Delayed parasite clearance after treatment of falciparum malaria in Thailand

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Artemisinin combination therapy is currently the mainstay of treatment of falciparum malaria worldwide. Artemisinin derivatives (such as artesunate) are thought to slow down the spread of resistance of their partner drug. In addition, resistance to artemisinin derivatives has never been definitively documented. However, recently there has been increased treatment failure of artesunate-mefloquine on the Cambodia-Thailand border. It is unclear if the increased treatment failure is due to increasing mefloquine resistance or artesunate resistance. Since mefloquine is more slow acting, artesunate is the major determinant of parasite clearance. Therefore, examining parasite clearance time may be a way to distinguish mefloquin and resistance. To determine if parasite clearance time varies over time and space, we analyzed data obtained from the in vivo monitoring of artesunate-mefloquine therapeutic efficacy by the Thai National Malaria Control Program. In total, 1,412 patients infected with *P. falciparum* from 1997-2007 from 2 provinces bordering Cambodia and 5 provinces bordering Myanmar were included. On the Thailand-Cambodia border, prevalence of day 2 parasitemia increased from 0% in 1997 to 43% in 2007 while during the same time period on the Thailand-Myanmar border, it increased only from 6% to 12%. After controlling for age, site, weight and initial parasitemia, the odds ratio for each year for the Cambodian border was 1.3 (95% CI: 1.2, 1.5) and was 1.0 (95% CI: 0.9, 1.2) for the Myanmar border. Day 2 parasitemia was associated with treatment failure (OR = 2.5, 95%CI: 1.4, 4.5). These data suggest that parasite strains on the Cambodian border may be becoming less sensitive to artesunate. Therefore increased malaria control efforts focusing on this multi-drug resistant hotspot is urgently needed.
Association of Environmental Aeroallergens in Chronic Idiopathic Urticaria

Background: Chronic idiopathic urticaria is a common clinical entity which can be debilitating to patients and frustrating to providers secondary to difficulty in elucidating specific causes and thus in targeting therapy to these causes. Recent studies have suggested that 30-50% of these cases may be secondary to autoimmune urticaria with the remainder of cases representing true idiopathic urticaria. Though environmental allergens are known to play a role in acute urticaria, they are not typically believed to be associated with chronic urticaria. However, it is possible that environmental allergens may play a role with continuous exposure.

Purpose: To review the clinical data of patients with chronic urticaria seen at UNC Hospitals, to describe characteristics of the patient population and to determine the prevalence of positive skin and RAST testing to environmental allergens.

Methods: A retrospective chart review of 75 patients with a diagnosis of chronic urticaria between the years of 2005-2009 was conducted. Information regarding basic demographic information was extracted as well as complement levels, h. pylori status, history of autoimmune disease and ANA titers, thyroid function tests and status of thyroid disease, anti-IgE receptor antibodies, and results of skin prick and RAST testing to environmental allergens.

Results: In patients with a diagnosis of chronic idiopathic urticaria, 43% tested positive for either IgE receptor antibodies, thyroglobulin antibodies, or thyroid peroxidase antibodies. However, the test for IgE receptor antibody was performed in only 56% of patients while testing for thyroid receptor antibodies was performed in 92% of patients. 20% of patients who tested positive for thyroid receptor antibodies tested negative for IgE antibodies and 5% of patients who tested positive for the IgE receptor antibodies tested negative for thyroid receptor antibodies. In patients who underwent skin prick or RAST testing, no significant difference was found in prevalence of atopy between the patients with autoimmune urticaria (77% positive to either food or environmental testing) and non-autoimmune urticaria (63% positive). However, more patients with non-autoimmune urticaria were found to be positive to environmental aeroallergens (81% versus 66%, p<.05).

