

## Henry Ford Health System Publication List November 2008

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### **Biostatistics & Research Epidemiology**

Russmann, S., L. Lamerato, S. P. Motsko, J. C. Pezzullo, M. D. Faber and J. K. Jones (2008). "Risk of further decline in renal function after the use of oral sodium phosphate or polyethylene glycol in patients with a preexisting glomerular filtration rate below 60 ml/min." American Journal of Gastroenterology **103**(11): 2707-16.

### [PDF Full-Text](#)

Henry Ford Hospital, Biostatistics & Research Epidemiology, Detroit, Michigan. Henry Ford Hospital, Nephrology and Hypertension, Detroit, Michigan.

**OBJECTIVES:** The aim of this study was to estimate the risk of further creatinine increase in patients with preexisting renal disease after the use of oral sodium phosphate (OSP) versus polyethylene glycol (PEG), and to study usage patterns of OSP in relation to renal function.

**METHODS:** A cohort study was done using clinical records and electronic patient information from the Henry Ford Health System (HFHS) in patients who had used either OSP or PEG for colonoscopy between February 1999 and April 2006. Among patients with an estimated GFR <60 ml/min before colonoscopy, we identified cases with an unexplained creatinine increase of  $\geq 0.5$  mg/dl within 14 days after colonoscopy.

**RESULTS:** We identified 7,971 OSP and 1,511 PEG users. Relative use of OSP versus PEG decreased from 88.0% before 2004 to 48.4% in 2006. 70.2% of OSP users had no recorded creatinine determination within 60 days before colonoscopy, and this proportion did not decrease over time. The study population included 317 patients with a baseline GFR <60 ml/min, and we identified one case with an unexplained creatinine increase  $\geq 0.5$  mg/dl among 191 PEG users (0.5%) versus eight cases among 126 OSP users (6.3%). Unadjusted and adjusted relative risk estimates on comparing OSP with PEG were 12.1 (95% CI, 1.5-95.8) and 12.6 (95% CI, 1.5-106.5), respectively.

**CONCLUSIONS:** In patients with preexisting renal disease, OSP use was associated with an increased risk of aggravated renal dysfunction versus PEG. Creatinine measurement with GFR estimation should be done before OSP administration in order to avoid its use in patients with renal disease.

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### **Biostatistics & Research Epidemiology**

Yang, J. J., E. G. Burchard, S. Choudhry, C. C. Johnson, D. R. Ownby, D. Favro, J. Chen, M. Akana, C. Ha, P. Y. Kwok, R. Krajenta, S. L. Havstad,

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Hours  
8:30am-7:30pm M-Th  
8:30am-5:00pm F

C. L. Joseph, M. A. Seibold, M. D. Shriver and L. K. Williams (2008). "Differences in allergic sensitization by self-reported race and genetic ancestry." J Allergy Clin Immunol **122**(4): 820-827 e9.

[PDF Full-Text](#)

Department of Biostatistics and Research Epidemiology, Henry Ford Health System, Detroit, MI 48202, USA.

**BACKGROUND:** Many allergic conditions occur more frequently in African American patients when compared with white patients; however, it is not known whether this represents genetic predisposition or disparate environmental exposures. **OBJECTIVE:** We sought to assess the relationship of self-reported race and genetic ancestry to allergic sensitization. **METHODS:** We included 601 women enrolled in a population-based cohort study whose self-reported race was African American or white. Genetic ancestry was estimated by using markers that differentiate West African and European ancestry. We assessed the relationship between allergic sensitization (defined as  $>$  or  $=1$  allergen-specific IgE results) and both self-reported race and genetic ancestry. Regression models adjusted for sociodemographic variables, environmental exposures, and location of residence. **RESULTS:** The average proportion of West African ancestry in African American participants was 0.69, whereas the mean proportion of European ancestry in white participants was 0.79. Self-reported African American race was associated with allergic sensitization when compared with those who reported being white (adjusted odds ratio, 2.19; 95% CI, 1.22-3.93), even after adjusting for other variables. Genetic ancestry was not significantly associated with allergic sensitization after accounting for location of residence (adjusted odds ratio, 2.09 for urban vs suburban residence; 95% CI, 1.32-3.31). **CONCLUSION:** Self-reported race and location of residence appeared to be more important predictors of allergic sensitization when compared with genetic ancestry, suggesting that the disparity in allergic sensitization by race might be primarily a result of environmental factors rather than genetic differences.

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### **Bone & Joint Center**

Sethi, A., S. Lee and R. Vaidya (2008). "Transforaminal lumbar interbody fusion using unilateral pedicle screws and a translaminar screw." Eur Spine J **Epub Ahead of Print**.

[PDF Full-Text](#)

Department of Orthopedics, Henry Ford Health System, Detroit, MI, USA,  
[drsethi11@rediffmail.com](mailto:drsethi11@rediffmail.com).

Lumbar spinal fusion is advancing with minimally invasive techniques, bone graft alternatives, and new implants. This has resulted in significant reductions of operative time, duration of hospitalization, and higher success in fusion rates. However, costs have increased as many new technologies are expensive. This study was carried out to investigate the clinical outcomes and fusion rates of a low implant load construct of unilateral pedicle screws and a translaminar screw in transforaminal lumbar interbody fusion (TLIF) which reduced the cost of the posterior implants by almost 50%. Nineteen consecutive patients who underwent single level TLIF with this construct were included in the study. Sixteen patients had a TLIF allograft interbody spacer placed, while in three a polyetheretherketone (PEEK) cage was used. Follow-up ranged from 15 to 54 months with a mean of 32 months. A clinical and radiographic evaluation was carried out preoperatively and at multiple time points following surgery. An overall improvement in Oswestry scores and visual analogue scales for leg and back pain (VAS) was observed. Three patients underwent revision surgery due to recurrence of back pain. All patients showed radiographic evidence of fusion from 9 to 26 months (mean 19) following surgery. This study suggests that unilateral pedicle screws and a contralateral translaminar screw are a cheaper and viable option for single level lumbar fusion.

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### **Bone & Joint Center**

Yang, M., X. Wang, L. Zhang, C. Yu, B. Zhang, W. Cole, G. Cavey, P. Davidson and G. Gibson (2008). "Demonstration of the interaction of transforming growth factor beta 2 and type X collagen using a modified tandem affinity purification tag." J Chromatogr B Analyt Technol Biomed Life Sci **875**(2): 493-501.

## [Article Request Form](#)

Bone and Joint Center, Henry Ford Hospital, 2799 West Grand Blvd., MI 48202, USA.

Like other members of the transforming growth factor beta (TGF-beta) family of growth factors, the biological activity of TGF-beta2 is believed to be regulated by the formation and dissociation of multiprotein complexes. To isolate the molecular complex formed by TGF-beta2 secreted by hypertrophic chondrocytes we have used expression of TGF-beta2 fused with the humanized, tandem affinity purification (hTAP) tag and mass spectrometry for the identification of interacting proteins. The hTAP synthetic gene was assembled by systematically replacing the rare codons of the original TAP tag with codons most preferred in highly expressed human genes to circumvent the poor translation efficiency of the original TAP tag in animal cells. TGF-beta2 was shown to interact with Type X collagen and this interaction confirmed using V5 tagged TGF-beta2. Functional interaction was suggested by the inhibition of TGF-beta2 activity by type X collagen in culture and the influence of a mutation in type X collagen on the distribution of TGF-beta2 in growth cartilage.

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### **Bone and Joint Center**

Norman, T. L., T. M. Little and Y. N. Yeni (2008). "Age-related changes in porosity and mineralization and in-service damage accumulation." Journal of Biomechanics **41**(13): 2868-73.

## [PDF Full-Text](#)

Henry Ford Hospital, Bone and Joint Center, Detroit, Michigan.

It has been proposed that bone damageability (i.e. bone's susceptibility to formation of damage) increases with the elevation or suppression of bone turnover. Suppression of turnover via bisphosphonates increases local bone mineralization, which theoretically should increase the susceptibility of bone to microcrack formation. Elevation of bone turnover has also been proposed to increase bone microdamage through an increase in bone intracortical porosity and local stresses and strains. The goal of this paper was to investigate the above proposals, i.e., whether or not increases to mineral content and porosity increase bone in-service damageability. To do this, we measured in vivo diffuse damage area (Df.Dm.Ar, %) and microcrack density (Cr.Dn) (cracks/mm<sup>2</sup>) in the same specimen from human cortical bone of the midshaft of the proximal femur obtained from cadavers with an age range of eight decades and examined their relationships with porosity, mineralization and age. results of this study showed that Cr.Dn and Df.Dm.Ar increased with a decrease in bulk mineralization. This finding does not appear to support the proposal that damage accumulation increase with low bone turnover that results in increases mineralization. it was proposed however that the negative correlation between damage accumulation and mineralization may be attributed to highly mineralized regions of bone existing with under-mineralized regions resulting in an overall decrease in average bone mineralization. It was also found that microdamage accumulates with increasing porosity which does appear to support the proposal that elevated bone turnover that results in increased porosity can accelerate microdamage accumulation. Finally, it was shown that linear microcracks and Df.Dm.Ar accumulate with age differently, but because they correlate with each other, one may be the precursor for the other.

