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ABSTRACTS

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1 Inhibition of Caspases 3/7 Enzyme Activity With an Infusion of Tissue Inhibitor of Metalloproteinases-3 (TIMP-3) Minimizes Apoptosis in Normal Livers During Sublethal Total Hepatic Ischemia in Rats

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Background: The inflammatory response to ischemia/reperfusion injury involves a critical mediator, tumor necrosis factor-α (TNF-α) converting enzyme (TACE). The published literature suggests that the cytokine TIMP-3, a naturally occurring inhibitor, results in healthier-appearing livers in histology and lowered alanine transaminase levels measured in recipients' serum. For this study, we administered TIMP-3 as a continuous infusion 1 hour after the ischemic injury to investigate whether the inhibitor has any effect on the regulation of apoptosis.

Methods: Forty-eight male Wistar rats (n = 4 per group at 4 time points: 6, 24, and 48 hours or 7 days) underwent our established total warm ischemia model for 30 minutes. One hour after ischemia, all animals were cannulated for 1 hour with either 0.9% NaCl solution (control groups) or TIMP-3 at 1000 ng per kg of body weight (treatment groups). After 6, 24, and 48 hours or 7 days of reperfusion, blood and liver tissue samples were collected. Quantitative caspases 3/7 enzyme activity was measured.

Results: All animals survived sublethal hepatic ischemia. In control livers at 6 hours, histological evaluation revealed notable early ischemic changes with pronounced features of apoptosis. Treated samples had intact cytoarchitecture. With a continuous TIMP-3 infusion, notable inhibition of caspases 3/7 enzyme activity was seen.

Discussion: A continuous infusion of TIMP-3 resulted in an inhibited inflammatory cascade that appeared to minimize apoptosis as shown by a decrease in hepatic caspases 3/7 enzyme activity. This study augments the existing evidence that TIMP-3, administered as an infusion after ischemia/reperfusion injury, could be applied clinically to save injured livers in humans.

2 In Vitro Synergy of Telavancin and Rifampin Against *Enterococcus faecium* Resistant to Both Linezolid and Vancomycin

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Background: An emerging pathogen is *Enterococcus faecium* resistant to both linezolid and vancomycin. Antimicrobial combinations may be required for therapy and need to be evaluated. The combination of daptomycin and rifampin has shown good in vitro activity against gram-positive bacteria, including *E. faecium*. Telavancin, a newer lipoglycopeptide, has shown in vitro activity against *E. faecium*. We evaluated the combination of telavancin and rifampin against linezolid- and vancomycin-resistant *E. faecium*.

Methods: Twenty-four genetically unique (by pulsed-field gel electrophoresis) clinical isolates resistant to both linezolid (minimum inhibitory concentrations [MICs] 8 to > 256 μg/mL) and vancomycin (MICs > 256 μg/mL) were collected in the United States. Telavancin MICs were 0.064-8 μg/mL and rifampin MICs 0.012 to > 32 μg/mL. In vitro synergy testing was performed in triplicate by an Etest MIC:MIC ratio method. The resulting combination ellipses were read after 24 hours of incubation at 35°C, and ∑FIC (summation fractional inhibitory concentration) was calculated: synergy < 0.5; indifference > 0.5 to < 4; antagonism > 4.

Results: The Etest synergy method showed synergy (∑FICs, 0.1-0.5) with telavancin plus rifampin in 20/24 (83%) isolates and indifference (∑FICs, 0.6-0.8) in 4/24 (17%) isolates. No antagonism with the combination was found.

Conclusion: The combination of telavancin and rifampin showed in vitro synergy (83%) by Etest against these linezolid- and vancomycin-resistant *E. faecium* isolates. Further in vitro synergy testing with this combination should be performed against additional *E. faecium* and other gram-positive cocci. In vitro synergy may or may not translate into in vivo effectiveness.

3 Nebivolol Prevents Myocardial Fibrosis and Diastolic Heart Failure in Salt-Loaded Spontaneously Hypertensive Rats

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Background: We sought to examine the effects of nebivolol, a novel beta-adrenergic blocking drug with vasodilatory action, in spontaneously hypertensive rats that were given salt excess (HS) (8% NaCl in food).

Methods: Rats were divided into 4 groups: controls received normal salt food; the other 3 were given HS. The second group received a placebo; the third received nebivolol (2×10 mg/kg/day) orally; and the fourth was given the same dose of nebivolol by osmotic minipump. Left ventricular weight index (LVWI), LV hydroxyproline concentration (LVHy), mean arterial pressure (MAP), coronary flow reserve (CFR), minimal coronary vascular resistance (MCVR), maximal rate of ventricular pressure rise (+dP/dT) and decline (-dP/dT), and diastolic time constant (Tau) were determined after 8 weeks of respective therapies.

Results: The results demonstrated that the HS diet induced further rise in MAP (161 ± 7 to 184 ± 8 mmHg), increased cardiac mass (2.85 ± 0.05 to 5.36 ± 0.22 mg/g), LV fibrosis (LVH from 4.12 ± 0.11 to 5.73 ± 0.14 mg/g), coronary insufficiency (decreased CVR from 5.84 ± 0 to 1.63 ± 0.71 mL/g and increased MCVR from 12.22 ± 1.33 to 24.25 ± 1.77 units), and LV diastolic dysfunction (decreased -dP/dT from $-8{,}754 \pm 747$ to $-4{,}234 \pm 754$ mmHg/sec and increased Tau from 12.9 ± 07 to 18.5 ± 1.6 ms). Nebivolol did not prevent the increase in MAP but ameliorated the adverse cardiac effects of HS, as indicated by decreased LV mass and fibrosis and improved coronary hemodynamics and LV function. Nebivolol was more effective when given by continuous infusion (minipump), probably because of its short half-life after oral administration in rats.

Discussion: Nebivolol prevented adverse cardiovascular effects of salt excess through mechanisms independent of arterial pressure, which may involve its antioxidant and antiproliferative properties.

4 Establishment of In Vitro and In Vivo Experimental Models for Lymph Node Microenvironment Influence on Bladder Cancer Cells

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Background: Bladder cancer is the fifth most common carcinoma, the second most frequently seen urologic malignancy, and one of the most expensive diseases to treat. Its resilience may derive from its cancer stem cells (CSCs), which are responsible for tumor recurrence and resistance to treatment. Certain cell markers indicate the presence of CSCs and metastasizing tendencies in an endothelial carcinoma. A lymph node (LN) metastasis gives a negative prognosis because follicular dendritic cells (FDCs), a type of LN stromal cell, foster a protumor microenvironment by encouraging drug resistance. We sought to investigate bladder CSC tumorigenicity and the microenvironment provided by FDCs.

Methods: Human bladder cancer cell lines SW 780 and UM-UC-3 and FDC stromal cell line HK were used to test in vitro sphere formation and proliferation assays and in vivo nonobese diabetic/severe combined immunodeficiency mice xenograft models. Assessment of CSC properties was first performed using cell lines and then confirmed by patient specimens.

Results: SW 780 cells expressed biomarkers CD24, CD44, and CD47. UM-UC-3 cells expressed CD44, CD47, and CD166. UM-UC-3 cells proliferated at a higher rate than SW 780. In both cell lines, cell proliferation and tumor formation were greatly supported by the presence of HK cells in both in vitro and in vivo experimental models, respectively. Under slide examinations, xenoplants resembled clinic patient specimens.

Discussion: We identified a CSC-like fraction in both cell lines that interacted with FDCs. Closer scrutiny of protumor factors provided by LN stromal cells may lead to a novel treatment protocol to prevent bladder cancer relapse.

5 Identification of Prognostic Markers for Follicular Lymphoma Patients

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Background: Follicular lymphoma (FL) is the second most common form of non-Hodgkin lymphoma in the Western Hemisphere. FL arises from B cells, frequently indolent and responsive to initial chemotherapy. However, multiple relapse is common. More than half of relapsed patients become refractory to treatment and do not survive more than 5 years. Because of the variable clinical course of FL, it is important to identify prognostic markers to predict patient outcomes at diagnosis. We sought to establish an FL patient database grouped according to length of survival after diagnosis—$<$ 6 years and $>$ 10 years—and construct a tissue microarray (TMA). Afterward, we identified specific prognostic markers differentially expressed between these 2 groups.

Methods: Pathology reports and chart records were reviewed to confirm FL diagnosis and collect patient prognosis information. Archival paraffin tissue blocks were collected from the Ochsner pathology department, organized as a TMA, and selectively stained for candidate prognostic markers, including cancer stem cell (CSC) markers.

Results: Between 1982 and 2008, 227 patients were diagnosed with FL at Ochsner. Pathology records were retrieved for these patients, and 110 cases were confirmed with available paraffin blocks. The results from pathology reports yielded 35 patients who fell into long- and short-survival groups by a Kaplan-Meier survival curve. Immunological methods were established to stain for ABCG2, Oct-3/4, and aldehyde dehydrogenase FL-CSC markers in these patients.

Discussion: A TMA linked with an FL patient outcome database was established to study differential expression of prognostic markers. Identification of biomarkers associated with clinic prognoses may lead to novel therapies.

6 Follicular Lymphoma Patient Cells Contain Cancer Stem Cells and Depend on Follicular Dendritic Cells for Proliferation and Tumor Formation

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Background: Follicular lymphoma (FL) is the second most common form of non-Hodgkin lymphoma in the Western Hemisphere. Clinically, it is sensitive to initial chemotherapy but followed by eventual relapses, which may involve the interaction between tumorigenic FL cells and stromal cells, such as follicular dendritic cells (FDCs) in the lymph node. We investigated FL tumorigenicity and the microenvironment provided by FDCs.

Methods: After informed consent was obtained, ascitic fluid from an untreated FL patient was collected in which B lymphoma cells (FLA-1) were isolated. Fluorescence-activated cell sorting was used to detect a side population (SP) and determine FLA-1 phenotype. The interaction between FLA-1 and FDC cell line (HK cells) was investigated by in vitro growth assay and in vivo nonobese diabetic/severe combined immunodeficiency mice xenograft experiments. The drug resistance gene ABCG2 was detected by immunohistochemistry. The capacity for colony formation was also evaluated. A small molecule inhibitor to the stromal cell-derived factor-1 receptor CXCR4 (AMD3100) was applied to the migration assay.

Results: FLA-1 cells are dependent on HK cells for growth and tumor formation. FLA-1 cells contain a Hoechst low stain and verapamil-sensitive SP with cancer stem cell (CSC) characteristics, expressing ABCG2 and CXCR4, having the capacity for colony formation and drug resistance. FLA-SP cells migrate toward stromal cell-derived factor-1 alpha (SDF-1α) with a significantly higher index compared with unsorted cells. AMD3100 inhibited the migration.

Discussion: We identified a CSC-like fraction in FL that interacted with FDC in an SDF-1α/CXCR4–dependent manner to resist chemotherapy. Targeting the signals provided by stromal cells may have therapeutic potential to prevent FL relapse.

7 A Retrospective Study of Biomarkers for Colorectal Cancer Recurrence

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Background: A majority of colorectal cancer (CRC) recurrence results from metastatic transmission through the lymphatics. Lymph node (LN) metastasis is a strong negative prognostic factor for CRC. Follicular dendritic cells (FDCs), unique LN stromal cells, were shown to nurture drug-resistant CRC cells responsible for recurrence through the production of various cytokines and growth factors (biomarkers). Thus, these biomarkers can be used to develop a model predictive of recurrence. We sought to identify prognostic biomarkers of CRC recurrence and establish a model to predict recurrence and response to traditional regimens.

Methods: From more than 300 stage II/III CRC patients treated at Ochsner from 1995 to 2005, chart records of 60 age-, sex-, and stage-matched patients were reviewed for prognosis within 5 years of postcurative surgery for primary tumor. These patients' archival specimens were obtained from the Ochsner pathology department and used for tissue microarray (TMA) construction. TMA sections were stained for immunohistochemical evaluation to assess the predictive value of biomarkers with respect to recurrence.

Results: A database of 60 demographically matched CRC patients was established and linked to a TMA to analyze biomarkers of recurrence. Work is constantly in progress to validate identified biomarkers, including markers for cytokines, cancer stem cells, inflammatory cells, and angiogenesis. This tool can be used to develop a mathematical model predictive of CRC recurrence.