Conclusions: Autoimmune urticaria may be the diagnosis for many patients with chronic idiopathic urticaria. As autoimmune urticaria may be optimally treated with different agents than those typically used in chronic idiopathic urticaria, it is important to conduct the appropriate testing for this subgroup in all patients with a diagnosis of chronic idiopathic urticaria. Though there is believed to be a direct relationship between thyroid disease and the IgE receptor antibody, there were patients who did not have thyroid receptor antibodies but did test positive for the IgE receptor antibody. Additionally, it is possible that for the remaining patients with chronic idiopathic urticaria, environmental allergens may play a role. It would be useful to further elucidate this relationship in future studies.
Mental disorders frequently occur in conjunction with medical illness. Prevalence of mood disorders also increases with chronic illness. A quality improvement project was designed in the UNC Internal Medicine Clinic to evaluate management of mood disorders in the clinic, including rates of under diagnosis, mood assessment and intervention in patients with mood disorders. Chart review of resident clinic was followed by administration of systematic mental health screening using the Patient Health Questionnaire 9 (depression) and Generalized Anxiety Disorder 7 (anxiety) was done. 32.3 % (57/177) patients were noted to have mood disorder prior to systematic screening and 48.1% (51/106) patients were found to have mood disorders after systematic mental health screening, demonstrating greater than 30% under diagnosis of mood disorders in the clinic population. Systematic screening improved rate of mood assessment and intervention by physician providers. It preferentially improved rates of diagnosis, assessment, and intervention of mood disorders in patients with higher number of medical co-morbidities. Despite improvement of mental health care delivery using systematic screening, many patients fail to receive mental health treatment by medical providers. A primary care based mental health care delivery system is proposed to implement systematic screening, to address medication adherence and titration, and to allow robust access to psychiatric sub-specialty resources.
DIFFERING ClOT DISTRIBUTION IN BLACK COMPARED TO WHITE PATIENTS PRESENTING WITH ACUTE LOWER EXTREMITY DEEP VENOUS THROMBOSIS.

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Venous thromboembolism (VTE) is a major cause of morbidity and mortality in the United States. There is growing evidence that VTE incidence and mortality rates differ among ethnic/racial groups. Specifically, it has been demonstrated previously that blacks with VTE have a higher proportional rate of pulmonary embolism (PE), as well as a higher case fatality rate from PE compared to whites (*Arch Int Med* 2003;163(15):1843-8). We therefore compared the location of DVT (proximal vs. distal) in blacks and whites at the time of diagnosis. The null hypothesis was that there is no difference in the location of DVT between white and black patients at the time of diagnosis. We reviewed all lower extremity Doppler ultrasound studies that were positive for acute DVT at our Institution over a 3-year period to create a retrospective case series of 941 patients. Subjects were further classified by self-reported race (black or white), disposition at diagnosis (inpatient or outpatient), and clot location (proximal or distal). Distal DVT was defined as thrombus in one or more deep veins distal to -- but not including -- the popliteal vein. Results were analyzed using Stata version 10. We found that the rate of any proximal (proximal or both proximal and distal) DVT compared with distal only was significantly higher in black patients (OR = 1.4; 95%CI: 1.03, 1.8; P = 0.032), both for 637 inpatients (OR = 1.3; (0.94, 1.9); P = 0.11) and for 304 outpatients (OR = 2.0; (1.01, 3.8); P = 0.048). These differences persisted after controlling for sex and age. We conclude that blacks with acute lower extremity DVT are more likely to present with proximal DVT than whites. These results confirm earlier suggestions that the proportion of proximal lower extremity DVT is higher in blacks, which might account in part for the higher rate of PE (*Arch Int Med* 2004;164(12):1348-9). We are further examining the possible causes of this disparity. Possibilities include genetic factors (such as factor V Leiden which is associated with more distal DVT presentation and is rare in blacks), co-morbid conditions (such as diabetes which is more prevalent in blacks), and access to healthcare and diagnostic services, which may lead to more delayed evaluation. Efforts will also be made to determine rates of idiopathic and provoked DVT in these sub-groups.
A randomized, controlled, double-blind trial of air vs carbon dioxide insufflation during ERCP

Background: Insufflation of carbon dioxide (CO2) has been shown to decrease patient pain and bloating after colonoscopy, but has not been as extensively studied for use during ERCP.

Aim: To assess the safety (transcutaneously measured pCO2; respiratory complications) and efficacy (post-procedural abdominal pain and distention) of CO2 insufflation during ERCP.

