

**SPP INTERIM MEETING ABSTRACTS**  
**October, 2008 - Louisville, KY**

**Platform Presentations (#1-15)**

**Abstract 1 - Congenital anomalies in stillborn: an analysis of 965 cases**

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**Background:** Although congenital anomalies have been reported to be more frequent in stillborn, their distribution have not been defined recently in a large series stillborn.

**Design:** We employed uniform postmortem examination protocol to evaluate the fetuses and placentas in 962 consecutive stillbirths <sup>3</sup> 20 weeks submitted to the Women and Infants Hospital Division of Perinatal Pathology from 1990 through 2005. Classification of anatomic abnormalities was based on a priori criteria. For this purpose, each case was assigned a primary diagnosis based on the organ system most severely involved or defects occurring earliest in embryogenesis. Information about any available diagnostic test was also collected.

**Results:** Of 962 stillbirths, 387 (40%) had malformations. 59 of these had phenotypic attributes that resulted in a preliminary diagnosis of aneuploidy, all of which had later karyotype confirmation. Nine cases were identified to have a single gene disorder. 34 cases had neural tube closure defects, 19 cases had congenital heart malformations and 17 cases had non-immune hydrops fetalis of undetermined etiology. There were 38 cases with complex malformations that did not conform to any specific diagnosis. The rest of the cases (211) had minor malformations.

**Conclusions:** Congenital malformations in stillborn show a wide spectrum. In only a minority of cases conventional diagnostic tests such as karyotype analysis was useful. In cases without specific diagnoses, comprehensive tests like human genomic hybridization or other similar techniques are needed and their clinical use should be expedited.

**Abstract 2 - A Novel 16q Deletion In An Infant With Cardiac Anomalies, Abnormal Situs, And Multifocal Pulmonary Artery Dissection**

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**Background:** Interstitial deletions involving the long arm of chromosome 16 have been linked to a variety of congenital anomalies distinct from the phenotype associated with 16q- syndrome. To date, the majority of reported interstitial 16q deletions have been proximal, occurring between 16q11.1 and 16q22.3. Only rarely have more distal deletions been observed. Callen, et al. [1993] described a patient [46,XX,del(16)(q23.1q24.1)] with minor skeletal and craniofacial anomalies and mental retardation. Werner et al. [1997] described a similar but milder phenotype in a patient [46,XY,del(16)(q23.1q24.2)] with bilateral iris coloboma. We report a case of a patient with a distal 16q deletion with severe cardiac anomalies, situs anomalies, and multifocal pulmonary artery dissection.

**Design:** The patient was a 3 week old female infant born at 35 weeks gestation with multiple congenital cardiovascular anomalies (e.g. transposed great arteries, ASD, VSD, persistent left SVC, PDA). She underwent surgical intervention, but eventually required extracorporeal membrane oxygenation (ECMO) and ultimately succumbed to intracranial hemorrhage. She became known to our service at the time of autopsy and cytogenetic analysis of peripheral blood

lymphocytes.

**Results:** Autopsy confirmed the known cardiac anomalies and further identified left atrial isomerism, bilateral atypical lung lobation, and malpositioned tripartite pancreas. Microscopic sections of the pulmonary parenchyma revealed multifocal pulmonary artery dissection. Finally, cytogenetic analysis uncovered an abnormal karyotype [46,XX,del(16)(q23.3q24)].

**Conclusions:** The present case report represents a departure from phenotypes observed in other cases of distal interstitial 16q deletions. The cardiac and situs anomalies are seen in more proximal deletions, but the pulmonary artery dissections are novel. In an attempt to make sense of these findings, we surveyed the known genes in the deleted region using the OMIM gene map. Interestingly, a gene (DYNLRB2) encoding a dynein light chain resides at 16q23.3. Given the link between the ciliopathies and the varied heterotaxy syndromes, this gene seems a reasonable starting point for future research. The genesis of the arterial dissections, however, remains a complete mystery. Ultimately, we submit this report in order to contribute to the relatively sparse data regarding distal 16q deletion syndromes.

### Abstract 3 - **Fetal Inflammation of Umbilical Cord is Often Present at Early Stage of Intraamniotic Infection and Its Distribution Along Cord is Variable**

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**Background:** The fetal inflammatory response to intraamniotic infection is thought to occur later than the maternal inflammatory response and to portend a worse clinical outcome. This study investigates the pattern of fetal inflammatory response to amniotic infection.

**Design:** All placentas accessioned in our surgical pathology department from June 2004 onward had two cord sections taken: one within 5 cm of the placental cord insertion site (inked, proximal section) and one that was at least 10 cm distal to the first section (uninked, distal section). Cases from June 2004 to May 2008 were prospectively evaluated for degree of cord inflammation. Those cases with a differential in umbilical vessel inflammation between the two sections were graded from 0 to 4 (0 - no inflammation; 1 – neutrophil margination; 2 – neutrophils involving inner half of vessel wall; 3 - neutrophils extending into outer half of vessel wall; 4 - neutrophils extending into Wharton's jelly). Cases in which cord vessels in both sections had equal amounts of acute inflammation were excluded. Cases were evaluated for presence or absence of acute chorionic vasculitis and extent of maternal inflammatory response.

**Results:** 1004 of 5566 total placentas had any cord inflammation (18%) and 120 of those cases (12%) had a differential in cord inflammation at the two cord sites. 77 of 120 cases (64%) had only one section involved by inflammation. Greater cord inflammation was divided almost equally between proximal section (59) and distal section (61). 24 cases had one or both arteries involved in one cord section only. In 21 of these 24 cases (88%) the proximal section had the greater degree of inflammation. Only acute subchorionitis or deciduitis were seen in 59 of 120 cases (49%). Acute chorionic vasculitis was identified in 57 of 106 cases (54%) with at least 2 vessels seen on the fetal surface.

**Conclusion:** A fetal inflammatory response is seen in a significant number of cases of early amniotic infection. Often this response is seen only in the cord and not in chorionic vasculature. Sampling a single cord section is inadequate to rule out fetal inflammatory response to infection. The absence of a differential in cord vein inflammation depending on cord site suggests that the slower venous blood flow makes the microenvironment around the cord more important than

where the neutrophils are in the vein. In contrast, the faster artery blood flow precludes significant neutrophil margination until farther towards the fetal surface. Cord undersampling might explain the previously reported low incidence of fetal inflammatory response accompanying early maternal response.

**Abstract 4 - Villitis and Clotting - Is There an Association? a retrospective statistical analysis**

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**Background:** Villitis of unknown etiology (VUE) is a frequent yet still a largely unexplained finding in 3rd trimester placentas. VUE can be recurrent and severe cases are associated with IUGR and IUFD. An infectious etiology has never been shown and immune theories alone do not explain discordance in monozygotic twins. Previous studies have found an increased incidence of villitis in the placentas of patients with lupus and anticardiolipin syndrome, but the association of maternal and fetal circulatory problems to VUE has not been otherwise evaluated.

**Design:** Diagnoses in 223 sequential cases of VUE from the files of the authors were tabulated for other specific findings including those related to fetal and maternal circulation, ascending infection, meconium, excess fibrin deposition and cord abnormalities. Fetal vascular lesions included avascular villi and intravascular thrombosis. Avascular villi were only considered when they were clearly separate from areas of villitis. Maternal vascular lesions included infarcts and/or villous ischemia and decidual vasculopathy. Control cases consisted of 222 sequential cases without villitis from the same time period. All were signed out by a single pathologist at each site. Multiple gestations, outside consultations, fetal demise and second trimester placentas were excluded. Data was analyzed by SPSS 11.0 statistical program. Chi square values with  $p < .05$  were considered significant.

**Results:** The following findings were significantly more common in the villitis group: retroplacental hematoma ( $p = .016$ ), avascular villi ( $p = .036$ ), remote thrombi ( $p = .031$ ), prematurity/immaturity ( $p = .012$ ), intervillous thrombi ( $p = .040$ ), increased fibrin ( $p = .036$ ) and meconium ( $p = .003$ ). No significant differences were found in ascending infection, ischemic change/infarcts, decidual vasculopathy and cord abnormalities.

