Each recording underwent a second analysis at 2 weeks following the first analysis to evaluate reproducibility. The effect of data sampling (5-min segment/hour), the system sensitivity to detect 5 ms increase in Q–T, and the ability to assess circadian variation were also evaluated. **Results:** The fully AQA resulted in identical QT for the first and second analyses, but with obvious errors in Q–T measurements. Compared to the complete onscreen MOR, the 24-hour mean Q–T was longer with AQA (416 ± 41 vs 387 ± 30 ms, $p < .001$, $r = .3$). The reproducibility of automatic analysis with complete MOR was very good (Q–T: 387 ± 30 vs 387 ± 30 ms), coefficient of variation (CV) = 0.2%, $r = .986$, $p < .001$. The 5-minute mean Q–T intervals correlated well with the hourly mean Q–T intervals ($r = .994$, $p < .001$, CV = 1 ms) and both showed a similar circadian variation. The system was sensitive to detect a 5 ms change in Q–T intervals (5 ± 2 ms, CV = 0.6%, $r = .998$, $p < .001$). **Conclusions.** The fully automatic Q–T analysis is not an acceptable method, while the automatic analysis with MOR is a highly sensitive and reproducible method. Data sampling by analyzing 5-minute segments per hour is also sensitive and reproducible. The 12-lead digital Holter technique is suitable for Q–T analysis and may have advantage compared to the serial recordings of large number of standard 12-lead ECGs in the evaluation of drug effects on the Q–T interval.

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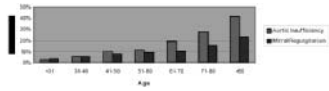
HOW PREVALENT IS UNSUSPECTED MITRAL AND AORTIC REGURGITATION?
G.T. Stefano, K. Fox, M. Schluchter, B.D. Hoit, University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH.
Introduction: Doppler echocardiography plays a critical role in identifying valvular insufficiency that may complicate the use of phen-fen and related drugs. However, the prevalence of unsuspected, preexisting valvular regurgitation in a large, heterogeneous population is poorly defined. **Methods:** 6,861 records were examined from consecutive individuals without known or suspected valve disease referred to the UHC echo laboratory for nonvalvular-related indications from 2001–2003. Mitral (MR) and aortic (AI) regurgitant severity was graded using a clinical composite of published 2-D, spectral, and color flow-Doppler methods. Multiple logistic analysis (*SPSS*, v13) was used to model clinical variables (age, gender, left ventricular ejection fraction [LVEF], body mass index [BMI], history of hypertension [HTN], LV hypertrophy [LVH], history of coronary disease [CAD]) and valvular morphology. **Results:** Prevalence estimates for moderate or greater MR and mild or greater AI as a function of age are shown in the figure. Female gender predicted MR (OR 2.12, 95% CI 1.78–2.53), but AI was gender neutral. Regurgitant severity increased with decreasing EF and BMI, and the presence of LVH, HTN, and CAD were not predictive. Regurgitation prevalence was significantly influenced by both nonspecific and specific valve abnormalities. **Conclusions:** The prevalence of moderate or greater MR and mild or greater AI is substantial, increases exponentially with age, and is predicted by commonly used clinical variables. These prevalence estimates should be considered when assessing the finding of unanticipated MR or AI on echocardiogram.



