ABSTRACTS

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Adverse Drug Reactions/Drug Interactions

1. Incident reports do not reflect antimicrobial adverse events in a hospital setting. *Katherine Y. Yang, Pharm.D.*, B. Joseph Guglielmo, Pharm.D.; University of California, San Francisco, San Francisco, CA.

BACKGROUND: According to the recent report by the U.S. General Accounting Office, an individual medication error (ME) rarely causes adverse drug events (ADE). However, because so many drug doses are given, an estimated quarter to half of all ADE result from ME. Incident reports (IR) are the most widely utilized mechanism of reporting ME. A significant consumption of resources is associated with the evaluation and summarization of IR. The value of IR in documenting ADE, particularly due to antimicrobials, has never been evaluated.
METHODS: All antimicrobial-related IR from 1999 were collated. Only those in critical care areas (ICU) were included. IR were assessed for impact on patient outcomes and nursing/physician response to IR.
RESULTS: Two hundred twenty antibiotic IR were reported (calculated rate: 1.08 per 100 hospital admissions). Twenty-five percent of the incident reports occurred in the ICU. Forty percent of ME were due to omission of antimicrobial administration; 24% were due to incorrect timing of administration. Extra doses encompassed 22% of all IR. Patient harm, as assessed by the nurse, was documented on the IR 2.3% of the time. However, follow-up review documented additional instances of patient harm. The physician was notified of the ME 77% of IR; physician interventions were made in response to the IR 27% of the time. Fifty percent of the interventions were considered inappropriate or unnecessary.
CONCLUSION: IR do not adequately capture significant ADE due to ME and are associated with consumption of resources. Interventions made to rectify the ME may be inappropriate or unnecessary.

2. Provider-identified adverse drug reactions in HIV patients: prevalence and characterization. *Mark J. Shelton, Pharm.D.*, Yuliya Ritterman, Pharm.D, Lori D. Esch, Pharm.D., Sue Ksiazek, R.Ph., Sue Rozek, Pharm.D., Ross G. Hewitt, M.D.; Erie County Medical Center, University at Buffalo, Buffalo, NY.

PURPOSE: This study evaluated provider-identified adverse drug reactions (ADRs) in an urban HIV clinic.
METHODS: Routine patient progress notes of patients seen between October 1, 1999, and December 31, 1999, were reviewed to document acute (new onset), provider-identified ADRs. Adverse drug reaction description, suspected agents, and management schemes (monitor condition, add symptomatic medications, dose reduction, or discontinuation of suspected medications), were noted, in addition to concurrent medications.
RESULTS: A total of 90 acute ADRs were identified during 1050 (8.6%) visits for 80 patients. HIV-RNA and CD_4 counts at the time of ADR spanned wide ranges, with 46% < 500 HIV-RNA copies/ml and 53% CD_4 > 200 cells/mm^3. Peripheral neuropathy was the most common ADR (n=20), followed by diarrhea (n=14), nausea (n=9), lipodystrophy (n=6), rash (n=5), and others (n<5 each). Monitoring of condition and prescribing of symptomatic medications were the most common responses (n=31 each), followed by drug discontinuation (n=23) and dose reduction (n=5). The most common medications implicated by name were nelfinavir (n=10), ritonavir (n=7), didanosine (n=6), and abacavir (n=5). Antiretrovirals as a class were implicated in another 10 instances. Comparisons of demographics, medication profiles, and surrogate marker responses between subjects with and without ADRs will be reported.
CONCLUSION: New onset ADRs were identified by providers occurred at approximately 9% of visits, although unidentified and unacknowledged ADRs were not addressed. The frequent use of symptomatic medications (31/90 instances) is likely to increase further the medication burden imposed upon HIV patients. A formalized ADR reporting system and management algorithm should be implemented in this population.

3. Lack of drug-interaction with combination of linezolid and monoamine oxidase inhibitor-interacting medications. *Charlotte S. Hartman, Pharm.D.*, Timothy S. Leach, M.D., Wesley M. Todd, M.D., Barry Hafkin, M.D.; Antibacterial Development, Pharmacia Corporation, Kalamazoo, MI.