Methods: We performed a randomized, controlled, double-blind trial of air vs CO2 insufflation for patients undergoing ERCP at University of North Carolina. Exclusion criteria were age <18, COPD requiring oxygen, known CO2 retention, same-day second endoscopy, use of chronic opiates for pain, and pregnancy. Randomization was by variable block size. CO2 insufflation was regulated by the Olympus UCR. Patients, endoscopists, nurses, and data analysts were blinded as to allocation. A nurse not involved with the procedure or data collection set-up and masked the equipment. Conscious sedation with midazolam and fentanyl was used. Primary outcomes were abdominal pain assessed on a 100mm visual analogue scale pre- and 1, 3, 6, and 24 hrs post-ERCP, and abdominal girth (cm) pre- and post-ERCP. Key secondary outcomes were pCO2 levels (mm Hg) measured with transcutaneous capnography and procedural complications. Outcomes were compared using t-tests and chi-square. This is a planned interim analysis.

Results: Baseline demographic characteristics, indications for ERCP, and comorbidities were similar in the air (n=26) and CO2 (n=24) groups, though cannulation time, procedure time, and procedure failure rate were all higher in the CO2 group. Mean pain scores in the air and CO2 groups were 11 and 12 at baseline (p=0.89), 8 and 18 at 1 hr (p=0.08), 12 and 23 at 3 hr (p=0.12), 13 and 20 at 6 hr (p=0.41), and 14 and 17 at 24 hr (p=0.66). Abdominal girth increased a mean of 0.8 cm in the air group and 0.3 cm in the CO2 group (p=0.73). Baseline pCO2 levels were 41 in the air group and 40 in the CO2 group (p=0.68), and increased to a mean of 50 in the air group and 48 in the CO2 group (p=0.57). One patient in the air group and none in the CO2 group had respiratory depression. There were no differences in other complications.

Conclusions: The use of CO2 for insufflation during ERCP was safe in a tertiary care referral population. While there was a mild rise in pCO2 in both groups, this was not associated with respiratory complications. Despite procedures being more difficult in the CO2 group, there was no difference between the air and CO2 groups in pain scores or abdominal distention. Patient accrual is ongoing for this study.
Question of local or global health addressed:

Hepatocellular Carcinoma (HCC) deaths are increasing in the U.S. Surveillance imaging of cirrhotic livers may permit earlier diagnosis of HCC and better outcomes. But if cirrhosis is unrecognized, HCC is rarely detected at a curable stage. The US Dept. of Veterans Affairs (DVA) Health System employs a comprehensive electronic medical record system. Using routinely collected data from this system, it may be possible to 1) identify individuals with possible undiagnosed cirrhosis in need of further evaluation; and 2) assess the adequacy of individual and institutional HCC surveillance.

Research conducted:

For my research I queried the Richmond DVA Medical Center's data warehouse to identify all patients seen at that facility between 10/1/06 & 11/1/07. For this interval I extracted most recent laboratory values (ALT, AST, platelets), and ICD codes and dates for abdominal imaging (ultrasound, CT, MR). I also searched these patients' records for the preceding 10 years for results of HCV antibody testing and encounter ICD diagnosis codes for cirrhosis, complications of cirrhosis, and HCC, as well as components of metabolic syndrome and alcohol abuse. I was able to take the data extracted and compute a Fib-4 score, which is a non-invasive index of liver fibrosis, as well as perform statistical analysis.

In conclusion, I found that routinely collected computerized patient record data can identify patients with probable undiagnosed cirrhosis as well as patients with known cirrhosis needing additional HCC surveillance. I found that the Fib-4 score may help identify patients with undiagnosed cirrhosis, especially in high risk subgroups, but may be falsely elevated in patients with advanced age or terminal illness.
Reduced Exercise Tolerance in Patients with Diastolic Dysfunction