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### **Cardiology**

Cavalcante, J. L., S. Khan and M. Gheorghide (2008). "EVEREST study: Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan." Expert Rev Cardiovasc Ther **6**(10): 1331-8.

## [Article Request Form](#)

Henry Ford Heart and Vascular Institute, 2799 W Grand Blvd - K14, Detroit, MI 48202, USA.

[icavalc1@hfhs.org](mailto:icavalc1@hfhs.org)

Acute heart failure syndromes are a common cause of emergency department visits and hospitalization in North America and Europe. Although in-hospital mortality is relatively low, the postdischarge mortality and rehospitalization rates can be as high as 10-15 and 30%, respectively, within 60-90 days following discharge. It appears that the main reason for admission and readmission for heart failure is related to congestion manifested by dyspnea, jugular venous

distension and edema. Often, congestion is associated with dilutional hyponatremia that is difficult to treat. Hyponatremia is an important predictor of increased mortality and the available therapies to treat congestion and/or hyponatremia are often ineffective and/or unsafe. Accordingly, there is an unmet need to develop a new agent that effectively relieves congestion due to high filling pressure without worsening renal function and improving or normalizing serum sodium in hyponatremic patients. This paper provides an overview of a new compound, tolvaptan, an oral selective V(2)-vasopressin antagonist in light of the recently published Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial. The biochemical and pharmacological properties are discussed in conjunction with its clinical efficacy and safety, exploring the potential role of tolvaptan in the management of acute heart failure syndromes presenting with or without hyponatremia.

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## Cardiology

Rastogi, S., M. Imai, V. G. Sharov, S. Mishra and H. N. Sabbah (2008). "Darbepoetin Alfa Prevents Progressive Left Ventricular Dysfunction and Remodeling in Non-Anemic Dogs with Heart Failure." Am J Physiol Heart Circ Physiol **Epub Ahead of Print**.

### [PDF Full-Text](#)

Henry Ford Health System, Cardiology, Detroit, Michigan.

In anemic patients with heart failure (HF), erythropoietin type drugs can elicit clinical improvement. This study examined the effects of chronic monotherapy with darbepoetin alfa (DARB) on LV function and remodeling in non-anemic dogs with advanced HF. HF (LV ejection fraction, EF ~25%) was produced in 14 dogs by intracoronary microembolizations. Dogs were randomized to once a week subcutaneous injection of DARB (1.0 microg/kg, n=7) or to no therapy (HF, n=7). All the procedures were performed during cardiac catheterization under general anesthesia and sterile conditions. LV end diastolic (EDV) and end-systolic volumes (ESV) and EF were measured before initiating therapy and at the end of 3 months of therapy. mRNA and protein expression of caspase-3, hypoxia inducible factor-1 alfa (HIF-1alpha) and bone marrow-derived stem cell (BMSC) marker c-Kit were determined in LV tissue. In HF dogs, EDV and ESV increased and EF decreased after 3 months of follow-up. Treatment with DARB prevented the increase in EDV, decreased ESV and increased EF. DARB therapy also normalized the expression of HIF-1alpha and active caspase-3 and enhanced the expression of c-Kit. We conclude that chronic monotherapy with DARB prevents progressive LV dysfunction and dilation in non-anemic dogs with advanced HF. These results suggest that DARB elicits beneficial effects in HF that are independent of the presence of anemia. Key words: Erythropoietin, Anemia, Ventricular function, Ventricular remodeling.

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## Cardiology

Sinno, M. C., M. Kowalski, D. N. Kenigsberg, S. C. Krishnan and S. Khanal (2008). "R-wave amplitude changes measured by electrocardiography during early transmural ischemia." J Electrocardiol **41**(5): 425-30.

### [Article Request Form](#)

Henry Ford Hospital, Detroit, MI 48202, USA. [msinno1@hfhs.org](mailto:msinno1@hfhs.org)

**BACKGROUND:** Changes in the amplitude of the R wave (RWA) on the electrocardiogram (ECG) have been described during acute myocardial ischemia and infarction. However, this has not been well studied in a controlled setting. We hypothesized that significant increase in RWA occurs during early transmural myocardial ischemia. **METHODS:** We prospectively evaluated changes in RWA in 50 patients during brief episodes of transmural ischemia induced by first balloon occlusion (mean, 38 seconds at 6-10 atmospheric pressures) during elective percutaneous coronary intervention. We recorded 12-lead ECGs at 20-second intervals before and during balloon inflation in 16 right coronary arteries, 14 left circumflex arteries, and 20 left anterior descending arteries. R wave amplitude was digitally measured in each of the 12 leads in every ECG using the ECG interval editor (General Electric HC, Menomonee Falls, WI). Intracoronary (IC) ECGs were also recorded in 4 patients. The mean of the RWA in each lead before balloon inflation was compared to the mean RWA during balloon inflation. **RESULTS:** R wave amplitude significantly increased during balloon inflation from baseline in limb leads I, II, aVL, and all the precordial leads with the exception of lead V(1). The RWA increase did not reach statistical significance in leads III, aVF, and V(1). Mean RWA increase was consistent in all leads except aVR during the brief episodes of ischemia during initial balloon inflation because of the

inverse polarity of this lead. The increase in RWA was seen in most patients (mean, 75%) in whom transmural ischemia was induced by first balloon inflation. Besides, the RWA showed an increase from baseline in 3 patients who had IC-lead recordings. CONCLUSION: R wave amplitude increases significantly in precordial leads (V(2)-V(6)) and limb leads (I, II, aVL) of the surface ECG during brief episodes of transmural ischemia. The increase in RWA might be consistent with the expansion of the left ventricular cavity during ischemia and/or alterations in conduction that are intrinsic to the myocardium.

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### **Center for Health Services Research**

Lafata, J. E., M. Cerghet, E. Dobie, L. Schultz, K. Tunceli, J. Reuther and S. Elias (2008).

"Measuring adherence and persistence to disease-modifying agents among patients with relapsing remitting multiple sclerosis." J Am Pharm Assoc **48**(6): 752-7.

### [Article Request Form](#)

Center for Health Services Research, Henry Ford Hospital, Detroit, MI 48202, USA.

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OBJECTIVES: To measure disease-modifying agent adherence and persistence among patients with multiple sclerosis (MS). DESIGN: Retrospective cohort study. SETTING: Multispecialty, salaried group practice in southeast Michigan, between June 1, 2004, and June 30, 2006. PATIENTS: 224 insured adult patients with relapsing remitting MS with an outpatient visit. MAIN OUTCOME MEASURES: Medical record-documented receipt of medication recommendation and prescription. Pharmacy claims data-derived measures of dispensing and among patients with two or more dispensings, medication possession ratios (MPRs), and proportion of gap days were estimated. Among those initiating agent use, persistence was estimated. RESULTS: Mean cohort age was 47.6 years, while 77% of participants were women and 39% were black. Of patients, 81.8% had a recommendation for a disease-modifying agent, 75.0% had a prescription, and 66.5% had two or more dispensings. Among those with two or more dispensings, mean MPR between the first and last dispensing date was 83.8% (95% CI 80.8-86.8), while mean MPR for the entire 24-month period was 68.0% (64.4-71.7). MPR for the 24-month period decreased with increasing drug copayments and was lower among black patients, while MPR between the first and last dispensing date increased with increasing age. Among those initiating therapy, 43% were nonpersistent with medications within 14 months. CONCLUSION: Medication adherence and persistence among patients with relapsing remitting MS is far from monolithic. Measuring medication adherence and persistence among defined populations is useful for understanding the relationship between medication use and outcomes in practice and for targeting patients and programs to improve medication adherence.

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### **Dermatology**

Adams, B. and T. Shwayder (2008). "Steatocystoma multiplex suppurativum." International Journal of Dermatology **47**(11): 1155-6.

### [PDF Full-Text](#)

Henry Ford Hospital, Dermatology, Detroit, Michigan

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### **Diagnostic Radiology**

Babajani-Feremi, A., H. Soltanian-Zadeh and J. E. Moran (2008). "Integrated MEG/fMRI model validated using real auditory data." Brain Topogr **21**(1): 61-74.