**Conclusion:** Our findings support a strong association of villitis with disorders of fetal vascular thrombosis as well as evidence of coagulation in the intervillous space. As villitis often appears to be of shorter duration than vascular changes, a secondary inflammatory process is favored, but the pathogenic mechanism is unclear. The increase in immature placentas and meconium may relate to fetal stress and early delivery.

**Abstract 5 - Immunohistochemical Evaluation of Immune Markers in Chronic Villitis of Unknown Etiology**

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**Background:** The etiology of chronic villitis of unknown etiology (CVUE) is often attributed to an autoimmune process, especially when recurrent. The absence of MHC class Ia and II molecules on the cell surface of syncytiotrophoblasts is thought to play a role in mediating the

exclusion of maternal inflammatory cells from the villous stroma as a mechanism to prevent rejection of the fetus. One previous report demonstrated aberrant expression of the MHC class II antigen HLA-DR on trophoblast cells in CVUE placentas. To date, the JAK-STAT pathway, which controls cellular responses to inflammatory cytokines has not been examined in CVUE. We hypothesize that CVUE is an autoimmune process in which there is abnormal upregulation of the interferon- $\alpha$ -induced JAK-STAT pathway, that would subsequently increase production of MHC class Ia and II molecules, promote apoptosis through caspase, and inhibit cell growth through p21.

**Design:** Hematoxylin & eosin-stained paraffin embedded tissue sections from 8 third trimester placentas with CVUE, 1 second trimester placenta with chronic intervillitis, and three 2nd and 3rd trimester control placentas were stained by immunohistochemistry using markers for CD3, CD4, CD8 (T-cell markers), CD20 (B-cell marker), CD25 (IL-2 receptor alpha), CD56 (NK-cell marker), CD68 (macrophage marker), IL-17 (pro-inflammatory cytokine), interferon-  $\alpha$ , HLA-DR (class II MHC marker), IRF-1 (immune regulatory factor-1), STAT-1, and phosphorylated STAT-1 (pSTAT-1). Cases of CVUE were defined as those cases of chronic villitis in which appropriate stains for organisms were performed and were negative.

**Results:** T-cells and histiocytes were confirmed as the primary inflammatory infiltrate in CVUE with a mixture of CD4+ and CD8+ T-cells. CD68+ histiocytes strongly expressed HLA-DR, STAT-1 (cytoplasmic) and pSTAT-1 (nuclear). In several cases of CVUE and the single case of intervillitis there was patchy nuclear expression of pSTAT-1 in syncytiotrophoblasts most extensively involved by villitis but no other marker, including HLA-DR, was expressed in the trophoblast cell layer.

**Conclusion:** We have confirmed the presence of CD4+, CD8+, and CD68+ inflammatory cells in CVUE. Moreover, our results suggest that aberrant MHC class II expression in the trophoblast layer is not associated with CVUE. The detection of isolated pSTAT-1 expression in syncytiotrophoblasts in regions of inflammation suggests that the trophoblast layer may be responding to inflammatory stimuli, but further studies are required to confirm this possibility.

#### Abstract 6 - **IMP-3 expression in rhabdomyosarcomas is associated with translocation-negative tumours**

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**Background:** Rhabdomyosarcoma (RMS) is the most prevalent paediatric soft-tissue sarcoma. Morphologically, it consists of two subtypes – embryonal (ERMS) and alveolar (ARMS). Accurate subclassification has clinical and therapeutic implications, and is achieved by a variety of morphological and molecular techniques. However, differentiation of ERMS from ARMS can be a challenge. Recent studies in our laboratory have shown that expression of the IGF2 ligand can differentiate RMS subtypes. The aim of the present study was to determine the expression pattern of the IGF2 RNA binding protein, IMP3, within RMS.

**Design:** The IMP3 antibody (Dako) was optimized using heat-induced epitope retrieval and a variety of different dilutions and incubation temperatures. Normal tissues known to express IMP3 were used as controls (ovary, lymph node) and the optimal staining parameters were determined to be a 1:40 dilution incubated at room temperature. The antibody was applied to tissue microarrays containing 31 RMS (21 ERMS, 9 ARMS, 1 mixed tumour), and a six-tiered

scoring system was used combining strength and distribution of the protein. A score of 4 or more was considered positive.

**Results:** Overall, 22 of 31 RMS were positive (71%). Within the different subtypes, 90% of ERMS were positive, whereas 33% of ARMS were positive ( $p = 0.0031$ , Fisher exact test). By looking at the molecular subtyping, 14% of RMS harbouring a PAX/FKHR translocation were positive, whereas 91% of translocation-negative RMS were positive ( $p = 0.0003$ , Fisher exact test).

**Conclusion:** The results have both diagnostic and biological relevance, and suggest a role for the IGF2-IMP3 axis in translocation-negative RMS.

### Abstract 7 - Utility of immunohistochemical stains in confirming foci of morphologically Yolk-Sac tumors in children's Germ Cell Tumors

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**Background:** Germ cell tumors (GCT) in children differ from their adult counterpart both in their biology and prognosis. The most common malignant component in pediatric GCT is yolk sac tumor (YST) and it is also the most valid predictor of recurrence. Morphologically, the biggest challenge appears to be the recognition of small foci of YST in immature teratomas. The hallmark appears to be the "piano-key" appearance of the glands as well as the reticular pattern. Recently, glypican-3 has been shown to be a reliable marker for YST and can be used in conjunction with AFP (a more soluble and hence unpredictable marker) for diagnosis of these foci. The aims of this study were to morphologically identify small foci of YST in H&E stains in cases of GCT in children, and to apply immunohistochemistry for AFP, Glypican-3, C-kit, AE1/AE3 and B-catenin in these tumors to localize these foci.

**Design:** 28 cases of GCT were identified and classified as mature teratomas (MT, n=15), immature teratoma (IT, n=5), dysgerminoma (D, n=2), mixed germ cell tumor (MGCT, n=3) and Yolk Sac Carcinoma (YSC, n=7). Positive and negative controls were run for each stain and staining was accomplished using the automated Ventana stainer.

**Results:** Glypican was positive in 1/15 MT, 2/5 IT, 3/3 MGCT, and 5/7 YST. In MT glypican stained the choroid plexus and in IT it stained immature renal tubular cells and salivary glands. No foci of YST were identified in IT. In MGCT, 3/3 were positive for glypican in areas of YST, the same areas were also reactive for C-Kit, B-catenin, AE1/AE3 and AFP in 2/3 cases. In pure YST, 5/7 were strongly positive for glypican in a membranous and cytoplasmic granular pattern, the two negative cases being treated YST with no residual viable tumor. In YST, the smaller glandular structures are more uniformly positive rather than the large intestinal/endometrial appearing glands, the latter being a feature more commonly seen in MGCT. Hepatoid foci, bile ducts structure and some pancreatic tissue also stain for glypican in a similar pattern as B-catenin. However, B-catenin also stained epithelial components of MT and large glandular structures in a cytoplasmic and membranous pattern. AE1/AE3 stained all YST and AFP some.

**Conclusion:** Combination of Glypican-3, AE1/AE3 and AFP stains appear to be the best available panel for identify small foci of YST. It is clear that the small hepatoid foci present in many immature GCT (excluding MT) stained with glypican-3 confirming their fetal nature, but their relationship with YST is still not clear. Small glands with "piano-key" features, which were positive for glypican, rather than large glands appear to be a better indication of YST in pediatric germ cell tumors, especially IT.

**Abstract 8 - Atypical Histiocytic lesions following Acute Lymphoblastic Leukemia and sharing the same molecular marker**

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**Background:** Histiocytic lesions can follow acute lymphoblastic leukemia (ALL) and follicular lymphomas. The lesions are often difficult to classify and are phenotypically and cytologically "atypical". Some demonstrate the molecular signature of the ALL, IgH or TCR rearrangement, or clonal identity by specific chromosomal change.