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Background- Diastolic dysfunction (DDfx) is of increasing importance as an etiology of heart failure with preserved systolic function. It is known that patients with diastolic dysfunction and typical heart failure symptoms have decreased exercise tolerance. It has not been previously reported whether patients presenting with chest pain without a previous diagnosis of diastolic dysfunction will have abnormalities in their exercise tolerance. Methods- A retrospective chart review of 574 subjects admitted to a Chest Pain Diagnostic Unit (CDU) at UNC Hospitals in Chapel Hill, NC was performed. Subjects had a chief complaint of chest pain on admission and were determined to be low risk based on a predetermined algorithm. Results- Of the 574 patients admitted to the CDU, 410 patients had an echocardiogram as part of their evaluation. Twelve percent of this population (n=50) were identified as having DDfx by echocardiography while the remaining 88 percent did not (n=360). These two groups did not differ significantly in most historical characteristics including: sex, race, diabetes mellitus, tobacco use, family history of coronary artery disease, or insurance status. When the group with DDfx was compared to those without, they were found to be significantly older, 52.5 yrs vs. 46.8 yrs (p<0.001) and had a higher incidence of hypertension 60% vs. 31% (p<0.001). 326 of the 410 patients with echocardiograms had documented exercise times with ETT using the Bruce protocol. The group identified with DDfx was found to have a significantly lower exercise tolerance as indicated by time on the treadmill. Those with DDfx had a mean exercise time of 6.19 minutes vs. 7.67 minutes (p<0.001) for those without DDfx. There was no significant difference in stress test outcomes or cardiac catheterization between the two groups. Conclusions- The prevalence of DDfx in a young low risk CDU population is not insignificant. The statistically significant difference in exercise time found in this study suggests DDfx may lead to exercise intolerance early in the disease process.
Title: Ventilator-induced Lung Injury in A2A and A3 Adenosine Receptor-deficient Mice

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Background. Acute lung injury (ALI) is a major cause of morbidity and mortality in the intensive care unit for which there is no effective pharmacological therapy. Adenosine is a small molecule released during cell injury which has been proposed to influence ALI development. To study the mechanisms by which adenosine may influence the pathophysiology of ALI, A2A and A3 adenosine receptor-deficient mice were subjected to injurious mechanical ventilation.

Methods. After measuring baseline respiratory mechanics, wild type (wt), A2A-deficient (A2AKO), and A3-deficient (A3KO) C57BL/6 mice were ventilated for 3 hours using high tidal volumes (30cc/kg) and 0 PEEP. Pressure-volume curves, dynamic resistance and compliance, and oscillatory mechanics were measured every 30 minutes.

Results. After 3 hours of mechanical ventilation, the static compliance in 10 month, 5 month and 2.5 month old wt C57BL/6 female mice were respectively 66.6%±6% (p<0.001), 86%±5% (p<0.01) and 95%±4% (p=0.3) of basal level. The tissue elastance (H) in these groups were respectively 144%±15% (p=0.01), 105%±6% (p>0.05); and 115%±6% (p>0.05). Lung histology in these groups showed edema and neutrophil influx. A2AKO and A3KO mice showed no physiological differences from age-matched wt controls during the course of mechanical ventilation (static compliance after 3 hours: 86%±5% in wt vs. 85.7%±3% in A3KO (p=0.83)(5 months); 66.6%±6% in wt vs. 74.4%±13% in A2AKO (p=0.54)(10 months).

Conclusions. High tidal volume ventilation for 3 hours without PEEP produced physiologically significant ALI in C57BL/6 mice. VILI-induced changes in lung compliance were age-dependent. Although A3 and A2A receptors have been shown to mediate deleterious and protective signals by adenosine, respectively, in many pathophysiological processes, we found no impact of adenosine signaling through these receptors in experimental ALI.
Increasing incidence of eosinophilic esophagitis: A persistent trend after accounting for procedure indication and biopsy rate

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Background: Multiple studies document the increasing incidence of eosinophilic esophagitis (EoE). However, most are unable to control for the overall increase in endoscopy utilization, or to adjust for differences due to evolving diagnostic practices, for example performing biopsies of an endoscopically normal esophagus in patients with dysphagia.

Aim: To assess trends in the annual incidence of EoE, after taking into account changes in EGD volume, indication and biopsy rate over time.

Methods: We performed a retrospective study of all upper endoscopies performed at University of North Carolina (UNC) Hospitals between 1/1/2002 and 12/31/2006. Our health system provides both primary and tertiary care for gastroenterology patients. Cases of EoE, defined as ≥ 20 eosinophils/high-powered field, were identified from the UNC pathology database reporting system. The total number of upper endoscopies performed each year was recorded, as were the number of procedures performed for an indication of dysphagia, the number of esophageal biopsies performed overall, and the number of esophageal biopsies performed during procedures evaluating dysphagia. Incidence rates for each category were calculated. This study was approved by the UNC IRB.

