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Resident Abstracts

HISTONE-COMPLEXED DNA LEVELS ARE ASSOCIATED WITH COAGULOPATHY, INFLAMMATION AND ENDOTHELIAL DAMAGE EARLY AFTER PEDIATRIC TRAUMA

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Introduction:
The release of damage-associated molecular pattern molecules (DAMPs) after injury has been suggested to activate innate immunity and may form a key link between inflammation and coagulation in trauma. We aimed to study the presence of circulating DAMPs in the form of histone-complexed DNA (hcDNA) in our pediatric trauma population and investigated the association between hcDNA, trauma induced coagulopathy, inflammation and endothelial damage.

Methods:
Prospective cohort study of pediatric trauma patients at a level 1 pediatric trauma hospital. Inclusion: highest level trauma activation and arrival within 6 hours of injury. Exclusion: >18 years of age, burns > 20% TBSA and primary asphyxiation. Blood samples were collected within 20 minutes of arrival, analyzed for hcDNA and linked to biomarkers of hypoperfusion, coagulopathy, fibrinolysis, endothelial glycocalyx shedding, complement and outcome. Platelet function was assessed by measuring platelet responsiveness to adenosine diphosphate (ADP) and thrombin receptor-activating peptide (TRAP) using multiple electrode impedance aggregometry.

Results:
120 consecutive patients were enrolled. Mean age was 9.16 ± 10.73 years with 84% sustaining blunt trauma. Mean injury severity score (ISS) was 25±20 and overall mortality was 12%. Median hcDNA level at admission was 4.49 AU. HcDNA levels were higher in patients with ISS >25 versus <25 (5.5 AU ± 4.7 vs 3.6 AU ± 3.6 p< 0.0258) and in patients with a base deficit <6 mEq/L versus >6 mEq/L (6.9 AU ±4.7 vs 3.6 AU ±3.4 p < 0.0001). The overall incidence of coagulopathy, defined by PT ratio >1.2 was 26%. Coagulopathic patients had higher levels of hcDNA (6.3AU ±4.8 vs 4.1AU ±3.8 p <0.0143). Patients with aggregometry levels below normal range for ADP and TRAP had significantly higher levels of hcDNA (ADP 5.3 AU ±4.2 vs 3.7 ±3.6 AU p < 0.0243 and TRAP 4.8 AU ±4.0 vs 2.6 AU ±3.0 p < 0.0003). HcDNA levels correlated with fibrinolytic marker D-dimer, syndecan-1 and terminal complement complex (sC5b-9) (all p < 0.0001). Finally, significantly higher hcDNA levels were seen in non-survivors versus survivors, 7.0 AU ±3.9 and 4.2 AU ±3.7 respectively (p < 0.0105).

Conclusion:
HcDNA levels are elevated in response to injury and correlate with coagulopathy, inflammation and endothelial damage observed early after severe pediatric trauma.

Injectable shear-thinning hydrogels to deliver endothelial progenitor cells, enhance cell engraftment, and improve ischemic myocardium

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INTRODUCTION: The clinical translation of cell based therapies for ischemic heart disease has been limited due to low cell retention and poor targeting to ischemic myocardium. To address these issues, we developed an injectable shear-thinning hyaluronic acid hydrogel and endothelial progenitor cell construct (STG-EPC). The STG assembles due to interactions of adamantane and β-cyclodextrin modified hyaluronic acid. It is shear-thinning to permit delivery via a syringe, and self-heals upon injection. This directed therapy to the ischemic myocardial borderzone enables direct cell delivery to reduce adverse remodeling. We hypothesize that this system will enhance vasculogenesis to improve myocardial stabilization in the context of a clinically translatable therapy.