PURPOSE: Linezolid, the first oxazolidinone, has broad activity against susceptible and resistant Gram-positive infections. Based on preclinical and phase I data, linezolid (LZD) is a weak, reversible monoamine oxidase (MAO)-inhibitor. Vital sign data were analyzed for phase III patients receiving both LZD and a medication known to interact with classic MAO-inhibitors.
METHODS: Vital signs from baseline (BL) and day 3 (D3) were compared within and between treatment groups for phase III patients receiving an MAO-interacting medication ≤ 24 hours before the first dose of study drug and continuing until at least D3. MAOI-interacting medications included sympathomimetics, vasopressors, select analgesics, selective seratonin reuptake inhibitors, cyclic and miscellaneous antidepressants, and others.
RESULTS: For patients with vital sign measurements at BL and D3, 271 LZD and 251 comparator patients received an MAOI-interacting medication. Baseline temperature (Centigrade), blood pressure (mm Hg), and pulse (per minute) were similar for LZD patients (37.5, 129/70, and 94) vs comparator patients (37.6, 127/71, and 92). D3 vital signs were analyzed for changes that may indicate a potential MAOI-related drug interaction. No difference between treatment groups was detected. D3 vital signs in the LZD group were 37.0, 130/72, and 85.4 vs 37.0, 128/71, and 86 in the comparator group (all p values > 0.17). As expected and consistent with resolution of infection, temperature and pulse were significantly lower at D3 than at BL within both groups ($p \leq 0.0001$).
CONCLUSION: Patients receiving LZD in combination with an MAOI-interacting medication had similar changes in vital signs relative to comparator, suggesting a lack of clinically significant MAO inhibition by LZD.

4. Analysis of adverse drug events in the intensive care unit. *Sandra L. Kane, Pharm.D.*, Joseph F. Dasta, M.S., Phillip J. Schneider, M.S., Mark E. Boye, M.Ph., Charles H. Cook, M.D.; Ohio State University, Columbus, OH.

PURPOSE: To determine the incidence and severity of adverse drug events (ADEs) in the intensive care unit (ICU) using adverse medical events (AMEs) as the identification tool. Secondary objectives include identifying both medication errors and drugs causing ADEs.
METHOD: A clinical pharmacist prospectively reviewed patient records daily for AMEs during a 3-month period. AMEs included: abnormal electrolytes, bleeding, diarrhea, elevated creatinine, hepatic dysfunction, hypotension, rash, seizures, and thrombocytopenia. AMEs caused by medications were considered ADEs based on Naranjo's criteria and were assessed for medication errors. The severity of ADEs was ranked using a published five-point scale.
RESULTS: Five hundred ninety patients (mean age 57 ± 17 years) with mean lengths of stay of 4.6 ± 7.1 days were evaluated. Of the 2876 AMEs (4.7 ± 8.5/patient) 184 (6.4%) were ADEs and 36 patients experienced > 1 ADE. ADEs were categorized as 107 (58%) definite, 50 (27%) probable, and 27 (15%) possible. Ninety-one (49%) ADEs required additional monitoring, 60 (33%) required additional laboratory tests or drug discontinuation, and 26 (14%) required treatment. The most common type of ADE (55%) was abnormal serum electrolytes caused by diuretics or excessive electrolyte replacement. Using abnormal serum potassium as an indicator of ADEs was specific for 21% of cases. Five (3%) ADEs were associated with an error. Only six ADE reports were generated by the voluntary reporting system.
CONCLUSION: AMEs frequently occur in ICU patients and are mechanisms of identifying ADEs, especially electrolyte disturbances. ADEs are difficult to identify, voluntary reporting systems underestimate occurrences, and more accurate surveillance systems are needed.

5. Cocktail purpura and OTC quinine as causes for severe blood dyscrasias: two unusual case presentations. *Dorothea C. Rudorf, Pharm.D., M.S.*; Massachusetts College of Pharmacy and Health Sciences; Beth Israel Deaconess Medical Center, Boston, MA.