**Design:** 15 consult cases of histiocytic lesion following ALL were compiled for histopathology, cytology and phenotype using CD14, CD68, CD163, S-100, CD1a, Langerin, Factor 13a and Ki-67. Molecular results were from FISH or cytogenetic studies. Treatment and outcome details were provided by contributors.

**Results:** There were 22 lesions from 15 patients (7 recurrences) in 13 children and 2 adults, 7 followed T-cell and 8 B-cell ALL. Interval from leukemia was 3-18 months. Lesions were solitary or multiple mostly in bone, skin and soft tissue, rarely liver, lung or lymph node. The lesions were classed as high grade, histiocytic sarcoma, Langerhans' cell sarcoma in 5 patients and low grade JXG (4), LCH (1), Rosai-Dorfman (1), reticulohistiocytoma (1) and unclassifiable "atypical lesions in 4 (2 patients had high + low grade). Shared clonal identity with the ALL did not necessary confer poor outcome, all 3 patients with IgH/TCR in common are alive, as are 3/4 with cytogenetic identity. Biological behavior is, however, commonly aggressive with local or distant recurrence despite resection. Of the 9 patients treated with chemotherapy, 5 died (1 presumed), 3 are alive with recurrences and one is alive without disease on treatment.

**Conclusion:** A common T-cell/myeloid precursor has recently been identified (in the mouse) that could explain conservation of the ALL molecular signature in a histiocyte still amenable to degrees of differentiation. Those following the B-cell ALL may require lineage switching with greater plasticity. The post-ALL histiocytic lesions have a wide range of biological behavior, not all malignant.

**Abstract 9 - Hyper IgD Syndrome and Macrophage Activation Syndrome: Overlapping**

## **Lymph Node Pathology**

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**Background:** A nine year old female with a complicated past medical history (Sweets syndrome, inflammatory bowel disease treated with mesalamine, and recurrent fevers, lymphadenopathy and pharyngitis) presented to the hospital with fever and upper respiratory tract symptoms.

Physical exam revealed hepatosplenomegaly as well as a discrete, enlarged right cervical lymph node, and a lymph node biopsy was performed. Histologic examination of the lymph node raised the possibility of macrophage activation syndrome (MAS) or some other underlying immune dysregulation. Laboratory studies included an elevated ferritin (740ng/ml, nl=10-60ng/ml) with normal fibrinogen and triglyceride. Immunoglobulin studies revealed an elevated IgA (529mg/dL, nl=34-181mg/dL), with normal IgM, IgG and IgD. The history of recurrent fevers, skin and gastrointestinal complaints and elevated IgA level led to genetic testing for hyper IgD syndrome (HIDS), and yielded two missense mutations in the mevalonate kinase gene (MVK).

**Design:** The histologic findings in skin biopsies are well characterized, but previous reports of lymph node biopsies describe only a non-specific reactive hyperplasia. The histologic and immunohistochemical findings in a lymph node biopsy obtained during a period of febrile illness in HIDS are reviewed here.

**Results:** Histologic examination of the lymph node revealed marked lymphocyte depletion with the few remaining follicles composed predominately of Bcl-2+ mantle B cells. CD21 staining of follicular dendritic cells identified a single residual germinal center. In addition, there was an extensive parafollicular infiltrate composed of numerous histiocytes, some with hemophagocytosis, mixed with a few residual T-lymphocytes and plasma cells.

**Conclusion:** HIDS is characterized by recurrent fever, accompanied by cervical lymphadenopathy, abdominal pain, diarrhea, skin rash and hepatosplenomegaly. Laboratory analysis generally shows elevated levels of IgD and IgA, although elevated IgD levels are not always detected in young children, and genetic studies reveal mutations in MVK. This lymph node biopsy, obtained during a period of febrile illness, shows a markedly atypical inflammatory response with features overlapping with MAS. MAS and HIDS represent biologically different disorders. In both instances, however, increased cytokines are present. The pattern of inflammation within lymph nodes from these patients may reflect the underlying cytokine imbalance.

## **Abstract 10 - Intraoperative Frozen Section In Management Of Massive Ovarian Edema**

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**Background:** Solid ovarian masses in children are malignant until proven otherwise. Massive ovarian edema (MOE) is an unusual non-neoplastic lesion that presents as solid ovarian enlargement, usually in adolescents or young women. The role of intra-operative frozen section in the management of this lesion has not been addressed.

**Design:** Patients with MOE were identified by a search of the Surgical Pathology files from July, 2004 through December, 2007. Medical records were reviewed to determine presenting symptoms, results of imaging studies, intraoperative management and final pathologic diagnosis.

**Results:** Five patients were identified with a mean age of 15.4 years (range 14 to 18 years). Presenting symptoms were abdominal pain, nausea and vomiting in 4 patients and amenorrhea in 1 patient. Preoperative ultrasound was performed in all 5 patients and showed an enlarged ovary (right in 4 and left in 1) with reduced ovarian arterial blood flow in 4 of these patients. In 2 patients, intraoperative frozen section was not done and oophorectomy was performed. The other 3 patients had a frozen section which showed ovarian stroma, with stromal edema noted in 2, and these patients underwent biopsy (n=2) or partial oophorectomy (n=1). The sizes of the 2 resected ovaries were 4.9 x 3.5 x 2.7 and 8.5 x 4.5 x 2.5 cm. Ultrasound measurements of the enlarged ovary in the other 3 patients were 7.5 x 5.8 x 4.9, 5.7 x 4.9 x 4.8 and 9.7 x 7.8 x 5.5 cm. Final histopathology showed ovarian stromal edema in all patients. Follow-up ultrasound at 2 and 5 months following ovarian biopsy and partial oophorectomy, respectively, showed normal size bilateral ovaries. No follow-up imaging was found in the medical record of the other patient who underwent ovarian biopsy.

**Conclusion:** The diagnosis of MOE should be considered in enlarged solid ovaries in pediatric patients. Frozen section may establish the correct diagnosis during surgery and help limit unnecessary oophorectomy. The enlarged ovary returned to normal size within 5 months by follow-up imaging in 2 patients, supporting the management decision to only biopsy the enlarged ovary.

#### Abstract 11 - **Childhood fibroadenomas: histologic patterns and varieties of ductal hyperplasia distinguishing giant forms: A review of 43 fibroadenomas**

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**Background:** Fibroadenomas in childhood are not unusual (constituting 4% of all fibroadenomas). Giant fibroadenomas are less common. Giant fibroadenomas include those that are large, weighing over 500 grams, or tumors appearing large in relation to the size of the breast. We studied 43 fibroadenomas to look for specific histologic patterns of hyperplasia that may distinguish Giant fibroadenomas from usual fibroadenomas.

**Design:** We retrospectively reviewed all fibroadenomas diagnosed at a tertiary children's hospital over a 5 year period (43 cases). The pathology and clinical features were reviewed.

**Results:** 29 cases were African American, 10 were Caucasian and the race of 4 was classified as 'other'. The ages ranged from 10 to 17 years. One tumor was over 10 cm, and six were over 5 cm in greatest dimension. Six were multiple lesions while two were bilateral. Among the 44 cases there were 2 Tubular adenomas, 10 Giant fibroadenomas and 31 Fibroadenomas not otherwise specified (NOS). The Giant Fibroadenomas were larger on average (largest: 13cm, median: 7.5cm) and consistently showed foci of laciform, cribriform and micropapillary patterns of ductal hyperplasia and a very prominent myofibroblastic population around the perimeter of ductules. The largest non giant fibroadenoma was 4.5cm, with a median of 2.2cm. The combination of laciform, cribriform and micropapillary ductal hyperplasia subtypes was not consistently identified in the non giant fibroadenomas.

**Conclusion:** Giant fibroadenomas represent a distinct group of benign breast tumors. They are more common in African American children (8/10, 80% versus 19/31 fibroadenomas NOS, in African American children, 61%), are usually single masses characterized by large size, and variable ductal hyperplasia. of laciform, cribriform, and micropapillary patterns. These patterns

were rarely seen in Fibroadenomas which were histologically indistinguishable from their more common adult counterpart.