### [PDF Full-Text](#)

Image Analysis Laboratory, Radiology Department, Henry Ford Hospital, One Ford Place, 2F, Detroit, MI 48202, USA. [abbasb@rad.hfh.edu](mailto:abbasb@rad.hfh.edu)

The main objective of this paper is to present methods and results for the estimation of parameters of our proposed integrated magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) model. We use real

auditory MEG and fMRI datasets from 7 normal subjects to estimate the parameters of the model. The MEG and fMRI data were acquired at different times, but the stimulus profile was the same for both techniques. We use independent component analysis (ICA) to extract activation-related signal from the MEG data. The stimulus-correlated ICA component is used to estimate MEG parameters of the model. The temporal and spatial information of the fMRI datasets are used to estimate fMRI parameters of the model. The estimated parameters have reasonable means and standard deviations for all subjects. Goodness of fit of the real data to our model shows the possibility of using the proposed model to simulate realistic datasets for evaluation of integrated MEG/fMRI analysis methods.

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### **Emergency Medicine**

Rivers, E. P. and T. Ahrens (2008). "Improving outcomes for severe sepsis and septic shock: tools for early identification of at-risk patients and treatment protocol implementation." Crit Care Clin **24**(3 Suppl): S1-47.

#### [Article Request Form](#)

Department of Emergency Medicine, Henry Ford Hospital, Detroit, MI, USA.

Sepsis is a significant problem, and septicemia is the 10th leading cause of death in the United States. Sepsis incidence is increasing, and the mortality rate is 20% to 50% for patients with severe sepsis. This article identifies methods for improving outcomes of severe sepsis and septic shock. Included are recommendations for diagnosis and treatment. Case studies are included.

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### **Emergency Medicine**

Rivers, E. P., V. Coba, A. Visbal, M. Whitmill and D. Amponsah (2008). "Management of Sepsis: Early Resuscitation." Clin Chest Med **29**(4): 689-704.

#### [Article Request Form](#)

Department of Emergency Medicine, Henry Ford Health Systems, 270-Clara Ford Pavilion, 2799 West Grand Boulevard, Detroit, MI 48202, USA; Department of Surgery, Henry Ford Health Systems, 270-Clara Ford Pavilion, 2799 West Grand Boulevard, Detroit, MI 48202, USA.

Key links in the chain of survival for the management of severe sepsis and septic shock are early identification and comprehensive resuscitation of high-risk patients. Multiple studies have shown that the first 6 hours of early sepsis management are especially important from a diagnostic, pathogenic, and therapeutic perspective, and that steps taken during this period can have a significant impact on outcome. The recognition of this critical time period and the robust outcome benefit realized in previous studies provides the rationale for adopting early resuscitation as a distinct intervention. Sepsis joins trauma, stroke, and acute myocardial infarction in having "golden hours," representing a critical opportunity early on in the course of disease for actions that offer the most benefit.

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### **Hematology, Medical Oncology and Josephine Ford Cancer Center**

Yates, T. J., M. Abouljoud, A. Lambing and P. Kuriakose (2008). "Risk of venous thrombosis in patients with hepatic malignancies undergoing surgical resection." Indian J Gastroenterol **27**(4): 159-61.

#### [PDF Full-Text](#)

Department of Hematology and Oncology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, Michigan 48202, USA. [oncheme@yahoo.com](mailto:oncheme@yahoo.com)

The risk of venous thrombosis is well documented in patients with malignancies, those undergoing abdominal surgery, and those undergoing hepatic resection for malignancy. This study was undertaken to determine whether there was a

difference in the risk of thrombosis between those undergoing resection for hepatic metastases and primary hepatic malignancies. We performed a retrospective chart review of patients undergoing initial surgical resection for hepatic malignancies, primarily to determine whether there was a difference in the incidence of venous thrombosis between those with primary and secondary malignancies. Ninety-nine patients underwent surgical resection for either primary or secondary hepatic malignancies from 2001 to 2006. Seven of these patients, all with secondary hepatic malignancy, developed venous thrombosis within 3 months of resection. This retrospective review reveals that a clinical presentation of venous thrombosis is significantly more common among patients undergoing hepatic resection for secondary malignancy than those undergoing resection for primary cancer of the liver. Special attention with regard to prophylaxis for thrombosis may be required in these patients.

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### **Hypertension & Vascular Research**

Silva, G. B. and J. L. Garvin (2008). "Angiotensin II-dependent hypertension increases Na transport-related oxygen consumption by the thick ascending limb." Hypertension **52**(6): 1091-8.

[PDF Full-Text](#)

Division of Hypertension and Vascular Research, Henry Ford Hospital, Detroit, Michigan 48202, USA.

Renal medullary superoxide (O<sub>2</sub><sup>-</sup>) increases in angiotensin (Ang) II-dependent hypertension. O<sub>2</sub><sup>-</sup> increases thick ascending limb Na transport, but the effect of Ang II-dependent hypertension on the thick ascending limb is unknown. We hypothesized that Ang II-dependent hypertension increases thick ascending limb NaCl transport because of enhanced O<sub>2</sub><sup>-</sup> production and increased protein kinase C (PKC) alpha activity. We measured the effect of Ang II-dependent hypertension on furosemide-sensitive oxygen consumption (a measure of Na transport), O<sub>2</sub><sup>-</sup> production, and PKCalpha translocation (a measure of PKCalpha activity) in thick ascending limb suspensions. Ang II-dependent hypertension increased furosemide-sensitive oxygen consumption (26.2±1.0% versus 36.6±1.2% of total oxygen consumption; P<0.01). O<sub>2</sub><sup>-</sup> was also increased (1.1±0.2 versus 3.2±0.5 nmol of O<sub>2</sub><sup>-</sup>/min per milligram of protein; P<0.03) in thick ascending limbs. Unilateral renal infusion of Tempol decreased O<sub>2</sub><sup>-</sup> (2.4±0.4 versus 1.2±0.2 nmol of O<sub>2</sub><sup>-</sup>/min per milligram of protein; P<0.04) and furosemide-sensitive oxygen consumption (32.8±1.3% versus 24.0±2.1% of total oxygen consumption; P<0.01) in hypertensive rats. Tempol did not affect O<sub>2</sub><sup>-</sup> or furosemide-sensitive oxygen consumption in normotensive controls and did not alter systolic blood pressure. Ang II-dependent hypertension increased PKCalpha translocation (5.7±0.3 versus 13.8±1.4 AU per milligram of protein; P<0.01). Unilateral renal infusion of Tempol reduced PKCalpha translocation (5.0±0.9 versus 10.4±2.6 AU per milligram of protein; P<0.04) in hypertensive rats. Unilateral renal infusion of the PKCalpha inhibitor Go6976 reduced furosemide-sensitive oxygen consumption (37.4±1.5% versus 25.1±1.0% of total oxygen consumption; P<0.01) in hypertensive rats. We conclude that Ang II-dependent hypertension enhances thick ascending limb Na transport-related oxygen consumption by increasing O<sub>2</sub><sup>-</sup> and PKCalpha activity.

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### **Hypertension & Vascular Research**

Sun, Y., O. A. Carretero, J. Xu, N. E. Rhaleb, J. J. Yang, P. J. Pagano and X. P. Yang (2008). "Deletion of Inducible Nitric Oxide Synthase Provides Cardioprotection in Mice With 2-Kidney, 1-Clip Hypertension." Hypertension **Epub Ahead of Print**.

*Sladen has electronic subscription. Issue for this article not available online at the time of this publication.*

Hypertension and Vascular Research Division, Department of Internal Medicine, and Department of Biostatistics and Research Epidemiology, Henry Ford Hospital, Detroit, Mich; and the Department of Pathology, North China Coal Medical College, Tangsan, China.

Inducible NO synthase (iNOS) has been implicated in the pathogenesis of hypertension and target organ damage. We hypothesized that induction of iNOS contributes to left ventricular (LV) hypertrophy and dysfunction in mice with 2-kidney, 1-clip hypertension. Deletion of iNOS diminishes oxidative stress, thereby attenuating LV hypertrophy and enhancing cardiac performance. 2-Kidney, 1-clip hypertension was induced in mice lacking iNOS and wild-type controls (C57BL/6J). Sham-clipped mice served as controls. Systolic blood pressure was measured weekly by tail cuff.

