 5–7).

I was still in my Army Reserve unit, and in 1990 the Iraqis invaded Kuwait. Then President Bush activated the reserves for Desert Shield, which became Desert Storm. I wound up at Fort Bragg, North Carolina, as a general hospital pathologist but soon received an order from the Armed Forces Institute of Pathology and Office of the Armed Forces Medical Examiner to be transferred to their forensic unit in Washington, DC, where I was assigned during the Gulf War (Figure 8).

**Roberts:** What dates did that occur?

**Guileyardo:** That was in late 1990 through part of 1991. After the Gulf War ended, I returned to the Dallas Medical Examiner’s Office. Dr. Petty retired, Dr. Jeffrey Barnard took his place, and he offered me the deputy chief position, which I held for the next 10 years. Then, in 2001, I established a forensic consulting company in partnership with Dr. Linda Norton called Forensic Medicine of Dallas. Dr. Norton subsequently retired, and I have continued with my own consulting company since then.

**Roberts:** How did you come to work at Baylor?

**Guileyardo:** In 2004, I got a call from Dr. Elizabeth Burton, who was then the director of autopsy services at BUMC. I had recently consulted with her sister, who is a criminal defense attorney in Round Rock, involving a baby that was born in a hotel room, and an autopsy had been performed at the local medical examiner’s office. They reached the conclusion that the baby died of blunt force trauma, and the mother was charged with murder. Through my private company I was asked to review the case prior to trial. Doing some additional microscopic work, I discovered severe acute chorioamnionitis. What appeared to be blunt trauma was really coagulopathy and bleeding from sepsis. In my opinion, this was not a homicide, and we were able to exonerate the mother of this murder charge (Figure 9).

Dr. Burton was interested in switching 50% of her time to research activities, and they were looking for somebody to cover the autopsy service part time. Her sister suggested me, and Dr. Peter Dysert offered me the job. I accepted and immediately fell in love with Baylor.

**Roberts:** You came to Baylor when?

**Guileyardo:** I was asked to cover the autopsy service in late 2004 during lab renovations, and I worked part-time until 2010. Then Dr. Burton left and Dr. Dysert asked if I would take over as director.

**Roberts:** Were you a good student in school? Did studies come easy for you?

**Guileyardo:** Yes, they did, but I had a lot of health problems. I had frequent and severe sinus infections, and masses were discovered in my right maxillary sinus. I underwent a Caldwell-Luc surgical procedure, and fortunately the lesions were benign inflammatory polyps.
Roberts: *You didn’t have any problem after the surgery?*
Guileyardo: No, except for chronic migraines, which appeared around that time. My father had similar migraines, and as a child I remember several trips to the emergency room for his incapacitating headaches.

Roberts: *Do you still have migraines?*
Guileyardo: I do, but they are much less frequent, and better medications are now available.

Roberts: *Do you have siblings?*
Guileyardo: I have one sister, and she lives in Mississippi.

Roberts: *What’s her name?*
Guileyardo: Mary Elizabeth Hastings. She is 6 years younger.

Roberts: *What were your parents like?*
Guileyardo: My dad owned a small beer distributing company, but he drove the trucks himself. He was a wonderful man and very caring. The townpeople had great respect for him, and he is my role model for how people should be treated.

Roberts: *You two got along very well.*
Guileyardo: We did, but he was interested in sports and I was more interested in books. I enjoyed music but to please him I went to football practice and then walked across the street for piano lessons. I don’t think he understood me very well, but he was always kind and supportive. There was also a pretty well known physician from Bogalusa, Dr. Gerald “Jerry” Berenson, who became a very prominent cardiologist at Tulane and LSU Medical Schools in New Orleans. He and my dad were close friends. My dad told me to go look up “Jerry” when I got into medical school, and he became my advisor. The first thing he told me when I introduced myself was that I needed to lose some weight. My dad said he was always a little abrasive, but Jerry was the only one who had a car so we hung around with him. Jerry’s parents had an eminent clothing store in Bogalusa—Berenson’s. If you wanted to buy a nice suit, that’s where you went. Jerry was a fine person and a brilliant teacher and mentor. He established what was called the “Score Project” in Bogalusa where they monitored blood pressures of everyone in town for a long time, similar to the Framingham studies.

Roberts: *When you were growing up in Bogalusa, what was the population?*
Guileyardo: It was around 18,000. It was a paper-mill town. Most of the people in town worked for the paper mill.

Roberts: *What about your mother’s family?*
Guileyardo: They were from north Louisiana. My dad’s side had Italian-Sicilian heritage. My mother’s parents were farmers. She was all-American.

Roberts: *What was your mother’s name?*
Guileyardo: Patsy Faye Huff, and she was also a very kind, intelligent, and supportive person.

Roberts: *How did she and your father meet?*
Guileyardo: I’m not sure. They met in Bogalusa (Figure 10). Her father was a barber and died from a stroke at a relatively young age. Her sister and brother-in-law lived in Bogalusa, and he worked for the paper mill. When her father died, they moved from north Louisiana to Bogalusa to be closer to the remaining family.

Roberts: *Your father was born when?*
Guileyardo: He was born in 1921 and died in 1993. We had always celebrated his birthday on November 25, but when we got his birth certificate so he could apply for Social Security, we found that he had been born on Christmas day. We asked my older aunt, who said that their mother felt it would not be fair for him to share his birthday with Christmas, so she arbitrarily decided to tell him he was born on November 25th! He celebrated his birthday on the wrong day his whole life.

Roberts: *Your mother?*
Guileyardo: She was born in 1931 and died in 1995.

Roberts: *Were they close? Was it a good marriage?*
Guileyardo: They were a good match. They supported each other.

Roberts: *In high school, did you play sports?*
Guileyardo: I played football for a year and, to my surprise, I enjoyed it. I think physical contact sports can give a kid...
confidence, and I learned the importance of a team approach to problems, which I still use today.

Roberts: How many students were in your high school?
Guileyardo: About 170 in each class.

Roberts: How did you end up in your class standings?
Guileyardo: I am not sure. I was sick so much and missed most of my junior year.

Roberts: Did you read a lot?
Guileyardo: I read a lot of fiction and began a lifelong love of Joseph Conrad’s works. At that time I was interested in photography, so I read a lot of technical books.
were profusely illustrated, and was fascinated by it all. The local library was also within a short walking distance from our house.

Roberts: Did your parents read much?
Guileyardo: My mother read a lot of fiction. My dad read several newspapers every day, and he listened to sports on the radio. He would have two radios going and would often read two newspapers (with special attention to the sports pages).

Roberts: Did either of your parents or grandparents go to college?
Guileyardo: No. I was the first person in my extended family to go to college.

Roberts: How did you get interested in medicine?
Guileyardo: I had often thought of becoming a medical doctor, mainly because I was curious about how the body worked, but I more or less gave up on the idea since I was always sick and doubted I could handle it academically. When I started college to do photography, I did better than I expected, and people suggested that I may want to aim a little higher. I also loved my introductory science courses, and I was concerned that photography may not provide a reliable income.

Roberts: What kind of courses made you look at medicine?
Guileyardo: Biology, chemistry, and mathematics. For a small college, the professors and teachers were excellent and enthusiastic.

Roberts: Were there any teachers throughout your school years who had a major impact on you?
Guileyardo: I remember a high school English teacher who had been an Army nurse and was a little eccentric. I didn’t have her courses, but a friend of mine and I would discuss books with her on our own. She had a library, mainly paperback books, in her classroom and she would lend out those books. She said that if you are successful, your associates will be discussing these books. It had nothing to do with specific school courses or grades, but she contributed toward my education as much as anyone. I still have many of those titles in my library. Also, my faculty advisor in college, Dr. Danny Acosta, was very supportive, and he got me a job at his uncle’s New Orleans shipyards so that I could pay my first year’s tuition to medical school.

Roberts: Do you read fast?
Guileyardo: No.

Roberts: Did your parents harp on you to make good grades, or did they not say too much about it?
Guileyardo: They didn’t say too much about it. My grades were usually good except for “conduct” during grammar school. The nuns generally felt that my behavior wasn’t up to their standards, and they were right. They did provide an excellent education, however, and by the eighth grade in their school, I probably knew more than most high school seniors.

Roberts: You mentioned music and playing the piano. Was music part of your life growing up?
Guileyardo: It was. I took piano lessons for many years, and I played keyboards and guitar in several small bands around Bogalusa. Later in Dallas I primarily played bass guitar.

Roberts: Are you still playing?
Guileyardo: Not professionally. Now there is no time to rehearse, and playing at late night venues is just not feasible. My time now is more focused on work, teaching, and writing.

Roberts: Did you sing?
Guileyardo: No. I have a terrible singing voice. They let me have a microphone, but I had to keep it switched off.

Roberts: You mentioned that your first wife was ill. What happened?
Guileyardo: She had a renal stone and had surgery to remove it. She developed an open fistula between her kidney and her back after that. She was too sick to move, and I couldn’t continue with my education when we needed a steady income. Dr. Strong was gracious enough to let me stay in New Orleans, and I am grateful for that.
Roberts: Do you have children?
Guileyardo: Yes. I have a son and daughter. My daughter is a nurse in Louisiana. My son died suddenly at the age of 24.

Roberts: When did you get married?
Guileyardo: I got married in 1971 to my first wife, Claudine Killen.

Roberts: When was your son born?
Guileyardo: Joseph Manuel Guileyardo Jr. was born in 1977.

Roberts: What is your daughter's name?
Guileyardo: Carla Dean Guileyardo, born in 1979. She has three children, one son and twin girls.

Roberts: When did you divorce?

Roberts: How did you meet Sara Tucker, and when did you marry?
Guileyardo: Sara and I were both working at the Dallas County Medical Examiner's Office when we met in 1994. She was an administrator. We got married in 2000. In addition to being a wonderful and supportive wife, Sara became my administrator and assistant when we established our private forensic consulting firm in 2001. I owe any success that I've had to her organizational abilities, friendship, and support.

Roberts: It seems to me that you have done a terrific job at Baylor. You have gotten the departments of internal medicine, surgery, and radiology very much involved and interested in what you do. You communicate beautifully with individuals and other departments. Is it true that because of you Baylor does more autopsies than any other hospital in Dallas?
Guileyardo: Parkland probably does more, but I don't know their death rates.

Roberts: What percent of deaths at BUMC have an autopsy?
Guileyardo: Around 4%.

Roberts: But you do autopsies of deaths from all of the Baylor hospitals in the Dallas area?
Guileyardo: Yes, we cover most of the local Baylor system hospitals.

Roberts: What is your day like? What time do you get up in the morning?
Guileyardo: I get up at 5:15. I then go to my little neighborhood restaurant, Norma's, where my iced tea and breakfast are usually already prepared and waiting for me.

Roberts: What time do you get to work?
Guileyardo: About 6:45 AM.

Roberts: What time do you leave the hospital?
Guileyardo: Around 4:00 PM unless we have a late case or I'm slipping behind on my turnaround times.

Roberts: So you work about 10 hours a day. What about weekends? Do you have to go to the office much on weekends?
Guileyardo: Not that often, but I'm on call if there is a case.

Roberts: You participate in virtually all autopsies done at BUMC?
Guileyardo: Yes.

Roberts: What time do you go to bed at night?
Guileyardo: Usually about 8:30 to 9:00 PM.

Roberts: You've always been a morning person?
Guileyardo: Yes.

Roberts: Do you have hobbies outside of medicine?
Guileyardo: Music was a big hobby, but reading is my only hobby now. Sara and I like to take cruises. We love ships and usually don't care where the ship is going. When I retire, we plan to cruise around the world.

Roberts: How much time do you take off a year for vacation?
Guileyardo: Between 2 and 3 weeks right now.

Roberts: What are you reading now?
Guileyardo: I'm reading the Selected Works of Bertrand Russell.

Roberts: How did you get interested in that?
Guileyardo: One of my favorite books is Men of Mathematics by E. T. Bell. There are some quotes by Russell in that book, and I became interested in knowing more about his life. He's written so much you can't read it all, but there is a collected set of basic writings from his essays and books.