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NOVEL THERAPIES FOR RESISTANT FOCAL SEGMENTAL GLOMERULOSCLEROSIS: A PHASE I STUDY.
H. Trachtman,[1] A. Way,[1] D. Gipson,[2] A. Morris,[2] M. Mitchell,[2] M. Joy,[2] K. Bozik,[2] T. Greene,[3] J. Gassman,[3] [1]Department of Pediatrics, Division of Nephrology, Schneider Children's Hospital of North Shore-LIJ Health System, New Hyde Park, NY; [2]Department of Pediatrics, Division of Nephrology, University of North Carolina, Chapel Hill, NC; [3]Cleveland Clinic Foundation, Cleveland, OH.
Background: Primary focal segmental glomerulosclerosis (FSGS) accounts for 10–15% of pediatric and adult patients with end-stage renal disease. The prognosis is poor in patients who are unresponsive to corticosteroids. The NIDDK has initiated a multicenter, randomized clinical trial comparing the efficacy of cyclosporine versus the combination of mycophenolate mofetil and oral dexamethasone pulses in this patient cohort. Some prevalent patients will be ineligible because of prior treatment with the study drugs and others will fail to respond to the test medications. Their long-term outcome may be improved by therapeutic strategies that reduce progressive glomerulosclerosis and tubulointerstitial fibrosis. **Objective:** To conduct a phase I study to assess pharmacokinetic (PK) parameters, safety, and tolerance of novel agents that may reduce renal fibrosis in patients who are screen or treatment failures in the FSGS-Clinical Trial. **Patients and Methods:** Patients, age 2–42 years, GFR ≥ 40 mL/min/1.73 m^2, biopsy-confirmed FSGS, and who are screen or treatment failures in the FSGS-clinical Trial are eligible for inclusion. Two novel agents are being tested: (1) rosiglitazone, 3 mg/m^2, daily, PO, and (2) adalimumab, 24 mg/m^2, every other week, SC injection. The treatment phase is 16 weeks with PK evaluation prior to first dose and at end of treatment. DNA, plasma, serum, and urine samples will be obtained for storage in the NIDDK FSGS Biorepository. The study is being performed at sites with an NCRR-funded GCRC. **Results:** The Manual of Operations and Clinical Report Forms have been written and are posted on the FSGS study Web site (<www.fsgstrial.org>). IRB and GCRC approval has been obtained at 4 sites and is pending at 8 sites. One 18-year-old male adolescent has been enrolled. The target sample is 20 patients, 10 assigned to each agent. **Conclusion:** This phase I clinical trial represents an important step in improving the treatment of resistant FSGS. The results of this phase I studies will be incorporated into phase II clinical trials as part of a Phased Innovation Award. This project will establish an infrastructure that will facilitate the evaluation of novel agents that reduce renal fibrosis and improve the prognosis in patients with resistant primary FSGS.

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THE EFFECT OF LEFT VENTRICULAR ASSIST DEVICE THERAPY ON MYOCARDIAL FIBROSIS AND HEMODYNAMIC FUNCTION.
A.R. Travis, Z. Zhou, Y.J. Kang, S.C. Koenig, University of Louisville School of Medicine, Louisville, KY.
Purpose: Left ventricular assist device (LVAD) therapy has emerged as a viable means for bridging to transplantation in end-stage heart failure patients. There has been conflicting evidence for the effect of this therapy on myocardial interstitial fibrosis, which may play a role in LVAD-induced myocardial recovery. We seek to elucidate the relationship(s) between changes in fibrosis during LVAD support and the following factors: the type of device implanted (continuous vs pulsatile), the duration and mode of support, and the hemodynamic impact of device operation. **Methods:** Left ventricular pressure, aortic pressure (AoP), aortic flow, and VAD flow waveforms were recorded intraoperatively at the time of LVAD implant and explant. Myocardial tissue samples were obtained from the left ventricle at time of implant and explant. Collagen-stained tissue samples (1 pre- and 1 post-VAD slide for each of three patients) were analyzed for percent fibrosis. All methods were executed as part of an IRB-approved clinical study, with appropriate informed consent of all involved patients. **Results**: At present, three patients have undergone both LVAD implantation and explantation. Those patients receiving a continuous-flow LVAD (CF-LVAD, $n = 2$) demonstrated a reduction in percent fibrosis from time of LVAD implant to time of explant, whereas those receiving a pulsatile-flow LVAD (PF-LVAD, $n = 1$) demonstrated an increase in percent fibrosis. Furthermore, of the two continuous-flow patients, the patient with lower preimplant fibrosis demonstrated a greater reduction in percent fibrosis during the duration of support, evidenced by changes from 4.9 to 2.4% fibrosis and 9.8 to 9.0% fibrosis during LVAD support in these two patients. Hemodynamic recordings indicate a marked reduction in pulsatility of AoP with the CF-LVAD vs the PF-LVAD, which preserves physiological pulsatility. Also, following LVAD support in a CF-LVAD patient, baseline AoP was decreased from pre-VAD status. **Conclusions:** The type of device and level of preimplant fibrosis may play a role in determining the direction and magnitude of change in myocardial fibrosis due to LVAD support. Moreover, clear differences in the hemodynamic impact of these two devices might reflect an underlying mechanism for the different changes in fibrosis seen with these two device types. In future work, more complete hemodynamic data will be used to calculate indices of function that will be correlated with histological findings in order to strengthen our understanding of the relationship between structural and functional changes brought about by LVAD support.