METHODS: EPCs (DiLDL+VEGFR2+CD34+) were harvested from adult male rats and suspended in STG. In vitro viability was quantified. STG-EPC constructs were injected at the borderzone of ischemic rat myocardium after acute MI (LAD artery ligation). The migration of the eGFP+ EPCs from the construct was analyzed using fluorescent microscopy. Vasculogenesis, myocardial-remodeling, and hemodynamic-function were analyzed in 4 groups: control (PBS injection), intramyocardial injection of EPCs (EPC), injection of the STG (STG), and treatment with the gel-EPC construct (STG-EPC). Hemodynamics and ventricular geometry were quantified using echocardiography and pressure-volume analysis.

RESULTS: EPCs demonstrated viability within the STG. A marked increase in EPC engraftment was observed one-week post-injection within the STG-EPC treated myocardium compared to EPC injection (17.2±0.8 cells/HPF vs. 3.5 cells±1.3 cells/HPF,p=0.0002). A statistically significant increase in vasculogenesis was noted with the STG-EPC construct (15.3±5.8 vessels/HPF) when compared to control, EPC, and STG
groups \((p<0.0001)\). Statistically significant improvements in ventricular function, scar fraction, and geometry were also noted after STG-EPC treatment compared to the control.

**CONCLUSIONS:** A novel injectable shear-thinning hyaluronic acid hydrogel seeded with EPCs enhanced cell retention and vasculogenesis after delivery to ischemic myocardium. This therapy limited adverse myocardial remodeling while preserving contractility.

**The Role of Inflammatory Monocytes in Human Metastatic Colorectal Cancer**

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**Intro:**
Colorectal cancer (CRC) is the most common gastrointestinal malignancy. 60% of CRC patients are diagnosed with metastatic (m)CRC and the 5-year survival is <20%.

Myeloid cells, particularly inflammatory monocytes (IM), are recruited from the bone marrow to the tumor microenvironment where they become tumor associated macrophages and play a crucial role in tumor progression, metastasis, and chemoresistance. While the importance of IM have been shown in other malignancies, little is known about their role in human CRC.

**Methods:**
Human tissue was collected under an IRB approved protocol at Washington University. Flow cytometry was performed on PBMCs and single cell suspensions of normal tissue and tumor samples. Qualitative RT-PCR and confocal microscopy were performed for CCL2. T-cell suppression assays were performed using CD14+ IM isolated from patient peripheral blood and tumor samples.

**Results:**
Analysis of pre-operative blood revealed that monocyte levels correlate with the extent of disease burden. Monocytes were elevated in CRC patients compared with controls \((p<0.0001)\), additionally patients with liver metastasis had further elevation in monocytes compared with patient’s with primary disease \((p=0.01)\). In metastatic patients, monocyte levels also correlate with survival following resection of hepatic metastasis \((p=0.0002)\). FACS analysis confirmed these findings and demonstrated that the circulating CD11b+/CD14+/CCR2+ subset of IM was responsible for the increase.

Both primary CRC and liver mCRC had increased expression of CCL2 compared to uninvolved tissue \((p=0.008 \text{ and } p=0.03, \text{ respectively})\). Production of CCL2 was localized to CRC cells. FACS analysis showed CCR2+ tumor infiltrating macrophages were elevated in CRC liver metastasis compared to adjacent normal liver and a paucity of effector T-cells.
CD14+ TAMs isolated from mCRC inhibited T-cell proliferation, illustrating the immune suppressive phenotype of these cells.

**Conclusion:**
Inflammatory monocytes are critical in the progression of mCRC. Therefore, targeting CCR2+ myeloid cells may improve anti-tumor immunity and patient survival in metastatic disease.

**Intraoperative Molecular Imaging For Detecting Subcentimeter Pulmonary Tumors**

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**Objective:** Subcentimeter lung tumors are frequently discovered by computed tomography, however, they can be difficult to locate intraoperatively. We propose using intraoperative molecular imaging with a novel folate receptor alpha targeted optical contrast agent (EC17) to localize intrapleural tumors.

**Methods:** We used a well-described intrapleural murine model of lung cancer (N=56) and performed a right thoracotomy on 8 mice each day for 7 days following tumor initiation. Traditional visualization and molecular imaging were used to localize tumor nodules. Tumor fluorescence was measured using tumor-to-background ratio (TBR). All lungs and suspected tumors were biopsied for H&E and fluorescence microscopy.