Roberts: Bertrand Russell was an atheist?
Guileyardo: At times he called himself an agnostic, but he probably was an atheist.

Roberts: Are you religious?
Guileyardo: Not in a formal sense, but there were times in my life, such as after the death of my son, that spiritual people helped me greatly. Therefore, I have tremendous respect and a sense of gratitude to them and their work. People like Dr. Timothy Warren who led the Baylor Bible Study Group for a while and Mike Mullender, head chaplain of Baylor, have stood by me and supported me as well. All the Baylor chaplains have been extremely supportive of what I have tried to accomplish in our department, and we work closely together every day.

Roberts: I understand that you usually come to Baylor on a motorcycle. How long have you been riding a motorcycle?
Guileyardo: Over 30 years, since about 1982.

Roberts: Does Sara ride with you?
Guileyardo: No, she's too precious to me to take the chance.

Roberts: What kind of motorcycle do you have?
Guileyardo: A 2004 Harley Davidson "Fat Boy" (Figure 11).

Roberts: Is that 1400 cubic centimeters? Have you ever had an accident?
Guileyardo: It's 1450 cc (88 cubic inches). I've had a couple of minor falls, but I've never been seriously injured.

Roberts: Do you wear a helmet?
Guileyardo: Not on a regular basis, only when it's cold or raining.

Roberts: Why not?
Guileyardo: It's more comfortable and I can see and hear better without one. I've actually avoided accidents because I could hear a vehicle in my blind spot. Nobody believes that, but I enjoy the experience more without a helmet, although I understand the concerns and drive very carefully.

Roberts: You come in so early that the traffic isn't too bad. Do you ride much on the weekends?
Guileyardo: No. I mainly just ride back and forth to work. I enjoy getting up early and getting out in the fresh air. It gives
me a sense of peace and relaxation. I am a member of a small motorcycle group called “The Big Dog Crewe” (mostly FBI agents and SWAT team guys), but I no longer have time to take trips with them.

Roberts: How many motorcycles have you owned?
Guileyardo: Just a few. My present one is over 10 years old with 45,000 miles, but I’ve had two other ones. With proper maintenance and a little luck, they last a long time.

Roberts: How far is your home from Baylor?
Guileyardo: About 5 miles.

Roberts: What’s your home like?
Guileyardo: I live in North Oak Cliff very near Methodist Hospital.

Roberts: You’ve lived there a long time?
Guileyardo: Sara and I moved there in 1999.

Roberts: Are there other topics you would like to talk about?

Guileyardo: I want people to understand how grateful I am to be given this opportunity to work at Baylor. This institution clearly was founded on and operates by altruistic and spiritual principles. Furthermore, the case material is so rich and interesting that I am constantly learning new things, even after all my years of practice. Working with giants such as you, Dr. Roberts, and others such as John Fordtran, John Krause, Michael Emmett, Randy Rosenblatt, the cardiologists, and the surgical teams has rekindled my passion for medical science and pathology (Figure 12). It’s also interesting to see which doctors show up in the autopsy room in order to learn more about their patients. They are generally the top men and women in their fields, and I have a tremendous respect for them and their work. These are the doctors that I want treating me and my family.

Roberts: You have fulfilled a unique role at Baylor and have blended a lot of different groups together to increase the knowledge base.

Guileyardo: When I took over the autopsy department, I immediately implemented suggestions by Dr. Bill Sutker and Dr. Irving Prengler to streamline our reports and improve the turnaround times in response to the needs of the medical staff. John Fordtran also took an interest in the autopsy department, and his support and suggestions have been invaluable as well. And finally, I wish to acknowledge Dr. Peter Dysert, the chairman of the Department of Pathology. The only reason I’m here is that Pete thinks that autopsy work is important for medical education and patient safety. There is no financial reimbursement for autopsies, and there are few private hospitals in this country willing to expend the resources that he does for this type of work.

Dr. Dysert reaches into his wallet and takes out the cash because he thinks it’s important. That needs to be on the record. Also, the other excellent pathologists at Pathologists Bio-Medical Laboratories, such as David Watkins, Jack Snipes, and Michelle Shiller, have been extremely helpful and supportive. Autopsy pathology around the world is in a bad state. Many pathologists performing hospital autopsies are not particularly interested in doing it, and not surprisingly, the results are often less than optimal.

Roberts: Joe, thank you for giving us a look into your life. It was great.
Fueled in part by recent bestselling books that warn of the evils of gluten in our diets, a significant proportion of our population is now either avoiding foods that contain gluten or eliminating gluten entirely from their diets, and these numbers continue to grow. The gluten-free trend—and the accompanying multibillion-dollar industry it has created—stems from the spreading belief that eating foods containing wheat or other gluten-laden grains may not only result in weight gain and obesity, but can also lead to a laundry list of ailments ranging from depression and anxiety to arthritis and autism. One popular book contends that current recommendations for a high-grain/low-fat diet underlie much of today’s chronic health problems and that a low-carbohydrate, high-fat/cholesterol diet is ideal. Every major change in our diet carries with it the possibility of unforeseen risks. Concern about the impact of such popularized dietary recommendations on overall well-being—and on cardiovascular health in particular—warrants discussion in the medical community.

Fueled in part by recent bestselling books—and the television talk shows and celebrity endorsements that accompany them—that warn of the evils of gluten in our diets, a significant proportion of our population is rapidly changing its eating habits. Approximately 30% of all Americans are now either avoiding foods that contain gluten or eliminating gluten entirely from their diets, and these numbers continue to grow (1). The gluten-free trend—and the accompanying multibillion-dollar industry it has created—stems from the spreading belief that eating foods containing wheat or other gluten-laden grains may not only result in weight gain and obesity, but can also lead to a laundry list of ailments ranging from depression and anxiety to arthritis and autism. One popular book contends that current recommendations for a high-grain/low-fat diet underlie much of today’s chronic health problems and that a low-carbohydrate, high-fat/cholesterol diet is ideal. Every major change in our diet carries with it the possibility of unforeseen risks. Concern about the impact of such popularized dietary recommendations on overall well-being—and on cardiovascular health in particular—warrants discussion in the medical community.

From State University of New York Upstate Medical University, Syracuse, New York.

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Note: This article will also appear in The American Journal of Cardiology.
led international panels to issue guidelines that recommend minimizing intake of saturated fats and trans fats and including whole grains as a primary staple of the diet (7).

Flaws in the arguments presented in the book have not entirely escaped the notice of health care professionals. Some have spoken up, calling the book “comfortably simplistic” (8), one of “brawn, not brain” (9). Others have charged the author with ignoring “the bulk of science,” exaggerating the truth, and making false assumptions (10), and have noted that the book makes claims that are contrary to “what some pretty reliable sources have to say,” referring to recommendations from the World Health Organization and Consumer Reports (11). Yet, the book remains a New York Times bestseller after 43 weeks, and sales of gluten-free products are projected to grow at an annual rate of 10.2% over each of the next 5 years (12).

Every major change in our diet carries with it the possibility of unforeseen risks. Many readers—the general public, as well as medical professionals—accept what they read at first glance. Myths have been part of our medical lore for millennia (13). Those jumping on the gluten-free/high-fat bandwagon may be disappointed when their symptoms are not mitigated; more critically, they may be at increased risk for other, more dangerous ailments. At the very least, concern about the impact of encouraging a high-cholesterol, high-saturated-fat diet warrants discussion in the medical community. In short, it is time to review some of the most egregious misinformation being spread and separate some of the wheat from the chaff.

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Notes on a stroke

Allen B. Weisse, MD

Last April we were about to celebrate the Passover Seder at my home. Just before calling the guests to the table, as the officiator of the celebration, I decided to take a quick look in the Passover guide, the Haggadah. I found that I could read no more than three or four words before the next, like some concrete traffic barrier, tripped up my progress. When I attempted to overcome this deficiency by uttering the words out loud, what came forth was an inchoate collection of muffled gibberish and gargles. It was clear that I was not going to be able to symbolically guide my family out of Egypt on the way to the Promised Land. It was all I could do to make my distress known to my wife and have her guide me to the nearest emergency room. At the age of 84, I was having a stroke.

During the 10-minute drive to the hospital, my articulation worsened and I began to experience numbness and tingling in my hands. I was able to walk into the emergency room. When I informed the clerk that I believed I was having a stroke, within minutes I was rushed to the back into the hands of the stroke team. Intravenous lines were inserted and a medical resident was right on the scene. Looming over her shoulder on a two-way television set-up was the neurology attending physician at her home assisting in examining me and making critical decisions. A computed tomography (CT) scan ruled out cerebral bleeding, which would have ruled out the administration of tissue plasminogen activator (t-PA). Since some of my symptoms were persisting, an infusion of the clot-dissolving agent was begun. Within 15 minutes all symptoms had disappeared. The time delay between the onset of symptoms at home and the administration of t-PA was between 2 and 3 hours.

Magnetic resonance imaging (MRI) was performed before I was admitted to the neurology intensive care unit. No specific arterial occlusion was seen, but there were multiple changes in the brain consistent with aging as well as old embolic-related small infarctions. The carotid vessels were clear. A transthoracic echocardiogram was normal. A Holter-like electrocardiographic monitoring device was attached to me to detect any episodes of asymptomatic atrial fibrillation over a 2-week period. (None found.)

Prior to this episode, I had been taking a regular aspirin (365 mg) daily along with atorvastatin for hypercholesterolemia. The aspirin dose was lowered to 80 mg, and clopidogrel was added to my medical regimen on discharge.

Twelve days following discharge, there were new cerebral rumbings. I felt the sudden onset of moderately severe lightheadedness with a transient unilateral facial droop. The 911 team delivered me to the hospital, where another CT and MRI were performed. These were unchanged from the previous studies. My symptoms rapidly abated and I was admitted for further observation and testing. This included electroencephalographic monitoring for 3 days, which was nondiagnostic. A transesophageal echocardiogram revealed a patent foramen ovale. A “bubble study” indicated shunting of blood across the defect from the right to left atrium, indicating this course of small thrombi reaching the heart from the systemic veins and lodging in the brain instead of the lungs, where they could not do as much damage. The aspirin and clopidogrel were discontinued, and I was placed on an oral anticoagulant (rivaroxaban).

I emerged from this episode remarkably free of sequelae. Motor and sensory functions are intact. I do have a slight unsteadiness of gait but can walk without assistance of any kind. I believe I am still mentally acute but, as a writer, I cannot escape the feeling that, on occasion, I find it more difficult than previously to retrieve just the right word from the memory bank inside my brain.

By any measure, one can say that I received the very best care that 21st century medicine can provide. So why did I have this lingering sensation that my care was somehow incomplete? It had to do with the performance of the neurological examination by nearly a dozen or more physicians and other health care workers during the course of my hospitalizations. Not one person checked my deep tendon reflexes. Examination of the cranial nerves was cursory and incomplete. I was checked for sensation of light touch but not pain or temperature perception. No one even attempted to elicit a positive Babinski sign! Even a second-year medical student would have been expected to perform better than this.

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When I began the practice of medicine over 50 years ago, its technological revolution was just getting into full swing. At that time I and my contemporaries were not too far removed from the teachings of the towering figures like Austin Flint and William Osler, who epitomized the ideals of the profession. Their keen interpretation of symptoms and signs of disease often put them on the right diagnostic track. No wonder they were often called “diagnosticians.” And, at a time when little could be done to alter the outcome of most diseases, they were quite adept at predicting the course of a disease in any patient they attended. Even when the outcome was death, their ability to foresee how and when it would occur gave the patients’ families a kind of comfort in knowing what to expect. Walter Alvarez encapsulated this skill in the lines, “Blessed be the physician who takes a good history, looks keenly at his patient and thinks a bit.”

Modern technology has dimmed the lights of the past. Nowhere has this been more marked than in the management of stroke, where time to treatment is so critical. If doing a full neurological examination adds nothing to this, should it still be performed? My neurologist assured me that the abbreviated neurological examination has become standard for all stroke teams such as his. Why waste time ascertaining the level of flooding in the valley when, upstream, a crack in the dam can be found and possibly be repaired?