Left ventricular ejection fraction (by echocardiography) and cardiac response (maximum and minimum dP/dt, as well as an indicator of isovolumic contraction) to isoproterenol (50 ng per mouse, IV) were studied at the end of the experiment. 4-Hydroxy-2-nonenal (a byproduct of lipid peroxidation and an indicator of oxidative stress) was measured by immunohistochemical staining. gp91(phox), endothelial NO synthase, and iNOS protein expression were determined by Western blot. We found that systolic blood pressure, LV weight, myocyte cross-sectional area, interstitial collagen fraction, ejection fraction, and cardiac response to isoproterenol did not differ between strains with sham clipping. 2-Kidney, 1-clip hypertension increased systolic blood pressure, LV weight, myocyte cross-sectional area, and interstitial collagen fraction similarly in both strains. However, in mice lacking iNOS, maximum and minimum dP/dt, as well as an indicator of isovolumic contraction, markedly increased in response to isoproterenol, associated with decreased cardiac 4-hydroxy-2-nonenal expression and urinary nitrate/nitrite. We concluded that deletion of iNOS does not seem to play a significant role in preventing 2-kidney, 1-clip hypertension-induced hypertension and cardiac hypertrophy; however, it does enhance preservation of cardiac function, probably because of a reduction of iNOS-induced oxidative stress.

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## **Hypertension and Vascular Research**

Liao, T. D., X. P. Yang, Y. H. Liu, E. G. Shesely, M. A. Cavasin, W. A. Kuziel, P. J. Pagano and O. A. Carretero (2008). "Response to Inflammation, angiotensin II, and hypertension." Hypertension **52**(5): E136.

### [Letter to the Editor](#)

Henry Ford Hospital, Hypertension and Vascular Research, Detroit, Michigan

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## **Nephrology**

Novak, J. E. and L. A. Szczech (2008). "Phosphate Binders in Chronic Kidney Disease and End-Stage Renal Disease: A Patient-Centered Approach." Semin Dial **EPub Ahead of Print**.

### [PDF Full-Text](#)

Division of Nephrology & Hypertension, Henry Ford Health System, Detroit, Michigan.

Disorders of calcium and phosphorus metabolism are associated with significant morbidity and mortality in patients with advanced chronic kidney disease. These patients typically require oral phosphate binders to maintain phosphorus homeostasis, but the choice of which among several agents to use has been actively investigated and debated. Recent debate has been polarized between those who favor calcium-based binders for their proven efficacy and relatively low cost and those who favor sevelamer for its putative beneficial effects on inflammatory biomarkers and vascular calcification. This review summarizes the current state of the art of prescribing phosphate binders, ranging from large-scale clinical trials to focused mechanistic studies, and proposes that the available evidence does not conclusively prove the relative superiority of any one binder.

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## **Neurology**

Bowyer, S. M., L. Hsieh, J. E. Moran, R. A. Young, A. Manoharan, C. C. Liao, K. Malladi, Y. J. Yu, Y. R. Chiang and N. Tepley (2008). "Conversation effects on neural mechanisms underlying reaction time to visual events while viewing a driving scene using MEG." Brain Res **EPub Ahead of Print**.

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Department of Neurology, Henry Ford Hospital, MEG Lab Clara Ford Pavilion 78/79, 2799 West Grand Boulevard, Detroit, MI 48202, USA; Department of Physics, Oakland University, 190 Science and Engineering Building, Rochester, MI 48309, USA; Department of Neurology, Wayne State University School of Medicine, University Health Center Suite 8D, Detroit, MI 48201, USA.

Magnetoencephalography (MEG) imaging examined the neural mechanisms that modulate reaction times to visual events while viewing a driving video, with and without a conversation. Twenty-four subjects ages 18-65 were monitored by whole-head MEG. The primary tasks were to monitor a driving video and to depress a foot pedal in response to a small red light presented to the left or below the driving scene at unpredictable times. The behavioral reaction time (RT) to the lights was recorded. The secondary task was a hands-free conversation. The subject pressed a button to answer a ring tone, and then covertly answered pre-recorded non-emotional questions such as "What is your birth date?" RTs for the conversation task (1043 ms, SE=65 ms) were slightly longer than for the primary task (baseline no conversation (944 ms, SE=48 ms)). During the primary task RTs were inversely related to the amount of brain activity detected by MEG in the right superior parietal lobe (Brodmann's Area 7). Brain activity was seen in the 200 to 300 ms range after the onset of the red light and in the visual cortex (BA 19) about 85 ms after the red light. Conversation reduced the strengths of these regression relationships and increased mean RT. Conversation may contribute to increased reaction times by (1) damping brain activation in specific regions during specific time windows, or (2) reducing facilitation from attention inputs into those areas or (3) increasing temporal variability of the neural response to visual events. These laboratory findings should not be interpreted as indicative of real-world driving, without on-road validation, and comparison to other in-vehicle tasks.

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## Neurology

Cerghet, M., B. Redman, L. Junck, J. Forman and L. R. Rogers (2008). "Prolonged survival after multifocal brain radiation necrosis associated with whole brain radiation for brain metastases: case report." J Neurooncol **90**(1): 85-8.

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Radiation necrosis of the brain is a well documented adverse effect of radiation therapy. The authors report an unusual case of relapsing multifocal radiation necrosis following whole brain radiation therapy (WBRT) for brain metastases from a systemic germ cell tumor. Anticoagulation with warfarin may have had therapeutic benefit. The patient is alive without a neurological deficit 10 years after the diagnosis of radiation necrosis.

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## Neurology

Hong, X., F. Jiang, S. N. Kalkanis, Z. G. Zhang, X. Zhang, X. Zheng, H. Jiang, T. Mikkelsen and M. Chopp (2008). "Increased chemotactic migration and growth in heparanase-overexpressing human U251n glioma cells." J Exp Clin Cancer Res **27**: 23.

### [Article Request Form](#)

Department of Neurology, Henry Ford Health Science Center, Detroit, MI, USA.

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Heparanase is an endoglycosidase that degrades heparan sulfate, the main polysaccharide constituent of the extracellular matrix (ECM) and basement membrane. Expression of the heparanase gene is associated with the invasion and metastatic potential of a variety of tumor-derived cell types. However, the roles of heparanase in the regulation of gene expression and the subsequent cell function changes other than invasion are not clear. In the current study, we overexpressed the human heparanase gene in a human U251n glioma cell line. We found that heparanase-overexpression significantly increased cell invasion, proliferation, anchorage-independent colony formation and chemotactic migration towards fetal bovine serum (FBS)-supplied medium and stromal cell-derived factor-1 (SDF-1). These phenotypic appearances were accompanied by enhanced protein kinase B (AKT) phosphorylation. Focal adhesion kinase (FAK) and extracellular signal-regulated kinase 1 (ERK1) signaling were not altered by heparanase-overexpression. These results indicate that heparanase has pleiotropic effects on tumor cells.

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## Neurology

Lewitt, P. A., W. G. Ondo, B. Van Lunen and P. B. Bottini (2008). "Open-Label Study Assessment of Safety and Adverse Effects of Subcutaneous Apomorphine Injections in Treating "Off" Episodes in Advanced Parkinson Disease." [Clin Neuropharmacol](#) **Epub Ahead of Print**.

*Sladen has electronic subscription. Issue for this article not available online at the time of this publication.*

Department of Neurology, Wayne State University School of Medicine and Henry Ford Hospital, Detroit, MI; Department of Neurology, Baylor College of Medicine, Houston, TX; and Mylan Laboratories, Morgantown, WV.

**OBJECTIVE::** To assess the safety and adverse effect profile of continued use of intermittent subcutaneous apomorphine to treat "off" episodes in subjects with advanced Parkinson disease. **SUBJECTS AND METHODS::** The study enrolled subjects with Hoehn and Yahr stage II-V Parkinson disease who were experiencing "off" events despite an optimized oral medication regimen. After baseline assessment and subcutaneous apomorphine dose titration (2-10mg/dose), subjects received  $\geq 12$  months of open-label treatment, as needed, for "off" episodes. **RESULTS::** Of the 546 subjects in the study population, the majority used apomorphine on a daily basis; the average dose was 4.0 mg. A total of 187 subjects discontinued treatment because of adverse events (AEs). Most AEs were mild to moderate and expected with apomorphine. The AEs most commonly classified as definitely, probably, or possibly treatment related were nausea and vomiting, dyskinesia, dizziness, somnolence, hallucination, yawning, and injection site bruising. Serious AEs occurred in 199 subjects, but only 27 were considered to be probably or possibly treatment related. None of the 45 deaths recorded in the study were attributed to apomorphine. **CONCLUSIONS::** Long-term use of intermittent apomorphine dosing for treatment of "off" episodes was generally associated with mild-to-moderate AEs.

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## Neurology

Santra, M., S. Santra, C. Roberts, R. L. Zhang and M. Chopp (2009). "Doublecortin induces mitotic microtubule catastrophe and inhibits glioma cell invasion." [J Neurochem](#) **108**: 231-45.

[PDF Full-Text](#)

Department of Neurology, Henry Ford Health System, Detroit, Michigan.