**Abstract 12 - N-Chlorotaurine: Bronchopulmonary Tolerability of a New Endogenous Antiseptic**

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**Background:** N-chlorotaurine, an important representative of the long-lived oxidants produced by human leukocytes, can be applied in human medicine as an endogenous antiseptic. This study was designed to evaluate the tolerability of N-chlorotaurine (NCT) in the pig model.

**Design:** Anesthetized pigs inhaled test solutions of 1% NCT (n = 7), 5% NCT (n = 6), or 1% NCT plus 1% ammonium chloride (n = 6), and 0.9% saline solution as a control (n = 7), respectively. Applications were performed every hour within four hours, i.e. 4 inhalations in total, with 5 ml each. Lung function, blood oxygenation, and circulation were monitored. Pharmacokinetics was investigated by oxidation capacity in bronchial fluid and by determination of taurine and chloride in serum. One hour after the last dosing the animals were euthanized, and lung samples near the bronchial carina as well as in the periphery at the same level were removed for histology.

**Results:** Two animals did not achieve >90% oxygen saturation and were excluded, so that 26 were evaluated and finished the experiment completely.

Arterial pressure of oxygen (PaO<sub>2</sub>) decreased significantly over the observation period of 4 hours in all animals. Compared to saline, only 1% NCT + 1% NH<sub>4</sub>Cl led to significantly lower PaO<sub>2</sub> values at the 4 hours measurement (62mmHg ± 9.6 vs. 76mmHg ± 9.2, p = 0.014). The corresponding increase in alveolo-arterial difference of oxygen partial pressure (AaDO<sub>2</sub>) was significantly higher only in the 1% NCT + 1% NH<sub>4</sub>Cl than in the control group (P < 0.01), too. Pulmonary artery pressure increased about 9.7 mmHg by 5% NCT, about 7.8 mmHg by 1% NCT + 1% NH<sub>4</sub>Cl (P < 0.05 versus control), about 4.3 mmHg by 1% NCT (P > 0.05 versus control), and about 6.7 mmHg by saline. Histological investigations revealed focal inflammatory reactions, districts with atelectasia, districts with emphysema, and districts with fragmentation of fibers in both the test groups and in the saline group with no statistical difference. NCT was not detectable in the systemic blood. Local inactivation of NCT below detectable levels took place within 30 min. The concentration of NCT tolerated by A549 lung epithelial cells in vitro was 0.25-0.5 mM, which was similar to that known from other body cells and 25-fold higher than that of chloramine T.

**Conclusion:** The endogenous antiseptic NCT was well tolerated at a concentration of 1% upon inhalation in the pig model. Addition of ammonium chloride in high concentration provokes statistically significant impact on blood oxygenation, which would require adjustment of dose. The advantage of using NCT might be that to reduce the dosage of antibiotics in some infections.

**Abstract 13 - Tumor Necrosis Factor Induced Mucin Release and Goblet Cell Depletion; A Potential Early Histologic Change in Necrotizing Enterocolitis?**

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College

**Background:** Necrotizing enterocolitis (NEC) is primarily a disease of premature infants affecting 1 in 10 infants with a birth weight of less than 1000 grams. Infants who develop NEC have a mortality of up to 50% and survivors are frequently left with severe sequelae. The immaturity of the intestinal tract is felt to be a major risk factors predisposing infants to NEC. The intrauterine environment of the fetuses is a sterile environment. Accordingly the fetal immune needs are geared towards prevention of rejection by the maternal immune system, accomplished by an anti-inflammatory (TH2) immunologic balance through the innate immune system. After birth, the newborn's immune system rapidly adapts to the non-sterile extra-uterine life by developing the more pro-inflammatory (TH1) adaptive immunity. During this transition time, the infant may be susceptible to infections or to unregulated inflammatory damage. In the gut, the innate immune system relies on the physical and antimicrobial properties of the mucin released by the goblet cells. It is postulated here that the earliest response of the newborn to pathogenic infections in the intestinal lumen is to release an increased amount of mucin into the lumen, in an attempt to isolate and neutralize the bacteria. The subsequent inadequate replenishing of the goblet cell's mucin predisposes the mucosa to infection and development of NEC. The purpose of this abstract is to describe early histopathologic changes identified in mouse models for NEC. Tumor Necrosis Factor (TNF), a potent cytokine that induces both inflammation and apoptosis in the intestinal tract, is instrumental in the propagation of inflammation in NEC.

**Design:** Day 0 newborn C57BL/6J mice were given intraperitoneal injections of TNF (0.5micrograms/gbw) or saline at an equivalent volume. Pups were sacrificed eight hours after injection, and the small and large bowel were harvested for histopathologic evaluation. Intestinal samples were scored a 0 for normal mucin amounts, 1 for mild loss, or 2 for moderate loss. All data are the average of 4 separate mice. All scores were obtained from a single blinded pathologist.

**Results:** Mice treated with TNF show a greater loss of mucin in the goblet cells of the epithelium when compared to mice injected with PBS. This decrease is seen in both the small intestine (PBS=1, TNF=1.75) and in the colon (PBS=0.5, TNF=1.25).

**Conclusion:** Theses studies demonstrate that there is an early release and delay of replenishment of mucus into both the small intestinal and colonic lumens with a decrease in the amount of mucin in goblet cells when newborn mice are challenged with TNF. Further studies into the physiology of mucin replenishing in the goblet cell is needed.

#### Abstract 14 - **PHOX2B Immunolocalization of the Putative Retrotrapezoid Nucleus in the Human Brain**

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**Background:** Research with animal models implicates the retrotrapezoid nucleus (RTN) as the primary central chemoreceptor that regulates respiratory drive during sleep. The RTN has yet to be identified in humans, but in mice, cats and goats, it is located in the caudal pons, immediately ventral and caudal to the facial nucleus. It is composed of neurons that co-express the tachykinin receptor, NK1R, and the transcription factor, PHOX2B. PHOX2B is active during development in visceral brainstem nuclei and some neural crest derivatives (e.g., enteric neurons). In humans,

dominant mutations of PHOX2B cause congenital central hypoventilation syndrome (CCHS), with or without Hirschsprung disease. Mice with comparable Phox2B mutations model the human phenotype and show a congenital loss of RTN neurons. Our goal is to localize PHOX2B in the central and enteric nervous systems at different stages of development, compare the patterns of expression observed in the two nervous systems, and, if possible, to localize the human RTN.

**Design:** PHOX2B and NK1R immunohistochemistry were used to evaluate histological sections of the caudal pons and medulla at various developmental stages in autopsy specimens from patients with no known brainstem abnormalities (corrected age ranges 22-40 gestational weeks). PHOX2B immunostaining was also performed on a series of intestinal specimens ranging from 22 gestational weeks to early adulthood.

**Results:** Although presumed autolysis interfered with immunostaining of some samples, nuclear PHOX2B-immunoreactivity was detected in several brainstem nuclei at the earliest and latest developmental stages examined. These sites correlated well with established sites of murine PHOX2B expression, including the putative RTN, located ventral to the facial nucleus and lateral to the superior olivary nucleus. In the putative RTN, the neurons also have NK1R immunoreactive perikarya. In intestinal samples from midgestation fetuses, PHOX2B was detected in the entire population of enteric neuroglial precursors. As pre- and postnatal development proceeds, PHOX2B immunoreactivity gradually is lost from enteric glial cells and a subset of neurons.

**Conclusion:** The putative RTN in humans shares anatomical and immunohistochemical properties with the RTN of other species, including expression of PHOX2B and NK1R. PHOX2B is also expressed in enteric neuroglial precursors, but is restricted postnatally to a subset of enteric neurons. We hope to study the influence of Phox2B mutations on RTN morphogenesis and enteric neurodevelopment in CCHS patients.

### Abstract 15 - An Unusual Form of Disseminated Low-grade Glioma in Children. Report of 3 Cases

CJ Klonek, DP Agamanolis, HM Bartkowski, Akron Children's Hospital, Akron, OH, Akron Children's Hospital, Akron, OH

**Background:** We report three cases of disseminated glioma with an indolent clinical presentation and course, unique MRI findings and characteristic histopathology. Two cases had deletion of 1p with intact 19q. Eight similar cases have been described previously. The chromosomal changes are being reported for the first time.