However, there are many clinical scenarios that allow for a more cognitive approach. My harping on the history and physical examination might not just represent foolish nostalgia. Osler’s aphorism still has the ring of truth: “Listen to your patient. He is telling you the diagnosis.” He is also telling you much else about himself and, as you persist in your bedside attention to him, you are responding in kind.
Book Review

Houston Hearts: A History of Cardiovascular Surgery and Medicine and The Methodist DeBakey Heart & Vascular Center Houston Methodist Hospital by William L. Winters Jr., MD, MACC, with Betsy Parish

Houston, TX: Elisha Freeman Publishing, 2014. 449 pp., $29.95, hardcover.

Reviewed by William C. Roberts, MD

When Dr. William Winters Jr. calls and makes a request, it is very difficult to say “no.” “Would you be willing to review my book?” “I would be honored,” I replied, not realizing that in a few days a 607-page manuscript by him and Betsy Parish would be received. After reading only a few pages, I realized that I had been given the privilege of reviewing a masterpiece. It was difficult to put down, and also for me difficult to review because the quantity of detailed information was enormous.

The book actually began in the early years of the 20th century when Dr. Winters began conducting video interviews, eventually numbering over 70, with longstanding members of The Methodist Hospital (TMH) staff to record the extraordinary changes that had taken place, particularly in cardiovascular disease, in the previous 60 years. Not long after starting the interviews, Dr. Winters suggested to Ms. Betsy Parish, a longtime friend and patient of his, who had just finished writing interviews, Dr. Winters suggested to Ms. Betsy Parish, a longtime friend and patient of his, who had just finished writing Legacy, 50 Years of Loving Care at Texas Children’s Hospital 1954–2004, to collaborate with him on a history of cardiovascular medicine and surgery at TMH in Houston. She obviously agreed.

The product is a magnificent story. The book is divided into 20 chapters with an appropriate quote under each chapter title and what they call a “blip”—a mini-story—at the end of each chapter, followed by numerous endnotes documenting their many sources—the interviews, Dr. Winters’ inside 40-year recollections of the events, newspaper and magazine accounts, and medical publications. The book ends with an epilogue by Dr. Winters in which he details the accomplishments of TMH since the 2004 tumultuous rupture of its 50-year relationship with Baylor College of Medicine (BCM). Following the epilogue are a collection of poems penned seemingly effortlessly by Dr. Winters. This section is entitled ‘Addendum for Rhyme and Reason’ and includes “Odes” to Antonio M. Gatto, William Zoghbi, Don and Mary Louise Chapman, Miguel Quiñones, Jimmy Howell, Richard Wainerdi, and Michael E. DeBakey, plus a poem entitled “Healthcare Reform—A Political Plea.”

A detailed timeline of events affecting TMH also is included near the end of the book.

The star of the book, and deservedly so, is Michael E. DeBakey, who came to Houston in 1948 as chairman of the department of surgery of Baylor University College of Medicine (BUCM; later the “University” was dropped), which had moved from Dallas only 5 years earlier. On arrival, he had no hospital in which to operate, but the visionary man from Lake Charles (initially) saw the potential. He was instrumental in rapidly setting up an affiliation of BUCM with the VA Hospital (years later to be named the Michael E. DeBakey VA Hospital), the Jefferson Davis Hospital, and beginning in 1950, TMH, where he eventually limited his practice. In 1963, the Ben Taub General Hospital opened and also affiliated with BUCM. His surgical innovations and unique skills and his multiple publications (eventually totaling >1200) and presentations rapidly attracted patients from the world over. As the patients increased, Mr. Ted Bowen, TMH’s dynamic president, increased the facilities accordingly—from 300 to eventually >1500 beds. It was not long before Dr. DeBakey attracted many talented associates, including Oscar Creech Jr. (1949), Denton A. Cooley (1951), E. Stanley Crawford (1954), Arthur C. Beall Jr., H. Edward Garrett, J. (Jimmy) E. Howell, Gerald Lawrie, and George Noon, among others, and Dr. DeBakey gave them space to shine. For many years, Dr. DeBakey daily averaged 100 patients on his hospital service, and in 1965, an additional 100 patients were waiting outside to get a bed. He would tell the cardiologists that he had gotten the patient out of the operating room and now it was their task to get the patient out of the hospital.

As his reputation grew, not only as an innovative and skilled surgeon but also as a major researcher, Dr. DeBakey expanded his national and international responsibilities. He became the US’s top proponent for expanded cardiovascular research, advising congressional committees, the National Heart Institute, and Mrs. Mary Lasker’s initiatives, among others. He traveled worldwide extensively giving presentations, receiving awards (he eventually received 32 honorary degrees and the Congressional Medal, the highest award available to a US civilian), and consulting with prominent citizens and government leaders. Additionally, Dr. DeBakey was chairman of BUCM’s department of surgery for 40 years and also either president or chancellor of BUCM for 20 years.

Although cardiovascular surgery drew the most attention at TMH in the 1950s and 1960s, the huge number of cardiovascular surgery patients at TMH led to a major expansion in the number

*This review was also published as a Foreword to the book and is reprinted with permission.*
of cardiologists, both full-time at BUCM and also in the private realm (volunteer faculty). Dr. Don Chapman, the first cardiologist in Houston and the first to perform a cardiac catheterization in Houston, started "the Chapman Group" in 1955 at TMH, and Dr. Chapman became the "preeminent practicing cardiologist in Houston." At the same time, Dr. Edward W. Dennis, a cousin of mine by marriage, became the first full-time BUCM cardiologist at TMH and remained so until his untimely death in 1975 at age 52.

The book describes in exquisite detail the development of cardiology at TMH and the town-gown relations that ensued. When coronary bypass became a successful procedure in the late 1960s, the number of patients further increased, the need for more cardiologists and cardiac catheterization laboratories expanded, and then when coronary angioplasty was introduced in the late 1970s further expansion was required. The hospital president, Mr. Ted Bowen, also a visionary, did all he could to expand TMH facilities adequately to accommodate the additional onrush of patients.

Dr. DeBakey, as BUCM’s president and chief executive officer beginning in 1969, worked among other endeavors to strengthen the nonsurgical departments. Dr. Henry D. McIntosh became chairman of the department of medicine in 1970, and during his “tumultuous” 7-year reign a number of subsequently prominent cardiologists were recruited, including Dr. Antonio M. Gotto, who later succeeded him as department chairman; Albert E. Ruizner, who later headed the cardiac catheterization laboratories and was the instigator behind the Methodist DeBakey Heart Center, which unified all cardiovascular services; as well as Miguel Quiñones, Mario S. Verani, Craig M. Pratt, James B. Young, William A. Zoghbi, Neal S. Kleiman, and later Richard Miller, Douglas L. Morris, and Christie M. Ballantyne, to name a few. Simultaneously, the Chapman Group expanded to include William L. Winters Jr., Miguel Quiñones, and William Zoghbi). As the years went by, Drs. Chapman and Winters and many other TMH cardiologists received many local, national, and international awards from many organizations.

When coronary angioplasty entered the scene in the early 1980s at TMH, the cardiac catheterization laboratories, as elsewhere, were converted from a purely diagnostic laboratory to a therapeutic laboratory as well, and this change altered for a spell the relations between the cardiovascular surgeons and the cardiologists. Interestingly, Dr. DeBakey was a strong supporter of percutaneous coronary intervention from the beginning.

All the while, TMH kept growing through the efforts of its fine leaders: Ted Bowen, Larry Mathias, Peter Butler, Peter Traber, and Ron Girotto. The damage caused by Tropical Storm Allison in 2001 was a game changer in many ways. The major game changer, however, occurred in 2004 when the Baylor College of Medicine (BCM) and TMH ended their 50-year affiliation. Nearly all of the TMH staff stayed with the hospital and resigned from BCM. Mr. Ron Girotto vowed to make TMH “an academic hospital” unassociated with a local medical school. Another wave of expansion occurred. By 2012, TMH was listed in the U.S. News & World Report as the number 1 hospital in Texas, as one of the best hospitals in 12 specialties, and as one of the top 15 major teaching hospitals in the USA. The TMH was listed as among the 100 best companies to work for 7 years in a row by Fortune magazine and one of the best places to work for by Forbes. Mr. Girotto established ICARE (integrity, compassion, accountability, respect, and excellence) to instill these values in every employee. As a consequence, hospital turnover and vacancy rates dropped, and patient and employee/physician satisfaction grew to the highest in its history.

And its physicians kept gaining prominence. Dr. Antonio Gotto served 1 year as president of the American Heart Association, and four others at TMH have each been president of the American College of Cardiology (Don W. Chapman, William L. Winters Jr., Miguel Quiñones, and William Zoghbi). As the years went by, Drs. Chapman and Winters and many other TMH cardiologists received many local, national, and international awards from many organizations.

This book presents a remarkable and inspiring story of how physicians and hospital administrators, by working together, can produce an awe-inspiring institution.

The reviewer, William C. Roberts, MD, is executive director of the Baylor Heart and Vascular Institute at Baylor University Medical Center at Dallas, dean of the A. Webb Roberts Center for Continuing Medical Education of Baylor Health Care System, and editor in chief of Baylor University Medical Center Proceedings and The American Journal of Cardiology.
Facts and ideas from anywhere

DOCTORS OF ANOTHER CALLING

Dr. David K. C. Cooper has edited a splendid book describing in detail 35 physicians who became famous not in medicine but in a nonmedical arena (1). Each chapter describes one of these distinguished men (no women were among the 35), and an appendix entitled “Who Could Have Been Chosen” provides a lengthy list of physician writers, entertainers, explorers, athletes, politicians, military men, humanitarians, and educators, as well as a philanthropist, a few criminals, and prominent scientists in areas other than medicine.

The book begins with St. Luke, the most widely read physician, called by St. Paul “the beloved physician.” It then describes other famous physicians. Dante Alighieri (1265–1321), a physician in Florence, Italy, was exiled by political rivals in 1302 and never allowed to return. He devoted the remaining 19 years of his life to writing his famous trilogy, The Divine Comedy. Nicholas Copernicus (1473–1543), the Polish celestial physician, demonstrated that the Earth, rather than being the center of the universe, orbited around the sun. Thus, this physician is tied to the origins of astronomy and astrophysics. John Locke (1632–1704) was one of the greatest minds of the 17th century, a philosopher and political theorist but also a pragmatic and progressive physician. Hans Sloane (1660–1753) collected plants, animals, minerals, antique coins, and many other objects that became the foundation for the British Museum and the Natural History Museum of London. Thomas Dover (1660–1742) made a fortune as a buccaneer and returned to practice in England thereafter and popularized Dover powder, which made him another fortune. Five physicians signed the Declaration of Independence and were prominent practitioners in their day. Mongo Park (1771–1806), a Scottish physician, led two expeditions into the heart of West Africa. Thomas Young (1773–1829) was stated to be the smartest person ever and contributed vastly to many areas of science, engineering, and numerous other fields. Peter Mark Roget (1779–1869) produced the thesaurus after he retired from his medical practice.

Several physicians became poets, including John Keats (1795–1821) and Oliver Wendell Holmes (1809–1894). Other writers included Conan Doyle (1859–1930), who created Sherlock Holmes; Anton Chekhov (1860–1904), the famous Russian writer; W. Somerset Maugham (1874–1965), whose plays were seen by tens of thousands and whose books sold in the millions; Archibald Joseph Cronin (1896–1981), a bestselling novelist; Khaled Hosseini (1965–), an acclaimed novelist and humanitarian; and Abraham Verghese (1955–), professor of medicine at Stanford University and the author of My Own Country, The Tennis Partner, and Cutting for Stone. And then there were the famous explorers: David Livingstone (1813–1873) and Edward Wilson (1872–1912), Antarctic explorer, painter, and naturalist. The military leaders included Leonard Wood (1860–1927) and Ernesto “Che” Guevara (1928–1967). Other physicians were prominent in business, including Abraham Gesner (1797–1864), the Canadian father of the petroleum industry, and Armand Hammer (1898–1990), an entrepreneur, diplomat, and philanthropist. Jules Stein (1896–1981) was a visionary extraordinaire—and his chapter was written by our own Marvin J. Stone and his son, Rob. Athletes included Roger Bannister (1929), who completed the first 4-minute mile while a medical student in London. He went on to have a distinguished career as a neurologist and subsequently was the head of an Oxford College. Henry Stallard (1901–1973) was a 1924 Olympics middle-distance runner (1500 meters) immortalized in the 1981 epic British film Chariots of Fire. He went on to have a distinguished career in ophthalmology.