Results: EoE was diagnosed in 2, 5, 9, 15, and 48 patients from 2002 to 2006, a 2400% increase over 5 years. During this time frame, the total number of upper endoscopies also increased from 2949 to 4228 (43%), the number of upper endoscopies for dysphagia increased from 516 to 797 (54%), the total number of endoscopies obtaining esophageal biopsies increased from 525 to 717 (37%), and the total number endoscopies during which esophageal biopsies were taken for evaluation for dysphagia increased from 91 to 134 (47%). The incidence of EoE per 1000 EGDs performed increased from 0.68 to 11.2 from 2002 to 2006, the incidence per 1000 procedures with esophageal biopsies performed increased from 3.8 to 67.8, and the incidence per 1000 biopsies in patients with dysphagia increased from 22.0 to 358.2.

Conclusions: The incidence of EoE has increased markedly at our center from 2002 through 2006. This increase far outstrips the relatively modest increases seen in procedure and biopsy volume, indicating that the increase is not due to detection bias alone.
Availability of experimental therapy outside of randomized clinical trials in oncology

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**Abstract:**

**Background:** Investigational cancer therapies may be available outside of trials, or “off protocol” (OPRx), with implications for patient safety, trial accrual, and access to care. Previous studies suggest OPRx is prevalent in oncology, but there is little consensus on when it should or should not be considered. We evaluated the scope and impact of OPRx through assessment of availability of the experimental arms of recent randomized trials (RCT), and evaluation of study outcomes and accrual. **Methods:** We conducted a Medline search to identify all English language phase III RCT of medical interventions in oncology over a 2 year period ending April 17th 2008. We determined availability of experimental interventions based on FDA approval for any indication. We limited assessment of accrual (time to trial completion, patients/month) to studies with US sites. Significance of results was assessed by Fisher’s exact test and unpaired t-test. **Results:** We identified 172 eligible RCT. The majority of RCT (108, 63%) evaluated drugs that were available OPRx at trial initiation, while an additional 19 (11%) trial drugs became available during the trial. 64 (55%) were available due to FDA approval for the same cancer in a different setting, 40 (35%) for a different cancer, and 12 (10%) for a non-cancer indication. 25% of trials were conducted at only US sites, 15% included US and international sites, and 60% were international only. Trials in which OPRx was available had slower time to completion compared to trials in which OPRx was unavailable (48 vs. 26 months, P=0.04) and a trend towards slower accrual (14.0 vs. 40.7 patients/month, P = 0.06). For the majority of RCT (66%), there was at least one grade III/IV toxicity that was greater in the experimental arm, for 47% the experimental interventions proved superior for 1 major outcome, and 27% demonstrated improvement in overall survival. These outcomes did not vary based on availability OPRx. **Conclusions:** The majority of recent oncology trials involve experimental regimens that are available outside of a trial. The safety and efficacy of novel interventions must be determined by trials but availability of OPRx may impact accrual. Guidelines are needed for OPRx in oncology.
During the course of residency, I have focused on caring for the underserved, both in our local community and in South America and Latin America. In November 2007, I spent a month working at a Christian, free medical clinic set among the mountains of Cusco, Peru. There I saw a broad range of acute and chronic conditions, as well as illnesses specific to a tropical climate. Issues ranged from care of children with congenital hypothyroidism and an atrioventricular septum defect, to newly diagnosing sporotrichosis and rheumatoid arthritis. Social issues are always forefront with the Spanish and Quechua-speaking population I served, and were a daily challenge. I further focused my efforts on basic clinic management, fundraising, and how to incorporate spiritual needs into a busy medical practice.

In late summer of 2008, I spent a week in Nicaragua stationed at a government health post located four hours and two rivers from the nearest hospital. In the RAAN, an often-neglected, poorer area of Nicaragua that was devastated by Hurricane Felix, I served as one of the senior physicians in the health post, supervising both UNC and Nicaraguan medical students. In the clinic, we saw children with malnutrition, subcutaneous emphysema, and probable pertussis, while in adults I treated a machete wound, acute asthma exacerbations, hepatocellular carcinoma, and a dislocated shoulder. Further, I assisted UNC medical students involved in public health projects that were being carried out in the region. In Leon, I served in an ambassadorial role for UNC, meeting with the CEO of the hospital and Dean of the medical school, as well as a number of the Nicaraguan public health scholars.
Improved clinical response from neoadjuvant taxane chemotherapy across breast cancer subtypes

Author Block: E. O. Jenkins MD, A. M. Deal, E. Burrows, A. Drobish, L. A. Carey MD; University of North Carolina Chapel Hill, Chapel Hill, NC.