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THE NUMBER OF LYMPHATIC CHANNELS DOES NOT AFFECT METASTASIS TO THE SENTINEL LYMPH NODE IN BREAST CANCER.
D.T. Tzou,[1,4] Y.-Y. Tan,[1] J. Hwang,[2] M. Florero,[1] C. Ewing,[1] L. Esserman,[1] S. Hwang,[1] E. Morita,[3] S.P.L. Leong,[1] Departments of [1]Surgery, [2]Radiology, Epidemiology, and Biostatistics, and [3]Nuclear Medicine, UCSF Medical Center at Mt. Zion and UCSF Comprehensive Cancer Center, San Francisco, CA; [4]Medical Student Research Program, University of Arizona College of Medicine, Tucson, AZ.
Introduction: The lymphatic channels are the routes by which cancer metastasizes. This study investigates whether a correlation exists between the number of channels and the likelihood of metastasis from the primary breast cancer site to the sentinel lymph node (SLN). Further, it examines the relationship of primary tumor characteristics with respect to these channels and SLN metastasis. **Materials and Methods:** This study was a retrospective review of a large database of 695 patients with primary invasive breast carcinoma undergoing selective sentinel lymphadenectomy at a single institution from November 1997 to June 2005. Only patients with successful preoperative lymphoscintigraphy (with either channels or nodes identified) and pathology-determined SLN status were included. There were 532 patients who fit our study criteria. **Results:** One hundred thirty-seven patients (24.8%) had one or more positive SLNs. A comparison of the percentages of positive SLN versus negative SLN for the different channel groups showed 0 channels, 25/137 (18.2%) with positive SLN vs 62/395 (15.7%) with negative SLN, $p = .4865$; 1 channel, 78/137 (56.9%) with positive SLN vs 244/395 (61.8%) with negative SLN, $p = .3182$; 2 or more channels, 34/137 (24.8%) with positive SLN vs 89/395 (22.5%) with negative SLN, $p = .5845$. No significant statistical relationship was found between number of lymphatic channels and frequency of SLN metastasis. The quadrant, type, and size of the tumor were also found to have no significant statistical relationship with the number of lymphatic channels. Metastasis was significantly associated with tumor size greater than 15 mm, poor tubular formation, and lymphovascular invasion. **Conclusion:** An increased number of lymphatic channels identified by preoperative lymphoscintigraphy does not appear to predict a higher likelihood of metastasis within the sentinel lymph node for all types of breast cancer. Metastasis to the sentinel lymph nodes is governed by the primary characteristics of the tumor rather than the number of lymphatic channels.