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## Neurology

Santra, M., S. Santra, J. Zhang and M. Chopp (2008). "Ectopic decorin expression up-regulates VEGF expression in mouse cerebral endothelial cells via activation of the transcription factors Sp1, HIF1alpha, and Stat3." [J Neurochem](#) **105**(2): 324-37.

[PDF Full-Text](#)

Department of Neurology, Henry Ford Hospital, Detroit, Michigan 48202, USA.

We demonstrate that a proteoglycan decorin (DCN) up-regulates the vascular endothelial growth factor (VEGF) expression with activation of VEGF regulating transcription factors Sp1, hypoxia-inducible factor 1alpha (HIF1alpha), and signal transducer and activator of transcription 3 (Stat3) via epidermal growth factor receptor (EGFR), mitogen-activated protein kinase extracellular signal-regulated kinase 1/2 (ERK1/2), and protein kinase B (AKT) pathways in DCN transfected mouse cerebral endothelial (MCE) cells. Treatment with pharmacological inhibitors and small interfering RNAs reveal that induction and activation of Sp1, HIF1alpha, and Stat3 facilitate their nuclear localization and binding to their specific motifs of the VEGF promoter and induce VEGF expression via two independent pathways, DCN/EGFR/phosphoinositide-3 kinase/AKT and DCN/EGFR/ERK1/2, respectively, in DCN synthesizing MCE cells. The cell type specific glycosylation protects Sp1 and HIF1alpha from proteasome degradation and plays an important and novel role in the regulation of VEGF in DCN transfected MCE cells. Induction of gelatinases (matrix metalloproteinase 2 and 9), the serine protease tissue plasminogen activator and plasmin by DCN transfection in MCE cells leads to extracellular proteolysis and to release of matrix-bound VEGF and activation of angiogenesis. In this

study, we demonstrate that two independent downstream signal pathways, DCN/EGFR/ERK1/2 and DCN/EGFR/phosphoinositide-3 kinase/AKT, mediate up-regulation and activation of transcription factors of VEGF such as HIF1alpha, Stat3, and Sp1 and increase VEGF transcription and angiogenesis in MCE cells.

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## Neurosurgery

Golembieski, W. A., S. L. Thomas, C. R. Schultz, C. K. Yunker, H. M. McClung, N. Lemke, S. Cazacu, T. Barker, E. H. Sage, C. Brodie and S. A. Rempel (2008). "HSP27 mediates SPARC-induced changes in glioma morphology, migration, and invasion." *Glia* **56**(10): 1061-75.

### [PDF Full-Text](#)

Barbara Jane Levy Laboratory of Molecular Neuro-Oncology, Department of Neurosurgery, Henry Ford Hospital, Detroit, Michigan 48202, USA.

Secreted protein acidic and rich in cysteine (SPARC) regulates cell-extracellular matrix interactions that influence cell adhesion and migration. We have demonstrated that SPARC is highly expressed in human gliomas, and it promotes brain tumor invasion in vitro and in vivo. To further our understanding regarding SPARC function in glioma migration, we transfected SPARC-green fluorescent protein (GFP) and control GFP vectors into U87MG cells, and assessed the effects of SPARC on cell morphology, migration, and invasion after 24 h. The expression of SPARC was associated with elongated cell morphology, and increased migration and invasion. The effects of SPARC on downstream signaling were assessed from 0 to 6 h and 24 h. SPARC increased the levels of total and phosphorylated HSP27; the latter was preceded by activation of p38 MAPK and inhibited by the p38 MAPK inhibitor SB203580. Augmented expression of SPARC was correlated with increased levels of HSP27 mRNA. In a panel of glioma cell lines, increasing levels of SPARC correlated with increasing total and phosphorylated HSP27. SPARC and HSP27 were colocalized to invading cells in vivo. Inhibition of HSP27 mRNA reversed the SPARC-induced changes in cell morphology, migration, and invasion in vitro. These data indicate that HSP27, a protein that regulates actin polymerization, cell contraction, and migration, is a novel downstream effector of SPARC-regulated cell morphology and migration. As such, it is a potential therapeutic target to inhibit SPARC-induced glioma invasion.

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## Neurosurgery

Mikkelsen, T., T. Doyle, J. Anderson, J. Margolis, N. Paleologos, J. Gutierrez, D. Croteau, L. Hasselbach, R. Avedissian and L. Schultz (2008). "Temozolomide single-agent chemotherapy for newly diagnosed anaplastic oligodendroglioma." *J Neurooncol* **EPub Ahead of Print**.

### [PDF Full-Text](#)

Hermelin Brain Tumor Center, Henry Ford Health System, 2799 W Grand Blvd, Detroit, MI, 48202, USA, [nstom@neuro.hfh.edu](mailto:nstom@neuro.hfh.edu)

The treatment of patients with anaplastic oligodendroglioma (AO) has been significantly impacted by the molecular detection of loss of sequences on chromosomes 1p and 19q. We performed a clinical trial to prospectively evaluate the safety of treating patients with AO with temozolomide (TMZ) alone in patients with chromosome 1p/19q loss and with chemo-radiation in patients not harboring this loss. Forty-eight patients were enrolled, 36/48 (75%) with evidence of chromosome 1p/19q loss treated with TMZ alone and 12/18 (25%) without such losses, treated with pre-radiation TMZ followed by chemo-radiation. Despite more aggressive treatment, patients without 1p/19q loss had a shorter progression-free survival (PFS) of 13.5 months. With a median follow-up time of 32 months, patients with 1p/19q LOH had a median TTP of 28.7 months. Patients with AO with 1p/19q LOH can be safely treated with single-agent TMZ and do not appear to experience earlier or more frequent tumor progression. This treatment regimen should be studied as part of a formal randomized clinical trial.

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## Neurosurgery

Seyfried, D. M., Y. Han, D. Yang, J. Ding, S. Savant-Bhonsale, M. S. Shukairy and M. Chopp (2008). "Mannitol enhances delivery of marrow stromal cells to the brain after experimental intracerebral hemorrhage." Brain Res **1224**: 12-9.

[PDF Full-Text](#)

Department of Neurosurgery, Henry Ford Health System, 2799 W Grand Boulevard, Detroit, MI 48202, USA. [nsdos@neuro.hfh.edu](mailto:nsdos@neuro.hfh.edu)

Previous studies show that intravascular injection of human bone marrow stromal cells (hBMSCs) significantly improves neurological functional recovery in a rat model of intracerebral hemorrhage (ICH). In the present study, we tested the hypothesis that mannitol improves the efficiency of intraarterial MSC delivery (i.e., fewer injected cells required for therapeutic efficacy) after ICH. There were four post-ICH groups (N=9): group 1, negative control with only intraarterial injection of 1 million human fibroblasts in phosphate-buffered saline (PBS); group 2, intravenous injection of mannitol alone in PBS (1.5 g/kg); group 3, intraarterial injection of 1 million hBMSCs alone in PBS; and group 4, intravenous injection of mannitol (1.5 g/kg) in PBS followed by intraarterial injection of 1 million hBMSCs in PBS. Group 4 exhibited significantly improved neurological functional outcome as assessed by neurological severity score (NSS) and corner test scores. Immunohistochemical staining of group 4 suggested increased synaptogenesis, proliferating immature neurons, and neuronal migration. The number of hBMSCs recruited to the injured region increased strikingly in group 4. Tissue loss was notably reduced in group 4. In summary, the beneficial effects of intraarterial infusion of MSCs are amplified with intravenous injection of mannitol. Preadministration of mannitol significantly increases the number of hBMSCs located in the ICH region, improves histochemical parameters of neural regeneration, and reduces the anatomical and pathological consequences of ICH.

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### Neurosurgery

Zuniga, R. M., R. Torcuator, R. Jain, J. Anderson, T. Doyle, S. Ellika, L. Schultz and T. Mikkelsen (2008). "Efficacy, safety and patterns of response and recurrence in patients with recurrent high-grade gliomas treated with bevacizumab plus irinotecan." J Neurooncol **EPub Ahead of Print**.