Discussion: We established a tool to predict probability of CRC recurrence and identify patients at high risk for recurrence. This tool may assist in developing targeted therapy to minimize recurrence in high-risk CRC patients.

8 Combining Gamma Secretase Inhibitors (GSIs) With Vincristine Offers a Therapeutic Advantage in GSI-Resistant T-Cell Acute Lymphoblastic Leukemia (T-ALL)

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Background: Activating Notch-1 mutations are common in T-ALL. Since Notch signaling contributes to leukemic growth and survival, Notch-1 is an attractive pharmacological target for the treatment of T-ALL. Mutant Notch-1 still requires gamma secretase activity to generate critical downstream signals, which provides the rationale for using GSIs to intervene with Notch signaling. Now several GSIs are in clinical trials for T-ALL. However, not all Notch-1 mutations carrying T-ALL are sensitive to GSI treatment. Hence, we tested whether GSIs in combination with other anticancer drugs offered a therapeutic advantage in these GSI-resistant cells.

Methods: Several GSI-resistant T-ALL cell lines were treated with anticancer drugs or GSI alone, or anticancer drugs in combination with GSI, and then apoptosis assay and cell cycle analysis were performed. To elucidate the molecular mechanisms by which GSI enhances the effect of vincristine, both siRNA technique and pharmacological approaches were introduced.

Results: GSIs significantly augmented vincristine-induced apoptosis in GSI-resistant T-ALL cell lines, although GSIs alone did not affect cell viability. Cell cycle analysis showed that mitotic arrest by vincristine was further increased by GSIs, which preceded an increase in the sub-G1 apoptotic/dead cell population. Furthermore, loss-of-function experiments using siRNA and pharmacological drugs revealed that GSIs enhanced vincristine-induced apoptosis by blocking presenilin, a subunit of gamma secretase complex, independent of Notch signaling.

Discussion: Combining GSIs with vincristine would be a promising therapeutic strategy for GSI-resistant T-ALL.

9 Elucidating the Ideal Murine Model for Metastatic Colon and Rectal Cancer

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Background: The disease-free survival of colon and rectal cancer (CRC) has remained unchanged in the past decade, hence the need to study CRC on a cellular and molecular level using predictable heterotopic and orthotopic CRC metastatic cancer models (CRCMMs). In this study, we hypothesized that the most physiologic CRCMMs would provide the highest yield of metastatic human CRC.

Methods: An established human CRC cell line HT-29 tagged with luciferase was further fluorescence-activated cell sorted for CD133 and CXCR4 positivity. Cells were injected into the mice subcutaneously, via the dorsal tail vein (IV), in the colonic mesentery (IM), transrectally (TR), or via the intracecal wall. Tumor growth was followed by caliper measurements of the subcutaneous tumors and by luciferase activity as detected by the IVIS imaging system (Caliper, Waltham, MA). The presence of metastatic disease was also confirmed by the presence of human DNA using quantitative reverse transcription-polymerase chain reaction analysis.

Results: Although the IV model showed the earliest uptake of cancer cells, the TR model showed the most progressive statistically significant tumor growth and metastasis by 30 days ($P < .05$). The IM injection model was not specific in that at necropsy, the location of the primary tumor appeared to be on the anterior abdominal wall.

Discussion: The TR model is minimally invasive, requires little equipment, and is rapid. It also closely mimics the expected pattern of the spread of rectal cancer. This study could serve as a launching pad for other studies evaluating the mechanism of metastatic CRC and testing novel drugs.

10 A Combination Therapy Targeting Colorectal Cancer Tumor-Initiating Cells

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Background: Lymph node (LN) involvement positively correlates to poor prognosis of colorectal cancer (CRC). CRC tumors contain a small population of drug-resistant CD133+CXCR4+ tumor-initiating cells (Co-TICs). The LN stromal microenvironment, specifically follicular dendritic cells (FDCs), significantly promotes the survival and growth of Co-TICs that metastasize to the LN by providing stromal cell-derived factor-1α (SDF-1α), a ligand of CXCR4, and enhancing CRC tumor formation and angiogenesis. We investigated an in vivo combination therapy targeting the Co-TIC population and its LN stromal support.

Methods: Human colon cancer cell line HT-29 cells with or without FDC cell line HK cells were subcutaneously injected into the posterior flank of immunodeficient mice. In some experiments, the CXCR4 inhibitor AMD3100 was delivered to CRC cells by preincubation or by using ALZET microosmotic pumps. Also, 5-FU was delivered via the tail vein. Tumorigenesis was assessed once a week by measuring solid tumors with calipers or through fluorescent and bioluminescent imaging. Tumors were removed and weighed when they became 1 cm^3, and a fluorescence-activated cell sorting (FACS) analysis was performed from tumor cell suspensions.

Results: AMD3100 partially inhibited FDC-enhanced tumor formation in immunodeficient mice. Mice treated with the combination therapy recorded smaller tumor masses. Fluorescent and bioluminescent imaging displayed decreased tumor growth in combination therapy-treated mice. FACS analysis of tumors treated with combination therapy indicated a significant decrease in the Co-TIC population.

Discussion: Therapy-resistant Co-TICs placed in an in vivo LN microenvironment were successfully targeted using combination therapy. Targeting the SDF-1α/CXCR4 interaction along with standard treatments may elucidate treatment methods for minimizing extranodal CRC recurrence.

11 Ectopic Follicular Helper T Cells Support Ongoing Autoantibody Production in Lupus Patients

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Background: Systemic lupus erythematosus is a chronic autoimmune disease characterized by autoantibody production. Follicular helper T (Tfh) cells, a specialized T cell subset that resides in the germinal center (GC) of lymphoid organs, are a key participant in controlling antibody production. We observed that the accumulation of circulating Tfh cells correlated to the levels of plasmablasts and autoantibodies in lupus patients. Here, we further investigated the pathophysiological role of Tfh cells by comparing the ectopically located (peripheral blood and synovial fluid) Tfh cells in lupus patients to the normal GC-Tfh cells in tonsils.

Methods: Peripheral blood from 27 lupus patients and 25 healthy controls was collected after consent. Synovial fluid from an inflamed joint of a lupus patient was collected. Tonsils were obtained from surgery and used to obtain GC-Tfh cells. Mononuclear cells were isolated by Ficoll, stained with fluorescent-conjugated antibodies, and detected via flow cytometry. Tfh cells, non-Tfh cells, and B cells were purified by MACS Columns (Köln, Germany) and cocultured for 10 days. Immunoglobulin G (IgG) in the culture supernatant was detected by enzyme-linked immunosorbent assay.

Results: Tfh cells existed not only in the peripheral blood but also in the synovial fluid in lupus patients. These ectopically located Tfh cells, which share similar phenotypes and signature cytokines with GC-Tfh cells, are capable of driving B cells to differentiate into IgG-secreting cells in vitro.

Conclusions: By driving self-reactive B cell clones to further differentiate into antibody producing plasmablasts, the ectopic Tfh cells contribute to the pathogenesis of systemic autoantibody-driven autoimmune disease and may serve as a promising therapeutic target.

12 Identification of Follicular Helper T Cells as a Novel Cell Population Potentially Involved in the Pathogenesis of Rheumatoid Arthritis

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Background: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of the synovium, causing progressive joint destruction. The treatment for RA is largely based on the clinic manifestations, which are likely to be remote from the fundamental pathophysiologic defects. The identification of cellular subsets or biomarkers according to the pathophysiologic defects is a necessary first step toward more accurate prognosis and better therapeutic decisions. Here, we identified a special T cell subset, follicular helper T (Tfh)-like cells in RA patients and examined the hypothesis that Tfh-like cells may account for the pathogenesis in RA by providing a fostering environment for self-reactive B cells, resulting in autoantibody production.

Methods: Diagnosis of RA is established according to the 2010 revised American Rheumatism Association criteria. RA patients were divided into remission, mild/moderate, and severe groups based on their disease activity score. Laboratory measurements, such as autoantibodies, were obtained. Peripheral blood was collected from RA patients and healthy controls after obtaining informed consent. Flow cytometry was used to determine the surface phenotype (CXCR5, CD57, ICOS, PD-1) and intracellular cytokine production (interleukin-21). Cell staining was analyzed by FlowJo (TreeStar, Ashland, OR) and WinMDI 2.8 (Scripps Research Institute, La Jolla, CA) software.

Results: A novel T cell subset with a Tfh cell signature molecule and cytokine was expanded in the peripheral blood of active RA patients. The percentage of Tfh-like cells correlated with the level of pathogenic autoantibody (anticyclic citrullinated antibody) and disease activity.

Discussion: Circulating Tfh cells may serve as a biomarker indicating the pathogenesis in RA patients. Targeting RA-Tfh cells may provide earlier and precise treatment strategies.

13 Effect of Chronic Sodium Nitrite Therapy on Monocrotaline-Induced Pulmonary Hypertension

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Background: Pulmonary hypertension (PH) is a rare disorder that without treatment is progressive and often fatal within 3 years. The treatment of PH involves the use of a diverse group of drugs and lung transplantation. Nitrite was once thought to be an inactive metabolite of endothelial-derived nitric oxide (NO), and increasing evidence shows that nitrite may be useful in the treatment of PH, but the mechanism by which nitrite exerts its beneficial effect remains uncertain. The purpose of this study was to investigate the effect of chronic sodium nitrite treatment in a PH model in rats.

Method and Results: Following induction of PH with an intravenous (IV) injection of monocrotaline (60 mg), daily intraperitoneal (IP) injections of sodium nitrite (3 mg/kg) starting on day 14 and continuing for 21 days resulted in a significantly lower pulmonary arterial pressure on day 35 when compared to values in untreated animals with monocrotaline-induced PH. In monocrotaline-treated rats, daily treatment with IP nitrite injections for 21 days decreased right ventricular mass and pathologic changes in small pulmonary arteries. Nitrite therapy did not change systemic arterial pressure or cardiac output when values were measured on day 35. The decreases in pulmonary arterial pressure in response to IV injections of sodium nitroprusside, sodium nitrite, and BAY 41-8543 were not different in rats with monocrotaline-induced PH and rats with chronic nitrite therapy when compared to responses in animals in which pulmonary arterial pressure was increased with U46619, suggesting that the mechanisms that convert nitrite to vasoactive NO, activate soluble guanylyl cyclase, and mediate the vasodilator response to NO are not impaired.

Discussion: The present data are consistent with the results of a previous study about monocrotaline-induced PH in which systemic arterial pressure and cardiac output were not evaluated and are consistent with the hypothesis that nitrite is effective in the treatment of monocrotaline-induced PH in rats.

14 Peroxynitrite Has Potent Pulmonary Vasodilator Activity in the Rat

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Background: Peroxynitrite (PN), a reactive oxygen species, is generated in the body by the rapid reaction of nitric oxide (NO) and superoxide. Although PN reportedly worsens pathologic conditions associated with oxidative stress and inflammation, beneficial biologic effects of this molecule have also been found. PN has been reported to have vasodilator as well as vasoconstrictor properties that are dependent on experimental conditions and the vascular bed studied. The mechanism by which PN relaxes vascular smooth muscle reportedly involves the interaction of tissue constituents to form substances that act as NO donors.

Methods: The present study investigated responses to PN in the pulmonary and systemic vascular beds of the intact-chest rat and the hypothesis that formation of S-nitrosothiols is involved in the response to PN using experiments with L-penicillamine (L-PEN), a known PN scavenger.

Results: The present study showed that PN has significant vasodilator activity in the pulmonary and systemic vascular beds and that responses to PN and glyceryl trinitrate (GTN) were not attenuated by L-PEN, whereas responses to sodium nitroprusside (SNP) were markedly decreased. PN had no significant effect on the decreases in systemic arterial pressure in response to SNP and GTN but had a small significant inhibitory effect on the decreases in systemic arterial pressure in response to DEA/NO and S-nitrosoglutathione. PN partially reversed the hypoxia-induced increase in pulmonary arterial pressure. L-PEN had no significant effect on responses to PN compared to control animals, U46619-infused animals, and L-nitro-arginine methyl ester–treated animals. Responses to PN were attenuated by the soluble guanylate cyclase inhibitor (sGC) ODQ. Cardiovascular responses to PN and the putative PN precursor SIN-1 were different in the rat.