Abstract:
Background: Adjuvant trials suggest that taxane (T) after doxorubicin and cyclophosphamide (AC) has little benefit in hormone receptor positive (HR+) patients compared to hormone receptor negative (HR-) patients, particularly if HER2 negative. Primary chemotherapy sensitivity is best determined from the neoadjuvant setting, therefore we sought to determine if HR+ primary tumors are less sensitive to taxane chemotherapy than HR- tumors.
Methods: Clinical stage II-III breast cancer patients from the UNC Neoadjuvant Database who received sequential AC and T chemotherapy were evaluated. Clinical and radiographic responses were determined after AC and again after T allowing intrapatient sensitivity comparison, and included RECIST-defined complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Hormone receptor status was determined at diagnosis, and subtypes included ER or PR positive, HER2 negative (HR+), ER and PR negative, HER2 positive (HER2+/ER-), and ER, PR and HER2 negative (TN). The ER or PR+, HER2+ group was too small for analysis. Patients who received neoadjuvant trastuzumab were excluded. Relationships of subtype and clinical response to AC and to T were assessed using Fisher’s exact test.
Results: 157 patients received neoadjuvant AC sequentially followed by T and were eligible for analysis. The majority of TN patients had PR to AC (56%), while the majority of HR+ patients had SD (54%). Of those with measurable disease after AC (n=127), a higher proportion of TN and HER2+/ER- patients had CR to T (43% and 45%, respectively) than HR+ patients (13%, p = 0.008 and p = 0.0393, respectively). While the majority of HR+ patients again had SD (52%), 42% responded to T.
Conclusions: Our data suggests that TN and HER2+/ER- patients benefit more from neoadjuvant taxane chemotherapy than HR+ patients, however HR+ patients clearly derived benefit from T administered after AC.
Title: Prognostic implication of NFkB and BCL3 activation in metastatic colorectal cancer.

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Background:
NF-κB is an anti-apoptotic transcription factor that has been shown to be a mediator of treatment resistance. The goal was to correlate the activation status of NF-kB (determined by IHC) in colorectal cancers (CRC) with clinical outcomes particularly overall survival in a group of patients with resected metastatic CRC. Differences in NF-kB expression between primary tumors (T) and metastatic deposits to liver (LM) and/or lymph nodes (LN) were also explored.

Methods:
Retrospective study of 23 patients who underwent surgical resection of metastatic CRC at UNC more than 8 years ago. Clinical data was collected under IRB approval. Tissue microarray (TMA), created from cores of normal mucosa (NM), T, LN and LM in triplicate from disparate areas of the blocks was scored by blinded pathologists. Activation of NF-kB was defined by nuclear expression (NE) of select components of NF-kB (p50, p65) and BCL3. An intensity score was generated by multiplying intensity (0-3+) by percent of positive tumor cells. Generalized estimating equations were used to note differences in intensity scores among NM & non-normal tissues. Cox regression models were fit to see if scores were significantly associated with overall survival.

Results:
BCL3-NE did not differ significantly between normal mucosa and tumor site. P65 NE was significantly higher in T and LM than NM (p<0.01, p<0.05 respectively). P50 NE was significantly higher for all tumor sites than for NM (PT and LN p<0.0001, LM p<0.01). NE in T for each of these components was strongly associated with survival: the increase in hazard for each half point in NE was 59% for BCL3, 45% for p65, and 50% for p50 (all p<0.05).

Conclusion:
Activation (NE) of canonical NFkB subunits p50 and p65 are both strongly associated with survival in the study suggesting NFkB as a prognostic factor in this disease. Primary tumor NE appears to be as good as or better than metastatic sites at predicting prognosis. BCL3 is a regulator of NFkB activity that has not been studied in CRC to date. Our study suggests that BCL3 may also be important in colorectal cancer.
**In Vitro Catecholamine Exposure Produces Variable Effects on the B7 Costimulatory Pathway in Human Monocytic Cells**

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**Rationale:** Catecholamines have been associated with immunomodulation of the adaptive immune system towards a TH2 response *in vitro*. We therefore examined the role of *in vitro* epinephrine (EPI) and norepinephrine (NE) exposure upon the B7 costimulatory expression of antigen presenting cells (APC) and CTLA4/CD28 on CD4+ T-cell populations by using human monocytic cell lines and human peripheral blood mononuclear cells (PBMC) as *in vitro* models.