**Results:** No tumors were discovered by traditional inspection or molecular imaging on post-injection days 1 through 3. On days 4 and 5, of the nodules confirmed to be tumor on H&E, 43% were discovered by traditional inspection, whereas molecular imaging discovered 86%. The mean tumor size was 0.93 mm (IQR 0.76-1.01) with a mean TBR of 3.06 +/- 0.22. On days 6 and 7, larger tumors with a mean size of 1.94 mm (IQR 1.84-2.12) were localized with both traditional inspection (75%) and fluorescent imaging (100%). Mean TBR of these tumors was 3.05 +/- 0.16. Overall, the sensitivity of tumor detection using molecular imaging was significantly greater than traditional inspection alone (85% vs. 55%, p-value <0.01, McNemar's chi-square test).

**Conclusions:** Intraoperative molecular imaging is superior to conventional surgical techniques in identifying subcentimeter intrapleural tumors. This may have important implications to minimally invasive thoracoscopic surgery for pulmonary resections.
Implications of new lumpectomy margin guidelines for breast-conserving surgery: Changes in re-excision rates and predicted rates of residual tumor

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Background: 2014 guidelines endorsed by the SSO, ASBS and ASTRO advocate “no tumor on ink” as the new margin standard for breast conserving surgery. We used our lumpectomy margins database to predict the effect of these new guidelines on rates of positive margins, re-excisions, and extent of residual tumor in the lumpectomy cavity.

Methods: We performed retrospective review of lumpectomies for invasive breast cancer at our institution from 2004-2006. Patients with neoadjuvant therapy, pure DCIS or incomplete margin data were excluded. We applied new (“no tumor on ink”) and old (≥ 2 mm) margin guidelines and compared rates of positive margins and re-excision. Rates of residual tumor found on re-excision for “tumor on ink” versus tumor <2mm from the margin, but “not on ink”, were determined.

Results: 437 lumpectomies met eligibility criteria. Median age was 55 yrs (29-91). 86% had invasive ductal carcinoma (IDC), 12% invasive lobular carcinoma (ILC) and 2% IDC and ILC. Using a ≥2mm margin standard, 36% of lumpectomies had positive margins compared with 19% using new guidelines (p<0.0001). 77% of patients with “tumor on ink” had residual disease found at re-excision. 50% of those re-excised for margins <2mm (but “not on ink”) had residual disease (p=0.0013), but would not have been re-excised with new guidelines. Residual tumor was more common in re-excisions for DCIS <2mm from a margin than in those for invasive cancer (53% vs. 40%), although this was not statistically significant.

Conclusions: Use of new lumpectomy margin guidelines would have reduced re-operation for BCT by half in our patient cohort. However, residual disease was present in many patients who would not have been re-excised with the new guidelines. Long-term follow-up of local recurrence rates is needed to determine if this increase in residual disease is clinically significant.
EPICARDIAL INFARCT REPAIR WITH EXTRACELLULAR MATRIX BIOMATERIAL PROMOTES VASCULOGENESIS AND MYOCARDIAL RECOVERY

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INTRODUCTION: Infarcted myocardium continues to remodel after successful reperfusion resulting in LV dilatation and heart failure. Epicardial infarct repair (EIR) using a bio-inductive extracellular matrix (ECM) biomaterial is a novel surgical approach to promote endogenous myocardial repair and functional recovery after ischemic injury. Using a preclinical porcine model of coronary ischemia-reperfusion, we assessed the effects of EIR on regional functional recovery, safety and feasibility of the procedure, and possible mechanisms mediating the observed functional benefits.

METHODS: An ECM-biomaterial (CorMatrix-ECM, CorMatrix Cardiovascular Inc. CA, USA) was applied to the epicardium after 75 minutes of coronary ischemia in a porcine model. Animals were randomized following ischemia-reperfusion injury to EIR therapy (n=8) or sham (n=4). Serial cardiac MRI was performed on normal (n=4) and study animals at baseline (1-week) and 6-weeks post-treatment. Myocardial function and tissue characteristics were assessed.