This is a splendid book making one proud to be a physician. Many of the authors of the individual chapters are members of the American Osler Society.

BANNING THE HANDSHAKE IN MEDICAL CENTERS

The handshake represents a deeply established social custom. In recent years, however, there has been increasing recognition of the importance of hands as vectors for infection, leading to formal recommendations and policies regarding hand hygiene in hospitals and other health care facilities (2). Such programs have been limited by variable compliance and efficacy. Regulations to restrict the handshake from the health care setting, in conjunction with more robust hand hygiene programs, may help limit the spread of disease and thus could potentially decrease the
clinical and economic burden associated with hospital-acquired infections and antimicrobial resistance. Given the profound social role of the handshake, a suitable replacement gesture may need to be adopted and then promoted with widespread media and educational programs. With the tremendous social and economic burden of hospital-acquired infections and antimicrobial resistance and the variable success of current approaches to hand hygiene in the health care environment, it would be a mistake to dismiss, out of hand, such a promising, intuitive, and affordable ban.

ANNUAL PHYSICAL EXAMINATION
The Society of General Internal Medicine argues against routine health checks (3). Despite its recommendation, an annual physical examination is the most common reason for visiting a primary care physician. During these visits, patients, physicians, and private insurers all expect a physical examination. In actuality, the value of an annual physical examination has not been tested. These annual examinations may introduce the danger of overdiagnosis. There is always a small possibility that this examination might detect some silent, potentially deadly cancer or aneurysm. Unfortunately, for the patients, these serendipitous, lifesaving events are much less common than the false-positive findings that lead to invasive and potentially life-threatening tests.

Almost nothing in the complete annual examination is based on evidence. For a generally healthy older person, the physical examination could reasonably be limited to blood pressure measurement and assessment of body mass index. As Michael B. Rothberg, MD, indicates, so many examination elements, such as testicular or thyroid exams to detect cancer, actually have evidence to recommend against them. But most simply have insufficient evidence to recommend for or against. Medicare, which has traditionally refused to pay for routine physicals, now covers an annual wellness visit. The physician exam component, however, is limited to measurement of blood pressure and body mass index. The rest of the visit includes updating medical history, testing for cognitive impairment, assessing risk factors, performing evidence-based screening (e.g., for colorectal cancer or diabetes mellitus), and providing personalized health advice.

VACCINE COSTS
Vaccination costs have gone from single digits to sometimes triple digits in the last 2 decades (4). Some physicians have stopped offering immunizations because they say they cannot afford to buy these potentially life-saving preventive treatments that insurance often reimburses poorly, sometimes even at a loss. Childhood immunizations are so vital to public health that the Affordable Care Act mandates their coverage without an out-of-pocket cost, and they are generally required for school entry. Once a loss leader for manufacturers, because they are usually more expensive to produce than conventional drugs, vaccines now can be very profitable. Old vaccines now cost more; new ones have entered the market at once unthinkable prices. Since 1986, the average cost to fully vaccinate a child with private insurance to the age of 18 has increased from $100 to $2200, according to the Centers for Disease Control and Prevention (CDC). Even with deep discounts, the costs for the federal government, which buys half of all vaccines for the nation’s children, have increased 15-fold since 1986. The most expensive shot for young children is Prevnar 13, which prevents diseases caused by pneumococcal bacteria from ear infections to pneumonia. Like many vaccines, Prevnar requires multiple jabs. Each shot is priced at $135, and every child in the US is required to get four doses before entering school. Pfizer, the sole manufacturer, had revenue of nearly $4 billion from the Prevnar vaccine line last year. Prevnar 13, which protects against 13 strains, has gone up 6% each year since it was approved by the Food and Drug Administration in 2010. There are some good reasons vaccines like Prevnar are more expensive than previous offerings. Vaccine trials, which once included thousands of volunteers, must now include tens or hundreds of thousands, as fears about side effects such as autism have grown. Additionally, some of the new vaccines are complicated to manufacture.

CIGARETTE SMOKING
According to the CDC, 18% of US adults, or 42 million, were cigarette smokers in 2012, down from 28% in 1992 (5). Smoking rates vary regionally: Kentucky, a major tobacco producer, had the highest smoking rate in the country in 2013, 30%, followed by West Virginia and Mississippi. Utah had the lowest rate (12%), followed by California and Minnesota. Smoking rates among lesbians, gays, and bisexuals are 28% compared to 17% among heterosexuals. According to Legacy, the higher smoking rates are tied to greater social stress, more frequent visits to bars, and higher rates of alcohol use. The adult smoking rate among Americans below the poverty line was 28% in 2012, compared to 17% for those above the poverty line. The smoking rate in households with annual incomes above $100,000 is 9%.

Cigarettes cost less in heavy smoking states. The 10 states with the highest smoking rates had an average cigarette tax of 82¢ a pack in 2012, compared with $2.42 in the 10 states with the lowest smoking rates. About 70% of American smokers say they want to quit, and about 50% try to quit every year. Many smokers indicate that they are ashamed of the habit, but kicking the habit remains tough. Only about 1 in 20 who try to quit actually succeed.

Forty-two million is still a lot of people. In some states a pack of cigarettes is now over $10. If one put $10 in the bank every day of the year from age 18 to 65, one would be quite well off when retiring, if still alive.

HIGH SCHOOL SMOKING
In 2013, just 16% of high school students in the US smoked cigarettes, down from 36% in the peak year of 1997, according to the CDC (6, 7). Other news from the survey of >13,000 teens: 25% of students were in physical fights in 2013, down from 42% in 1991; and 32% watched 3 hours of TV daily, down from 43% in 1999. Some of that time shifted to computers, with 41% using a computer for nonschool reasons at least 3 hours a day, up from 22% in 2003. In addition, 27%
HIV DIAGNOSIS RATE FALLING

The US HIV diagnosis rate fell to 16.1 per 100,000 persons in 2011, down from 24.1 a decade earlier (8). The World Health Organization estimates that 35 million people globally have the virus that causes AIDS. In the US, 1.1 million people are believed to be infected. The diagnosis rate is a direct measure of when people actually tested positive for the virus. The diagnosis rates dropped even as the amount of testing rose. In 2006, the CDC recommended routine HIV testing for all Americans aged 13 to 64, saying an HIV test should be as common as a cholesterol test. The percent of adults ever tested for AIDS increased from 37% in 2000 to 45% in 2010, according to CDC data.

TOO MANY POUNDS GLOBALLY

The obesity epidemic is global: 2.1 billion people, or about 29% of the world’s population, were either overweight (body mass index 26–30 kg/m²) or obese (body mass index >30) (9). The prevalence of overweight and obese people rose nearly 28% for adults and 42% for children between 1980 and 2013. In 1980, 857 million of the world’s population was overweight or obese. (Obese people are also overweight, of course, but this is the terminology now used everywhere.) These data involved 183 countries. No country reported a decrease in obesity during that period! In 2013, 24% of boys and 23% of girls were overweight or obese in developed countries; in developing countries, 13% of boys and 13% of girls were overweight or obese. The number of obese people in 1913, in millions, was as follows: USA, 87; China, 62; India, 40; Russia, 29; Brazil, 26; Mexico, 25; Egypt, 24; Germany, 17; Pakistan, 17; and Indonesia, 15. Body weight is not a good thing for the USA to lead the world in.

POULTRY, PORK, AND BEEF CONSUMPTION

According to the Organization for Economic Cooperation and Development, pork (porcine muscle) is the world’s most consumed meat, but in the next 5 years it is almost certain that poultry will become number one (10). By 2020, global meat consumption in millions of metric tons annually is expected to be the following: chickens, 134; pigs, 129; and cows, 75. The trend is expected to hold true for just about every region and country, developed or developing. Chicken is the cheapest and most accessible meat in the world. Both bovine and porcine meat prices are expected to well outpace prices for chicken. Poultry is also free of the sort of cultural barriers that affect pork. Some of the world’s largest chicken-eating countries per capita are those that consume almost no pork, namely Malaysia, Israel, and Saudi Arabia.

The good news is that the poultry industry is much kinder to the environment than the porcine or bovine industries. Per kilogram consumed, chicken’s carbon footprint is roughly half that of pork, a quarter that of beef, and nearly a seventh of lamb. According to a spokesman of the Environmental Working Group, “If every American stopped eating beef tomorrow and started eating chicken instead, that would be the equivalent of taking 26 million cars off the road!”

A 125-POUND WOMAN DOWNS 144 OUNCES OF BOVINE MUSCLE IN 15 MINUTES

At the Interstate 40 landmark in Amarillo, Texas, the Big Texan Steak Ranch, Molly Schuyler—a professional competitive eater who this year also broke the world record for consuming huge quantities of chicken wings in a certain amount of time—at the first 72-ounce steak dinner with all the trimmings in 5 minutes, and a second 72-ounce steak dinner with all the trimmings in <10 minutes. Amazing! I wonder how she felt the next day.

LIFE EXPECTANCY

People around the world are living longer, according to the World Health Organization (11). The average girl born in 2012 can expect to reach 73 years and the average boy, 68. That gives them an average of 6 more years of life than children born in 1990. The US does better than average, with a female life expectancy now of 81 and a male life expectancy of 76. Nevertheless, the US ranks 37th overall and does not make the top 10 for either gender. The life expectancy of the top 10 countries for females in years are the following: Japan, 87.0; Spain, 85.1; Switzerland, 85.1; Singapore, 85.1; Italy, 85.0; France, 84.9; Australia, 84.6; Republic of Korea, 84.6; Luxembourg, 84.1; and Portugal, 84.0. The top 10 countries for male life expectancy in years: Iceland, 81.2; Switzerland, 80.7; Australia, 80.5; Israel, 80.2; Singapore, 80.2; New Zealand, 80.2; Italy, 80.2; Japan, 80.0; Sweden, 80.0; and Luxembourg, 79.7.

OPTIMAL NIGHT’S SLEEP

Several sleep studies, according to Somathi Reddy (12), have found that 7 hours—not 8 hours—is the optimal amount of sleep when it comes to certain cognitive and health markers. Other recent studies have shown that skipping on a full-night’s sleep, even by 20 minutes, impairs performance and memory the next day. And, getting too much sleep, not just too little, is associated with health problems including diabetes mellitus, obesity, and certain cardiovascular diseases, as well as higher rates of death. The lowest mortality and morbidity is with 7 hours! The CDC is helping to fund a panel of medical specialists to review the scientific data on sleep and develop new recommendations, probably by 2015.

A study by Kripke and colleagues (13) in 2002 tracked over a 6-year period data on 1.1 million people who participated in a large cancer study. People who reported that they slept 6.5 to
7.4 hours had a lower mortality rate than those with shorter or longer periods of sleep. In that study, 32 health factors were controlled for, including medications. Another study, also by Kripke and associates (14) in 2011, recorded the sleep activity of about 450 older women using devices on their wrist for a week. Some 10 years later, the investigators found that those who slept <5 hours or >6.5 hours had a higher mortality.

Studies based on people reporting their own sleep patterns may have some inaccuracies. Timothy Morgenthaler, president of the American Academy of Sleep Medicine and professor of medicine at the Mayo Clinic Center for Sleep Medicine, advises patients to aim for 7 to 8 hours of sleep a night and to evaluate how they feel. Sleep needs vary between individuals, largely due to cultural and genetic differences. People should be able to figure out their optimal amount of sleep in a trial of 3 to 7 days, ideally while on a vacation. An alarm clock should not be used. Go to sleep when you get tired. Avoid too much caffeine or alcohol. Stay off electronic devices a couple of hours before going to bed. These investigators advise that during the trial, you should track your sleep with a diary or a device that records your actual sleep time. If you feel refreshed and awake during the day, you’ve probably discovered your optimal sleep time.