**Methods:** THP1 monocytic cells and CD14+ cells from normal human PBMC were stimulated with lipopolysaccharide (LPS) and are incubated with physiologic stress levels (10^{-6} – 10^{-8} M) of EPI or NE for 24 hours. Similarly CD4+ human T-cells Cells were subsequently stained with fluorochrome-labeled antibodies directed against CD3, CTLA-4, CD28, CD80, CD86, and CD14 and were analyzed by flow cytometry for changes in percent fluorescence and mean fluorescence intensity (MFI).

**Results:** Exposure of THP1 to EPI *in vitro* at concentrations of 10^{-6}, 10^{-7} and 10^{-8} M significantly decreased mean CD80 from 42±0.7% to 11±0.44%, 19.1±2.0%, and 30.7±2.1% expression, respectively (p<0.01). In addition, CD86 expression increased with EPI at 10^{-6}, 10^{-7} and 10^{-8} M from 9.2±0.52% to 41±3.8%, 26.4±1.9%, and 15.74±1.8% expression, respectively (p<0.01). Similar results for mean CD80 and CD86 percent expression were observed for CD14+ cells from PBMC with a sample size of N = 6 and for NE when substituted for EPI. Due to technical limitations, changes in CD28 and CTLA-4 were not appreciated.

**Summary:** The data show that *in vitro* exposure to catecholamines significantly decreases %CD80 expression and significantly increases %CD86 expression in THP1 cells and human CD14+ APC. Previous studies have suggested an association between increased CD86 expression and TH2 activity. Thus, the data suggest that immunomodulation by catecholamines results in part by the variable effects of the B7 costimulatory pathway in APC.
Differential timing and patterns of recurrence among breast cancer subtypes.
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Abstract:

Background: At present, effects of heterogeneity among breast cancer subtypes on timing and patterns of relapse are not fully understood. We characterized timing and patterns of distant recurrence among subtypes in women followed from initial diagnosis of breast cancer.

Methods: 345 pts with newly diagnosed predominantly stage II-III breast cancer were treated with multiagent neoadjuvant therapy and subtyped by IHC: LumA (ER/PR+, HER2-); LumB (ER/PR+, HER2+); Basal (triple neg); HER2(HER2+,ER/PR-). Site-specific patterns of distant metastasis (DM) were examined among pts with single site of first DM. Sites of relapse were bone, CNS, viscera, lymph node, and soft tissue. Time to progression (TTP) was from date of initial diagnosis.

Results: 108 patients developed metastatic disease; 65 demonstrated a single site of first DM. Basal subtype was associated with greater CNS and visceral metastases and fewer bone metastases than other subtypes. LumA subtype was associated with fewer CNS and greater bone metastases than other subtypes. [See table]. Dichotomizing as Basal v. non-Basal, bone v. no bone and CNS v. no CNS revealed identical trends with increased significance (p=0.01-0.03). TTP trended toward Basals demonstrating earliest DM and LumA latest. Excluding pts with DM at diagnosis, TTP differed between Basals and non-Basals within viscera (p=0.002, n=14/21, median TTP=10/21); CNS (p=0.047, n=8/7, median TTP=11/27); and bone (p=0.002, n=8/31, median TTP=9/21).

Conclusion: Subtypes exhibit distinct timing and patterns of relapse within this largely homogeneous cohort of pts with predominantly locally advanced breast cancer, despite modern multiagent neoadjuvant therapy. Specifically, Basal cancers exhibit earlier recurrence and greater involvement of sites more difficult to treat than non-Basals. Within individual sites TTP differences between Basal and non-Basal tumors persist and are even more pronounced, suggesting that tumor microenvironment does not appear to be driving these differences.
Case Report: Acute Esophageal Necrosis
Abstract:
Acute esophageal necrosis (AEN) is a rare disorder of unclear etiology. It has been ascribed many names in the past, including “black esophagus” and necrotizing esophagitis. AEN typically occurs in elderly patients with significant predisposing co-morbid conditions. AEN is usually diagnosed endoscopically by visualizing a “black esophagus.” The most commonly reported etiologies are ischemia, massive gastroesophageal reflux from gastroduodenal obstruction, and infections such as herpes and Candida. Because of the rare nature of this condition, little is known about the pathogenesis of AEN. It has been proposed that the pathogenesis of AEN relates to the presence of a low-flow state. However other predisposing factors must contribute, since the esophagus is relatively protected from ischemic injury because of its rich arterial supply. Cocaine use has not previously been described as a risk factor for AEN. This report will describe the unusual case of a young man who developed AEN in the setting of cocaine abuse superimposed on diabetic ketoacidosis (DKA).