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Department of Neurosurgery, Henry Ford Health System, 2799 W Grand Blvd., Detroit, MI, 48202, USA, [rzuniga1@hfhs.org](mailto:rzuniga1@hfhs.org)

Our objective is to assess treatment efficacy, safety and pattern of response and recurrence in patients with recurrent high-grade glioma treated with bevacizumab and irinotecan. We reviewed retrospectively 51 patients with recurrent high-grade glioma treated with this combination at the Henry Ford Hermelin Brain Tumor Center from 11/15/2005 to 04/01/2008. The 6-month progression-free survival (PFS) for anaplastic gliomas (AGs) was 78.6 and 63.7% for glioblastoma. The median PFS was 13.4 months for AG and 7.6 months for those with glioblastoma. The overall survival rate (OS) at 6 months was 85.7% for AG and 78.0% for glioblastoma. The 12-month OS was 77.9% for AG and 42.6% for glioblastoma. The median OS time for AGs was not reached and was 11.5 months for those with glioblastoma. Thirty-six out of 51 (70.59%) patients demonstrated partial (32/51) or complete (4/51) radiographic response to treatment and 8/51 (15.69%) remained stable. Of the 38 who demonstrated progression on post-gadolinium studies, 23 showed distant progression with or without local recurrence. Seven patients showed progression on FLAIR without concordant findings on post-Gd sequences. Six patients (11.76%) discontinued treatment due to a treatment-emergent adverse event, including one with end-stage renal failure and another with gastric perforation. No symptomatic intracranial hemorrhages were reported. Patients with recurrent high-grade glioma treated with bevacizumab plus irinotecan demonstrate an excellent radiographic response rate and improved clinical outcome when compared to historical data. The high rate of distant tumor progression suggests that tumors may adapt to inhibition of angiogenesis by increased infiltration and vascular co-option.

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### Pathology

Mammen, J. J. and M. Tuthill (2008). "Structuring data in pathology reports: overcoming challenges with new tools." AMIA Annu Symp Proc: 1041.

## [Article Request Form](#)

Henry Ford Hospital, Pathology and Laboratory Medicine, Detroit, Michigan.

Traditional pathology reports have been textual with a high degree of variability. Checklist based structured pathology reports contribute significantly towards standardization and error reduction. As implemented, most of these are text templates making data retrieval dependent on natural language search. We describe a toolset that has been used to construct Laboratory Information System (LIS)-integrated checklists with forward chaining inference capabilities and contextual decision support. Data is saved directly into the LIS database facilitating data extraction.

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### **Pathology**

Saglam, O., A. Pederson, Z. Y. Zhang, C. Stone and S. R. Kini (2008). "Retrospective review and analysis of pancreaticobiliary specimens with discordant cytohistologic correlation." Cancer Cytopathology **114**(5): 421-2 Suppl S.

## [Article Request Form](#)

Henry Ford Hospital, Pathology and Laboratory Medicine, Detroit, Michigan.

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### **Radiation Oncology**

Kumar, S., S. L. Brown, A. Kolozsvary, S. O. Freytag and J. H. Kim (2008). "Efficacy of suicide gene therapy in hypoxic rat 9L glioma cells." J Neurooncol **90**(1): 19-24.

## [PDF Full-Text](#)

Department of Radiation Oncology, Henry Ford Health System, Detroit, MI 48202, USA.

[skumar4@hfhs.org](mailto:skumar4@hfhs.org)

Viral vector mediated suicide gene therapy (SGT) involving thymidine kinase (TK) or cytosine deaminase (CD) have considerable promise in the treatment of malignant brain tumors. An unresolved issue is to what extent tumor hypoxia influences the outcome of SGT since brain tumors characterized by regions of hypoxia have potentially reduced cellular metabolism and SGT's cytotoxicity is manifest through cellular metabolism. We studied in vitro and in vivo, the effect of hypoxia on the cytotoxicity of SGT in rat 9L glioma cells. Neither acute nor chronic hypoxia affected the cell killing of SGT by TK or CD. In vivo confirmation that SGT efficacy was not adversely affected by tumor hypoxia using the hypoxic cell marker pimonidazole was shown by the absence of a change in tumor hypoxia by SGT. These studies support the use of SGT utilizing either TK or CD gene strategies even when tumors are characterized by a hypoxic microenvironment.

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### **Radiology**

Rad, A. M., X. Gao, D. Deeb, S. C. Gautam and A. S. Arbab (2008). "Imaging Mouse Prostate Gland by 3 Tesla Clinical MRI System." Open Magn Reson Rev **1**: 60-63.

## [Article Request Form](#)

Department of Radiology, Henry Ford Hospital, Detroit, Michigan.

In vivo detection of prostate tumor in animal model will facilitate the investigations that deal with the efficacy of different treatment strategies in different experimental settings. Recently higher field strength dedicated animal MRI system has been used successfully to detect mouse prostate glands and its lesions, however, usefulness of clinical system has not been utilized to its fullest extent. In this short communication we show the advantages and disadvantages of different in vivo imaging parameters of MRI to acquire images of the mouse prostate gland using clinical strength MRI systems.

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## Sleep Medicine

Scharf, M., R. Rogowski, S. Hull, M. Cohn, D. Mayleben, N. Feldman, L. Ereshefsky, A. Lankford and T. Roth (2008). "Efficacy and safety of doxepin 1 mg, 3 mg, and 6 mg in elderly patients with primary insomnia: A randomized, double-blind, placebo-controlled crossover study." Journal of Clinical Psychiatry **69**(10): 1557-64.

### [PDF Full-Text](#)

**Objectives:** Evaluate efficacy and safety of the histamine-H<sub>1</sub> antagonist doxepin at doses of 1 mg, 3 mg, and 6 mg in elderly adults with primary insomnia.

**Design:** A randomized, double-blind, placebo-controlled, crossover design was used in this population of elderly adults with primary insomnia (DSM-IV). Each treatment period consisted of 2 polysomnographic (PSG) assessment nights with a 5- or 12-day drug-free interval between periods. The study was conducted from September 2004 to January 2005.

**Setting:** Sleep laboratories in 11 sleep centers in the United States.

**Participants:** Elderly adults with primary insomnia.

**Intervention:** Doxepin 1 mg, 3 mg, and 6 mg.

**Measurements:** Efficacy was assessed using PSG and patient-reported measures.

**Results:** Seventy-six patients were randomly assigned. All 3 doxepin doses produced dose-related significant improvements in PSG-determined wake time during sleep ( $p < .0001$ ), wake time after sleep onset ( $p < .0001$ ), total sleep time ( $p < .0001$ ), and overall sleep efficiency ( $p < .0001$ ) versus placebo. At the 3-mg and 6-mg doses, sleep efficiency was significantly improved during all thirds of the night ( $p < .05$ ). There was a dose-related decrease in patient-reported sleep latency, with the 6-mg dose achieving statistical significance in latency to sleep onset ( $p = .0181$ ). The pattern of the remaining subjective efficacy results was consistent with PSG. All 3 doxepin doses had side effect profiles comparable to placebo, with no spontaneously reported anticholinergic effects, no memory impairment, and no significant next-day residual effects.

**Conclusions:** In this 2-night study of elderly adults with primary insomnia, doxepin doses of 1 mg, 3 mg, and 6 mg were well tolerated and produced significant improvement in objective and subjective sleep maintenance and duration endpoints that persisted into the final hour of the night. Positive effects on patient-reported sleep onset were observed at the highest dose. All 3 doxepin doses had a safety profile comparable to placebo. These data demonstrate that doxepin was efficacious in improving sleep in elderly adults.

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## Surgery

Carlin, A. M., D. S. Rao, K. M. Yager, N. J. Parikh and A. Kapke (2008). "Treatment of vitamin D depletion after Roux-en-Y gastric bypass: a randomized prospective clinical trial." Surg Obes Relat Dis **EPub Ahead of Print**.

### [Article Request Form](#)

Division of General Surgery, Henry Ford Hospital, Detroit, Michigan.

**BACKGROUND:** A high prevalence (60%) of vitamin D (VitD) depletion, defined as a serum 25-hydroxyvitamin D level of  $\leq 20$  ng/mL, is present in preoperative morbidly obese patients. Despite daily supplementation with 800 IU VitD and 1500 mg calcium after Roux-en-Y gastric bypass (RYGB), VitD depletion persists in almost one half (44%) of patients. However, the optimal management of VitD depletion after RYGB and the potential benefits of such treatment are currently unknown. **METHODS:** A total of 60 VitD-depleted morbidly obese women were randomly assigned to receive 50,000 IU of VitD weekly after RYGB (group 1;  $n = 30$ ) or no additional VitD after RYGB (group 2;  $n = 30$ ). All patients received a daily supplement of 800 IU VitD and 1500 mg calcium. The serum calcium, parathyroid hormone, 25-hydroxyvitamin D, bone-specific alkaline phosphatase, urinary N-telopeptide, and bone mineral density were measured preoperatively and 1 year after RYGB. Questionnaires were used to assess other potential sources of VitD, including sunlight exposure and ingestion of VitD-containing foods/liquids. **RESULTS:** At 1 year after RYGB, VitD depletion and mean 25-hydroxyvitamin D level had improved significantly in group 1 (14% and 37.8 ng/mL, respectively) compared with the values in group 2 (85% and 15.2 ng/mL, respectively;  $P < .001$  for both). A significant 33% retardation in hip bone mineral density decline ( $P = .043$ ) and a significantly greater resolution of hypertension was seen in group 1 (75% versus 32%;  $P = .029$ ). No significant adverse effects were encountered from pharmacologic VitD therapy. **CONCLUSION:** The results of our study have shown that 50,000 IU of VitD weekly after

RYGB safely corrects VitD depletion in most women, attenuates cortical bone loss, and improves resolution of hypertension.