Discussion: These data show that PN has potent vasodilator activity in the pulmonary vascular bed of the intact-chest rat and support the hypothesis that a PN interaction with S-nitrosothiols is not the predominant mechanism involved in mediating the vasodilator response. These data suggest that responses to PN are mediated by the activation of sGC and that PN has a small effect on NO bioavailability.

15 BAY 77-7549, an Azaindole-Based Rho-Kinase Inhibitor, Has Long-Acting Vasodilator Activity in the Pulmonary Vascular Bed of the Intact-Chest Rat

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Background: Cardiovascular responses to a highly selective azaindole-based Rho-kinase (ROCK) inhibitor, BAY 77-7549, were investigated in the intact-chest rat.

Results: Intravenous injections of BAY 77-7549 in doses of 10-300 μg/kg produced small decreases in pulmonary arterial pressure, larger dose-dependent decreases in systemic arterial pressure, and no significant change in cardiac output. Vascular responses to BAY 77-7549 were slow in onset and long in duration. When baseline pulmonary vascular tone was increased with U46619 or with L-nitro-arginine methyl ester, the decreases in pulmonary arterial pressure in response to BAY 77-7549 were higher. The ROCK inhibitor decreased the increase in pulmonary arterial pressure in response to ventilation with a hypoxic gas mixture. BAY 77-7549 significantly decreased pulmonary and systemic arterial pressures in rats with monocrotaline-induced pulmonary hypertension.

Discussion: The present study showed that BAY 77-7549 has significant vasodilator activity in the pulmonary and systemic vascular beds that are long in duration. BAY 77-7549 reversed the hypoxic pulmonary vasoconstrictor response and decreased pulmonary and systemic arterial pressures in a similar manner in rats with monocrotaline-induced pulmonary hypertension. These data provide support for the hypothesis that Rho-kinase is involved in regulating baseline tone in the pulmonary and systemic vascular beds and suggest that inhibition of Rho-kinase will promote vasodilation when tone is increased by diverse stimuli, including the plant alkaloid monocrotaline.

16 Antiinflammatory Mesenchymal Stem Cells (MSC2s) in the Treatment of Diabetic Peripheral Neuropathy

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Background: Mesenchymal stem cells (MSCs) are very attractive candidates in stem cell–based strategies that target inflammatory diseases. Preclinical animal disease models and clinical trials have demonstrated that human MSCs can be safely infused, that they selectively hone to inflamed tissue, and that they contribute to quelling the inflammatory process at the diseased tissue.

Methods: To optimize the antiinflammatory effects of MSCs, we primed the cells with toll-like receptor agonists to render them homogenous and capable of decreasing proinflammatory cytokines and chemokines. Such cells are termed MSC2s. Here, we tested the effects of MSCs versus MSC2s versus placebo in a streptozotocin-induced diabetic mouse model with diabetic peripheral neuropathy (DPN). The causes of DPN are multifactorial, with research pointing to the role of proinflammatory cytokines as a contributing factor. The Hargreaves behavioral assay was performed each day before treatment and at the end of the experiment.

Results: Although mice treated with placebo had no change in their behavioral assays, the ones treated with MSCs showed an improvement, with even greater improvement among the mice receiving MSC2s. Further, blood taken from the mice indicated that those treated with MSC2s had lower levels of inflammatory markers such as interleukin-2.

Discussion: This pilot study lays the groundwork for more extensive research that will help determine if MSC2 therapy is an effective treatment in DPN. Our long-term objective is to develop clinical trials for the treatment of DPN using MSC2s in the hope of relieving the pain of the disease and hampering its destruction.

17 Infusion of Cell-Penetrating Peptides Corresponding to the Angiotensin II Type 1 Receptor Reduces Blood Pressure in C57BL6/J Mice

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Background: In previous published studies, we demonstrated that gamma-aminobutyric acid receptor-associated protein (GABARAP) binds to the angiotensin II (AngII) AT1 receptor (AT_1R) and enhances cell surface expression and that a cell-penetrating peptide fused to an AT_1R peptide, (CPP-1), can block GABARAP:AT_1R interaction, effectively reducing AT_1R cell-surface accumulation. Our present study tested whether CPP-1 reduces blood pressure (BP) in whole animals.

Methods: C57BL6/J mice were maintained on a low-sodium diet to render BP as AngII dependent. At day 7, telemeters were implanted for BP measurement. At day 14, catheters were inserted in the right jugular vein in a second surgical procedure. On day 17, baseline BP was recorded for 24 hours. On day 18, CPP-1 (59 ug/100 uL) or corresponding control (cell penetrating peptide-2 [CPP-2] 59 ug/100 uL) was injected into the jugular vein port and then again after 8 hours (5 experimental and 5 control mice).

Results: Active cell-penetrating decoy peptide decreased 24-hour systolic blood pressure (SBP) from 129.8 $\pm$ 2.14 mmHg to 125.0 $\pm$ 2.66 mmHg (mean $\pm$ standard error of mean [SEM], $n = 5$, $P < .01$, paired *t* test, two tailed). Diastolic blood pressure (DBP) fell from 99.0 $\pm$ 3.2 mmHg to 95.0 $\pm$ 4.1 mmHg ($n = 5$, $P < .03$, paired *t* test, two tailed). Administration of a control peptide actually raised SBP from 128.7 to 131.7 mmHg and DPB from 93.9 to 95.9 mmHg, neither statistically significant.

Discussion: Cell-penetrating peptides that block GABARAP:AT_1R interaction effectively reduce whole mouse BP; CPP-1 or corresponding small molecule inhibitors are potential new therapeutic tools for hypertension.

18 Intracellular Angiotensin II Interacts With Mitochondrial Proteins: Identification of Binding Domains

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Background: In a previous study using yeast two-hybrid screening, we isolated 2 Complex I proteins of the electron transport chain—NduFAF4 (nicotinamide dinucleotide plus hydrogen [NADH] dehydrogenase-1a subcomplex assembly factor 4) and NduFS2 (NADH dehydrogenase iron-sulfur protein 2)—that interact with intracellular angiotensin II (AngII).

Methods: To identify the region of interaction within each mitochondrial protein, we cotransformed into yeast several deletion constructs of each protein fused to Gal4 activation domains together with constructs encoding AngII fused to Gal4 DNA-binding domains. We distinguished interacting pairs by growth on agar media lacking leucine, tryptophan, histidine, and adenine.

Results: N-terminal deletions of fibroblast-activating factor 4 (FAF4) (constructs retaining the amino acids 58-173, 100-173, or 116-173) preserved interaction with AngII, while C-terminal deletions (retaining the amino acids 1-150) eliminated interaction. N-terminal deletion of FS2 (retaining amino acids 340-463) preserved interaction with AngII, but further deletion (retaining amino acids 402-463) eliminated it. C-terminal deletions of FS2 (retaining amino acids 340-412 or 340-402) also inhibited interaction. We then quantified the strength of interaction by monitoring growth in liquid media over 72 hours. FAF4 (58-173) cells grew at a rate approaching that of the originally identified protein (1-173), while 100-173 and 116-173 cells grew at rates indicating weaker interactions. FAF4 (1-150) cells exhibited only baseline growth. FS2 (340-463) cells grew at a rate indicating lesser interaction, while all other FS2 constructs exhibited baseline growth.

Discussion: Intracellular AngII may modify electron transport through mitochondrial protein interactions, contributing to hypertension. The identification of the AngII binding domains is the first step in preventing binding.

19 Components of Renin-Angiotensin System in Mouse Kidney

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Background: We have previously reported evidence for kidney thrombotic microangiopathy (TMA) in enhanced cyan fluorescent protein/angiotensin II (ECFP/AngII) transgenic mice, which overexpress intracellular AngII and exhibit elevated blood pressure (BP). To define the role of intracellular AngII in the development of TMA and high BP, we sought first to define the renin-angiotensin system in wild-type C57BL6/J mice. The present study was designed to define the renin-angiotensin system in mouse kidney using 3-dimensional deconvolution immunofluorescence imaging.

Methods: Mouse kidneys were perfused with 4% paraformaldehyde and 10% sucrose, and the Ochsner Pathology Department generated 5 um paraffin sections. Sections were then incubated with antibodies against renin, angiotensinogen, AngII, AngII type 1 receptor (AT_1R), and synaptopodin and their corresponding secondary antibodies conjugated to Alexa Fluor (Invitrogen, Carlsbad, CA) 488 or 594. The slides were mounted with coverslips using mounting medium (Invitrogen) with DAPI (a nuclear stain).

Results: AngII staining was found at high levels in podocytes based on colocalization with synaptopodin. Little if any AngII was observed elsewhere in the kidney. Angiotensinogen and AT_1R staining, by contrast, were observed in the proximal tubules, primarily in the brush border as expected, but not in the glomeruli. Some staining for these proteins was also observed in loops of Henle. AT_1R was prevalent in the media of larger blood vessels. Renin was found as expected in juxtaglomerular cells, collecting ducts, and connecting tubules.

Discussion: AngII colocalization with synaptopodin suggests an important physiologic or pathophysiologic role for AngII in urine filtration during hypertension and other related diseases. Podocyte injury and high levels of AngII have been implicated in glomerular injury in hypertension.

20 Spatiotemporal Expression of Regeneration-Associated Genes After Transforming Growth Factor-Beta Treatment of Chronic Nerve Injuries

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Background: Despite the capacity of peripheral nerves to regenerate, it is common clinical knowledge that functional recovery is suboptimal. We have previously demonstrated that the slow rate of axonal regeneration results in chronic denervation of Schwann cells (SCs) of the distal injured nerve stump and chronic axotomy of the injured neurons. Whether changes in gene expression in SCs subjacent to the injury site and SC response to axon-derived signals during regeneration are identical along the whole length of the distal nerve stump is unknown.

Transforming growth factor-beta (TGF-β) secreted by activated macrophages and by SCs plays a central role in the regulation of SC proliferation and is essential for the neurotrophic effects of several neurotropins. We have shown that in vitro reactivation of 6-month chronically denervated distal nerve stumps with TGF-β reversed the deleterious effect of chronic denervation by quadrupling the numbers of injured neurons that regenerated their axons in vivo.

Methods: We extended these observations by the application of TGF-β in vivo to a 2-month chronic injury of the rat tibial nerve at the time of repair. After 6 weeks of recovery, 3 10-mm sections of nerve were harvested: proximal to repair, including the repair, and distal to the repair. Sections were analyzed by immunohistochemistry and gene expression analysis.

Results: Results suggested that the TGF-β application resulted in prolonged expression of recombination activating genes compared to saline control. Furthermore, expression patterns suggested a possible progression of response with respect to distance from the spinal cord and distance from the nerve repair and TGF-β treatment.

21 The Effect of Transforming Growth Factor-β After Chronic Nerve Injuries

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Background: Although peripheral nerves can regenerate after traumatic injury, functional recovery is often suboptimal, especially after injuries to large nerve trunks such as the sciatic nerve and brachial plexus. Current research with animal models suggests that the reason resides in the lack of sufficient mature axons reaching their targets, which is as a result of the loss of receptivity (lack of neurotrophic support) in the distal stump of the injured nerves, primarily from Schwann cells (SCs). Severed axons and their associated myelinated SCs undergo Wallerian degeneration distal to the nerve injury. Axons degenerate, as do the myelin sheaths, and are degraded and phagocytosed by the SCs and infiltrated macrophages. SCs actively interact with infiltrated macrophages via cytokines during Wallerian degeneration and secrete chemoattractants for macrophages, which in turn also secrete numerous growth factors, including transforming growth factor-β (TGF-β). TGF-β plays a central role in the regulation of SC proliferation and is essential for the neurotrophic effects of several neurotropins.

Methods: We tested the ability of forskolin and TGF-β plus forskolin to enhance the axonal regeneration of 8 weeks' delayed repair of the tibial nerve of the rat.

Results: Regeneration was monitored by immunohistochemistry tests of several indicative proteins such as S100, Ki-67, and CD68; tests revealed that the treatments resulted in the SCs that expressed proteins indicative of an enhanced period of SC receptivity.

Discussion: These results suggested that exogenous growth factors added at the time of surgical repair may be useful for increasing nerve regeneration in vivo.

22 Diabetes Induces Resistance to Mammalian Target of Rapamycin (mTOR) Inhibition via Down-Regulation of Cyclin-Dependent Kinase Inhibitor p27Kip1

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23 Clinical Outcomes in the Arthroscopic Management of Femoroacetabular Impingement

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Background: We contended that comparison of labral debridement to labral repair outcomes in the arthroscopic treatment of femoroacetabular impingement (FAI) would reveal no significant differences.