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INSULIN IS PRESENT IN HUMAN SALIVA AND NASAL MUCUS.
I. Velicu, R.I. Henkin, Taste and Smell Clinic, Washington, DC.
Measurement of insulin is an important marker for diabetes mellitus and other metabolic processes. Most insulin measurements are made in blood, although insulin has been previously found in saliva. Since we have described several of the proteins in both saliva and nasal mucus we wished to determine if insulin were present in these biological fluids and whether or not their measurements could be used to determine physiological and pathological processes. We measured insulin by colorimetric ELISA in a 96-plate assay in plasma and saliva in the fasted and nonfasted state and in nasal mucus in the nonfasted state in 60 patients with a variety of disease states. In plasma in the fasting state insulin was 17.1 ± 3.8 μIU (mean ± SEM), in saliva, 22.6 ± 1.9; in plasma in the nonfasting state insulin was 29.4 ± 4.4, in saliva 24.7 ± 2.4. In the fasted state, insulin in saliva was 32% higher than in plasma, whereas in the nonfasting state it was 15% higher. In the nonfasting state insulin in nasal mucus was 19.0 ± 2.2 or 35% lower than in plasma and 23% lower than in saliva. In patients with diabetes under biochemical control saliva insulin in fasting state was 62% higher than in plasma and in the nonfasting state it was essentially the same as in plasma. In patients with controlled diabetes in the nonfasted state insulin in nasal mucus was 47% lower than in plasma and 45% lower than in saliva. Relative changes in insulin in plasma, saliva and nasal mucus were also found in thin and obese subjects. These results indicate that insulin is present in both saliva and nasal mucus and physiological changes in this hormone can be measured in these fluids. Use of saliva and nasal mucus to monitor diabetes and other disorders offers noninvasive techniques to obtain data usually found in blood.

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IS METABOLIC SYNDROME AN INDEPENDENT RISK FACTOR FOR CORONARY ARTERY DISEASE?
A.J. Weissman, T.K. Bhatti, D. Hersh, G. Panagopoulos, M. Jimenez, N.L. Coplan, Lenox Hill Hospital, New York, NY.
Introduction: Metabolic syndrome consists of a constellation of metabolic abnormalities that include glucose intolerance, obesity, elevated blood pressure, and dyslipidemia. There are conflicting results in the medical literature as to whether the components of the metabolic syndrome, taken together or individually, can improve existing formulas such as the Framingham risk score for estimating the 10-year risk for cardiovascular disease. The purpose of this study was to determine if the metabolic syndrome is an independent risk factor for the presence of coronary artery disease (CAD). **Methods:** A total of 174 patients with

no known history of CAD who presented for elective cardiac catheterization were included in the study. These patients were evaluated for the presence (M+) or absence (M−) of the metabolic syndrome using the NCEP-ATP III criteria; CAD was defined as the presence of at least 70% stenosis in one of the three major coronary vessels or one of their significant branches or 50% stenosis in the left main coronary artery. The relationship between the metabolic syndrome and the presence of CAD was assessed by using the Pearson chi-square test. **Results:** Metabolic syndrome was present in 95/174 patients (54.6%), and M+ was significantly more likely to have CAD than M− (43% vs 28%, $p = .036$). There was no significant difference between M+/M− with regard to the mean Framingham risk score or for age, tobacco use, or family history of CAD; there was a significantly increased prevalence of DM (defined as fasting blood sugar > 126 mg/dL or DM Rx) in the M+ group ($p < .01$). Given that DM is a coronary risk equivalent, subgroups with DM and without DM were evaluated separately:

	Diabetic p = *NS*			*Nondiabetics* p = *NS*	
	No CAD	CAD		No CAD	CAD
M−	5	2	M−	52	20
M+	18	23	M+	36	18

Conclusion: Metabolic syndrome, independent of diabetes mellitus, is not a risk factor for obstructive coronary artery disease.

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METFORMIN-DIET AMELIORATES CORONARY HEART DISEASE RISK FACTORS AND FACILITATES RESUMPTION OF REGULAR MENSES IN ADOLESCENTS WITH POLYCYSTIC OVARY SYNDROME. M. Winiarska, D. Aregawi, G. Luo, J. Munjal, L. Sieve, P. Wang, C.J. Glueck, Cholesterol Center, Jewish Hospital, Cincinnati, OH.