RESULTS: Functional myocardial recovery was significantly increased by EIR as compared to shams (change in regional myocardial contraction at 6-weeks: 28.6±14.0% vs. 4.2±13.5% wall thickening; P<0.05). EIR-treated animals had reduced adhesions compared to shams (1.44±0.51 vs. 3.08±0.89; P<0.05). Myocardial fibrosis was not increased and EIR therapy did not cause myocardial constriction, as LV compliance by passive pressure distension at matched volumes was similar between groups (EIR: 13.9±4.0 vs. Sham: 16.0±5.2mmHg; P=0.609). EIR-treated animals showed evidence of vasculogenesis in the region of functional recovery.

CONCLUSIONS: These novel data show that, over and above the beneficial effects of successful reperfusion, EIR using a bio-inductive ECM can enhance myocardial repair and functional recovery. Clinical translation of EIR early after MI as an adjunct to surgical revascularization may be warranted.
DETERMINATION OF APPROPRIATE TIMING FOR INTRA-ABDOMINAL MESH PLACEMENT AFTER INCIDENTAL ENTEROTOMY IN A RODENT (RATTUS NORVEGICUS) MODEL

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Introduction:
Controversy exists regarding the most appropriate timing for placement of permanent intra-abdominal mesh following inadvertent enterotomy. The aim of this study was to examine mesh placement at variable postoperative periods and the subsequent risk of mesh infection.

Methods:
Fifty rodents were divided into five groups. Groups 1-4 underwent laparotomy, small bowel enterotomy, and primary repair. Physiomesh® was placed in Group 1 at the index operation and 1, 3, or 7 days post-operatively in Group 2, 3, and 4 respectively. Group 5 served as the control with mesh placement but no enterotomy. Necropsy with mesh harvest was performed 7 days after mesh placement. Cultures were obtained pre and post-sonication. Fisher's exact test was used to compare groups.

Results:
Pre-sonication of the samples from groups 1-4 yielded positive bacterial growth in 20%, 0%, 30%, and 30% of the samples compared to 10% of the controls. Bacterial growth post-sonication was identified in 30%, 30%, 50%, and 90% versus 20% in the controls. When compared to controls, there was a significantly increased risk of mesh infection when it was placed 7 days after enterotomy (p=0.006). There was no significant difference in bacterial growth when mesh was placed at the time of enterotomy, 1, or 3 days later.

Conclusion:
Our results suggest that the risk of bacterial contamination of permanent mesh placed immediately following enterotomy is as safe as placing mesh at 1 or 3 days. Mesh placed at 7 days after an inadvertent enterotomy significantly increased the risk of mesh infection.
Significant variation in surgical supply cost secondary to surgeon preference for laparoscopic cholecystectomy

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Introduction: Variation in surgical supply utilization among surgeons can lead to unwarranted increased costs within operating rooms (OR). The aim of this study was to determine the surgical supply cost variation among surgeons performing laparoscopic cholecystectomies (LCs).

Methods: Surgical supply cost data were collected retrospectively from financial accounting inclusive of all surgeons performing consecutive single procedure LCs from November 1st, 2011 and February 1st, 2015. Surgeons with fewer than 5 LCs within the study period were excluded. Utilization of trocars, scissors, clips, skin closure materials, drapes, hemostatic agents, suction irrigators, and specimen retrieval bags were selected for analysis.

Results: 1252 cases were performed by 20 surgeons. The surgical supply cost varied widely from $346 to $2829. The median supply cost was $818. Patient age and gender did not affect the mean cost in a statistically significant way (p=0.534 and 0.150, respectively). Variation between surgeon preference in supply utilization was responsible for 12.7% of total variability in supply cost (95% CI: 6.2 – 24.6). The surgeon preference variation breakdown by item was 17% for trocars, 32% for clips, 43% for skin closure materials, 35% for drapes, 7% for hemostatic agents, and 6% for specimen retrieval bags. No utilization variation existed for scissors and suction irrigators.