Methods: We prospectively assessed 124 patients who underwent arthroscopic management of FAI with associated labral pathology from February 2009 to February 2011. Outcomes were measured preoperatively and postoperatively with the modified Harris Hip Score, Short Form-12, and Visual Analog Scale for pain. Statistical analyses compared outcome differences between labral debridement (Group D) and repair (Group R).

Results: The mean follow-up for both groups (D = 49, R = 75) was 13 months (range, 6 months to 2 years). The debridement group had a larger percentage of hips with advanced arthritis ($P = .0089$). All median outcome scores were significantly improved ($P < .01$) in both groups. Comparative analysis of final median scores revealed no differences between the groups at final follow-up. Age $\leq$ 30 years was the only factor found to be predictive of a good outcome ($P = .003$).

Discussion: Preliminary results indicated that equivalent short-term outcomes can be expected with either repair or debridement when treating labral pathology in association with FAI.

24 Airway Risk Factors for the Miller Laryngoscope

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Background: Failure to intubate the trachea remains a leading cause of morbidity and mortality in anesthesiology. Many clinical studies have tested the predictability of airway risk factors for difficult intubation with the Macintosh laryngoscopy blade; however, less is known about the Miller blade. The purpose of this study was to analyze airway risk factors in the performance of Miller laryngoscopy in American Society of Anesthesiologists category I through III (ASA I-III) adult patients requiring general anesthesia for surgery.

Methods: Following Institutional Review Board approval, 9 airway risk factors were preoperatively assessed in 978 patients. Following induction of general anesthesia, orotracheal intubation was performed utilizing the Miller #2 laryngoscope blade. Multivariate analysis was used to predict airway risk factors for inferior modified Cormack-Lehane views and increasing attempts at orotracheal intubation.

Results: Successful orotracheal intubation occurred in 96.2% of patients with the Miller blade, with the remaining patients requiring alternate airway tools or 3 attempts. There were no failed intubations. Multivariate analysis revealed that modified Mallampati class, thyromental distance, and ability to prognath were predictors for inferior modified Cormack-Lehane views. Modified Mallampati class and head and neck extension were predictors for increased attempts at orotracheal intubation.

Discussion: The Miller blade was highly successful in the performance of direct laryngoscopy for orotracheal intubation. For patients requiring advanced airway tools, the intubating catheter or videolaryngoscopy was the tool of choice. Multivariate analysis suggested that different combinations of airway risk factors restrict the actions of the left and right hands. Finally, the Miller blade is highly effective and safe for orotracheal intubation.

25 Impact of Coenzyme Q10 in Older Athletes Treated With Statin Medications

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26 Which Echocardiographic Indexing Method for Left Ventricular Hypertrophy Best Predicts Mortality Risk in Women?

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Background: Cardiovascular (CV) disease is the leading cause of mortality in women. Although left ventricular hypertrophy (LVH) is a predictor of subsequent CV morbidity and mortality, only limited data are available on LVH in women, including whether LVH is best determined by echocardiography as left ventricular mass (LVM) indexed to body size (either body surface area [BSA] or height$^{2.7}$ [Ht$^{2.7}$]).

Methods: We evaluated 26,128 female patients with preserved ejection fraction to determine the impact of LVM indexed to either BSA (LVH = LVM index $>$ 96 g/m^2) or Ht$^{2.7}$ (LVH = LVM index $>$ 51 g/m$^{2.7}$) on prevalence of LVH and subsequent mortality during an average follow-up of 1.7 $\pm$ 1.0 years.

Results: During follow-up, 1,947 women died and had significantly higher LVM (157.3 $\pm$ 60.6 g vs 146.7 $\pm$ 53.8 g, $P < .0001$) and prevalence of LVH (by LVM/BSA [25.9% vs 13.8%, $P < .0001$] or by LMV/Ht$^{2.7}$ [26.5% vs 16.9%, $P < .0001$]) than did the 24,181 survivors. Both LVM indices were significantly correlated ($r = 0.74$, $P < .0001$) and were concordant in determining the presence or absence of LVH in 93% of women. In the 7% (n = 1,845) of women in whom categorical LVH was discordant between the 2 indexing methods, LVH determined by LVM indexed to BSA (15.4% vs 6.4%, $P < .0001$) predicted an increase in mortality compared to women without LVH, whereas LVH determined by LVM indexed to Ht$^{2.7}$ did not (7.0% vs 6.4%, P = not significant [NS]).

Discussion: Echocardiographically determined LVH strongly predicted mortality in women. Although both indexing methods predicted mortality, the classification of LVH using LVM indexed to BSA was superior to LVM indexed to Ht$^{2.7}$ in predicting mortality in female patients.

27 Echocardiographic Detection of Left Ventricular Hypertrophy in the Elderly: Which Indexing Method Is the Best Predictor of Mortality?

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Background: Left ventricular hypertrophy (LVH) is a powerful independent risk factor predicting subsequent cardiovascular morbidity and mortality in the elderly population and is clinically best determined by echocardiography as left ventricular mass (LVM) indexed to body size (either body surface area [BSA] or height$^{2.7}$ [Ht$^{2.7}$]). However, considerable controversy exists regarding which of these 2 methods is superior for determining LVH and its association with mortality.

Methods: We evaluated 16,901 elderly patients (age $\geq$ 70 years) with preserved ejection fraction to determine the impact of LVM indexed to either BSA (LVH = LVM index $>$ 96 g/m^2 in women and 116 g/m^2 in men) or Ht$^{2.7}$ (LVH = LVM index $>$ 51g/m$^{2.7}$) on prevalence of LVH and subsequent mortality during an average follow-up of 1.7 $\pm$ 1.0 years.

Results: Deceased patients (n = 2,404) had significantly higher LVM (174.1 $\pm$ 66.8 g vs 169.4 $\pm$ 63.2 g, $P < .0001$) and prevalence of LVH (by LVM/BSA [26.4% vs 21.0%, $P < .0001$] or by LMV/Ht$^{2.7}$ [26.0% vs 22.1%, $P < .0001$]) than survivors (n = 14,497). Both LVM indices were significantly correlated (r = 0.80, $P < .0001$) and were concordant in determining the presence or absence of LVH in 93% of patients. In the 7% (n = 1,189) of patients where categorical LVH was discordant between the 2 indexing methods, LVH determined by LVM indexed to BSA predicted an increase in mortality compared to patients without LVH (20.0% vs 13.4%, $P < .0001$) whereas LVH determined by LVM indexed to Ht$^{2.7}$ did not (13.8% vs 13.4%, P = not significant [NS]).

Discussion: Although both echocardiographic LVH indices predicted higher mortality, the classification of LVH using LVM indexed to BSA was superior to LVM indexed to Ht$^{2.7}$ in predicting subsequent mortality in elderly patients.

28 The Impact of Inflammation/C-Reactive Protein and Body Fat on Mortality in Coronary Heart Disease: A New Twist on the Obesity Paradox

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Background: Despite the well-known adverse effects of obesity on almost all aspects of coronary heart disease (CHD), many studies of CHD cohorts have demonstrated an inverse relationship between obesity and subsequent prognosis (the obesity paradox). The etiology of this paradox and the potential role of inflammation in this process remain unknown.

Methods: We studied 513 patients with CHD following major CHD events, who were divided into low ($\leq$ 25% men and $\leq$ 35% women) and high body fat (BF) ($>$ 25% in men and $>$ 35% in women) as determined by the sum of the skin-fold method. Similarly, they were divided into low ($\leq$ 3.0 mg/L) and high ($>$ 3 mg/L) inflammatory states based on high-sensitivity C-reactive protein (CRP). Four groups were analyzed by total mortality over a 3-year follow-up period by the National Death Index: low BF/low CRP (n = 160), high BF/low CRP (n = 201), low BF/high CRP (n = 55), and high BF/high CRP (n = 97).

Results: During 3-year follow-up, all-cause mortality was highest in the low BF/high CRP group (15%), which was significantly ($P < .0001$) higher than the other 3 groups (2.1% for the high BF/high CRP, 3.5% for the high BF/low CRP, and 4.4% for the low BF/low CRP group, respectively). Using a proportional hazard model, after adjusting for BF, age, gender, ejection fraction, and peak oxygen consumption, both low BF (hazard ratio [HR] 0.907, confidence interval [CI] 0.849-0.969) and high CRP were associated with higher mortality (HR 2.78, CI 1.14-6.76).

Discussion: Although low BF and high CRP are independent predictors of mortality in patients with CHD, patients with combined low BF and high inflammatory state appear to be at particularly high risk for mortality. Obese patients with high inflammation, on the other hand, do not seem to share the same high mortality risk.

29 Is Psychosocial Stress an Independent Predictor of Mortality in Patients With Stable Coronary Heart Disease?

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Background: In many coronary heart disease (CHD) cohorts, depression, anxiety, and hostility are associated with a worse prognosis. We examined the relationship between total psychosocial stress—as defined by a composite of depression, anxiety, and hostility—and mortality in a cohort with stable CHD.

Methods: We studied 538 patients with CHD following major CHD events. Using validated questionnaires (Kellner Symptom Questionnaire), we measured stress in 3 domains: depression, anxiety, and hostility. The number of positive stress sources as a categorical variable was aggregated into a psychosocial stress score from 0 to 3, and the raw scores for each domain were also added to determine a composite of total stress. Subjects at the 4 levels were analyzed by total mortality over 3-year follow-up using the National Death Index.

Results: During 3-year follow-up, mortality was highest in individuals with the highest stress score, 3 (n = 8; 37.5%); mortality was 10.3% (n = 29), 4.9% (n = 41) and 3.5% (n = 460) for scores 2, 1, and 0, respectively ($P < .0001$, $< .0001$, and $= .011$, respectively). The group with the second level of stress (score of 2) had a significantly increased mortality risk compared with the group with stress score of 0 ($P = .04$). Mortality was significantly higher in patients above the 90th percentile of total stress raw score compared with other patients (13.7% vs 3.5%; $P < .0001$). In multiple logistic regression analysis, after adjusting for age, gender, ejection fraction, and peak exercise oxygen consumption, psychosocial stress score was an independent predictor of higher overall mortality (odds ratio 1.89; confidence interval 1.03-3.44).

Discussion: Psychosocial stress is an independent predictor of mortality in stable CHD patients. Greater attention directed at psychosocial stress and intervention is needed in primary and secondary CHD prevention.

30 Discordant Effects of Metabolic Syndrome and Central Obesity on Mortality in Stable Coronary Heart Disease

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Background: Metabolic syndrome (MetS) is associated with an increased risk of developing type 2 diabetes mellitus and major cardiovascular events. However, in light of the obesity paradox, where overweight/obese patients with coronary heart disease (CHD) have a better prognosis than do leaner patients, the impact of MetS on prognosis in CHD is largely unknown.

Methods: We evaluated 392 consecutive patients with stable CHD (241 with MetS and 151 without MetS) to determine the impact of standard CHD risk factors, including central obesity or waist circumference (WC; high is $\geq 40''$ in men and $\geq 35''$ in women), on 3-year mortality.

Results: During 3-year follow-up, mortality trended higher in those with MetS (4.6% vs 1.9%; $P = .18$). However, the group with MetS but low WC (n = 48) had a nearly sixfold higher mortality (12.5%) vs all others combined (2.3%; $P = .0004$). In multivariate analysis, MetS was not an independent predictor of mortality (odds ratio [OR] 1.87; confidence interval [CI] 0.50-7.0), whereas high WC as a continuous variable was an independent predictor of lower mortality (OR 0.86; CI 0.75-0.99).

Discussion: Although MetS was associated with a trend to higher mortality, this result was not significant in univariate or multivariate analyses. On the other hand, central obesity appeared to be protective in patients with MetS, supporting the obesity paradox, and those with MetS and low WC had the highest mortality risk during follow-up.

31 Relationship Between Arterial Impedance and Concentric Remodeling in Patients With Normal Systolic Function: Impact on Prevalence and Survival

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Background: Cardiac remodeling, including the development of concentric remodeling (CR), frequently develops in response to increased hemodynamic loads. Although the development of CR is independently associated with increased morbidity and mortality, little is known regarding the interaction of arterial impedance (IMP) on survival in patients with CR.