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### **Surgery**

Dulchavsky, D., X. H. Gao, Y. B. Liu, D. Deeb, A. S. Arbab, K. McIntosh, S. A. Dulchavsky and S. C. Gautam (2008). "Bone marrow-derived stromal cells (BMSCs) interact with fibroblasts in accelerating wound healing." Journal of Investigative Surgery **21**(5): 270-9.

### [Article Request Form](#)

Henry Ford Hospital, General Surgery, Detroit, Michigan. Henry Ford Hospital, Diagnostic Radiology, Detroit, Michigan.

Bone marrow-derived stromal cells (BMSCs) exhibit extraordinary degree of plasticity and growth factor repertoire for which they have been investigated for repair and regeneration of damaged tissues, but have not been adequately examined for wound healing. The ability of BMSCs to accelerate healing of surgically inflicted cutaneous and fascial wounds was tested in vivo in rats and in vitro using a fibroblast monolayer wound model. Intravenous treatment with BMSCs augmented healing of both cutaneous and fascial wounds as determined by an increase in the biomechanical strength of wounds. In vitro experiments showed that incorporation of BMSCs in fibroblast monolayers accelerates the closure of mechanically disrupted monolayers, which was attributed to the enhanced migration of fibroblasts onto the denuded surfaces. Furthermore, culture medium conditioned by activated BMSCs promoted the closure of defects in monolayers and enhanced the proliferation/growth and directional migration (chemotaxis) of fibroblasts. This study demonstrates that BMSCs significantly augment healing of cutaneous and fascial wounds in vivo at least in part through interaction with fibroblasts in which BMSCs promote growth and chemotaxis of fibroblasts.

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### **Surgery**

Hans, S. S., D. DeSantis, R. Siddiqui and M. Khoury (2008). "Results of endovascular therapy and aortobifemoral grafting for Transatlantic Inter-Society type C and D aortoiliac occlusive disease." Surgery **144**(4): 583-9; discussion 589-90.

### [PDF Full-Text](#)

Henry Ford Macomb Hospital, Clinton Township, MI, USA. [sshans@comcast.net](mailto:sshans@comcast.net)

**OBJECTIVE:** The purpose of this study was to compare the outcomes of aortoiliac stenting (AIS) to those of aortobifemoral grafting (ABF) for patients with TransAtlantic Inter-Society Consensus (TASCII) C and D aortoiliac occlusive disease. **METHODS:** From 1998 to 2007, 32 patients underwent ABF and 40 patients underwent AIS. Kaplan-Meier estimates for patency were used. **RESULTS:** Patients undergoing AIS were older (66.6 years ABF vs 59.2 years AIS; P=.006). The ABF group had simultaneous profundoplasty (n = 8) and femoral-popliteal graft (n =1). Six patients had treatment for concomitant infrainguinal disease at the time of AIS. There was no mortality in either group. Average hospital stay in the ABF group was 7 +/- 2 days and 1 +/- 0.3 days for AIS (P = .0001). Pulmonary complications predominated in the ABF group (13%). Four patients in the AIS group (10%) developed intraprocedural complications. Primary patency at 48 months was 69 +/- .12% for AIS and 93 +/- .07% for ABF (P = .013). There was a significant increase in ankle-brachial indices after revascularization in both groups. **CONCLUSIONS:** TASC type C and D lesions can be treated with either ABF or AIS with satisfactory results. Compared with ABF, AIS is associated with decreased primary patency, decreased perioperative morbidity, and shorter hospital stay.

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### **Surgery**

Kakkos, S. K., T. Andrzejewski, J. A. Haddad, G. K. Haddad, D. J. Reddy, T. J. Nypaver, M. M. Scully and D. L. Schmid (2008). "Equivalent secondary patency rates of upper extremity Vectra Vascular Access Grafts and transposed brachial-basilic fistulas with aggressive access surveillance and endovascular treatment." J Vasc Surg **47**(2): 407-14.

[PDF Full-Text](#)

Division of Vascular Surgery, Department of Surgery, Henry Ford Hospital, Detroit, Michigan

**OBJECTIVES:** The 2006 update of the DOQI guidelines has stated that in patients with end-stage renal disease, autogenous radial-cephalic, or brachial-cephalic fistulas are the preferred access modalities, followed by transposed brachial-basilic (TBB) fistulas and prosthetic arteriovenous (AV) grafts. AV grafts are in general least preferred; however, there is very limited data comparing directly the last two modalities. The aim of the present study is to compare outcomes of the TBB fistula and the Vectra Vascular Access Graft. **METHODS:** Seventy-six patients had a prosthetic brachial-axillary Vectra graft placed, while in 41 patients brachial-basilic upper arm transposition was performed. Graft surveillance to detect a failing/failed access was followed by endovascular treatment, rheolytic thrombectomy (AngioJet, Possis Medical), and/or angioplasty +/- stenting of the responsible anatomical lesion(s). **RESULTS:** Use of Vectra grafts and TBB fistulas started after a median (interquartile range) of 14 (7-30) and 70 (52-102) days, respectively ( $P < .001$ ), as early as the operative day in some patients with grafts. Postoperative complications were more frequent in TBB fistulas and late complications (mainly access thrombosis) in Vectra grafts. Total number of thrombectomy sessions performed for graft or fistula occlusion was 45 and 7, respectively ( $P = .032$ ); total number of isolated angioplasty sessions, performed for failing graft or fistula was 31 and 45, respectively ( $P = .004$ ). Although primary patency of the two access modalities was equivalent, primary assisted patency was significantly reduced in Vectra grafts (70% at 12 months and 58% at 18 months), compared with TBB fistulas (82% at 12 months and 78% at 18 months,  $P = .033$ ); however, as a result of endovascular intervention, secondary patency rates at 12 months (87% vs 88%) and 18 months (87% vs 83%) were equivalent ( $P = .91$ ). Presence of arterial anastomosis stenosis treated with angioplasty at any stage had a significant negative predictive value on secondary patency rates at 12 and 18 months which were 61%, compared with 96% for Vectra grafts that had any intra-graft, venous outflow, draining or central vein stenosis treated with angioplasty at any stage ( $P = .010$ ). **CONCLUSIONS:** Aggressive graft surveillance and endovascular treatment methods can yield equivalent long-term secondary patency rates between Vectra graft and TBB fistulas. The advantage of earlier use of Vectra graft must be balanced against the need for more frequent secondary interventions and the risk of graft infection.

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**Surgery**

Kakkos, S. K., G. K. Haddad, J. A. Haddad and M. M. Scully (2008). "Percutaneous rheolytic thrombectomy with the angiojet system for thrombosed autogenous fistulae and prosthetic arteriovenous grafts: Outcome after aggressive surveillance and endovascular management." J Vasc Access **9**(Suppl 1): 7.

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Division of Vascular Surgery, Department of Surgery, Henry Ford Hospital, Detroit, Michigan.

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**Surgery**

Kakkos, S. K., R. Haddad, G. K. Haddad, D. J. Reddy, T. J. Nypaver, J. C. Lin and A. D. Shepard (2007). "Results of aggressive graft surveillance and endovascular treatment on secondary patency rates of Vectra Vascular Access Grafts." J Vasc Surg **45**(5): 974-80.

[Article Request Form](#)

Division of Vascular Surgery, Henry Ford Hospital, Detroit, Michigan.