This case describes a previously unrecognized risk factor for AEN. His cocaine use, in synergy with his poorly controlled diabetes and frequent bouts of DKA, predisposed him to AEN. Most patients who develop AEN are older and have significant vascular disease. Although the patient described in the present case has a long history of diabetes, a known risk factor for accelerated vascular disease, he is young and has no other complaints that can be attributed to vascular disease. The intravascular volume contraction seen in DKA, possibly in concert with gastroesophageal reflux related to impairment in gastric emptying, predisposed him to an unusual occurrence that would have been unlikely in the absence of the vasoactive properties of cocaine.
BACKGROUND. Primary care has been defined by the Institute of Medicine as, “the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients, and practicing in the context of family and community.” This is no small task for which to train. Further, qualities that make an effective primary care physician have proven difficult to define or to teach. In the spirit of an apprenticeship, this experience is one of observing masterful primary care physicians in the course of their practice in an effort to glean the skills that make an effective primary care physician.

METHODS. For this qualitative study five physicians were observed in the course of their primary care practice. These physicians were selected based on their outstanding reputation at our medical center. Notes were taken on what the physician did and said during patient visits. A convenience sampling of patients were asked more directly what made their physician a good one. Physicians also made more explicit comments regarding their ethos of primary care. These notes and comments were collated and reviewed for unifying themes.

RESULTS. Among the many activities observed, four were identified that were common to these primary care physicians. The first, being present, was manifested in the committed partnership between patient and physician. There was a mutual sense of ownership. The care physicians expressed engendered further trust from their patients. The second, listening, was clearly described by more than one physician as paramount. Patients want to be heard and respected as they relate their experience and interpretations of it. The third activity, reassuring, was a central component to almost every visit. Physicians used their knowledge to allay specific fears and their confidence to dispel more general anxiety. Finally, I observed physicians sharing authority with their patients. The physician provided information and advice but the patient retained the role of decision maker.

DISCUSSION. Four key activities undertaken by primary care physicians emerged from this experience. These activities are used by the physician to build a relationship over which medical care may be transmitted. The physicians observed exercise these activities skillfully. They are rewarded by seeing their medical knowledge effect positive change in the lives of their patients. These observations could serve as the basis for future research into their impact on patient outcomes and physician satisfaction.
**Hemodialysis Reduces Pulse Pressure via Changes in Extracellular Volume**

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**BACKGROUND:** Pulse pressure, an inexpensive, frequently measured parameter in hemodialysis patients, has been shown to impact mortality risk. The contribution of volume overload to elevated pulse pressure remains under-explored. **METHODS:** In a single-center, retrospective study, we examined pre- and post-dialysis pulse pressures in 109 patients. Whole body bioimpedance spectroscopy to measure extracellular and intracellular volume was measured on 5 of these patients during the study period. **RESULTS:** Conventional hemodialysis, with a mean ultrafiltration volume of 3 liters significantly lowered pulse pressure (p=0.0002 for comparison between mean pre- and post-dialysis pulse pressure). Analysis by quartiles of ultrafiltration volume revealed a threshold of 2 liters, above which ultrafiltration had the greatest impact on pulse pressure (p=0.037 for comparison against ultrafiltration volume < 2 liters). Pre-dialysis pulse pressure was linearly related to the whole body bioimpedance extracellular volume measurements (F-statistic 5.84, p=0.023). **CONCLUSIONS:** Hemodialysis with an ultrafiltration volume of 2 liters significantly reduces pulse pressure. The effect on pulse pressure seems to be mediated by reductions in extracellular volume. Interventions beyond hemodialysis to minimize extracellular volume expansion, such as salt and fluid restriction, should provide benefits to the hemodialysis population.