Methods: We evaluated 50,421 patients with normal systolic function to assess prevalence of CR and the impact of CR and IMP on survival during a mean follow-up of 3.9 $\pm$ 2.3 years. In a cohort of 2,636 patients with paired echocardiograms, we assessed the impact of IMP on mortality, based on maintaining a high or low IMP (above or below 4.0 mmHg/mL/m^2) over a follow-up of 3.0 $\pm$ 2.0 years.

Results: CR occurred in 21% of subjects and was associated with twice the mortality compared to subjects with normal left ventricular structure (7.7% vs 3.2%; $P < .0001$). The prevalence of CR increased with increasing levels of IMP ($P < .001$ for trend). In the paired-echo cohort, CR patients with an IMP < 4.0 had a mortality of 6.3%, with 58% converting to a normal LV structure. Mortality was higher (10%; $P < .0001$) and conversion to a normal LV structure was less frequent (46%; $P < .001$) in CR patients whose IMP remained ≥ 4.0.

Discussion: The prevalence of CR increases with higher degrees of IMP. Once CR is manifest, IMP < 4.0 mmHg/mL/m^2 is associated with a lower mortality and greater conversion to a normal LV structure over time. Further studies are needed to determine if reporting and targeting IMP are clinically beneficial in patients with CR.

32 Use of Porcine-Derived, Acellular Dermal Collagen Matrix Xenografts for Eyelid Reconstruction

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Background: The use of supportive and spacer grafts is often necessary in eyelid reconstruction. These grafts are traditionally made of autologous cartilage, hard palate, or fascia lata. Although structural integrity and host immune tolerance can be achieved, a second wound and limitations on the size of the harvested graft can be problematic. Recently ENDURAGen (Tissue Science Laboratories, Leeds, UK), a porcine-derived acellular dermis, has been suggested to have similar properties to those of autologous grafts.

Methods: We performed a retrospective chart review on 6 patients in whom ENDURAGen was used to reconstruct the periorbital adnexae.

Results: In 3 of the 6 cases, ENDURAGen was used as a spacer to correct for lower lid retraction from adhesions to the orbital rim following floor fracture repairs. One of the 6 cases was to reform a severely contracted congenital anophthalmic socket, which would not hold a prosthesis. Another case required upper lid reconstruction following 75% loss of the eyelid from trauma. The porcine graft was sandwiched in the first stage of a Cutler-Beard procedure. Finally, the xenograft was used for reconstruction of the posterior lamellae and fornices after loss of eyelid integrity secondary to chemical and thermal burns. None of the 6 cases was complicated by an infection or graft failure, and none of the cases required surgical revision.

Discussion: We found ENDURAGen to be rigid, durable, and unlikely to fail or become infected. In our experience, the xenograft was comparable to autologous grafts in restoring eyelid integrity in a variety of cases.

33 Repair of Medial Canthal Dystopia Made Simple and Safe Using Mitek Microanchors

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Background: Medial canthal tendon avulsion secondary to trauma or disruption from cancer resection results in eyelid malposition and causes ectropion, lagophthalmos, scleral show, epiphora, and distorted facial appearance. Treatment of telecanthus remains a challenge for oculofacial reconstructive surgeons because of the complex anatomy of the medial canthal tendon and the closely associated lacrimal excretory apparatus. Historically, techniques for repair included fixating plates with screws that required extensive dissection or transnasal wiring that necessitated a bilateral approach for a unilateral pathology. These methods, however, have high failure rates with risk to normal ipsilateral and contralateral structures. Even though the Mitek microanchor system (Mitek Products, Westwood, MA) has been used successfully in facial plastic and reconstructive surgery, little interest has been shown in the ophthalmology literature promoting its adoption as a primary tool for the repair of the periorbital adnexae.

Methods: We report our experience in 8 patients who underwent medial canthopexy using the Mitek microanchor device following medial canthal tendon loss.

Results: All 8 patients experienced successful fixation of the displaced medial canthus and perfect alignment of the lower eyelid with complete globe apposition. No iatrogenic injuries to surrounding structures were reported.

Discussion: The Mitek microanchor system uses a minimally invasive, unilateral approach in achieving safe, precise, and stable medial canthal fixation with reduced operative times. We believe this device should be deployed more frequently and is especially useful in cases requiring unilateral medial canthopexy.

34 Rosacea and Facial Dystonias

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Background: Benign essential blepharospasm is an involuntary, rhythmic, spasmodic closure of the eyelids with variable forcefulness, generally occurring in middle-aged and elderly patients. Therapy falls within several modalities, but periodic injection of the dystonic facial muscles with botulinum is the preferred choice. In addition to spasms, major symptoms are dryness and photophobia. Hemifacial spasm is believed to be caused by a mechanical irritation of the intracranial facial nerve as it turns forward around the posterior communicating cerebella artery, producing similar rhythmic facial spasms as in blepharospasm except unilaterally. When treating blepharospasm and hemifacial spasm patients with botulinum, it became apparent over years of facial injections that more patients than usual had rosacea.

Methods: The appearance of rosacea in these patients was studied retrospectively and included all patients from 1990 through 2011 at the Ochsner Medical Center: 87 benign blepharospasm patients and 53 hemifacial spasm patients.

Results: Given the accepted incidence of rosacea of 5% in our general populations (no Asians or African-Americans were excluded), the incidence approximately tripled in benign blepharospasm patients and in hemifacial spasm patients.

Discussion: Rosacea increased the incidence of facial dystonia threefold in our review of botulinum records since 1990. Rosacea embodies a constellation of clinical signs and symptoms, including facial flushing, telangiectatic vessels, rhinophyma, and significant dryness of the eyes. The spectrum of changes in the skin and eyes varies in each patient, but hypersensitivity to a variety of stimuli is generally present. Proinflammatory forms of interleukin-1 have been found to be increased in tear fluid samples obtained from patients with rosacea compared to normal patients. Given the inflammatory nature of rosacea on the lids and eyes, the link between rosacea and in both benign essential blepharospasm and hemifacial spasm through the chronic symptoms of dryness and photophobia remains hypothetical but very plausible.

35 Use of Botulinum Toxin for Epiphora in Children with Proximal Obstruction of the Lacrimal Drainage System

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Background: Epiphora resulting from proximal obstruction of the lacrimal drainage system in children is difficult to treat with current surgical options. Conjunctivodacryocystorhinostomy (CDCR) with Jones tube placement is the recommended treatment but is rarely performed in children because it requires excellent patient cooperation and compliance and has a high rate of complications. We sought to analyze the effectiveness of botulinum toxin injections to the lacrimal gland in treating epiphora secondary to proximal obstruction of the lacrimal drainage system.

Methods: We performed a retrospective chart review of children who underwent botulinum toxin injections of the lacrimal gland for epiphora secondary to proximal obstruction of the lacrimal drainage system. The primary outcome was subjective measurement of change in epiphora following injections. The study population consisted of 3 children—ages 8, 9, and 16 years—who received botulinum toxin injections over a 2-year period. Patients were seen as needed following the injections and were treated with repeat botulinum toxin injections as needed.

Results: All patients experienced either partial or full relief of epiphora within 2 to 8 weeks following botulinum toxin injection and lasting 6 to 13 months. Two of the patients received repeat injections after the recurrence of symptoms with similar results. No complications were noted.

Discussion: Botulinum toxin injection of the lacrimal gland in adults has been reported to successfully treat functional epiphora, hyperlacrimation (crocodile tears), and epiphora secondary to canalicular obstruction from docetaxel therapy. Botulinum toxin injection of the lacrimal gland should be considered as an alternative treatment for epiphora in children with proximal lacrimal system obstruction.

36 Fecal Impaction: Are There Any Missed Lesions?

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Background: Fecal impaction (FI) is the inability to evacuate inspissated fecal material. We hypothesized that after disimpaction there is no indication for colonoscopy outside of the normal screening recommendations.

Methods: Using the International Classification of Diseases, 9th Revision, number 560.39 (fecal impaction), 2,419 patients were identified. A total of 264 patients required treatment, and 16 patients were excluded for incomplete records. Patient demographics, the etiology of FI, the treatment modality, the recurrence rate, and the results of endoscopic evaluation and final pathology, if performed, were recorded.

Results: A total of 248 patients were included; the mean age was 69 years (range, 17 to 96 years). A majority of the patients were female (n = 167; 67%), 25 (10%) had a previous impaction, and 14 (6%) had a recurrence after treatment. A causative lesion was found in 2 (0.8%) on postdisimpaction endoscopic evaluation. One patient had distal rectal cancer; and the other patient had radiation proctitis. The most effective method of treatment was manual disimpaction by an endoscopy technologist; this was used in 93 patients (37%).

Discussion: FI remains a common problem in the elderly population. The presence of a clinically significant lesion noted by lower endoscopy was very low, < 1%. The incidence of polyps was 8.5%, similar to results in the literature. The risk-benefit ratio of colonoscopy combined with the risk of sedation-related issues in the elderly patient population does not warrant postdisimpaction colonoscopy outside current screening guidelines. Our data show that FI can be safely treated by physician extenders.

37 Discontinuation of Antiplatelet Therapy for Colonoscopy and the Associated Thromboembolic Risk

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38 Outcomes of Urgent Carotid Endarterectomies Performed in a Tertiary Referral Center

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Background: Stroke is the number one cause of adult disability in the United States and Europe. Patients presenting with acute carotid-related neurological symptoms are at increased risk of recurrent stroke. Urgent carotid endarterectomy (CEA) performed during the index hospitalization is increasingly advocated in some tertiary referral centers to improve outcomes. We assessed the outcomes of patients undergoing urgent compared to nonurgent CEA in symptomatic patients.

Methods: CEAs (n = 436) performed at a tertiary center between 2005 and 2011 were reviewed for 30-day postoperative myocardial infarction, stroke, and death. Fisher's exact and *t* tests were used to analyze the perioperative outcomes.

Results: During this 6-year period, 49 urgent CEAs and 49 symptomatic but elective CEAs were performed. Mean National Institutes of Health Stroke Scale (NIHSS) calculated preoperatively by the vascular-neurology service was 3.5 (0-24); mean transient ischemic attack score was 5 (scale of 1-8). A trend toward a higher combined stroke/death rate in the urgent compared to the elective symptomatic CEA group was present (6.1% [3/49] vs 2% [1/49]; $P = .36$); however, patients undergoing urgent CEA with an NIHSS < 10 had no perioperative complications. Length of stay was higher for urgent CEAs compared to elective but symptomatic CEAs (7.6 ± 0.67 days vs 2.6 ± 0.2 days, $P < .001$), as was the number of patients being discharged to a rehabilitation facility (19% [8/42] vs 0% [0/49], $P < .0001$).

Discussion: Patients presenting with mild-to-moderate stroke (NIHSS < 10) may undergo urgent CEA with periprocedural risks similar to those of electively performed CEAs.

39 Ultrasound Findings Following Endovascular Stent Deployment in Transplant Liver Hepatic Artery Stenosis

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Background: Endovascular stenting is a safe, effective treatment for hepatic artery stenosis post–liver transplant (HASPLT), but no detailed evaluation of ultrasound changes after stenting has been completed. This study aims to improve monitoring by delineating expected postoperative findings.

Methods: Fifteen stent procedures for HASPLT were performed at our institution between October 2008 and October 2011; 14 (93.3%) were technically successful. These procedures were followed with serial ultrasound beginning within 2 days of stenting. Follow-up examinations (mean 233 days) were compared to prestenting examinations to evaluate changes in peak systolic velocity (PSV), resistive index (RI), and tardus-parvus waveform (TPW). Data were analyzed to determine expected postprocedure values and time course of change in values.

Results: Of the 14 patients, 4 demonstrated restenosis. In all patients, PSV decreased an average of 233 cm/sec, and RI increased an average of 0.2 within 48 hours after stenting. PSV differed between success and failure groups only > 90 days poststenting (mean 279 and 493 cm/sec, respectively). Prestenting RI < 0.40 demonstrated a strong correlation with restenosis. Poststenting RI differed between success and failure groups only > 30 days (mean RI $< .50$ and $> .50$, respectively). TPW resolution was often delayed beyond 48 hours poststenting, and time to TPW resolution demonstrated no correlation with success or failure.

Discussion: Ultrasound is convenient and useful to follow stents in HASPLT. Prestent hemodynamics can have value in predicting restenosis. Diagnosis of restenosis can be made with RI and PSV, while resolution time of TPW is of less concern. These parameters can guide determining which patients require closer monitoring and aggressive treatment.