**Design:** Brain biopsies were processed for histology, electron microscopy (EM), and chromosome analysis. Paraffin sections were stained with hematoxylin and eosin, and immunostained using antibodies to Glial Fibrillary Acidic Protein (GFAP), S-100 protein, Synaptophysin, and Ki67. In addition to karyotyping, chromosome fluorescence in situ hybridization (FISH) was done on formalin fixed, paraffin-embedded tissue sections using 1q25 - 1p36, 19q13-19p13, and EGFR (7p11.1 - q11.1) (CEPT) locus specific probes.

**Results:** Three children ages 4, 5 and 9 years, presented with signs and symptoms of increased intracranial pressure and focal deficits. MRI in all patients showed hydrocephalus and extensive diffuse cystic lesions involving the surface of the cerebellum and adjacent areas of the cerebral hemispheres and brainstem without a tumor mass. There were also multiple intramedullary

lesions. Biopsies of the cerebellar and spinal cord lesions revealed moderately cellular diffusely infiltrating neoplasms composed of uniform cells with round nuclei and clear cytoplasm. The tumor cells expressed GFAP and S-100 weakly and were negative for Synaptophysin. Ki67 labeling ranged from 1% to 6%. There were microcysts filled with a loose proteinaceous material. On EM examination, the tumor cells had a moderate amount of cytoplasm rich in mitochondria and smooth endoplasmic reticulum. Some cells had cytoplasmic vacuoles with a granular material similar to the microcysts. Two tumors had a 46,XY karyotype. There was not sufficient sample to determine the karyotype of the third case. FISH analysis showed a reduction of 1p signals. No loss of 19q or EGFR amplification was seen.

**Conclusion:** These are unique low-grade gliomas that do not fit into any entity in the 2007 WHO classification of brain tumors. The MRI findings suggest that they are either multifocal or disseminated at presentation. The normal karyotype indicates that the 1p deletion involved a small segment, probably corresponding to the 1p36 locus, which is commonly deleted in astrocytic and other tumors. Microdeletion of 1p without loss of this chromosome or of 19q in two of our cases underscores their uniformity and sets them apart from pilocytic astrocytoma and oligodendroglioma.

Poster Presentations (# 16-29)

**Abstract 16 - Oromandiular Limb Hypoplasia Associated With Fetal Thrombotic Vasculopathy Of The Placenta: Support For A Vascular Disruptive Mechanism**

LM Ernst, R Jethva, D McDonald-McGinn, EH Zackai, The Children's Hospital of Philadelphia, Philadelphia, PA

**Background:** Oromandibular Limb Hypoplasia is part of a spectrum of syndromes including aglossia-adactylia, Hanhart syndrome, peromelia with micrognathism, and syndactyly-ankyloglossia. The oral manifestations include small mouth, micrognathia, abnormal tongue attachment and tongue aplasia/hypoplasia. The limb defects are reduction defects such as amputations, oligodactyly, and symbrachydactyly. The cause of these, likely sporadic, disorders is not known, but a vascular disruptive etiology has been postulated.

**Design:** We present a newborn with oromandibular limb hypoplasia whose clinical findings and placental histologic features lend further support for a vascular disruptive mechanism.

**Results:** The infant's prenatal course was significant for polyhydramnios and an abnormal prenatal ultrasound revealing mandibular hypoplasia/micrognathia with bilateral asymmetric limb deformities. The male infant was born by cesarean section at 35 2/7 weeks with tracheostomy placed while the infant was on placental bypass. Physical examination revealed unremarkable growth parameters, a broad nasal bridge, mandibular hypoplasia, marked micrognathia, cleft palate, and hypoglossia. The infant had right hand brachydactyly with aplastic first and second digits and 3-4-5 syndactyly. The left hand showed a proximal thumb, the left foot was absent, and the right lower extremity was unremarkable. The neurological exam was unremarkable. Brain imaging revealed small choroid plexus cysts and sinus venous thrombosis involving the superior sagittal sinus, transverse sinuses, right sigmoid sinus, vein of Galen, and straight sinus. Extensive coagulation and infectious workups were negative.

The placenta was small for gestational age weighing 220 grams and showed fetal thrombotic vasculopathy characterized by multifocal stem villous vessel thrombotic occlusion, multifocal villous stromal vascular karyorrhexis, and numerous avascular terminal villi. In addition, a possible maternal vascular perfusion disorder of the placenta was suggested by acute atherosclerosis of a maternal vessel and an area showing increased perivillous fibrin/infarct.

**Conclusion:** This is the first report of placental thrombi in the spectrum of oromandibular and limb disorders. The concurrence of thrombi in the placenta and newborn along with oromandibular and limb defects suggests a mechanism and timing of vascular disruption that allows for involvement of multiple developmental fields. The pathogenesis of the thrombotic lesions in the newborn might be an intrinsic fetal thrombophilia or embolization from placental thrombi. Finally, this report underscores the importance of careful placental examination in malformation syndromes without a known genetic etiology.

**Abstract 17 - Proposal for a New Web-Based Fetal Histology Atlas: A Promising New Resource for the Pediatric Pathology Community**

DV Spencer, JE Madory, MJ Caplan, Medical University of South Carolina (MUSC), Charleston, SC.

**Background:** Many medical textbooks offer accompanying websites which allow readers to

access images from the text and acquire additional information between editions. Very little information has been published regarding normal fetal histology, and the most recent concise atlas on the subject was published in 1979. A website for fetal and perinatal histology would be a valuable resource for residents and practicing pathologists. It would also offer the potential advantage of supplementing and improving the database with contributions from interested pathologists.

**Design:** We performed a cost analysis for the start-up and operation of a fetal histology website that would be accessible to the pathology community. Laboratory information system searches were performed to identify pertinent cases that would illustrate a broad spectrum of fetal development. Acquisition of images was performed using a high resolution microscope camera, with all images taken at maximum resolution. The expenses associated with providing the images online include domain name registration, domain hosting and storage, initial site design and maintenance costs.

**Results:** The estimated costs for developing and maintaining a website for an image archive can vary significantly. Domain name registration through a reliable registrar is \$8 per year. Hosting and storage of the site will vary based on the number of images stored on the site and the number of visitors. A package allowing storage space for approximately 655,000 high resolution images will cost \$19.99 per month. This package will also allow transmission of approximately 6.5 million images to end users. The initial design of the site is approximately \$1500. Maintenance costs contracted with the developer of the site are approximately \$85 per hour. The costs of owning and operating such a histology website could be offset by self-designing and maintaining the website, altering the quality and the number of images, and providing options for payment such as advertisements, subscription costs, and acquiring sponsors.

**Conclusion:** An online electronic fetal histology atlas would be a useful training resource for residents and fellows, and would provide a readily accessible reference for practicing pathologists. The initial set-up and operating costs for such a website would be amply compensated by the substantial benefit to the pathology community in providing access to a fully functional, comprehensive, and dynamic resource for fetal histology.

## Abstract 18 - Accessory (Lobe Of) Liver. Personal Experience And Review Of The Literature

P Florescu, PA Siegmund, University Children's Hospital, Cluj-Napoca, Romania

**Background:** Accessory liver (AL) is a rare malformation of the liver, incidentally found by peritoneoscopy, laparotomy, or autopsy. There are many alternative terms, sometimes synonymously used in the literature: accessory liver, ectopic liver, supranumerary liver, hepar succenturiatum, etc. Little is known about the pathogenesis of this lesion.

**Design:** We reexamined 2534 consecutive pediatric necropsies found in the files of the Department of Pathology of University Children's Hospital, Cluj-Napoca, Romania and reviewed the literature on the topic, beginning with the first description (Morgagni-1767). We have considered as AL: "a liver tissue mass connected to the liver" and as ectopic liver: "a liver tissue mass not connected to the liver".