In 35 postmenarchal adolescent females (17 ± 2 years, range 14–19) with polycystic ovary syndrome (PCOS), in a case-series prospective description, we assessed effectiveness of metformin-diet for 1 year for reduction of weight, insulin, HOMA insulin resistance (IR), cholesterol, triglycerides, and resumption of regular menses. By selection, all 35 girls met the 2003 consensus criteria for diagnosis of PCOS; all 35 had clinical hyperandrogenism, 37% were amenorrheic, and 60% oligomenorrheic. Pretreatment median weight was 82.7 kg, BMI 30.8 kg/m^2, and 19 (54%) girls had BMI > the CDC age-gender-specific 95th percentile (overweight). Calories (26% protein, 44% carbohydrate) were targeted to 1,500–1,800/day if BMI was < 25 or to 1,200–1,500/day if BMI was ≥ 25, along with 2,550 mg metformin. After 1 year on metformin-diet, median weight fell from 82.7 to 79.1 kg ($p = .009$); the median of the percent change was −5%. In 6 girls (17%) weight loss was ≥ 10 kg, in 8 (23%) was 5–10 kg, and in 11 (31%) was 0–5 kg. After 1 year on metformin-diet, fasting serum insulin 16.7 to 13.3 uU/mL ($p < .0001$), HOMA IR 3.41 to 2.74 ($p = .0004$), total cholesterol 164 to 151 mg/dL ($p = .002$), and triglyceride 103 to 85 mg/dL ($p = .006$). After 1 year on metformin-diet, reduction in insulin was associated with reduction in testosterone, $R^2 = 20\%$, $p = .008$. The percentage of cycles with normal menses rose from a pretreatment median of 8% to 100% after 1 year on metformin-diet, $p < .0001$. In 19/35 girls (54%) serum progesterone was ≥ 2.3 ng/mL (ovulatory range) at ≥ 1 of their follow-up visits. Because we did not randomize to diet-placebo vs diet-metformin, we cannot separate metabolic-endocrine benefits attributable to metformin alone or diet alone. The importance of the diagnosis of PCOS in adolescence lies in primary prevention of adult endocrinopathy, obesity, infertility, hyperinsulinemia, hypertriglyceridemia, type 2 diabetes, and increased cardiovascular morbidity-mortality. In adolescents with PCOS, metformin-diet reduces weight, insulin, IR, cholesterol, and triglycerides and facilitates resumption of regular menses. Successful reversal of endocrine and cardiovascular risks associated with PCOS soon after menarche should save the adolescent from the early and late stigmata of the syndrome and emphasizes the importance of the earliest diagnosis and treatment of PCOS in adolescence.

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GENE EXPRESSION PROFILING CAN DISTINGUISH PHYSIOLOGIC B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA CLONAL EXPANSIONS FROM PRELEUKEMIC AND LEUKEMIC CLONES. B. McCarthy,[1] X.-P. Wang,[2] S. Paul,[1] L. Goodwin,[2] A. Rawstron,[3] N. Chiorazzi,[1] [1]Laboratory of Experimental Immunology, The Feinstein Institute for Medical Research; [2]Molecular Genetics/Core Facility, The Feinstein Institute for Medical Research, Manhasset, NY; [3]Haematological Malignancy Diagnostic Service, Leeds General Infirmary, Leeds, United Kingdom.

B-cell chronic lymphocytic leukemia (B-CLL), the most common adult leukemia, is a clonal disease manifested by an absolute lymphocytosis. However, not all clonal lymphocytoses are B-CLL since monoclonal B-cell subpopulations can be detected in apparently healthy individuals using flow cytometry. This phenomenon is termed monoclonal B-cell lymphocytosis (MBL) or clonal lymphocytosis of uncertain significance (CLUS). CLUS has been identified in healthy volunteers with normal lymphocyte counts at a frequency of 3.5% and among first-degree relatives of B-CLL patients at a higher frequency (13.5%).* These findings suggest a transition from a B-CLL progenitor cell to overt B-CLL that occurs over time. Therefore, it would be useful, both therapeutically and mechanistically, to identify genes involved in this transition and to determine which cell population is vulnerable to leukemic progression. Using gene expression profiling, we and others have identified genes transcribed at significantly different levels between B-CLL patients and normal subjects. From these genes, a select panel was chosen, and the expression of these genes was quantified by rtQ-PCR from mRNA of patients with B-CLL as well as from normal subjects, with and without CLUS. Since the numbers of cells within the expanded clones from normal individuals with CLUS was limiting, in these instances we amplified mRNA using the Nugen OVATION RNA Amplification System. Using this rtQ-PCR approach, we accurately distinguished the clonal expansions of normal healthy subjects from those with CLUS and B-CLL. Therefore, expression of this gene panel may provide a novel way to identify genetic patterns that change during the transition from B-cell clonal expansions that occur physiologically from those that occur among preleukemic and leukemic B-cell populations.