40 Epidural Use During Pancreaticoduodenectomy

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Background: Data are limited regarding epidural anesthesia and analgesia (EAA) use during pancreatic head resection. The goal of the study was to critically evaluate outcomes in patients undergoing Whipple procedures with and without EAA.

Methods: A retrospective chart review of 100 pancreaticoduodenectomies (PD) was performed, including 50 patients without EAA but using narcotic patient-controlled analgesia and pain catheters and the 50 patients with EAA. Perioperative and immediate postoperative clinical outcomes were compared.

Results: EAA patients had a longer time from anesthesia start time to surgery start time ($P = .004$). The EAA group had higher rates of intraoperative hypotension ($P = .001$) and revealed a trend toward a higher intraoperative blood transfusion rate ($P = .071$). Postoperatively, EAA patients had delay of diet initiation ($P = .015$) and a higher requirement of postoperative fluid administration on postoperative day 1 ($P = .001$). Although overall morbidity was similar between the 2 groups, the EAA group had higher rates of urinary tract infections and intraabdominal abscess. Twenty percent of patients in the EAA group had premature discontinuation of epidural catheter secondary to hypotension or inadequate pain control. Length of stay was similar between the 2 groups.

Discussion: EAA during PD was associated with a statistically significant delay in surgery start time, increased episodes of intraoperative hypotension, a trend toward increased intraoperative blood transfusion, and a 20% device failure rate. Although pain relief may be excellent with EAA, these issues must be considered when selecting a perioperative pain control strategy.

41 Robot-Assisted Thorascopic Lobectomies for Early-Stage Lung Cancer: Report of 40 Consecutive Cases

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Background: Open thoracotomy with anatomic lobectomy and mediastinal lymph node dissection is the standard primary treatment for patients with early stage non-small cell lung cancer (NSCLC). Minimally invasive surgical techniques such as video-assisted thorascopic (VATS) lobectomy have been shown to be safe and efficacious while potentially decreasing perioperative complications. The use of robotics to augment VATS lobectomies has been shown to be feasible for anatomic lobectomies; however, no study to date has looked at the use of robotics throughout the entire procedure.

Methods: Over a 16-month period, 40 patients were identified with stage I to III NSCLC who underwent robot-assisted thorascopic lobectomy. Median age at diagnosis was 71 years.

Results: Lobectomies involved the right upper lobe in 8, the right middle lobe in 4, the right lower lobe in 10, the left upper lobe in 12, and the left lower lobe in 7. One patient had a bilobectomy. There were 4 emergent conversions to open thoracotomy. Tumor histology showed adenocarcinoma in 22, squamous in 8, adenosquamous in 3, and carcinoid in 7. Pathologic upstaging was noted in 7 cases. Complications included stroke, atrial fibrillation, pulmonary empyema, pneumonia, and incisional bleeding. Postoperative mortality was 2.5%. Median hospitalization was 6 days. Follow-up for 36 of the 40 patients was complete. Median follow-up was 8 months. One patient developed metastatic disease, and 2 patients developed local recurrence.

Discussion: The use of robotics during thorascopic lobectomy for definitive treatment of early-stage NSCLC is feasible. Further experience, follow-up, and comparisons to standard open lobectomies and VATS lobectomies are necessary.

42 Emergence of YMDD Lamivudine Resistance After Transplantation of Anti-Hepatitis B Core (HBc) Antigen–Positive Donor Livers Into Anti-HBc–Negative Recipients Using Lamivudine Monotherapy Prophylaxis

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Background: The use of livers from hepatitis B virus (HBV) HBc-positive donors in naïve HBV recipients for liver transplantation (LT) requires prophylaxis because of the risk of HBV reactivation. Lamivudine (lam) has been considered an effective agent with minimal or no emergence of resistance.

Methods: Between January 1999 and December 2010, 64 (6.05%) anti-HBc–negative patients received an LT from anti-HB–positive donors. Recipients received hepatitis B immunoglobulin (HBIG) during the anhepatic phase and lam postoperatively 150 mg/day.

Results: Mean age was 53.5 ± 8.5 years. All donor sera were negative for anti-HBc immunoglobulin M (IgM) and HBV-DNA by polymerase chain reaction. Mean follow-up was 40.7 ± 38.5 months (range 1-148 months). Nine (14.06%) patients developed de novo HBV. Patient and graft survival were identical between patients with and without HBV at 1, 3, and 5 years (92.1%, 87.2%, and 69.2%). No death or graft loss was related to HBV recurrence. Mean time from LT to de novo HBV was 21.4 ± 26.1 months (range 10.8-92.8 months). Two patients presented with de novo HBV lam-resistance (YMDD mutation) at 16.3 and 24.3 months post-LT. One patient received treatment with a combined therapy of HBIG and lam/tenofovir and the other one with tenofovir monotherapy. Both were successfully treated without modification in their immunosuppression regimen.

Discussion: Anti-HBc liver allografts may be safely used in HBV-naïve recipients. Lam is effective monotherapy to prevent de novo HBV, and the development of resistance is a rare event that does not increase risk of mortality or graft loss. If de novo infection occurs, therapies have been successful in seroconversion to HBV-DNA negative status.

43 Survival Outcomes Following Late Liver Retransplantation: A Single-Center Experience

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Background: Late liver retransplantation (LRTx) (retransplant > 90 days after the primary transplant) has lower published graft and patient survival rates than primary transplantation (Tx).

Methods: We compared LRTx at one large center to LRTx documented in the Organ Procurement and Transplantation Network (OPTN) database. Between January 1, 2005, and June 30, 2011, our center performed 663 liver transplants, including 41 (6.18%) LRTx. Kaplan-Meier calculations compared our LRTx survival rates with the most recent OPTN database rates for the same time period.

Results: OPTN and our patient demographics were similar. Our group had higher ratios of hepatitis C virus–positive patients (73% vs 44%) and non-Caucasians (46.3% vs 30.2%) and our patients trended toward higher average Model for End-Stage Liver Disease scores (27.6 vs 25.0). Our 3-month and 1-, 3-, and 5-year patient survival rates were 95.1%, 92.6%, 86.6%, and 86.6%, respectively, compared to OPTN rates of 86.5%, 77.1%, 66.2%, and 59.0% (all $P < .001$). Likewise, our graft survival rates were significantly higher than OPTN rates at all time points studied. We performed a higher percentage of LRTx as combined liver/kidney transplants (29% vs 17%) and recorded much shorter warm (29 ± 4 vs 54 ± 18 min) and cold ischemic times (5:49 ± 1:52 vs 7:42 ± 3:18 hr:min).

Discussion: In our experience, LRTx yielded patient and graft survival rates comparable to primary Tx survival rates and superior to OPTN LRTx survival rates. These very different results may be related to our shorter warm and cold ischemic times.

44 Validity and Clinical Utility of a Risk Calculator for Total Knee Arthroplasty

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Background: Using the Medicare Provider Analysis and Review dataset, a perioperative total knee arthroplasty (TKA) risk calculator was created based on select preoperative comorbidities.

Methods: We retrospectively identified and reviewed 2,284 primary TKAs at a single institution from 2000 to 2008. A numerical complication risk was established for each patient. Actual complications occurring within the first 14 postoperative days were recorded. Statistical analysis was performed using the C statistic and analysis of variance (ANOVA) test.

Results: Patients with higher predicted probability of a complication did show higher complication rates. The corresponding C statistic was 0.609 (95% confidence interval 0.542-0.677). When the patients were divided into 4 groups based on their calculated complication risk (0-5%, 5-10%, 10-25%, and $> 25\%$) the statistical significance of the associated ANOVA was $P < .001$, showing again that patients with higher predicted risk experienced more complications and those with lower predicted risk experienced fewer complications.

Discussion: Based on our results, the calculator is valid and clinically relevant.

45 Teaching Palliative Care in the Medical Intensive Care Unit: How to Break the News

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Background: A structured curriculum was developed to improve residents' confidence with end-of-life care.

Methods: The curriculum involved a 3-pronged approach, including role modeling, tutorials, and case-based debriefing at the end of each rotation. Case-based debriefing consisted of discussions by residents of real cases they had experienced during the rotation. These sessions were moderated by a staff physician and palliative care advanced practice nurse. Using a 4-point Likert scale–based survey instrument, residents were evaluated before and after the rotation with regard to their confidence in 9 areas of palliative care (conducting family conferences, delivering bad news, discussing do-not-resuscitate orders, discussing comfort care, discussing treatment withdrawal, managing pain, managing terminal symptoms, assessing decision-making capacity, and discussing advance directives).

Results: A total of 214 residents participated in the course from April 2007 to September 2011. Resident confidence improved across all 9 areas. The biggest changes were seen in discussing comfort care, discussing treatment withdrawal, managing terminal symptoms, assessing decision-making capacity, and discussing advance directives.

Discussion: Using a structured curriculum, including a novel case-based debriefing approach, to teach palliative care improves resident confidence in discussing and providing palliative care.

46 Using Avatars in an Online Virtual Community to Facilitate Peer Storytelling Among Grieving Oncology Nurses

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47 Exploring the Use of Mothers' Own Milk as Oral Care for Mechanically Ventilated Very Low Birth Weight Preterm Infants

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48 Hurricane Katrina–Related Experiences and Blood Pressure Control in Older Adults: Findings From the Cohort Study of Medication Adherence in Older Adults

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Background: Disaster events can negatively impact the health and well-being of residents, particularly among vulnerable populations such as older adults. We assessed the relationship between Hurricane Katrina–related experiences and blood pressure control among older adults living in greater New Orleans and the surrounding areas.

Methods: Data were analyzed for 2,194 participants in the Cohort Study of Medication Adherence in Older Adults. As part of the baseline CoSMO survey conducted between August 2006 and September 2007, participants were asked about their hurricane-related experiences, including property damage, life disruptions, and loss of life. Blood pressure measurements for the 24-month period following Hurricane Katrina were abstracted from patient medical records, and uncontrolled blood pressure was defined as systolic blood pressure (SBP) $\geq$ 140 mmHg or diastolic blood pressure (DBP) $\geq$ 90 mmHg.

Results: The mean age of study participants was 75 years (range 65-97). Overall, 30.5% of participants were African-American, 33.9% had uncontrolled blood pressure, 18.7% reported that they had a family member or friend who had died within 1 month of Hurricane Katrina, 22.2% had $\geq$ 50% damage to their residence, and 6.8% reported both of these latter two experiences. After adjustment for sociodemographic characteristics, participants with $\geq$ 50% damage to their residence and those with a family member or friend who died within 1 month of Hurricane Katrina were more likely to have uncontrolled blood pressure (prevalence rate [PR] = 1.18, 95% confidence interval [CI] = 1.03-1.35, $P = .020$, and PR = 1.13, 95% CI = 0.98-1.31, $P = .096$, respectively). The association with uncontrolled blood pressure was even stronger for participants reporting both of these disaster-related experiences compared to none or one (PR = 1.37, 95% CI = 1.14-1.66, $P = .001$).

Discussion: These data show that Katrina-related losses of property and life are associated with uncontrolled blood pressure in older adults. Further research is needed to examine the short and long-term impact of Katrina-related experiences on blood pressure control and cardiovascular outcomes.

49 Gender Disparities in Blood Pressure Control Among Older Adults: Findings From the Cohort Study of Medication Adherence in Older Adults

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Background: Previous studies indicate that gender disparities exist in blood pressure control among hypertensive adults. The purpose of this study was to identify gender differences in blood pressure control in a sample of older adults with hypertension.

Methods: A cross-sectional analysis of baseline data from the Cohort Study of Medication Adherence in Older Adults treated for hypertension was conducted. Data for sociodemographic and clinical characteristics were obtained from patient surveys. Blood pressure measures were obtained from outpatient medical records. Antihypertensive medications filled and comorbid conditions were obtained using an administration database. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure provided cut points for blood pressure levels: systolic blood pressure (SBP) $<$ 120 mmHg and diastolic blood pressure (DBP) $<$ 80 mmHg, SBP 120-139 mmHg or DBP 80-89 mmHg, and SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg. Blood pressure control rates (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg vs SBP $<$ 120 mmHg and DBP $<$ 80 mmHg) were compared between genders.