**OBJECTIVE:** The aim of the present study was to determine the effect of an aggressive graft surveillance and endovascular treatment protocol on secondary patency rates of a polyetherurethaneurea vascular access graft, specially designed to provide early access and rapid hemostasis. **METHODS:** One hundred and ninety Vectra Vascular Access Grafts (C. R. Bard, Inc, Murray Hill, NJ) were placed in 176 patients (78 females and 98 males, mean age 61.7 years). There were 41 forearm grafts, 145 upper arm grafts and four thigh grafts. Graft surveillance was performed by using clinical and hemodialysis parameters to detect a failing/failed graft and followed by endovascular treatment, rheolytic thrombectomy (AngioJet, Possis Medical Inc, Minneapolis, Minn) and/or angioplasty +/- stenting of the anatomical lesion (arterial anastomosis, graft, venous outflow, draining or central veins). **RESULTS:** Hemodialysis

started after a median of 15.5 days, as soon as from the day of the operation in some cases. Bleeding complications occurred in six patients (3.2%), venous hypertension in seven (3.7%), steal syndrome in two (1.1%), neurological complications in two (1.1%), while late infection (range 2.7-14.6 months) was seen in six patients (3.2%). Thrombectomy and angioplasty (median number of sessions 1, interquartile range 1-2) was performed in 43 grafts. Isolated angioplasty, not associated with thrombosis (median number of sessions 1, interquartile range 1-2), was performed in 50 grafts. These interventions increased primary assisted patency from 69% and 63% at 12 and 18 months, respectively to a secondary patency rate of 86%. Taking into account grafts removed for late infection, functional secondary patency rate dropped to 83% and 81%, at 12 and 18 months, respectively. Arterial anastomosis angioplasty was performed more frequently in thrombosed grafts (28.6%) than failing grafts (6.7%),  $P < .001$  and had a significant negative predictive value on secondary patency rates at 12 and 18 months, which were 60.5% compared with 89% for grafts that had no interventions performed ( $P = .007$ ) and 90.9% for grafts that had any intra-graft, venous outflow, or draining or central vein stenosis treated with angioplasty at any stage ( $P = .002$ ). Multivariate analysis identified the presence of arterial anastomosis stenosis as the single predictor of secondary patency (relative risk 0.247,  $P = .002$ ). CONCLUSIONS: Aggressive graft surveillance and endovascular treatment increases significantly secondary patency rates of Vectra Vascular Access Grafts. Longer follow-up will determine the effectiveness of this policy. The role of inflow stenosis on graft longevity and alternative treatment options warrant further investigation.

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## Surgery

Kharbutli, B. and V. Velanovich (2008). "Management of preoperatively suspected choledocholithiasis: A decision analysis." Journal of Gastrointestinal Surgery **12**(11): 1973-80.

### [PDF Full-Text](#)

Background: The management of symptomatic or incidentally discovered common bile duct (CBD) stones is still controversial. Of patients undergoing elective cholecystectomy for symptomatic cholelithiasis, 5-15% will also harbor CBD stones, and those with symptoms suggestive of choledocholithiasis will have an even higher incidence. Options for treatment include preoperative endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy (ERCP/ES) followed by laparoscopic cholecystectomy, laparoscopic cholecystectomy with intraoperative cholangiogram (LC/IOC), followed by either laparoscopic common bile duct exploration (LCBDE) or placement of a common bile duct double-lumen catheter with postoperative management. The purpose of this analysis was to determine the optimal management of such patients.

Methods A decision analysis was performed to analyze the management of patients with suspected common bile duct stones. The basic choice was between preoperative ERCP/ES followed by LC, LC/IOC followed by LCBDE, or common duct double-lumen catheter (Fitzgibbons tube) placement with either expectant management or postoperative ERCP/ES. Data on morbidity and mortality was obtained from the literature. Sensitivity analysis was done varying the incidence of positive CBD stones on IOC with associated morbidity and mortality.

Results One-stage management of symptomatic CBD stones with LC/LCBDE is associated with less morbidity and mortality (7% and 0.19%) than two-stage management utilizing preoperative ERCP/ES (13.5% and 0.5%). Sensitivity analysis shows that there is an increase in morbidity and mortality for LC/LCBDE as the incidence of positive IOC increases but are still less than two-stage management even with a 100% positive IOC (9.4%, 0.5%). If a double-lumen catheter is to be used for positive IOC, the morbidity would be higher than two-stage management only if the positive IOC incidence is more than 65% but still with no mortality.

Conclusion LCBDE has lower morbidity and mortality rates compared to preoperative ERCP/ES in the management of patients with suspected CBD stones even if the chance of CBD stones reaches 100%. Using a common duct double-lumen catheter may be considered if LCBDE is not feasible and the chance of CBD stone is less than 65%.

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## Surgery

Moser, S., S. K. Kakkos, G. K. Haddad and D. J. Reddy (2008). "Endovascular management of failing/failed haemodialysis access." Re-do vascular interventions.: 111-26.

### [Article Request Form](#)

Division of Vascular Surgery, Henry Ford Hospital, Detroit, Michigan.

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## Urology

Bhandari, A., R. S. Boris, R. G. Laungani and H. Stricker (2008). "Ureteral Inguinal Hernia in a Pelvic Kidney." J Urol **EPub Ahead of Print**.

[PDF Full-Text](#)

Vattikuti Urology Institute, Henry Ford Health System, Detroit, Michigan.

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## Urology

Elder, J. S. (2008). "Does antibiotic prophylaxis prevent renal scarring in children with vesicoureteral reflux?" Nat Clin Pract Urol **5**(12): 646-7.

[Article Request Form](#)

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Antibiotic prophylaxis has been the recommended management for most children with vesicoureteral reflux and urinary tract infection (UTI). This Practice Point commentary discusses the study of Pennesi and colleagues, one of three recent randomized controlled clinical trials of children with reflux, which suggested that antibiotic prophylaxis might be unnecessary in this setting, as similar rates of febrile UTI and renal scarring were seen in individuals who received prophylaxis and those who did not. However, because follow-up was short in one study, UTI was diagnosed by bag samples in infants and toddlers in another, and, overall, an insufficient number of children at high risk for UTI were included in the analyses, the results should be treated with caution. Further evidence from large, double-blind trials will help to better define the role of prophylaxis in children with vesicoureteral reflux.

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## Urology

Patil, N., L. Krane, K. Javed, T. Williams, M. Bhandari and M. Menon (2008). "Evaluating and grading cystographic leakage: correlation with clinical outcomes in patients undergoing robotic prostatectomy." BJU Int **EPub Ahead of Print**.

[PDF Full-Text](#)

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**OBJECTIVE** To classify cystographically detected urinary leaks in patients undergoing computer-assisted (robotic) radical prostatectomy (RP) and to evaluate its effect on postoperative outcomes. **PATIENTS AND METHODS** Between October 2001 and October 2007, 3327 patients had a RP using a technique described previously. The data were entered prospectively into an approved database. Before catheter removal, all patients had a gravity cystogram taken 7 days after RP. All patients who had a detectable urinary leak on cystography were stratified into three groups by two independent radiologists using a previously described grading system. Patients were evaluated with a validated International Prostate Symptom Score at 3-, 6-, 9- and 12-month intervals after RP. The continence status was determined based on a patient-reported questionnaire. Medical records in these patients were reviewed for the presence of complications requiring secondary interventions. **RESULTS** In all, 287 patients (8.6%) had a detectable leak on cystography, of which 179 (62.4%), 84 (29.3%) and 24 (8.4%) were grades I, II and III, respectively. Of the patients with a detectable leak 70% were continent within 3 months and 94% had no involuntary urinary leakage at 1 year. Eight of 287 (2.8%) patients required a secondary intervention to correct bladder neck contracture. All eight of these patients had a grade II or III leak on cystography. **CONCLUSION** The presence of a urinary leak might delay the time to continence, but has no adverse effect on long-term urinary control. Quantifying the gradation of leakage according to the described classification might provide the clinician with prognostic information about patients at risk for future interventions.

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## Urology

Siva, S., E. R. Barrack, G. P. Reddy, V. Thamilselvan, S. Thamilselvan, M. Menon and M. Bhandari (2008). "A critical analysis of the role of gut Oxalobacter formigenes in oxalate stone disease." [BJU Int](#) **EPub Ahead of Print**.

[PDF Full-Text](#)

Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA.

Hyperoxaluria is a major risk factor for the formation of calcium oxalate stones, but dietary restriction of oxalate intake might not be a reliable approach to prevent recurrence of stones. Hence, other approaches to reduce urinary oxalate to manage stone disease have been explored. The gut-dwelling obligate anaerobe Oxalobacter formigenes (OF) has attracted attention for its oxalate-degrading property. In this review we critically evaluate published studies and identify major gaps in knowledge. Recurrent stone-formers are significantly less likely to be colonized with OF than controls, but this appears to be due to antibiotic use. Studies in animals and human subjects show that colonization of the gut with OF can decrease urinary oxalate levels. However, it remains to be determined whether colonization with OF can affect stone disease. Reliable methods are needed to detect and quantify colonization status and to achieve durable colonization. New information about oxalate transport mechanisms raises hope for pharmacological manipulation to decrease urinary oxalate levels. In addition, probiotic use of lactic acid bacteria that metabolize oxalate might provide a valid alternative to OF.

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### **Urology**

Sivanandam, A. and M. Bhandari (2008). "How should patients with an overactive bladder manipulate their fluid intake?" [BJU Int](#) **102**(7): 903.

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Henry Ford Hospital, Vattikuti Urology Institute, Detroit, Michigan.