**Results:** We found five cases, four of them corresponding to our AL definition and one to ectopic liver in the right adrenal gland. We demonstrated three different macroscopic types of AL (of four described in the literature) and a modified microscopic structure. In three of AL

cases, we were able to demonstrate anatomic variations of the hepatic arteries and especially, the presence of an accessory hepatic artery.

**Conclusion:** Accessory liver defined as a liver tissue mass connected to the liver could be linked to the presence of an accessory hepatic artery. The ectopic liver could be a choristoma or, in other cases, an AL in which the pedicle atrophied

#### Abstract 19 - **Significance of macroscopic placental findings in stillborn.**

Halit Pinar, Brown Medical School - Women and Infants Hospital

**Background:** Macroscopic quantitative placental findings in stillborn and compared with findings in liveborn with similar gestational age have not been analyzed and their significance has not been determined.

**Design:** We employed a uniform placental examination protocol to evaluate a total of 418 placentas. 106 were from preterm stillbirths <sup>3</sup>20 and <sup>2</sup>36 and gestational age matched 104 preterm controls and 102 term placentas from stillbirths with gestational age matched 106 control placentas. Pathology records and macroscopic digital images were retrospectively reviewed. Quantitative parameters such as placental and fetal/newborn weights and sizes of the placentas and weights of circumscribed lesions were collected. Fixed and fragmented specimens and placentas from multifetal gestation, or with congenital malformations were not included in the analysis. The collected parameters were compared using the student's t test.

**Results:** The weights of the stillborns in both preterm and term groups were significantly smaller in comparison to the liveborn control groups (p=0.006). Similar results were obtained when placental weights were compared. When the relative size and weights of the placental lesions were compared though, there was no statistically significant difference.

**Conclusions:** Intrauterine growth impairment is arguably the most significant findings that is seen in stillborns and their placentas. On the other hand, the percentage of placental parenchyma involved with a lesion is not a reliable indicator of fetal demise.

#### Abstract 20 - **False knots: Clinically important?**

H Baldwin, D Shanklin, D Padgett, University of Tennessee, Memphis.

**Background:** Umbilical cord false knots are considered insignificant. Reference texts seldom mention them, and the vascular pattern of false knots is largely undescribed. We present two recent examples of striking vascular redundancy of the umbilical cord presenting grossly as "false knots," which on cross-section showed 9 vascular lumina. These raise the question of whether the clinical significance of "false knots" can be so easily dismissed.

**Design:** Placentas were received in formalin and examined. The medical records of the mothers and infants were reviewed.

**Results:** A female infant was born at 34 weeks to a 30-year-old, G3P2 mother with a history of hypertension, Class B diabetes mellitus, and previous stillbirth. She was delivered by section for pre-term labor and footling breech. She had a loose double nuchal cord, meconium, and apnea. At delivery her heart rate was <100 and she required brief intubation and chest compression. Birth weight was 2128 grams, and APGARs were 1 and 7. In intensive care, she was noted to have poor tone. She was eventually weaned from oxygen therapy and was discharged with

unresolved clinical concern for anoxic brain injury. The placenta weighed 294 grams (<10th %ile) and had hemodynamic lesions including an intraplacental hematoma, villous congestion and hemorrhage, hypervascularity and fibromuscular hyperplasia of stem vessels. The umbilical cord had a 2.5 cm false knot with 9 complex vascular lumina on cross-section. A male infant was born at 38 weeks to a 40-year-old, G3P1 mother with a history of severe pre-eclampsia and oligohydramnios. He was delivered by section, with meconium noted. Birth weight was only 2051 grams, and APGARS were 9 and 9. The placenta weighed 335 grams (<10th %ile) and had hemodynamic lesions including subchorial and cotyledonary fibrinosis, intervillous space collapse, exaggerated syncytial knotting and dilated veins. The marginally-inserted cord had a 2 cm false knot with 9 vascular lumina on cross-section.

**Conclusion:** These examples of extreme umbilical cord vascular redundancy were found in the setting of small placentas with numerous hemodynamic lesions. In both, the infants had significant clinical lesions, one with a very low birth weight, and one with low muscle tone and apnea requiring intensive care. These raise the question of the association of complex false knots with other major disorders. If not themselves clinically significant, false knots may yet be a marker for significant lesions, and should perhaps require microscopic examination. At the very least, their significance needs to be reevaluated.

#### **Abstract 21 - Ewing Sarcoma with 7;22 Translocation - Is it Occurring in a Younger Age Group with Predilection for Extrasketal Location? A Study of 35 Cases with Emphasis on Molecular Analysis**

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**Background:** Ewing sarcoma is a malignant bone or soft tissue tumor usually occurring in children and young adults. Gene fusion between EWS (22q12) and ETS-related gene family, either FLI1 (11q24) or ERG (21q22), resulting in t(11;22)(q24;q12) or t(21;22)(q22;q12), respectively, is the characteristic genotype of this tumor, in 90% of cases. The gene fusion involving EWS and ETV1, another member of the ETS family at 7q22, however, is extremely rare. Currently, a few cases with t(7;22)(q22;q12) have been reported, but information regarding this variant is still limited.

**Design:** We performed a retrospective study in 71 cases of Ewing Sarcoma at Children's Healthcare of Atlanta. The age of those patients range from 8 months to 20 years of age with a mean age of 13 years of age. Tumor karyotyping was available in 35 cases, the subject of this report.

**Results:** Thirty of the 35 tumors occurred in patients older than 4 years of age and 5 patients younger than 4 years of age. Twenty seven of the older patients (90%) showed the classic t(11;22) and three (10%) showed t(7;22) while 3/5 patients(60%) under 4 years of age showed t(7;22). Additionally, in the older age group the majority of Ewing Sarcoma occurred in the usual skeletal locations previously described with only 17% being extrasketal, while 2 of 5 (40%)the younger age patients had tumors in extrasketal sites.

**Conclusion:** Although this is a small study, it is suggested that when Ewing Sarcoma occurred in a younger age group, it shows more predilection for t(7;22) and extra skeletal presentation. Further studies with a larger number of patients are needed to confirm our findings.

**Abstract 22 - Unusual intra abdominal malignancies of childhood: The utility of cytogenetic analysis**

V. Prasad, J. Bedrnicek, E. Chenever, R. Houston A. Hughes, Nationwide Children's Hospital, Ohio State University, Columbus, OH

**Background:** Intra abdominal malignancies are not rare in childhood, with Wilms tumor, and neuroblastoma being the commonest. Other types of nonhematopoietic malignancies are unusual. It is important to submit lesional tissue for cytogenetic studies in all intra abdominal malignancies.

**Design:** We reviewed all non hematopoietic intra abdominal malignancies diagnosed over a 8 year period at a tertiary care dedicated children's hospital from 2000-2008. The pathology, clinical history and cytogenetic study results, when available, were reviewed. Excluded were common entities such as Wilms Tumor, germ cell tumors and neuroblastoma.

**Results:** We identified eight unusual intra abdominal malignancies. The cases included synovial sarcoma (1/8), undifferentiated embryonal sarcoma (2/8, one occurring in the liver), mucinous adenocarcinoma of colon (1/8), gastrointestinal stromal tumors (GIST, 2/8), clear cell sarcoma-like tumor of the stomach (1/8) and a desmoplastic small round cell tumor (DSRCT, 1/8, involving the liver, rectum and omentum). Cytogenetic analysis was done in only 5 of the 8 tumors, with results in 4. One of the tumors failed to grow and no result was possible. The clear cell like tumor of the stomach showed a translocation: t (12:22) involving the EWSR1 gene at 22q13 and the ATF1 gene at 12q12, confirmed by FISH analysis. The synovial sarcoma showed a t(X; 18) (p11; q11) translocation and was positive for SYT-SSX1 fusion by RT-PCR. The DSRCT showed a t (11; 22) (p13; q12) translocation and WT1 and EWSR1 fusion. One of the embryonal sarcomas (arising from liver) showed an abnormal complex composite karyotype that included: 40-77, XY, +X, + add (1) (p? 21), +Del (1) (p32).