Results: The mean age of the 1,957 participants was 75.0 $\pm$ 5.6 years, 30.5% were African-American, and 58.7% were women. Female gender was consistently associated with higher blood pressure levels. After adjustment for sociodemographic characteristics, women had 1.94 (95% confidence interval 1.31-2.89) higher odds of SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg than men. Gender differences in blood pressure control remained significant even after additional adjustment for clinical characteristics, the number and type of antihypertensive medications filled in the last year, and self-reported adherence to antihypertensive medications.

Discussion: Gender disparities exist in blood pressure control for older adults with hypertension. Further research to identify gender-specific determinants of blood pressure control is needed.

50 Collateral Benefits of Glycemic Control on Lipids

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Background: Diabetes is an illness with multiple quality indicators, and the discovery of cost-effective quality strategies has the potential to improve outcomes at a lower cost. This retrospective cohort study evaluated if interventions directed at improving hemoglobin A1c (HgA1c) quality indictors had collateral benefits on similarly measured low density lipoprotein (LDL) quality indicators in diabetic patients.

Methods: The deidentified Ochsner primary care diabetic patient electronic databases from 2008 (N = 16,503) and 2010 (N = 23,040) were initially analyzed. A cohort of patients that only appeared in both databases was then identified and selected for the study (N = 11,288).

Results: The proportion of patients with poor glycemic control and poor lipid control both decreased from 10.3% to 8.42% and 38.2% to 32.1%, respectively (both $P < .0001$). The no testing rate for HgA1c and LDL both increased from 6.41% to 11.1% and 15.1% to 16.8%, respectively (both $P < .0001$). The mean HgA1c and LDL levels also improved from 7.34% to 7.21% and 100.2 mg/dL to 95.6 mg/dL, respectively ($P < .0001$).

Discussion: This quality improvement initiative employed interventions that were directed strictly toward improving HgA1c levels. Interventions included prescribing a 3-month supply of diabetic medications, using ancillary personnel, and sustaining a focus on patients with elevated HgA1c and those without measurements. Additional recommendations included initiating insulin therapy earlier and enrolling patients in a diabetic boot camp. Sustained, physician-directed interventions targeting one quality metric in diabetic patients may have collateral benefits in improving other diabetes quality measures.

51 Use of an Automated Sedation Assessment Tool Reduces Complications in Patients Undergoing Moderate Sedation for Transesophageal Echocardiography

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Background: Conscious sedation (CS) is typically given to patients undergoing transesophageal echocardiography (TEE). Complications arising from CS (typically ventilatory impairment or hypotension) are heightened because of secretions related to esophageal intubation and the common comorbidities in patients referred for TEE—including acute stroke, atrial fibrillation with accompanying heart failure, and sepsis where endocarditis is of concern—that are more prevalent in hospitalized patients. These CS-related complications are initially managed by the administration of reversal agents, and when severe, may require endotracheal intubation and/or volume resuscitation.

Methods: We developed an automated computerized sedation-scoring instrument (SedRisk) to predict which patients are more likely to develop a CS-related complication and require consultation with an anesthesiologist to administer and oversee sedation. Patients were scored on a 0-22 point scale based on Mallampati class, American Society of Anesthesiologists class, and other clinical parameters predicting airway and sedation risk and categorized into low and high sedation risk. A CS-related complication was considered present if the patient required the use of a reversal agent or developed significant hypotension or an airway-related event. Outcomes were recorded before and after initiation of the SedRisk tool.

Results: The overall frequency of CS events was 1.5% prior to SedRisk (14/951 consecutive cases). In the 220 consecutive patients screened using SedRisk, no CS events were recorded in the 168 (76%) patients identified as low risk. In the 52 (24%) patients deemed high risk, CS events were present in 5 (9.6%, $P < .001$ versus low risk). These patients were managed in a more appropriate environment by an anesthesiologist working with a cardiologist than would have occurred by a cardiologist acting alone.

Conclusions: CS-related complications are infrequent but predictable using the SedRisk screening tool. High-risk patients can be identified in advance of TEE and more safely undergo CS by consultation with an anesthesiologist, thus minimizing potential catastrophic complications.

52 Resident Experience in Training May Not Improve Anesthetic Drug Cost Containment in Adult Cardiac Surgery

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Background: All physicians bear the responsibility of minimizing cost while providing care that meets or exceeds national quality benchmarks. Intraoperative anesthetic drug costs constitute a small but significant fraction of the total cost in the perioperative period. Previous studies have revealed that anesthesiologists are generally unaware of drug costs. To determine if experience improves anesthetic drug cost containment, we compared the total anesthetic drug cost per case as residents progressed through their rotations in cardiac anesthesia.

Methods: We studied the total anesthetic drug cost for 204 adult cardiac cases, including coronary artery bypass grafting, aortic valve replacement, mitral valve replacement, and left ventricular assist device placement. Seventy-two of the procedures analyzed were performed by residents in their first month of cardiac anesthesia, and 127 by residents in their subsequent months of cardiac anesthesia.

Results: The average total cost per case for residents in their first month ($192.60; SD = $81.80) was significantly less than the average total cost per case for residents in their subsequent months ($223.70; SD = $95.40) ($P = .018$).

Discussion: The results revealed that more experienced residents had a higher average total cost per case. One possible explanation for this finding is that complex cases may have been assigned to more experienced residents, and these patients may have required greater pharmacologic support. Also, more experienced residents may have anticipated the pharmacological needs for their patients, and this anticipatory dispensing of additional medications may have resulted in higher wastage. Drug wastage has already been shown to play a significant role in intraoperative drug costs.

53 Effect of Eye Dominance and Hering's Law on Surgical Outcomes of Bilateral Ptosis Repair

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Background: Eye dominance and eyelid interdependence as described by Hering's law are phenomena believed to influence eyelid position and thus affect surgical outcomes following blepharoptosis surgery. Pseudoretraction of the contralateral eyelid, usually observed in the nondominant eye, is a well-recognized phenomenon in the ophthalmic literature. Failure to recognize Hering's law dependence and eye dominance preoperatively could result in an increased incidence of postoperative eyelid asymmetry and in some cases further surgery to repair the manifested contralateral blepharoptosis.

Methods: In this retrospective cohort study, we investigated postoperative eyelid position and rates of reoperation in 50 patients with bilateral involutional ptosis who underwent bilateral levator advancement surgery. In addition to the standard ptosis preoperative evaluation, patients were tested for eyelid interdependence and eye dominance.

Results: None of the patients in the study had significant postoperative eyelid asymmetry or required reoperation. Patients in whom the dominant eye exhibited more ptosis preoperatively were more likely to have eyelid interdependence than patients in whom the nondominant eye was more ptotic (67% vs 33%).

Discussion: Eye dominance and eyelid interdependence did not affect the surgical outcomes of the patients included in this study who had bilateral ptosis repair performed. We postulate that this may be because of the balancing of these 2 phenomena intraoperatively, thus negating their effect on eyelid position postoperatively. Patients in whom the dominant eye is more ptotic should be counseled about the possible need for bilateral surgery rather than unilateral surgery because of the increased incidence of eyelid interdependence.

54 A Vascular Neurology Service Increases the Volume of Urgent Carotid Endarterectomies Performed in a Tertiary Referral Center

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Background: Urgent carotid endarterectomy (CEA) is increasingly recognized as a valuable tool in the management of select patients presenting with acute neurologic symptoms. The primary reason is the heightened risk of recurrent stroke after a transient ischemic attack (TIA) or small stroke, approximately 10% within 7 days. We aimed to determine whether implementation of a vascular neurology service increases the volume of urgent CEAs performed in patients presenting with acute neurologic symptoms.

Methods: All CEAs (n = 436) performed at a tertiary care center were analyzed between 2005 and 2011. Chi-square analysis compared the urgent CEA volume before (June 2005-August 2008) and after (September 2008-November 2011) the implementation of the vascular neurology service. Urgent CEA was defined as a patient presenting with stable or unstable neurologic symptoms and undergoing CEA during the same hospitalization as the symptoms' onset.

Results: The proportion of urgent CEAs performed increased significantly after the initiation of a vascular neurology service (4.1% [7/172] vs 22.2% [49/221], $P < .0001$). Per annum, the proportion of urgent CEA increased from 5.3% (4/75) in 2005 to 10.7% (9/84) in 2009, 27.9% (17/61) in 2010, and 39.6% (25/63) in 2011. Urgent CEA indications were stroke in evolution (10% [5/49]), crescendo TIAs (6% [3/49]), acute stroke (45% [22/49]), and cerebral/ocular TIAs (39% [19/49]). Evidence of cerebral infarction on the admission magnetic resonance imaging/computed tomography scans was evident in 61.5% (24/39) of patients.

Discussion: Close collaboration with a vascular neurology service at the time of symptom presentation increased the volume of urgent CEAs performed over a 3-year period.

55 Early Empiric Antibiotic Administration Decreases Hospital Length of Stay in Patients With Severe Sepsis and Septic Shock

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Background: Sepsis is one of the leading causes of death in the United States. Incidence continues to increase, with cost estimates of $17 billion per year. Shortened time to antibiotics appears to improve outcomes in patients with severe sepsis and septic shock (SS/SH) We sought to find out whether patients with SS/SH receiving antibiotics in < 2 hours had improved outcomes in hospital length of stay (LOS) and in-hospital mortality.

Methods: This prospective study included 813 consecutive patients with SS/SH admitted to the intensive care unit of a 530-bed tertiary referral medical center between July 2008 and June 2011. Time to antibiotics was calculated as the time from the diagnosis of SS/SH to the start of the first antibiotic infusion. Providing antibiotics in < 2 hours was defined a priori as one of the goals of the sepsis project.

Results: The antibiotics < 2 hours cohort consisted of 510 patients with a median age of 63 years. The antibiotics > 2 hours cohort consisted of 303 patients with a median age of 64 years. Hospital LOS was shorter for the antibiotics < 2 hours cohort (8.3 days vs 10.8 days [$P = .001$]). In-hospital mortality was 19.8 versus 25.6% for antibiotics < 2 hours versus antibiotics > 2 hours, respectively ($P = .05$). Emergency department (ED) bundle order set use was associated with receiving antibiotics within 2 hours. Eighty-three percent of patients receiving antibiotics < 2 hours used an ED order set.

Discussion: The use of the ED bundle order set was associated with patients receiving antibiotics within 2 hours. Patients with SS/SH receiving antibiotics within 2 hours had decreased hospital LOS and in-hospital mortality.

56 Peer Review, Performance Improvement, and the United Network for Organ Sharing Membership and Professional Standards Committee: One Center's Experience

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Background: In July 2005, published results from the Scientific Registry of Transplant Recipients (SRTR) showed that our liver transplant center's patient and graft survival rates were significantly lower than expected. The Membership and Professional Standards Committee (MPSC) placed our center under peer review.

Methods: After an initial period of denial, our center began to work closely with the MPSC, during which time a rigorous quality assurance and performance improvement (QAPI) program was established.

Results: We remained under MPSC peer review for the next 18 months, until our observed survival rates reached expected levels. But with our QAPI system in place, our liver transplant results continued to improve even after cessation of MPSC peer review. In July 2011, with all transplants performed after June 30, 2005, included in the SRTR analysis, our 1- and 3-year patient survival rates as well as our 1- and 3-year graft survival rates were all significantly higher than expected.

Discussion: Our liver transplant program had a long and difficult journey from the bottom 5% for outcomes to the top 5%. This same QAPI system has been successfully applied to other solid organ programs at our center, and we argue for the positive impact of MPSC peer review.

57 Safety for Collaboration: A Critical Care Imperative

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Background: Professional development, staff retention, quality outcomes, and cultural change present challenges in critical care. In 2008, the Intensive Care Unit Leadership Team initiated a Healthy Work Environment program to create a structure to provide and sustain safe, efficient, and cost-effective care using the 6 pillars of the Healthy Work Environment initiative.

Methods: Each pillar was achieved using specific strategies. True collaboration was addressed by clarification of physician expectations monthly and recognition of nurses as patient care coordinators. Effective decisionmaking involved data-driven decisions and the implementation of best practices. Appropriate staffing matched nurse competencies with assignments. Orientation was restructured to include hands-on information, a phased approach to skill acquisition, and individual learning maps. Didactic and patient simulation synergized clinical knowledge and critical thinking. Authentic leadership required strategies to generate enthusiasm, provide resources, share information, and appraise performance.