*Rawstron et al. Blood 2002;100:635–9.

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PHENOTYPIC AND GENETIC CHARACTERIZATION OF A COMMON DENTOFACIAL DEFORMITY: MANDIBULAR PROGNATHISM. S.A. Frazier-Bowers,[1] C. Bui,[1] T.M. King,[2] W.R. Proffit,[1] [1]Department of Orthodontics, University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Department of Pediatrics, University of Texas Health Science Center, Houston TX.

Although substantial evidence has supported the role of heredity in Class III dentofacial deformity (mandibular prognathism), the relative contribution of genetic and environmental factors that led to this dentofacial problem, however, continues to be debated. The objective of this study is to elucidate the role of genetics in the development of the Class III trait. We therefore performed a detailed phenotypic characterization of both isolated and familial cases of Class III dentofacial deformity to address the fundamental hypothesis that the Class III trait is an inherited trait with distinctly segregating subphenotypes. We further propose to categorize individuals based on these subphenotypes that can ultimately be correlated with specific haplotypes. It should be possible to eventually understand the contribution of genetic factors in the various expressions of Class III dentofacial problems and to apply this knowledge to improved treatment approaches. To date 15 families with multiple affected individuals have been identified within the existing database of the Dentofacial Clinic at the University of North Carolina through which surgical patients are followed and through the records of the graduate orthodontic clinic and faculty practice. Cluster and principal components analyses were performed using cephalometric variables to compare familial and isolated Class III individuals. Finally, a genome-wide scan followed by linkage analysis was conducted to identify the chromosomal locus of the Class III trait for four families with significant power. The results indicated that there are five clusters, from 309 individuals, representing clinically distinct phenotypes. A pedigree "analysis by inspection" revealed that the broad Class III phenotype is inherited as an autosomal dominant trait in 15 families analyzed. Linkage analysis reveals a locus suggestive of linkage with the Class III trait. We therefore conclude that the Class III dentofacial deformity is largely under strict genetic control and is made up of distinct subphenotypes.

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EPIDEMIOLOGY OF PEDIATRIC MASTOIDITIS IN THE PRE– AND POST–PNEUMOCOCCAL VACCINE ERAS. M.G. Roddy, S. Glazier, D. Agrawal, Children's National Medical Center, Washington, DC.

Background: Studies have shown that the epidemiology, clinical course, and bacterial pathogens for acute otitis media (AOM) have changed in the seven-valent conjugate pneumococcal vaccine (CPV) era. We hypothesize similar changes with mastoiditis, which may require an adjustment of empiric antibiotic therapy. **Objectives:** To describe the epidemiology, etiology, and clinical course of mastoiditis in the pre-CPV (1/95–12/00) and post-CPV (1/01–4/05) eras. **Methods:** We performed a retrospective chart review of patients admitted to a tertiary care pediatric hospital with a discharge diagnosis of mastoiditis from 1/95–4/05. Etiological agents were determined by culture results from mastoid fluid, middle ear fluid, and/or blood. **Results:** 139 charts were reviewed, with 78 pre-CPV and 61 post-CPV. Patient age ranged from 30 days to 18.2 years (median 4.4 years). Myringotomy tubes were placed in 60 (43%), and mastoidectomy was performed in 59 (42%). Etiological agents were determined in 68 (49%). The most common bacterial isolates from the 34 pre-CPV cases were *S. pneumoniae* (15), *P. aeruginosa* (10), *S. aureus* (6), and *S. pyogenes* (1) and from the 34 post-CPV cases were *S. pneumoniae* (12), *S. pyogenes* (8), *P. aeruginosa* (5), and *S. aureus* (5). *S. pneumoniae* was implicated in 15/34 (44%) of pre-CPV cases versus 12/34 (35%) of post-CPV cases ($p = .46$). Acute mastoiditis was diagnosed in 106/139 (76%), and chronic mastoidits (defined as ≥ 3 weeks of symptoms) was diagnosed in 33/139 (24%). *S. pneumoniae* was more likely to be implicated in acute vs chronic mastoiditis (30% vs 7%, $p = .06$), and *P. aeruginosa* was more likely to be implicated in chronic vs acute mastoiditis (40% vs 10%, $p = .003$). Sixty-seven percent of pre-CPV *S. pneumoniae* isolates were pansensitive compared to 33% in the post-CPV era ($p = .09$). Seven percent of pre-CPV *S. pneumoniae* isolates were resistant to ceftriaxone compared to 25% in the post-CPV era ($p = .18$). In the post-CPV era vs pre-CPV era, treating clinicians were more likely to choose empiric parenteral combination therapy with ceftriaxone (38% vs 6%, $p < .0001$). **Conclusion:** In this post-CPV era and in chronic mastoiditis, clinicians must consider choosing broader-spectrum initial antibiotic coverage than ceftriaxone alone.