**Conclusion:** In unusual intra abdominal malignancies, histologic patterns and cytogenetic alterations are crucial to diagnosis. Two of 8 cases showed classic cytogenetic changes known to occur (in DSRCT and Synovial sarcoma respectively). The clear cell sarcoma-like tumor of the stomach showed a translocation involving the EWSR1 and ATF1 genes. One of the embryonal sarcomas (liver) showed a very complex abnormal composite karyotype. Many tumors are not submitted for cytogenetic studies, It is imperative to submit tissue and study the cytogenetics of the tumor in order to diagnose and better understand unusual abdominal malignancies. It is critical to impart training to residents, fellows and pathology assistants to quickly and optimally save tumor tissue, when available, for cytogenetic analysis. The results of cytogenetic and molecular study can have vital diagnostic use.

**Abstract 23 - Bone Marrow Embolization: A Cause of Acute Chest Syndrome in Sickle Cell Disease**

J. Bedrnicek, K. Mast, A. Hughes, P. Baker, Nationwide Children's Hospital, Ohio State University, Columbus, OH

**Background:** Acute chest syndrome is the leading cause of death and hospitalization in patients with sickle cell disease. Bone marrow hematopoietic tissue embolization is one of several

etiologies for acute chest syndrome and may be interpreted at autopsy as a resuscitation-related finding.

**Design:** We report the autopsy findings in a 7 year old with sickle cell disease who developed acute chest syndrome preceded by abdominal pain and low grade fever. She presented to the Emergency Department in arrest and expired after one hour of attempted resuscitation.

**Results:** At autopsy, there was a red, soft embolus in a lobar pulmonary artery as well as multiple similar emboli in peripheral pulmonary arteries. Sequential compression from the ankle to the thigh produced expulsion into the pelvic cavity of material similar to the emboli. Microscopic sections of the embolic material as well as the material from the leg revealed bone marrow hematopoietic tissue with necrosis of the hematopoietic elements. Sections of vertebral body bone marrow revealed necrosis of the hematopoietic elements. There were no fractures of ribs or other bones and extensive red blood cell sickling was evident. There was a patent foramen ovale and the bone marrow removed from the vessels of the leg likely represented paradoxical bone marrow embolization.

**Conclusion:** Bone marrow embolization was the immediate cause of death in this patient with sickle cell disease and acute chest syndrome. In patients with sickle cell disease, bone marrow emboli occur in the absence of bone fractures and should be recognized as a cause of acute chest syndrome. Sections of bone marrow, especially in the vertebral bodies, may document necrosis from recent sickling crisis which is thought to have a role in the entrance of bone marrow hematopoietic elements into sinusoidal marrow vessels.

#### Abstract 24 - **Intestinal Spirochetosis in Children: Five New Cases and a Twenty-year Review of the Literature.**

DF Carpentieri; JS Gardetto; HM Ross; K Downey; K Ingebo; E Siaw, Phoenix Children's Hospital, AZ; University of Arizona, AZ; John Hopkins University, MD; Boston University Medical Center, MA.

**Background:** There is limited clinical awareness and variable therapeutic options among physicians involved in the care of children diagnosed with intestinal spirochetosis. This abstract summarizes the findings of five new cases and a twenty-year review of the pediatric literature.

**Design:** A retrospective study of all new cases diagnosed with spirochetosis at Phoenix Children's Hospital was performed after IRB approval. The findings were reviewed in the context of the available pediatric literature.

**Results:** Five new cases were identified at our institution and twenty-four upon review of the literature. Children often presented with pain (24/29), bleeding (14/29) and diarrhea (12/29). The endoscopic examination was reported in twenty-two patients. Of these, abnormal findings were reported in only 32% (7/22) and were limited to the distal colon (sigmoid-rectum) in three. Three patients presented with signs and symptoms of appendicitis. Two patients were also diagnosed with juvenile polyps and one with ulcerative colitis. Coexisting infections (*H. pylori*, *ascaris lumbricoides* and enterobiasis) were also seen in a few cases (4/29). The majority of patients had no or at most mild microscopic inflammation in the lamina propria. The reported therapeutic options included: Metronidazole, Erythromycin, Clarithromycin, Piperazine, Mebendazole, Doxycycline; Sulfasalazine with steroid, Omeprazole, Penicillin-V, Amoxicillin and Penicillin-G.

**Conclusions:** Spirochetosis is an uncommon worldwide disease of children. The diagnosis of spirochetosis requires a high degree of suspicion especially in cases presenting with diarrhea

and/or hematochezia and a normal endoscopic examination. The best therapeutic option for children, while still under debate, may be a macrolide antibiotic with or without metronidazole. Further investigations are needed to determine the correlation between spirochetosis and coexisting gastrointestinal diseases and/or possible immunodeficiencies.

**Abstract 25 - Fatal Respiratory Syncytial Virus (RSV) Lower Respiratory Infection in Children**

AM Gomez, A Mejias, JP Torres, Y Butt, O Ramilo O, University of Texas Southwestern Medical Center; Children's Medical Center, Dallas, TX.

**Background:** To study the pathogenesis of fatal RSV lower respiratory tract infection in children.

**Design:** All autopsies from patients diagnosed with RSV lower respiratory infection performed at Children's Medical Center of Dallas during the last 15 years were studied. H&E stained slides, and slides immunohistochemical stained for RSV, CD3 (pan T cells), CD4 (helper/inducer T cells), CD8 (cytotoxic/suppressor T cells), CD20 (B cells) and CD68 (macrophages) were examined. Real time quantitative PCR was performed on sections from paraffin embedded blocks.

**Results:** Fourteen autopsies of children diagnosed with RSV lower respiratory infection were performed at Children's Medical Center of Dallas during the last 15 years (1993-2008). Ages ranged between two months and 18 years, and there were 5 males and 9 females. In 5/14 patients (Group 1), no other infection was recognized. In 9/14 patients (Group 2), a secondary bacterial infection (1 Legionella, 2 S. pneumoniae, 2 Pseudomonas spp, 1 Serratia marcescens, 1 M. catarrhalis, 1 MSSA, and 1 Stenotrophomonas maltophilia) was identified. Lung sections from patients in Group 1 demonstrated a diffuse necrotizing bronchiolitis and a predominantly macrophagic pneumonitis with a few mixed in neutrophils present in the alveolar spaces. Two of the five patients in group 1 also had diffuse alveolar damage. Immunohistochemical phenotyping of the inflammatory infiltrate demonstrated a peribronchial lymphocytic infiltrate composed of B cells and CD4 and CD8 positive T lymphocytes. A mononuclear infiltrate present in the alveolar septa was composed of CD8-positive T cells and macrophages; the alveolar spaces contained abundant CD68-positive macrophages. Lung sections from 4/9 patients in Group 2 demonstrated acute pneumonia with necrosis. The remaining 5/9 patients demonstrated severe macrophagic pneumonitis with patchy necrosis and hemorrhage. In both groups, immunohistochemical staining demonstrated RSV antigens in the bronchial and bronchiolar epithelium and in the alveolar lining and alveolar macrophages. Real time PCR performed in paraffin sections immunosuppressed patient revealed the presence of RSV RNA in multiple organs including the lungs, liver, spleen, pancreas, adrenals, and Central Nervous System in an immunosuppressed individual in Group 2.

**Conclusions:** Fatal RSV lower respiratory infection is characterized by necrotizing bronchiolitis and severe macrophagic pneumonitis. Most patients show superimposed bacterial pneumonia. In immunosuppressed patients, RSV may cause a systemic infection.

**Abstract 26 - Intrauterine Fetal Heart Block and Demise Due to Fulminant Myocarditis in Maternal Sjogren's Syndrome**

AM Hughes, J Wheller, PB Baker, Nationwide Children's Hospital; The Ohio State University, Columbus, Ohio.

**Background:** Maternal Sjogren's syndrome with anti-SS-A and anti-SS-B antibodies has been associated with fetal congenital heart block, hydrops and intrauterine death. The pathologic basis for these complications has not been well-described.