The new sleep guidelines will be drawn by a panel of experts being assembled by the American Academy of Sleep Medicine, the Sleep Research Society, and the CDC. Another group, the National Sleep Foundation, has also assembled an expert panel that expects to release updated recommendations for sleep times in January 2015. These groups currently recommend 7 to 9 hours of nightly sleep for healthy adults. The National Heart, Lung, and Blood Institute recommends 7 to 8 hours. Most current guidelines say school-aged children should get at least 10 hours of sleep a night and teenagers, 9 to 10.

The average American adult sleeps 6 hours 31 minutes on an average weekday and 7 hours 22 minutes on weekends. About 70% of Americans get less sleep on workdays than they say they need. Sleeping with a partner is preferred by 60% of adults. About 20% of American adults sleep with a pet. Pajamas are worn by 73% of American adults and 12% sleep nude. A third of adults sleep with one pillow, 40% with two, and 15% with four or more pillows.

FROM BABY DIAPERS TO ADULT DIAPERS

In the past 4 years, sales of baby diapers in the US have fallen 8% and sales of adult incontinence products have increased 20% (15). Births peaked in the US at 4.32 million in 2007 and declined for 5 years before leveling off recently. Some 3.96 million babies were born in the US in 2013, up slightly from 2012. The country’s fertility rate has dropped to a record low of 63 births per 1000 women of childbearing age. At the same time, >3 million Americans are now turning 65 years every year. Over the past 15 years, US sales of incontinence products have roughly tripled to around $1.5 billion annually. Globally, sales of these incontinence products are growing at a rate of 84% annually, faster than paper-based household products. As many as 25 million Americans, or about 1 in 10 adults, have some form of urinary incontinence that can range from occasional small leaks when they cough or sneeze to a complete loss of bladder control.

While most infants and toddlers use diapers for 2 to 3 years, incontinence users typically have to buy products for much longer periods, as the problem seldom goes away. The average user spends about $80 a month. Retiring baby boomers—Americans born between 1946 and 1964—are driving a surge in the US population aged ≥65, which is expected to nearly double to 84 million by 2050 and make up 20% of the country.

KARL FRIEDRICH MEYER (1884–1974)

My introduction to Dr. Meyer was via a recent article published in Lancet by Mark Honigbaum (16). Meyer was born in Basel, Switzerland and began his research studies at the University of Basel in 1902, where he concentrated on biology, zoology, histology, and laboratory techniques. In 1909, he received a doctorate of veterinary medicine from the University of Zurich, and in 1924 during a sabbatical from the University of California, he obtained a PhD in bacteriology from the University of Zurich. His first employment was in South Africa, but in 1910 he moved to the Veterinary School of Pennsylvania, where he soon rose to full professor. There he worked on glanders, a bacterial disease in horses, mules, etc., which first affects the mucous membranes. It may be lethal and is dangerous to humans. He also helped elucidate the transmission of the bacteria causing a contagious abortion disease of cattle and also affecting humans via unsterilized milk, causing possibly lethal fever. This disease was called Brucellosis. In 1914, he moved to San Francisco and the University of California at Berkeley, where he stayed the rest of his life.

In 1950, Reader’s Digest invited Paul De Kruif to pen a tribute to his friend, veterinarian and bacteriologist Karl Friedrich Meyer. In 1926, when Sinclair Lewis was casting around for a real-life disease detective with which to populate his novel Arrowsmith, it is said De Kruif suggested Meyer as the model for Gustaf Sondellius, Lewis’s Swedish plague-hunter. In 1928, De Kruif, a Dutchman who had worked at the Rockefeller Institute, published Microbe Hunters, A History of the “Great Men” of Medical Microbiology. De Kruif called Meyer “the most versatile microbe hunter since Pasteur.” He described how Meyer from his laboratory in San Francisco had gone in search of the hidden factors of a series of deadly food-borne, animal-borne, and arthropod-borne diseases. In a career spanning over 3 decades, Meyer showed that botulism was a highly resistant spore found in soils across the USA; that psittacosis or “parrot fever” was an ornithosis spread by some 50 species of birds; and that the mysterious outbreaks of “staggers” seen in horses in the American Midwest during the 1930s and 1940s were due to equine encephalitis, a virus transmitted by mosquitoes that bred along irrigation ditches.

Just as in the 21st century concerns about food and security, climate change, and the incubation of humans into the natural habitats have led to the recognition of new emerging infectious diseases, so in the 1930s California’s rapid population growth and the incursion of settlers into valleys and deserts teeming with arthropod-bearing parasites and exotic fungi presented public health workers with new and unexpected disease
challenges. To solve these problems, Meyer ventured far from his laboratory, enlisting the aid of experts in entomology, animal ecology, and soil and climate science. At the same time, drawing on his expertise as a comparative pathologist, he had to convince often skeptical public health officials of the threat that animals, whether in the form of dairy herds (Brucellosis), parakeets (psittacosis), or ground squirrels (sylvatic plague), posed to human populations at a time when the importance of latent "infections" and "animal reservoirs" popularized by Meyer were not widely appreciated. This was no easy task. Thus, Meyer was an important bridge figure in mid-20th century medical research that sought to link microbial behavior to broader bacteriological, environmental, and social factors that affect host-pathogen interactions and the mechanisms of disease control.

As Honigsbaum describes, Meyer made many contributions to the burgeoning field, and one can get a sense of his methodology in changing thinking on disease from his investigation, particularly of psittacosis. Today, few people recall the hysteria about the parrot fever epidemics of the 1930s, but in the preantibiotic era, psittacosis was a disease that, like avian influenza or severe acute respiratory syndrome today, could provoke widespread panic. This was particularly the case in the US, where lurid stories about diseased Argentinean parrots were taken up by the prominent magazine American Weekly and the illness of the wife of a prominent US senator prompted Herbert Hoover to ban the interstate transport of lovebirds.

Although by 1930, it was known that psittacosis was transmitted by parrots, before Meyer, no one appreciated the extent to which the disease was also spread by parakeets, or that the large proportion of budgerigars bred in American aviaries harbored the "virus" (actually a small intracellular bacterium, Chlamydia psittaci) without displaying signs of illness. These silent infections were a particular problem in California where, during the Depression, many people supplemented their incomes by breeding budgerigars in backyard aviaries.

The urgent need for a study of psittacosis had been brought home to Meyer in December 1931, when three elderly California women had taken ill at a coffee club, dying soon thereafter. Meyer quickly established that the women had been infected by a pet budgerigar and that the bird had come from an aviary in Los Angeles. Meyer found that psittacosis was endemic to aviaries in the city, prompting the question of how the disease had been first introduced to southern California. To find out, Meyer paid a barber on a Pacific liner to bring him 200 wild shell parakeets from Australia. On arrival in San Francisco, these birds were placed in quarantine while Meyer waited to see what would happen. When one of the birds died 4 weeks later, Meyer did an autopsy. To his astonishment, he found typical lesions of psittacosis in the bird's spleen, the same as had been observed in California budgerigars. Meyer immediately shared the information with Charles Kellaway, who was in San Francisco at the time, and on his return to Australia Kellaway alerted Frank Macfarlane Burnet, who launched his own study in which he found that psittacosis was an endemic infection of wild parakeets and had probably been enzootic among Australian parrots for centuries. Burnet, who later was awarded the Nobel Prize, postulated that while the wild young birds were infected in the nest, these natural, mild infections could flare up under the stress of close confinement, resulting in the birds' losing their acquired resistance and shedding the virus. By questioning importers, Meyer established that it was common practice for shippers to throw wild unbanded birds into the same pens as clean birds, greatly facilitating the spread of the virus. He concluded that in the wild these virus strains were highly adapted to their avian hosts, but conditions in shipping containers in California aviaries had greatly increased their virulence—hence, the frequent spillovers of enzootic psittacosis infections into humans.

By 1934, Meyer had tested nearly 30,000 parakeets and certified 185 California aviaries as psittacosis-free. Although he insisted that test animals at his laboratory be kept in a special isolation room and that his laboratory workers wear rubber gloves and masks at all times, the rules were not always observed. In 1935, Meyer himself breached protocol when he removed his rubber gloves to take a phone call and developed psittacosis. Meyer fortunately made a full recovery. A fascinating investigator.

**ARNOLD S. RELMAN, MD (1923–2014)**

Dr. Marvin Stone recently called my attention to an article in The New York Review of Books entitled "On Breaking One’s Neck" by Arnold Relman (17). Dr. Relman served as editor in chief of the New England Journal of Medicine from 1977 through 1991 and before that was a renowned clinician and investigator (in nephrology). He was professor of medicine and director of the Boston University Medical Services at Boston City Hospital and, later, chair of the department of medicine at the University of Pennsylvania School of Medicine. He also was editor of the Journal of Clinical Investigation from 1962 through 1967 and was a member of the Institute of Medicine of the National Academy of Sciences.

The essay "On Breaking One’s Neck" by Dr. Relman describes his hospital experiences after an accident on June 27, 2013, 10 days after his 90th birthday, when he suddenly and disastrously fell down the stairs of his home, broke his neck, and nearly died. Subsequently, he made an astonishing recovery, in the course of which he learned how it feels to be a helpless patient close to death. He also learned some things about the US medical care system that he had not fully appreciated, even though it was a subject that he had studied and written about for many years. His essay regarding his own treatment and his impressions thereof is a fascinating read. Just a few months after his injury, he began to resume his previous activities and enjoy life again.

He called his recovery astonishing, and it would never have happened without the superb emergency treatment he received at the Massachusetts General Hospital and the rehabilitative care that followed in another institution. But as he indicated, he was convinced that other factors contributed to his survival: his family support, a strong body, an intact brain, and very good luck. He also believed that his previous medical training helped because it made him aware of the
The balance of nature—an ideal state in which every species is biologist in Canada calls what’s happening “global swarming.” numbingly homogenized as invasives spread across the globe. A planet is becoming a giant mixing bowl, one that could end up forcing species to move as they adapt to rising temperatures. The around in the ballast water of cargo ships. Climate changes are During any 24-hour period, some 10,000 species are moving around in the ballast water of cargo ships. Climate changes are

Species have been brought into the country by human beings Authorities at Los Angeles International Airport seized 67 live invasive giant African snails that were apparently intended for human consumption (20). The pythons are not alone. On nearly every border, the US is under biological invasion. A quarter of the wildlife in the world. There are more than 50,000 alien species in the world. They where they often compete or simply eat native flora and fauna. Invasive species are probably the second biggest threat to endangered animals after habitat loss. One study suggested that invasives could cost the US as much as $120 billion a year in damages. In Texas, feral hogs rampage through farmers’ fields; in the Northeast, Emerald Ash borers turn trees into kindling; in the Great Lakes, zebra mussels encrust pipes and valves, rendering power plants worthless. On July 1, 2014, authorities at Los Angeles International Airport seized 67 live invasive giant African snails that were apparently intended for human consumption (20).

Invasion biology has become a sprawling discipline with its own journals, academic centers, and graduate programs (20). Just because a plant or animal is alien does not automatically mean it will become a dangerous invasive. But all else being equal, it is better for nature if species stay at home, and it is estimated 20% more species now than it did before European colonization. On a global scale, unchecked invasions can lead to planetary homogenization. Just as global trade has allowed megabrands like Wal-Mart and McDonald’s to spread around the world, crushing local mom and pop shops, human activity has allowed jellyfish and Argentine ants to invade new territory, displacing natives along the way.

**ALIEN SPECIES INVADING THE USA**

As Bryan Walsh (20) indicates, Burmese pythons began appearing regularly in South Florida >15 years ago. It is likely pythons, brought in as pets, either escaped or were released into the wild and then like so many retirees before them, fell in love with the Sunshine State’s climate. Today, as many as 100,000 Burmese pythons may be living amid the wetlands of South Florida, though no one knows for sure. Scientists have linked a drastic decline in small mammals in South Florida’s Everglades National Park to the pythons, which can lay up to 100 eggs at a time, grow more than 7 feet in their first 2 years, and now face no natural predators.