Conclusions: There is significant variation in surgical supply utilization for laparoscopic cholecystectomy and most of the variation is due to differences within and not between surgeons. Institutional operational standardization should be implemented to improve cost efficiency in routinely performed general surgery procedures.
Analysis of Severe and Deadly Dog Bite Injuries in Children
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Introduction: Severe dog bites injuries frequently occur in the pediatric population. The purpose of this study was to examine the characteristics of severe and fatal dog bite injuries admitted to hospital.

Methods: Using the trauma database of a Level I pediatric trauma center located in St. Louis, Missouri we identified admissions due to dog bite injuries from 2009-2015. Demographics, length of stay (LOS), number of deaths, cause of death, dog breed, procedure required, wound complications, and zip codes were recorded. Pearson's correlation identified correlation between variables. P≤0.05 was considered to be statistically significant.

Results: Fifty four children were identified. The mean age was 5.9 years and 59.3% were male. Forty two patients were Caucasian, 10 African-American, and 2 Hispanic. Mean LOS was 1.9 days for all patients. The most common breed was pit-bull (42.5%). The most common procedure was laceration washout and wound closure (63.0%). Three children required diagnostic laparotomy. Infection was the most common wound complication (20.8%). One death occurred in a child that sustained major vascular injury to neck, severe anoxic brain injury, and C7 vertebral avulsion. Most dogs were familiar to the child (69.0%). Most bites occurred in the face/neck region (46.3%). A correlation was found between dog being familiar to child and Caucasian race (R=.469, p=.002); penetrating injury and procedure required (R=.700, p<.0001); disfigurement and location of incident being home (R=.317, p=.041). Majority of dog bites occurred in urbanized locations. No correlation was found between duration of ownership of dog and severity of injury.

Conclusion: Overall, severe dog bite injuries were more likely to be located in an urbanized location, more likely to occur in face and neck region, and more likely to be caused by dogs familiar to child if child was Caucasian. Additional dog bite prevention strategies are necessary.
**Sarcoma Resection With and Without Vascular Reconstruction: A Matched Case-Control Study**

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**Introduction:** En bloc resection and reconstruction of involved vessels is being increasingly performed during sarcoma surgery, however the perioperative and oncologic outcomes of this strategy are not well described. The objective of this study is to examine the impact of major vascular resection on sarcoma resection outcomes.

**Methods:** Patients undergoing sarcoma resection with (VASC) and without (NO-VASC) vascular resection and reconstruction were 1:2 matched on anatomic site, histology, grade, size, synchronous metastasis, and primary (vs. repeat) resection. R2 resections were excluded. Endpoints included perioperative morbidity, mortality, local recurrence, and survival.

**Results:** From 2000 to 2014, 50 sarcoma patients underwent VASC resection. These were matched with 100 NO-VASC patients having similar clinicopathologic characteristics (Table). The rates of any complication (74% vs. 44%, P=0.002), grade 3 or higher complication (38% vs. 18%, P=0.024), and transfusion (66% vs. 33%, P<0.001) were all more common in the VASC group. Thirty-day (2% vs. 0%, P=0.30) or 90-day mortality (6% vs. 2%, P=0.24) were not significantly higher. Local recurrence (5-year, 51% vs. 54%, P=0.11) and overall survival after resection (5-year, 59% vs. 53%, P=0.67) were similar between the two groups (Figure). Within the VASC group, survival was not affected by the type of vessel involved or the presence of vessel wall invasion.

**Conclusion:** Vascular resection and reconstruction during sarcoma resection significantly increases perioperative morbidity and requires meticulous preoperative multidisciplinary planning. However, the oncologic outcome appears equivalent to cases that did not require vascular resection and reconstruction. Major vascular involvement should not be a contraindication to sarcoma resection.