**Design:** The autopsy findings, maternal medical records and pregnancy course were reviewed on a stillborn infant of a mother with a 4 year history of Sjogren's syndrome.

**Results:** This 29 year old gravida 2 Para 1 was positive for anti-SS-A and anti-SS-B antibodies as well as anti-nuclear antibodies (1:1280, speckled pattern). She was negative for anti-cardiolipin antibodies. Her first pregnancy, 10 years prior, produced a liveborn female at term. Her second pregnancy was complicated by anemia and she was taking prednisone, 5 mg. daily. A fetal ultrasound at 19 1/7 weeks gestation revealed "bright" atria and evidence of complete heart block and she was started on dexamethasone, 4 mg. daily. Intrauterine fetal demise was documented at 19 6/7 weeks. At autopsy, the fetus was within the expected size for 20 weeks gestation and there were no dysmorphic features. Cytogenetics reported normal female karyotype. The heart revealed dilation of all four chambers with prominent areas of yellow discoloration in the atrial walls and the basilar ventricular myocardium. Microscopically, there was severe myocarditis with extensive necrosis of atrial and ventricular myocardium. There was patchy dystrophic calcification of the ventricular myocardium and extensive calcification of the atria. In addition to the myocardium, the inflammatory infiltrate involved epicardial soft tissue (especially along the atrioventricular junction) and endocardium. There was no inflammation in the valve leaflets, proximal aorta or pulmonary trunk. The large coronary arteries had no evidence of vasculitis. The placenta showed features associated with hypoperfusion.

**Conclusions:** Severe pancarditis represented the pathologic basis for heart block and intrauterine demise in this infant with maternal anti-SS-A and anti-SS-B antibodies. Irreversible heart block has been documented post-delivery in previously reported cases, and may be due to mild or limited myocarditis followed by post-inflammatory fibrosis involving the conduction system and/or adjacent myocardium. Fulminant myocarditis is likely the pathologic basis for fetal hydrops and intrauterine demise.

#### Abstract 27 - **Isolated Eosinophilic Coronary Periarteritis with Dilated Cardiomyopathy in a 10 year-old Girl**

H Correa, D Dodd, J Atkinson, V Exil, Vanderbilt University Medical Center; Monroe Carell Jr. Children's Hospital

**Background:** Isolated eosinophilic coronary periarteritis is a rare, poorly understood entity of unknown etiology. It is not associated with Churg-Strauss syndrome, Kawasaki disease, Takayasu arteritis, Wegener's granulomatosis or hypereosinophilic syndromes. Only five cases are identified in the literature, all in adult patients over 39 years of age. All of these have been identified during postmortem examination, which showed no other sites of eosinophilic arteritis or an eosinophilic process involving other organs. No cases of isolated eosinophilic coronary periarteritis have been described in children.

**Design:** We report the first pediatric case of a 10 year-old girl who presented with shortness of breath, exercise intolerance, and an increased heart size detected on chest x-ray. There was no

history of intercurrent illnesses, fever or infections, and there was no family history of heart disease. An echocardiogram demonstrated an enlarged heart with decreased function. The child received inotropic therapy and underwent a right endomyocardial biopsy which was normal. After 2 weeks of therapy her symptoms worsened. She underwent an orthotopic heart transplant. After transplant the patient has had a full recovery. There is no evidence of Kawasaki's disease, Churg-Strauss disease, Wegener's granulomatosis, or hypereosinophilic syndrome.

**Results:** The explanted heart showed a markedly enlarged heart, 345 grams (expected for age 116 grams). Histologically there was myocardiocyte hypertrophy, and a striking isolated coronary artery eosinophilic periarteritis, with no evidence of myocarditis.

**Conclusion:** This is the first reported pediatric case of isolated eosinophilic coronary periarteritis. Although the diagnosis can be made only post mortem or in explanted hearts, orthotopic heart transplantation should be strongly considered in suspected cases.

### Abstract 28 - **Morphological Supportive Evidence That Central Nervous System Abnormalities In Seckel's Syndrome Are Due To Premature Involution Of Germinal Layers**

B Fitzgerald, K Chong, S Keating, P Shannon, Mount Sinai Hospital, Toronto.

**Background:** Seckel's syndrome is a rare autosomal recessive disorder characterized by intrauterine growth retardation, dwarfism, microcephaly and mental retardation. The facial features are distinctive and include a prominent nose, which together with micrognathia and a receding forehead result in a "bird-like" appearance. The condition is genetically heterogenous and at present two mutations have been characterized. These involve the ataxia telangiectasia and Rad3-related protein (ATR) and the gene encoding pericentrin (PCNT). These gene products have a role in the DNA damage response and a defective DNA damage response appears to be one of the critical defects present in this disorder. Supernumerary centrosomes are also a feature of Seckel cells and it is postulated that these may contribute to premature cell death of affected cells, contributing to the clinical features observed in this condition. Documentation of cerebral abnormalities in Seckel's syndrome has mainly been through imaging techniques with only rare descriptions of the neuropathological findings.

**Design:** As part of a full autopsy, detailed neuropathological examination of a 30 week gestation foetus with Seckel's Syndrome was conducted with photographic documentation and extensive histological sampling. Morphology was compared to gestational age matched normal controls.

**Results:** Extensive severe neurological abnormalities were observed that included, micrencephaly, cortical neuronal migration disorder, hypoplasia of corpus callosum, aplasia of descending corticofugal tracts, ventriculomegaly, severe temporal lobe hypoplasia, premature involution of germinal matrix with involutinal cysts, hypoplasia of cerebellar cortex with patchy absence of the external granular cell layer and dysplasia of deep cerebellar and inferior olivary nuclei.

**Conclusion:** The evolving molecular understanding of Seckel's syndrome implicates defective DNA damage response and reduced cell survival as critical components in the pathogenesis of Seckel's syndrome. In this case we have demonstrated that there were defects present in germinal layers within the central nervous system. Most interestingly, we demonstrated that there were areas in the cerebellum where the external granular layer was absent. This observation provides the first direct morphological evidence for reduced cell survival/premature involution in

Seckel's syndrome and thus provides autopsy derived corroborative evidence for the emerging molecular hypotheses.

Abstract 29 - **Increasing The Efficiency Of Autopsy Reporting**

JR Siebert, Children's Hospital and Regional Medical Center; University of Washington, Seattle, WA

**Background:** As we assign priorities to our work days, the completion of autopsy reports may suffer. When sign-outs are protracted, tasks may need to be repeated or case histories revisited; CAP-designated deadlines may be missed; and families and their care givers may not receive information in a timely manner. Our group sought to improve its performance in this area.

**Design:** With our institution's Continuous Performance Improvement team, we set out to streamline the reporting process. In a 3-day workshop that included two pathologists, a pathology fellow, a histology technologist, and an administrative secretary, we identified the tasks, transfers of material, and queues involved in finishing a report. These steps were examined to see if any could be eliminated, abbreviated, or re-scheduled. We then established a set of intermediate deadlines for each case, corresponding to the various stages in the reporting process and totaling 30 work days; we designed loose-leaf binders for each case, with outside calendar and interior pockets that made tracking deadlines visible and storing material systematic; we created a wall-mounted status board to display the progress of each case; and, we initiated a weekly conference to review cases, with emphasis given to approaching deadlines.

**Results:** Following conversion to this system, an audit showed a reduction in average completion time from 53 days (N=47 cases) to 27 days (N=26 cases). One case requiring additional testing exceeded 30 days. Although we were able to reduce 77 individual steps in our reporting process by 8%, the larger gains came elsewhere. Eliminating redundancy, adopting a more systematic approach to work-ups, and increasing the visibility of unfinished tasks led to increased efficiency in our system. By increasing our vigilance at intermediate steps, we were able to eliminate an additional QA review.

**Conclusion:** In attaining a deadline of 30 days in virtually every case, we were able to rectify a chronic problem and meet national standards. We were able to identify and prevent delays, or at least anticipate them and take steps to minimize their effect. This program has proven sustainable nearly one year after initiation. We believe that increased efficiency and timeliness benefit pathologists and clinicians and enhance feedback to families.