The pythons are not alone. On nearly every border, the US is under biological invasion. A quarter of the wildlife in South Florida is exotic, more than anywhere else in the US, and the region has one of the highest number of alien plant in the world. There are more than 50,000 alien species in the US, where they often compete or simply eat native flora and fauna. Invasive species are probably the second biggest threat to endangered animals after habitat loss. One study suggested that invasives could cost the US as much as $120 billion a year in damages. In Texas, feral hogs rampage through farmers’ fields; in the Northeast, Emerald Ash borers turn trees into kindling; in the Great Lakes, zebra mussels encrust pipes and valves, rendering power plants worthless. On July 1, 2014, authorities at Los Angeles International Airport seized 67 live invasive giant African snails that were apparently intended for human consumption (20).

The problem seems to be getting worse (20). Most invasive species have been brought into the country by human beings either on purpose, in the case of exotic pets or plants, or accidently with alien species hitching a ride to new habitats. During any 24-hour period, some 10,000 species are moving around in the ballast water of cargo ships. Climate changes are forcing species to move as they adapt to rising temperatures. The planet is becoming a giant mixing bowl, one that could end up numbingly homogenized as invasives spread across the globe. A biologist in Canada calls what’s happening “global warming.” The balance of nature—an ideal state in which every species is in its right place—is seemingly being upended.

Life has always been on the move, but until recently that mobility was limited by oceans, mountains, and other geographic barriers. That separation allowed life to evolve into as many as 8.7 million separate species, if not far more. But then Homo sapiens arrived. As humans spread around the globe, they brought their favorite plants and animals with them, along with stowaways like black rats, which originated in tropical Asia before infesting the planet from the holds of sailing ships.

For a long time there was little concern about the effects of introducing alien species to new ecosystems; they were sometimes even sought after. It is not surprising that the growth of invasive species has closely followed the growth of global trade. As canoes and clippers gave way to container ships and jumbo jets, it became easier to move species around the globe. The sheer speed in which things move around the planet gives species coming from one part of the planet a much better chance to arrive alive, happy, and ready to reproduce in another part. Since the St. Lawrence Seaway was opened in 1959, oceangoing vessels have been able to sail into the lakes, bringing alien species with them. That is how the zebra mussel, one of the most tenacious aquatic invasives, found a home in the Great Lakes. There are now millions of the mussels in the Great Lakes; clusters encrust anchors and docks and disrupt the marine food chain. Zebra mussels can grow so plentiful that they block the intake valves of power plants and industrial facilities, causing hundreds of millions of dollars in damage. The mussels take all the plankton out of the water, pulling the rug out from under the entire ecosystem.

The reality is that we already live in a deeply invaded world. Alien species are everywhere. Almost all of the grasses in American lawns come from somewhere else, including Kentucky Blue Grass. More than one-quarter of the plants in Vermont and more than one-third in Massachusetts come from outside those states (20).

Invasive plants and animals have flocked to Florida for some of the same reasons that more than 600 people a day move there: the sunny climate, the plentiful land, and a generally welcoming attitude toward newcomers. And like the new human arrivals, invasive wildlife enters the state through the sprawling Miami International Airport, which ranks first in the US in international freight shipments and live-animal traffic, with about 3000 live wildlife shipments every month. While border control officials check cargo for invasive species, the sheer number of alien species entering Florida on any given day and a climate that seems designed to turbocharge the growth of anything living tilts the odds in the species’ favor.

Invasion biology has become a sprawling discipline with its own journals, academic centers, and graduate programs (20). Just because a plant or animal is alien does not automatically mean it will become a dangerous invasive. But all else being equal, it is better for nature if species stay at home, and it is worth spending billions of dollars worldwide to prosecute a war against aliens. Even though the spread of invasives can actually lead to an increase in local diversity, North America has an estimated 20% more species now than it did before European colonization. On a global scale, unchecked invasions can lead to planetary homogenization. Just as global trade has allowed megabrands like Wal-Mart and McDonald’s to spread around the world, crushing local mom and pop shops, human activity has allowed jellyfish and Argentine ants to invade new territory, displacing natives along the way.
BUNDLED HOSPITAL PAYMENTS

Traditionally, hospitals have charged patients separately for every service and supply they use (21). Fees for surgeons, anesthesiologists, and other providers come in complex bills of their own. Now, more hospitals see so-called “bundled” payments as the wave of the future. In bundled care, patients or insurers are charged one overall price for everything involved in, say, a hip replacement or coronary bypass—from the preoperative tests to postoperative care, for as long as 120 days after the surgery. If the hospital delivers that care for less than the stated price, it keeps the savings. If complications occur and the patient needs more care, the hospital absorbs the extra cost. Proponents say bundled payments, unlike fee-for-service billing, provide strong incentives for physicians and hospitals to work together to keep costs and complications low. Patients and insurers also know upfront what care will cost, which is usually much less than the sum of all those separate bills. The concept began with heart surgery and joint replacement and is expanding to cancer care and chronic conditions, such as diabetes mellitus. According to Melinda Beck, some 350 health care organizations are participating in pilot bundled-payment programs with Medicare, covering 48 health conditions. Several states are experimenting with bundles in their Medicaid programs.

Promising to deliver quality care at a specific price does put physicians and hospitals at risk, so agreeing on what the bundle includes and how to price it is critical. Geisinger Health System, a bundling pioneer, redesigned its procedures and eliminated unjustified variation in care, and outcomes improved and costs decreased. In its first 2 years, Geisinger’s coronary bypass bundle decreased costs by 5% and reduced the mortality rate by 67%. Its perinatal program reduced the rate of Cesarean sections by 36% and the average stay in the neonatal intensive care unit by 1.5 days. To date, however, the only health plan using Geisinger’s care bundle is its own, a nonprofit health maintenance organization with nearly 450,000 members. Commercial insurers have been slow to embrace bundled care because it requires them to process claims differently. More than 100 hospitals initially involved in Medicare’s pilot program decided not to continue, mainly due to administrative issues. Bundled payments pose significant challenges—including how hospitals should set prices, manage costs, distribute savings, and get physicians to think about delivering integrated care, rather than isolated care.

INTERNAL MEDICINE FELLOWSHIPS

The percentage of internal medicine specialty fellowships filled for positions starting in July 2014 were the following: cardiovascular disease, 99.6%; pulmonary disease/critical care, 99.4%; gastroenterology, 98.0%; hematology/oncology, 97.1%; rheumatology, 91.7%; endocrinology/diabetes and metabolism, 91.2%; infectious disease, 77.4%; nephrology, 75.9%; and geriatric medicine, 42.1%.

GRADUATE MEDICAL EDUCATION

As Chandra and colleagues (22) pose it, “A central health care–related policy question for the United States is whether the federal government’s role in financing graduate medical education (GME) increases the number of physicians trained and influences their specialty choices by subsidizing the cost of training.” As these authors indicate, total federal GME funding amounts to nearly $16 billion annually. Medicare’s contribution to GME is $9.5 billion, nearly $3 billion for direct medical education to pay the salaries of residents and supervising physicians, and about $6.5 billion for indirect medical education to subsidize the high cost that hospitals incur when they run training programs. Federal Medicaid spending adds another $2 billion for GME, and an additional $4 billion comes from the Veterans Health Administration and the Health Resources and Services Administration. States support GME through nearly $4 billion in Medicaid spending. These authors argue that direct medical education funding does little to offset the training of physicians; residents essentially pay the full cost of their training, while the direct medical education program simply transfers money to recipient hospitals. Indirect medical education is more controversial in terms of both the accuracy of the costs that are reimbursed and the underlying concept: paying institutions more because they spend more, rather than because they provide higher value. Such cost-based reimbursement runs counter to the direction that health care reimbursement is heading.

If the policy goal of federal funding for GME training is to alleviate physician indebtedness or to encourage more medical school graduates to go into primary care practice, other strategies may be more effective, such as offering selective loan forgiveness or vouchers to offset tuition for trainees who opt for careers in primary care. Such strategies, these authors argue, directly benefit the recipient physician instead of the training institution. Alternatively, if the current training system is not preparing residents adequately to practice using team-based strategies or to focus efficiently on improving health care outcomes, GME monies could be targeted for activities directed toward these goals, with appropriate metrics verifying the outcomes of the training.

WASHINGTON LOBBYING

From 1999 through 2013, 20 different interest groups or individual firms spent at least $150 million to influence Congress
and executive branch agencies (23). The biggest spender was the US Chamber of Commerce, spending $1,066,810,680; number 2 was the American Medical Association, which spent $306,077,500; the American Heart Association was number 5, with $259,177,661; number 6 was the Pharmaceutical Research and Manufacturers of America, with $255,146,420; and Blue Cross Blue Shield was number 8, at $231,835,532. The totals for the US Chamber were not limited to what was spent to lobby federal officials, but also included spending to influence state and local governments. The biggest spenders in 2013 included pharmaceuticals/health products, $226,114,456; followed by insurance, oil, and gas, computers/Internet, electric utilities, and TV/movies/music. These lobbying expenses do not include political donations to various candidates.

THE ATHENA DOCTRINE

The subtitle to this book by John Gerzema and Michael D’Antonio is “How Women (and the Men Who Think Like Them) Will Rule the Future” (24). These authors surveyed 64,000 people in 13 nations; two-thirds said the world would be a better place if men thought more like women. The sentiment was the same across the planet: “We’ve had enough of the winner-takes-all masculine approach to getting things done; it’s time for something better.”

In 2010, these authors wrote the book Spend Shift, and during the year afterwards they traveled the country and heard from many people who agreed with the thesis that a quiet revolution had taken place in “the way we buy, sell, and live” and applauded how individuals, families, businesses, and organizations were adapting to tougher economic conditions. These authors stressed the theme of adaptation and not merely survival because they saw that the effects of the “Great Recession” that began in 2008 would not be reversed quickly. Despite low interest rates, government spending, government cutbacks, and bank bailouts, full recovery seemed elusive. A growth did return, of course, to the US economy, but its pace was anemic and the previously high employment rates have not returned. Although the immediate insights offered in Spend Thrift were clear, these authors learned more as they presented them to audiences around the world and began to notice something they had not fully appreciated. Most of the traits exhibited by the successful entrepreneurs, leaders, organizers, and creators whom they profiled seemed to come from aspects of human nature that are widely regarded as feminine. That was not to say that these innovators were mainly women—indeed, they were not—or that they believed that human equality belonged primarily to one gender or the other. It was simply that time and again these authors heard people say the skills required to thrive in today’s world—such as honesty, empathy, communication, and collaboration—come more naturally to women. The authors decided that they needed to conduct research to discover how people in various parts of the world define traditionally masculine and feminine traits. Then the authors had to discover if the feminine qualities were more highly valued. If the answer turned out to be yes, then they could search for case studies to show that the trend worked in the real world.

To better define masculine and feminine, the authors sampled 32,000 people to classify 125 different behavioral traits as masculine, feminine, or neither. They chose words like selfless, trustworthy, curious, and kind from previous empirical studies in behavioral psychology and gender-related research. They found a strong consistency across countries in what was perceived as feminine, masculine, or neither. Some words defining masculine included rugged, dominant, strong, arrogant, rigid, leader, analytical, proud, decisive, ambitious, overbearing, hardworking, logical, aggressive, brave, daring, competitive, gutsy, stubborn, assertive, driven, and direct. Words defining feminine included free-spirited, charming, trustworthy, articulate, reliable, dedicated, dependable, reasonable, nimble, adaptable, obliging, healthy, popular, passive, committed, helpful, creative, flexible, intuitive, social, sincere, passionate, kind, supportive, giving, good listener, gentle, vulnerable, emotional, involved, friendly, selfless, empathetic, understanding, patient, poised, and trendy. After defining their terms, the authors developed a statistical model for how masculine and feminine traits related to solving today’s challenges. After getting the data, they saw that across age, gender, culture, and country, feminine traits correlated more strongly with making the world a better place than did masculine traits.