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INHIBITING GLUCONEOGENESIS PREVENTS THE EFFECTS OF FREE FATTY ACIDS ON GLUCOSE EFFECTIVENESS. S. Koppaka, D.E. Lee, P. Kishore, J. Tonelli, M. Hawkins, Albert Einstein College of Medicine, Bronx, NY.

Glucose effectiveness, the ability of hyperglycemia to suppress endogenous glucose production (EGP), is lost in type 2 diabetes mellitus (T2DM). Free fatty acids (FFA) modulate the effectiveness of glucose to suppress EGP, and increased FFA contribute importantly to the loss of glucose effectiveness in T2DM. Elevating FFA levels in nondiabetic subjects increases gluconeogenesis (GNG) and impairs glucose effectiveness. However, inhibiting GNG alone does not decrease EGP under normoglycemic conditions because of compensatory increases in glycogenolysis (autoregulation). Since hyperglycemia inhibits glycogenolysis, we hypothesized that inhibiting GNG in the presence of hyperglycemia would decrease EGP and prevent the negative impact of FFA on glucose effectiveness. To determine the impact of inhibiting GNG in the presence of elevated FFA, EGP ([3–3H]-glucose) was measured during three separate 7h normoglycemic/hyperglycemic 'pancreatic clamp' studies in $n = 7$ nondiabetic subjects (1F/6M; age = 45 6 5 years; BMI = 28 6 3.0 kg/m^2). Following an initial 210-minute interval of euglycemia (5 mM), blood glucose levels were raised to hyperglycemic levels (10 mM) from $t = 210$–420 minutes. The first pancreatic clamp study was a baseline study with saline infusions (Lip2/Et2) in which hyperglycemia suppressed EGP by 61%. Lipid emulsion (Liposyn 20%) was infused throughout the second and third study types (Lip+ and Lip+/Et+) to increase FFA to T2DM levels (≈500 mM). After raising plasma FFA to T2DM levels, suppression of EGP by hyperglycemia was impaired in Lip+ (34% suppression) and rates of GNG increased by 67% to 1.49 6 0.14 mg/kg.min ($p = .03$). In addition to Liposyn, ethanol (Et) was infused during hyperglycemia in the third study type (Lip+/Et+) to rapidly inhibit GNG (measured by deuterated water) by {223}80%. GNG inhibition significantly enhanced suppression of EGP by hyperglycemia (65.8% decrease, $p = .004$ vs Lip+) and thus restored glucose effectiveness ($p = .6$ vs Lip2/Et2). We conclude that increased FFA impair the ability of glucose to suppress EGP in large part due to FFA-induced stimulation of GNG. Inhibiting GNG with ethanol restored glucose effectiveness despite increases in FFA up to T2DM levels. Thus, inhibiting GNG is a potential approach to regulate glucose production in T2DM.