Results: By 2012, a staff survey showed staff awareness of the administrative strategic initiative about safety importance. Project improvement for 2008-2010 included sepsis mortality decreases from 18% to 2%; central line–associated bloodstream infection rate decreases from 3.6 to 2.1/1,000 patient days despite increased acuity; reduced RN turnover from 52.8% to 20.5%; improved National Database of Nursing Quality Indicators job satisfaction from 44.7% to 51.0%; and increased specialty certification from 7.5% to 30.0%.

Discussion: The project demonstrated positive trends in outcomes after the implementation of a healthy work environment. Additional study is needed regarding the impact of cultural adaptation in allowing creative solutions for sustaining change, quality measurement, novel research, and mutual learning.

C1 Treating One Disease Causes Another: Renal Sarcoidosis

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Introduction: Renal sarcoidosis (RS) is a multisystem granulomatous disorder of unknown etiology characterized pathologically by noncaseating granulomas. Common renal manifestations are nephrocalcinosis and nephrolithiasis. We present a rare case of etanercept (a tumor necrosis factor inhibitor)-induced RS.

Case Report: A 42-year-old African-American female with psoriasis treated with subcutaneous injections of etanercept 50 mcg twice weekly for 3 years presented to the renal clinic with weakness and acute kidney injury. Current medications were prednisone 10 mg, the etanercept, and multivitamins. Recent gastric biopsy for reflux gastropathy revealed multiple noncaseating granulomas. She had no pertinent family history or use of herbal medications, nonsteroidal antiinflammatory drugs, or intravenous drugs. Physical examination showed a heart rate of 89 beats per minute, blood pressure of 100/72 mmHg, and oxygen saturation of 100% on room air. The patient was a thin woman with multiple healing erythematous plaques on her joints. Laboratory results were creatinine of 3.8 mg/dL (increased from 1.3 mg/dL 7 months earlier), blood urea nitrogen of 29 mg/dL, hemoglobin of 9.3 mg/dL, calcium of 8.6 mg/dL, angiotensin-converting enzyme of 53 U/L, and no eosinophilia. Urine analysis was negative for sediments. Serological evaluation and renal ultrasound were normal. With worsening creatinine of 6.2 mg/dL, a renal biopsy reported subacute and chronic granulomatous interstitial nephritis. Etanercept was discontinued, and high-dose steroid treatment was started. Creatinine improved to 2.4 mg/dL with steroid taper in 4 weeks.

Discussion: Etanercept-induced sarcoidosis has previously been reported in the literature. With this in mind, we attributed etanercept as causing the patient's RS. This case highlights a rare cause of sarcoidosis and the importance of monitoring renal function while on etanercept.

C2 Intramural Colonic Splenosis: A Rare Case of Lower Gastrointestinal Bleeding

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Case Report: A 41-year-old man had left upper quadrant abdominal pain, constipation, and melena. About 6 years previously, he received a single gunshot wound to the abdomen, which required partial gastrectomy and small bowel resection. He subsequently developed bleeding gastric varices for which he underwent a splenectomy 2 years before the current admission. A computed tomography scan identified a 6.5×2.5 cm left upper quadrant mass. Upper endoscopy was unremarkable, but on colonoscopy a 3 cm polypoid mass partially obstructed the descending colon. A left hemicolectomy was performed with a primary colonic anastomosis and incidental appendectomy. The mass that involved the muscularis of the colon and caused ulceration of the mucosa was ectopic hypertrophic splenic tissue, indicating intramural colonic splenosis.

Discussion: We hypothesize that after the patient's splenectomy, a colonic focus of the heterotrophic spleen became hyperplastic and led to a clinically apparent lesion, resulting in lower gastrointestinal bleeding.

C3 Partial Müllerian Agenesis Causing Primary Amenorrhea

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Introduction: Primary amenorrhea—characterized by the absence of menarche by age 15 in women with normal physical and secondary sexual development—can have multiple etiologies spanning a variety of medical specialties, including gynecology, endocrinology, and psychiatry. A thorough history and physical examination can elucidate the underlying cause in a majority of cases. We present a patient who had previously been undiagnosed.

Case Report: An 18-year-old healthy, normally developed female presented with amenorrhea. She had never had a menstrual period. Breast and secondary sex characteristics developed normally around age 11. Her 2 sisters experienced menarche around age 14. When she initially presented last year to her physician, she was found to have normal female sex hormone levels. A 12-month trial of oral contraceptives produced no withdrawal bleeding or abdominal pain. She had normal external female genitalia but deferred a pelvic examination because she was not sexually active. Magnetic resonance imaging of the pelvis showed normal ovaries but an absent uterus.

Discussion: Primary amenorrhea rarely presents to the adult endocrinologist. Etiologies include hormonal, chromosomal, and structural causes. Although the differential is complex, a thorough history, physical examination, and basic laboratory testing should reveal the etiology. This patient's normal development with regard to breasts and secondary sexual hair suggested that she had functional ovaries, adrenals, and androgen receptors. Her normal female hormone levels ruled out primary and secondary gonadal failure. Her lack of withdrawal bleeding could only be caused by a congenital anatomic variant. Imaging confirmed uterine agenesis. The fallopian tubes, uterus, and upper vagina are formed from Müllerian ducts, and many defects can occur. Presentation varies depending on the defect involved, and infertility is a more common presentation than primary amenorrhea.

C4 Immunoglobulin G4–Related Sclerosing Disease in the Orbit

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Introduction: Immunoglobulin G4 (IgG4)-related autoimmune sclerosis is a complex disease entity that affects multiple organ systems, commonly the abdominal viscera. We report an unusual case of IgG4-sclerosing idiopathic orbital inflammation (IOI) and discuss the distinguishing characteristics of the ophthalmic disease subtype. We present a review of the pertinent literature and history of disease in the context of a new, atypical case.

Case Report: IgG4-sclerosing IOI is histopathologically identified by fibrosis, lymphoplasmacytic infiltration, and an increased percentage of IgG4-positive plasma cells. Even though lacrimal gland involvement has always been reported and elevated serum IgG4 is commonly observed, our case did not demonstrate any of these findings in light of biopsy-proven IgG4 orbital involvement. A course of systemic steroids completely resolved our patient's periorbital edema, erythema, and mechanical blepharoptosis. Future recurrence not totally responsive to steroid therapy may warrant a repeat biopsy because orbital IgG4 disease has been associated with development of mucosa-associated lymphatic tissue (MALT) lymphoma.

Discussion: IgG4-sclerosing orbital disease mandates a high index of suspicion and can only be confirmed by tissue biopsy. Possible progression to MALT lymphoma necessitates close surveillance and may require repeat biopsy.

C5 Cholesterol Granuloma of the Orbit From Remote Penetrating Facial Trauma

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Introduction: The etiology of cholesterol granulomas in the skull and sinuses has been a subject of controversy. We describe a rare case of cholesterol granuloma involving the orbit and frontal bone in a patient who had suffered remote penetrating facial trauma.

Case Report: A 39-year-old male presented with a 1-week history of left-sided frontal headache and a blind spot in his left eye. Visual field testing revealed a dense inferonasal quadranopsia. Imaging demonstrated a left superior orbital mass with possible intracranial extension. An orbitotomy revealed changes suggestive of a ruptured cyst or other inflammatory process. A craniotomy and complete excisional biopsy of the orbital roof and rim were then undertaken in conjunction with neurosurgery. The histopathology showed numerous foamy, hemosiderin-laden macrophages and foreign body giant cells surrounding cholesterol clefts with no epithelial elements, consistent with a cholesterol granuloma. Postoperatively, the patient's symptoms and visual field defect resolved completely. Of note, the patient reported experiencing 20 years earlier spontaneous extrusion of windshield glass from his left forehead following a motor vehicle accident.

Discussion: A cholesterol granuloma is a giant cell reaction to cholesterol crystals as foreign bodies. Reported cases suggest an association between orbital cholesterol granulomas and trauma. It has been hypothesized that bleeding into the bone introduces cholesterol where the foreign body inflammatory reaction occurs, distinguishing it from giant cell reparative granuloma. Our case supports this mechanism of development. In a patient with a painful, expanding, bone-eroding orbital mass, any history of trauma should be thoroughly investigated.

C6 Three Cases of Soft Contact Lens–Related *Paecilomyces* Keratitis Successfully Treated With Topical Voriconazole

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Introduction: We report 3 cases of *Paecilomyces* keratitis in contact lens wearers, as well as their successful treatment with topical voriconazole.

Case Report: Three cases of soft contact lens (SCL)-related *Paecilomyces* keratitis were unsuccessfully treated with conventional topical antifungal agents. Treatment was switched to topical or intrastromal voriconazole (10 mg/mL) when corneal cultures yielded *Paecilomyces*. In all 3 cases, the corneal infiltrates completely resolved. Two of the 3 patients also had significant improvement in final visual acuity.

Discussion: These cases support previous series suggesting that SCL wear is a risk factor for fungal keratitis from atypical organisms such as *Paecilomyces*. They also support recent evidence that voriconazole is an effective treatment option for *Paecilomyces* keratitis. Although no evidence supports voriconazole over natamycin as an initial treatment option in suspected fungal keratitis, it should be considered early if the patient is an SCL wearer, is unresponsive to natamycin, or has culture-proven *Paecilomyces* keratitis.

C7 Orbital Varix Thrombosis Following Surgical Prone Positioning for Spinal Decompression

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C8 A Rare Case of Primitive High-Grade Sarcoma with Features of Ewing in the Orbit

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Introduction: We report an exceedingly rare case of primary orbital sarcoma.

Case Report: A 50-year-old man presented with diplopia, blepharoptosis, proptosis, and globe displacement. Imaging found a 1.7 × 2.7 cm extraconal soft-tissue mass without bony invasion. There was no radiographic evidence of systemic disease on positron emission tomography. During orbitotomy, the mass was excised, although clear margins were not possible to achieve in the deep orbit. Microscopy showed a small round cell tumor; however, the morphological, molecular, and immunohistochemical findings were not specific to an established type of mesenchymal tumor. The tumor was positive for CD99, as seen in Ewing sarcoma, but negative for Ewing sarcoma–related genetic events as determined by reverse-transcription polymerase chain reaction and fluorescence in-situ hybridization testing. Even though the tumor was initially described as similar to Ewing sarcoma, the final designation was a nonclassified, high-grade sarcoma. Following resection, chemotherapy and high-dose radiation were recommended. At that time, the patient refused further treatment, but he returned 6 months later with worsening of his symptoms. Repeat imaging documented an orbital mass in the same location. He agreed to localized radiation therapy and will require total exenteration of the orbital contents.

Discussion: Primary orbital sarcoma is exceedingly rare, with only 6 cases of Ewing sarcoma in that location documented in the literature. Patients with orbital sarcoma should be counseled early regarding the aggressive nature of this malignancy and the guarded prognosis regardless of the treatment strategy employed.

C9 Electroretinogram Findings in Cancer-Associated Retinopathy

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Introduction: We report 2 cases of cancer-associated retinopathy (CAR) in which the electroretinogram (ERG) demonstrated a negative-waveform pattern.

Case Report: Case 1 involved a 74-year-old female with a history of bladder, breast, and lung cancer in remission since 2007 who presented with a painless rapid onset of nyctalopia. She demonstrated a mild decrease in visual acuity and field performance; and the fundus examination was otherwise unremarkable. Case 2 involved an 88-year-old female who presented with decreased visual acuity and retinal pigment epithelial changes in the right eye. For each patient, an ERG demonstrated a prominent negative waveform in the dark-adapted bright-flash condition. The negative-waveform ERG prompted further work-up for CAR. We determined Case 1 to have serum antiretinal antibodies against alpha-enolase and the optic nerve and positive immunohistochemical staining of photoreceptors. Case 2 had ophthalmic metastasis from a neuroendocrine tumor confirmed by an octreotide scan.

Discussion: CAR is a paraneoplastic syndrome with autoantibodies directed toward the retina and optic nerve. A negative-waveform ERG signifies disrupted photoreceptor-bipolar cell processing and is associated with CAR. Although the diagnosis of CAR is often elusive, a high index of suspicion substantiated by a negative-waveform ERG can guide the physician in making a correct diagnosis and developing a treatment plan. Case 1 represents the first diagnosis of CAR at our facility, and Case 2 represents the second report in the literature of CAR associated with a neuroendocrine tumor.