The authors found that many of the qualities of an ideal modern leader are considered feminine. We seek a more expressive style of leader, one who shares feelings and emotions more openly and honestly. Across the globe, societies want those in power to connect more personally—an understandable response to the hidden agendas and tightly wound power circles often associated with men. They found that an ideal leader must be a long-term thinker who plans for the future to bring about sustainable solutions, rather than posturing for expediency. The qualities of being decisive and resilient (identified as more masculine) are both important, but the definition of “winning” is changing. It is becoming a more inclusive construct rather than a zero-sum game. In a highly interconnected and interdependent economy, masculine traits like aggression and control, which are largely seen as “independent,” are considered less effective than the feminine values of collaboration and sharing credit. They found that being cause-focused rather than self-focused was a more valued leadership trait. This perhaps indicates that being loyal (feminine) was more important than being proud (masculine). We want our leaders to be more intuitive, more understanding of others’ feelings, and more able to access various angles of a problem or consequences of an action before taking action. They also found that being flexible is an essential modern skill. It permits people to listen, learn, and build consensus to get things done. They found that over 80% of their respondents said that relationships and respect of others count more toward success than money. When they explored the concept of morality, they found that it was strongly associated with loyalty, reason, empathy, and selflessness—all feminine traits. The value placed on this trait reflects society’s outrage over the greed, corruption, and self-interest of our times.

They found that in every country respondents were most in agreement when it came to linking feminine traits and values.
MEGACITIES

There are now 30 cities on planet Earth with populations of ≥10 million: Tokyo has 38 million; Delhi, 25; Shanghai, 23; Mexico City, 21; San Paulo, 21; Mumbai, 21; Osaka, 20; Beijing, 20; New York, 19; Cairo, 18; Dhaka, 17; Karachi, 16; Buenos Aires, 15; Kokata, 15; Istanbul, 14; Chongqing, 13; Rio de Janeiro, 13; Manila, 13; Lagos, 13; Los Angeles, 12; Moscow, 12; Guangzhou, 12; Kinshasa, 11; Tianjin, 11; Paris, 11; Shenzhen, 11; London, 10; Jakarta, 10; Seoul, 10; and Lima, 10. Of these megacities, only two are located in the US, six are in China, and three in India (25).

Eight of the 30 largest cities are in countries that the World Bank defines as high-income. By 2030, the United Nations projects that only 4 of the 30 largest cities will be in nations viewed as high income: Tokyo, Osaka, New York, and Los Angeles. In 1950, New York was the largest urban area in the world, with just over 12 million residents. Now, it has nearly 19 million but ranks only ninth. In 1950, only New York and Tokyo had more than 10 million people.

KEVIN Durant

What a guy! He saluted his mother while accepting the National Basketball Association’s Most Valuable Player award in May 2014 (26). Durant responded to the trophy presentation by talking about how much his mom sacrificed, moving the family from apartment to apartment and working long hours to make ends meet. Yet, she always found time to tell his sons that she loved them. She was, said Durant, at his games and his practices and involved in his life in ways that money couldn’t cover—in ways that only a mother’s heart could provide. He fought back tears as he detailed many of those tough moments. He declared that his mother, Wanda Pratt, was “the real MVP.” Her son’s teammates and fans gave her an emotional standing ovation. In Durant’s case, he is all too aware of what his mom selflessly endured to make him a responsible man as she fought the odds of raising a family alone in Washington. “We weren’t supposed to be here,” a sobbing Durant said. “You made us believe, and kept us off the streets, put clothes on our backs, and food on the table. When you didn’t eat, you made sure we ate. You went to sleep hungry. You sacrificed for us.” What a guy and what a mother!

GARRISON KEILLOR

A Prairie Home Companion is the live radio variety show founded and hosted by Mr. Keillor 40 years ago (27). He is a storyteller extraordinaire and his latest work, The Keillor Reader, is a treat. Some brief quotes: “Half of all people are below average.” “Whoever increases knowledge, increases sorrow.” “The rivers run into the sea and yet the sea is not full.” “The race is not to the swift nor the battle to the strong nor riches to men of understanding, but time and chance happeneth to them all.”

SAFEST FORM OF TRANSPORTATION: THE AIRPLANE

In 2013, out of 36.4 million flights, there were 81 accidents and 210 fatalities, down from 90 accidents and 685 fatalities in 2009, according to the International Air Transport Association.

ADVICE FROM A CURMUDGEON

In 2014, Charles Murray, PhD, published The Curmudgeon’s Guide to Getting Ahead: Dos and Don’ts of Right Behavior, Tough Thinking, Clear Writing, and Living a Good Life (28). I believe this is Dr. Murray’s 15th book. Charles Alan Murray (born 1943) is an American paleo conservative and a paleo libertarian-leaning political scientist, author, columnist, and pundit currently working as a fellow at the American Enterprise Institute, a conservative think tank in Washington, DC. He is best known for his controversial book The Bell Curve, coauthored with Richard Herrnstein in 1994, which argues that class and race are linked with intelligence. He first became well known for his book Losing Ground: American Social Policy 1950–1980, which appeared in 1984 and discussed the American welfare system.

His articles have appeared in Commentary Magazine, The New Criterion, The Weekly Standard, The Washington Post, The Wall Street Journal, and The New York Times. Dr. Murray was born in Newton, Iowa, and because of his high SAT score was accepted into Harvard University, where he graduated in history in 1965. His PhD was received in 1974 from Massachusetts Institute of Technology in political science.

The latest book, The Curmudgeon's Guide to Getting Ahead, is written mainly for young people who have recently graduated from college or have just received some type of postgraduate degree, and he advises on how to get ahead in life and how to have a happy one. The book is divided into four basic sections with anywhere from 6 to 13 chapters under each section. The first major section, entitled “On the Presentation of Self in the Workplace,” has the following titles: Don’t suck up; Don’t use first names with people considerably older than you until asked, and sometimes not even then; Excise the word like from your spoken English; Stop “reaching out” and “sharing” and other prohibitions; On the proper use of strong language; On piercings, tattoos, and hair of a color not known to nature; Negotiating the minefield of contemporary office dress; Office emails are not texts to friends; What to do if you have a bad boss; The unentitled shall inherit the earth; Manners at the office and in general; Standing out isn’t as hard as you think. Under the heading “On Thinking and Writing Well” are the following chapters: Putting together your basic writing tool kit; A bare bones usage primer; Writing when you already know what you
want to say; Writing when you don't know what you want to say; Don't wait for the muse; and Learn to love rigor. “On the Formation of Who You Are” has the following chapters: Leave home; Recalibrate your perspective on time; Get real jobs; Confront your inner hothouse flower; Think about what kind of itch needs scratching; Being judgmental is good and you don't have a choice anyway; Come to grips with the distinction between can do and may do; Come to grips with the difference between being nice and being good; Don't ruin your love affair with yourself. In the section “On the Pursuit of Happiness” are the following chapters: Show up; Take the clichés about fame and fortune seriously; Take religion seriously especially if you have been socialized not to; Take the clichés about marriage seriously; Be open to a start-up marriage instead of a merger marriage; Watch Groundhog Day repeatedly; and That's it! Try hard. Be true. Enjoy. Godspeed.

I love this book and I think we all can get a good deal from it.

William Clifford Roberts, MD
August 11, 2014


This exploratory phase II study evaluated the safety and efficacy of belatacept in de novo adult liver transplant recipients. Patients were randomized (N = 260) to one of the following immunosuppressive regimens: (i) basiliximab + belatacept high dose [HD] + mycopheno-late mofetil (MMF), (ii) belatacept HD + MMF, (iii) belatacept low dose [LD] + MMF, (iv) tacrolimus + MMF, or (v) tacrolimus alone. All received corticosteroids. Demographic characteristics were similar among groups. The proportion of patients who met the primary end point (composite of acute rejection, graft loss, death by month 6) was higher in the belatacept groups (42%–48%) versus tacrolimus groups (34%–38%), with the highest number of deaths and graft losses in the belatacept LD group. By month 12, the proportion surviving with a functioning graft was higher with tacrolimus + MMF (93%) and lower with belatacept LD (67%) versus other groups (90%: basiliximab + belatacept HD; 83%: belatacept HD; 88%: tacrolimus). Mean calculated GFR was 15–34 mL/min higher in belatacept-treated patients at 1 year. Two cases of posttransplant lymphoproliferative disease and one case of progressive multifocal leukoencephalopathy occurred in belatacept-treated patients. Follow-up beyond month 12 revealed an increase in death and graft loss in another belatacept group (belatacept HD), after which the study was terminated.


Background: Endovenous laser ablation (EVLA) of the saphenous vein has become one of the preferred treatments for saphenous vein reflux that has resulted in symptomatic lower extremity venous insufficiency or varicose veins. This procedure was noted during initial reports to have a low incidence of postoperative thrombosis of the femoral or popliteal vein adjacent to the treated great saphenous vein (GSV) or small saphenous vein (SSV). Later clinical experience suggested that the actual incidence of this event is higher and it was subsequently termed endothermal heat-induced thrombosis (EHIT).

Methods: We reviewed the office records and the pre- and post-treatment ultrasounds of patients undergoing EVLA in our office from 2005 to 2010 to determine the frequency of EHIT in patients we had treated and then graded them according to a previously published classification.

Results: There were 528 veins treated in 192 men and 336 women. The clinical, etiology, anatomy, pathophysiology (CEAP) class for these patients was I (0), 2 (291), 3 (65), 4 (104), 5 (26), and 6 (40), respectively. The GSV was treated in 496 patients, the SSV in 22, and both were treated in 10 patients. EHIT occurred in 29 of the legs treated for an incidence of 5.1%. The EHIT in the femoral vein were of level 3 (3), 4 (7), 5 (12), and 6 (3), respectively. Two patients developed EHIT in the popliteal vein after EVLA of the SSV. Treatment for the EHIT consisted of observation (13), anticoagulation (9), antiplatelet therapy (2), and nonsteroidal anti-inflammatory agents (1). Duration of therapy was usually 1 week, but 7 patients were treated for periods ranging from 1 to 7 weeks. No pulmonary emboli occurred in any of these patients. The EHIT resolved completely in all patients.

Conclusions: EHIT after EVLA occurs frequently and mainly consists of low-risk level 3, 4, and 5 deep vein thrombosis. The risk of pulmonary embolism is low and the EHIT typically resolves after 1 week. It can be treated with a short course of antiplatelet or anticoagulation therapy, although observation appears to be sufficient as well for lesser grades of EHIT.

CLINICAL AND EXPERIMENTAL DERMATOLOGY

Genetic markers of treatment response to tumour necrosis factor-α inhibitors in the treatment of psoriasis


Background: Anti-tumour necrosis factor (TNF)-α therapies have revolutionized the treatment of psoriasis; however, up to 50% of patients do not respond satisfactorily. Identification of pharmacogenetic markers of treatment response is an important step in the development of individually tailored treatment. The objective of this study was to assess the association of human leucocyte antigen (HLA)-C, killer immunoglobulin receptor (KIR) and vitamin D receptor (VDR) genotypes with response to treatment by etanercept and adalimumab.

Methods: This was a study of 138 patients with severe chronic plaque psoriasis who were treated with etanercept and/or adalimumab. Patients were classified as responders if they achieved a 75% reduction in PASI (PASI75) or were almost clear of psoriasis after 24 weeks of therapy. The frequencies of HLA-C and KIR haplotypes and VDR polymorphisms were compared in responders and nonresponders. The frequency of all HLA-C and KIR genotypes were compared between responders and nonresponders. Th e frequencies of HLA-C and KIR haplotypes and VDR polymorphisms were compared in responders and nonresponders.

Results: The number of patients classified as responders was 46 of 94 (49%) in the etanercept group and 50 of 76 (66%) in the adalimumab group. None of the HLA-C, KIR or VDR genotypes examined was predictive of treatment response. Compared with healthy controls, patients with psoriasis were more likely to have the HLA-C*06 genotype ($P < 0.001$)
and less likely to have the HLA-C*07 genotype \( (P<0.001) \), whereas there was no significant difference in frequencies of any KIR subtype.

**Conclusions:** Using the candidate gene approach to identify biomarkers of treatment response in psoriasis may have limited utility. This was a small study with limited power. Future larger studies are needed to further examine these findings and to explore alternative approaches to identify predictors of treatment response to biological agents.

**CURRENT CARDIOLOGY REPORTS**

*Ischemic and functional mitral regurgitation in heart failure: natural history and treatment*

Benjamin MM, Smith RL, Grayburn PA

*Carr Cardiol Rep* 2014;16(8):517. Reprinted with permission from Springer.

Functional mitral regurgitation (FMR) occurs when normal or nearly normal mitral leaflets are prevented from proper coaptation by underlying left ventricular (LV) dysfunction, mitral annular dilation, or both. FMR is associated with an adverse prognosis in nonischemic or ischemic LV dysfunction. Multiple studies have confirmed that even mild FMR portends a worse prognosis, and that the risk of FMR is independent of LV volumes and other clinical risk factors. FMR can be difficult to quantitate echocardiographically because it is load dependent and can vary considerably from exam to exam. There is a systematic tendency to underestimate FMR severity by echocardiography because the regurgitant orifice in FMR is typically elliptical, but the formula for calculating regurgitant orifice area assumes circular geometry. Treatment of FMR begins with guideline-directed medical therapy (GDMT) for LV dysfunction and heart failure, including cardiac resynchronization, if indicated. Revascularization should be considered for ischemic FMR, when indicated. Finally, mitral valve surgery should be considered in patients undergoing CABG in whom moderate or greater FMR is present, and also when severe asymptomatic FMR persists despite optimal GDMT and revascularization. Percutaneous options for treatment of FMR are in development but are not currently approved in the US.

**INTERNATIONAL JOURNAL OF ENDOCRINOLOGY**

*Inflammatory response in islet transplantation*

Kanak MA, Takita M, Kunnapathodi F, Lawrence MC, Levy MF, Naziruddin B


Islet cell transplantation is a promising beta cell replacement therapy for patients with brittle type 1 diabetes as well as refractory chronic pancreatitis. Despite the vast advancements made in this field, challenges still remain in achieving high frequency and long-term successful transplant outcomes. Here we review recent advances in understanding the role of inflammation in islet transplantation and development of strategies to prevent damage to islets from inflammation. The inflammatory response associated with islets has been recognized as the primary cause of early damage to islets and graft loss after transplantation. Details on cell signaling pathways in islets triggered by cytokines and harmful inflammatory events during pancreas procurement, pancreas preservation, islet isolation, and islet infusion are presented. Robust control of pre- and peri-transplant islet inflammation could improve posttransplant islet survival and in turn enhance the benefits of islet cell transplantation for patients who are insulin dependent. We discuss several potent anti-inflammatory strategies that show promise for improving islet engraftment. Further understanding of molecular mechanisms involved in the inflammatory response will provide the basis for developing potent therapeutic strategies for enhancing the quality and success of islet transplantation.

**JOURNAL OF THE AMERICAN COLLEGE OF SURGEONS**

*Compliance with recommended care at trauma centers: association with patient outcomes*


**Background:** State health departments and the American College of Surgeons focus on the availability of optimal resources to designate hospitals as trauma centers, with little emphasis on actual delivery of care. There is no systematic information on clinical practices at designated trauma centers. The objective of this study was to measure compliance with 22 commonly recommended clinical practices at trauma centers and its association with in-hospital mortality.

**Study design:** This retrospective observational study was conducted at 5 Level I trauma centers across the country. Participants were adult patients with moderate to severe injuries \( (n = 3,867) \). The association between compliance with 22 commonly recommended clinical practices and in-hospital mortality was measured after adjusting for patient demographics and injuries and their severity.

**Results:** Compliance with individual clinical practices ranged from as low as 12% to as high as 94%. After adjusting for patient demographics and injury severity, each 10% increase in compliance with recommended care was associated with a 14% reduction in the risk of death. Patients who received all recommended care were 58% less likely to die \( (\text{odds ratio} = 0.42; 95\% \ CI, 0.28–0.62) \) compared with those who did not.

**Conclusions:** Compliance with commonly recommended clinical practices remains suboptimal at designated trauma centers. Improved adoption of these practices can reduce mortality.

**JOURNAL OF NURSING ADMINISTRATION**

*Development of a tool to measure user experience following electronic health record implementation*

Xiao Y, Montgomery DC, Philpot LM, Barnes SA, Compton J, Kennerly D


**Objective:** The aim of this study was to develop a survey tool to assess electronic health record (EHR) implementation to guide improvement initiatives.

**Background:** Survey tools are needed for ongoing improvement and have not been developed for aspects of EHR implementation.

**Methods:** The Baylor EHR User Experience (UX) survey was developed to capture 5 concept domains: training and competency, usability, infrastructure, usefulness, and end-user support. Validation efforts included content validity assessment, a pilot study, and analysis of 606 nurse respondents. The revised tool was sent to randomly sampled EHR nurse-users in 11 acute care facilities.

**Results:** A total of 1,301 nurses responded (37%). Internal consistency of the survey tool was excellent \( (\text{Cronbach’s } \alpha = .892) \). Survey responses including 1,819 open comments were used to identify and prioritize improvement efforts in areas such as education, support, optimization of EHR functions, and vendor change requests.
Conclusion: The Baylor EHR UX survey was a valid tool that can be useful for prioritizing improvement efforts in relation to EHR implementation.

The impact of opening visitation access on patient and family experience
Nuss T, Kelly KM, Campbell KR, Pierce C, Entzminger JK, Blair BK, Wissinger L, Bryant L, Walker JL.

Restrictive visiting hours have been an obstacle to family participation in care. To support increased and consistent access to patients, Baylor Health Care System implemented a system-wide approach to open access for visitation across all facilities. Nursing and medical leadership led the communication efforts, and shared nursing governance guided revisions to existing policies. Data collected from 13 hospitals demonstrated that patients and families felt more informed; that the nursing staff were more courteous and respectful and explained things in a way that could be understood; that the staff attitude toward visitors was markedly improved; and that comfort and accommodations for guests were extended and improved. The resources needed to deploy these changes are outlined as well as the iterative process needed to create a positive impact on the family partnership in care.

LUNG CANCER

BRAF V600E-mutated lung adenocarcinoma with metastases to the brain responding to treatment with vemurafenib
Robinson SD, O’Shaughnessy JA, Cowey CL, Konduri K

Somatic BRAF mutations have been reported in 1–4% of non–small cell lung cancer (NSCLC), primarily in adenocarcinomas with the BRAF (V600E) mutation in about 50% of the cases. The role of BRAF mutation in NSCLC and the treatment for tumors with such mutations is still evolving. Our patient had metastatic NSCLC with metastases to her brain. Due to the BRAF (V600E) mutation in her tumor and her poor functional status, we offered her off-label treatment with vemurafenib, a BRAF inhibitor approved for use in metastatic melanoma. Our patient’s visceral disease improved, supporting vemurafenib’s efficacy in the treatment of metastatic BRAF-mutated NSCLC. The regression of intracranial disease indicated vemurafenib was able to cross the blood-brain barrier and was efficacious in treating brain metastases in this patient with lung cancer.

MEDICINE

Morphologic features of the recipient heart in patients having cardiac transplantation and analysis of the congruence or incongruence between the clinical and morphologic diagnoses
Roberts WC, Roberts CC, Ko JM, Filardo G, Capehart JE, Hall SA

Cardiac transplantation (CT) has been one of the great medical advances of the last nearly 50 years. We studied the explanted hearts of 314 patients having CT at Baylor University Medical Center Dallas from 1993 to 2012, and compared the morphologic diagnoses to the clinical diagnoses before CT. Among the 314 patients the morphologic and clinical diagnoses were congruent in 272 (87%) and incongruent in 42 (13%). Most of the incongruity occurred among the 166 patients with non-ischemic cardiomyopathy (non-IC) (36/166 [22%]), and of that group the major incongruity occurred among the patients with hypertrophic cardiomyopathy (7/17 [41%]), non-compaction left ventricular cardiomyopathy (NCLVC) (3/3 [100%]), mononuclear myocarditis (3/3 [100%]), arhythmogenic right ventricular cardiomyopathy (ARVC) (4/4 [100%]), and cardiac sarcoidosis (8/8 [100%]). The phrase “non-IC” is a general term that includes several subsets of cardiac diseases and simply means “insignificant narrowing of 1 or more of the epicardial coronary arteries,” but it does not specify the cause of the heart failure leading to CT. A number of cardiac illustrations are provided to demonstrate the morphologic variability occurring among the patients with IC and non-IC.

PLOS ONE

MicroRNA miR-J1-5p as a potential biomarker for JC virus infection in the gastrointestinal tract
Link A, Balaguer F, Nagasaka T, Boland CR, Goel A

Introduction: JC virus (JCV), a human polyomavirus that causes progressive multifocal leukoencephalopathy (PML), has been linked to colorectal cancer (CRC). However, determination of JCV infection and its role in carcinogenesis has been challenging, highlighting the need for better diagnostic strategies for this virus. JCV-specific microRNAs (miRNAs) were identified and shown to negatively regulate oncogenic JCV T-Ag. Herein, we determined the pattern of JCV miRNA expression in clinical specimens from healthy subjects and CRC patients.

Material and methods: JCV miRNA expression was validated in CRC cell lines transfected with the JCV T-Ag. Results were confirmed using CRC tissues that expressed T-Ag. Expression of JCV-specific miR-J1-5p was measured in fresh stool samples from healthy volunteers, and samples from fecal occult blood test kits from healthy subjects and patients with colorectal neoplasms.

Results: JCV miR-J1-5p was detected in JCV-transfected, but not vector-transfected, CRC cells, and was stable between cell passages. MiR-J1-5p was present in all six JCV T-Ag+ CRC samples. Surprisingly, JCV miRNA was detectable in all normal tissues, but the expression was much lower in CRC tissues. Similarly, miR-J1-5p expression was present in all fecal samples, but expression was lower in CRCs compared to controls or adenoma patients.

Conclusion: JC virus–specific miR-J1-5p miRNA is a potential biomarker for viral infection, and the lower expression in patients with colonic neoplasia highlights its biological role regulating oncogenic T-Ag expression in CRC.

Impact: JCV-specific miRNA is a candidate for the development of a non-invasive screening test, as well as therapeutic intervention for JCV-associated diseases.
Instructions for authors

Baylor University Medical Center Proceedings welcomes submissions from Baylor and non-Baylor authors. Send all manuscripts and editorial correspondence to William C. Roberts, MD, Editor in Chief, Baylor Scientific Publications Office, 3500 Gaston Avenue, Dallas, Texas 75246; phone: 214-820-9996; fax: 214-820-4064; e-mail: cynthiao@BaylorHealth.edu. This page presents a shortened version of the instructions. For the complete version, see http://www.baylorhealth.edu/Research/Proceedings/SubmitManuscript/Pages/default.aspx.

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Conclusions: Conclusion paragraphs at the end of the discussion section are rarely needed and are often cut if included.

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Use of color: Authors are asked to pay $100 for each color figure or table. Generally, color is suggested only when clinically required (as with certain pathology and radiology images).

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- A single-paragraph abstract of 150 to 250 words is included.
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“That kind of care is unique.”

— David McFarland, MD
Retired surgeon and Trust Rewards beneficiary

David McFarland, MD successfully practiced General Surgery for 31 years before retiring this year. He now enjoys working on his cattle ranch in the Bastrop area.

We recently paid him a visit to ask about his 22 years of being insured by TMLT. We also asked him about Trust Rewards, our financial benefit program that thanks physicians for their loyalty and commitment to TMLT. Since its inception in 2012, TMLT has allocated $150 million to the Trust Rewards program.

Dr. McFarland told us, “TMLT truly understands the stresses and risks we, as doctors, face in our profession. That understanding makes TMLT more responsive to our needs. That kind of care is unique. I wouldn’t expect any less from a trust governed by Texas physicians.”

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