PURPOSE: The purpose of presenting these case reports is to alert health care professionals of potentially unrecognized severe hematological adverse drug reactions associated with quinine.
METHOD: Between September 1998 and April 2000 two patients were identified who had developed severe blood dyscrasias. One patient, a 55-year-old male, presented with petechiae and purpura on his trunk and extremities, blood blisters and gum bleeding in his mouth, and was found to have significant thrombocytopenia (platelet count of < 5,000 mm^3). The other patient, a 78-year-old woman presented with rapid onset of shortness of breath, fever, and constitutional symptoms and was diagnosed with

disseminated intravascular coagulopathy of unknown origin.
RESULTS: Hematological adverse reactions of quinine have been described in the literature. In both patients, quinine was initially not identified as probable and highly likely, respectively, cause for the observed complications. Only careful history taking revealed that the male patient had ingested two to three glasses of gin and (quinine containing) tonic water (cocktail purpura) prior to admission, and also 1-2 weeks before with similar signs and symptoms that disappeared after 3 days. The woman, a physician, remembered having taken one tablet of 200 mg quinine sulfate for leg cramps just hours prior to the onset of her symptoms. Quinine intake on one other occasion was uneventful. Both patients recovered and could be discharged after a few days.
CONCLUSION: Quinine-containing products may not be recognized, and potential blood dyscrasias after their ingestion may not be identified or underestimated in a clinical setting. Health care professionals need to be aware of these problems, and careful history taking and patient information is essential.

Analgesia

6. Saliva as an alternative to blood samples in acetaminophen monitoring. *Tina W. Hahn M.S.*, Mette Rasmussen Ph.D.; The Royal Danish School of Pharmacy, Copenhagen, Denmark.

PURPOSE: A correlation between acetaminophen concentrations in serum and saliva has been shown in volunteers but is not confirmed in adult or pediatric postoperative patients.
METHODS: In four studies (I-IV) secondary purposes were to determine the saliva-serum correlation of acetaminophen in postoperative patients. The following patients were studied subsequent to different routes of administration: (I) Twenty-four women after one rectal (2 g) and two oral (2 x 1 g tablets) doses; (II) Forty-eight women after intravenous injection of 10-40 mg/kg of propacetamol (pro-drug to acetaminophen); (III) Forty women on a fixed postoperative dosing schedule 1 g q6h (regular tablets) or 2 g q12h (sustained release); (IV) Twenty-three children (9 weeks-11 years) following a peri- and postoperative rectal dosing schedule of 25 mg/kg q6h. Scheduled coincident saliva and serum samples were obtained using a cotton wool swab (Salivette®) for collection of saliva and venous blood samples were drawn from a peripheral vein. All samples were analyzed by high performance liquid chromatography.
RESULTS: The correlation coefficients (r) between saliva and serum calculated by linear regression were $0.98_{rectal(I)}$ (n=61) and $0.95_{oral(I)}$ (n=53), 0.95 (n=147), 0.87 (n=88), and 0.91 (n=32) for studies I-IV respectively (n represents number of paired samples). The correlation was statistical significant in all studies (P_{slope}<0.05). The saliva/serum-ratios were (mean ± SD) 0.99 ± $0.24_{rectal(I)}$ and 1.00 ± $0.11_{oral(I)}$, 1.04 ± 0.29, 1.12 ± 0.30, and 0.92 ± 0.26 for studies I-IV, respectively.
CONCLUSION: Saliva sampling represents a non-invasive method which is not associated with pain and the risk of infection present in blood sampling. The good correlation between saliva and serum concentrations of acetaminophen found in both adult and pediatric patients in our studies, suggests that saliva samples can replace blood samples in assessment of acetaminophen concentrations in the postoperative period.

7. Pharmacokinetics of rectal acetaminophen (paracetamol; 25 mg/kg) after repeated dosing in children. *Tina W. Hahn M.S.*, Steen W. Henneberg, M.D., Rolf J. Holm-Knudsen, M.D., Kirsten Eriksen M.D., Søren. N. Rasmussen, M.S., Mette Rasmussen, Ph.D.; The Royal Danish School of Pharmacy, Copenhagen, Denmark; Copenhagen University Hospital, Copenhagen, Denmark.

PURPOSE: There is very limited knowledge of the pharmacokinetics after repeated rectal dosing of acetaminophen in children and it is unknown whether the doses recommended cause accumulation, resulting in supratherapeutic serum concentrations. A good correlation between serum and saliva concentration has been established in adult patients, but it remains to be shown in children.
METHODS: Twenty-three children (9 weeks to 11 years) were given acetaminophen suppositories 25 mg/kg every 6 hours up until 5 days after major surgery and serum and saliva concentrations were measured by high performance liquid chromatography (HPLC). Saliva sampling was used as a means of extending the collection period of pharmacokinetic data to several days.
RESULTS: There was a good correlation (r=0.91, p<0.05) between saliva and serum concentrations. A one compartment linear model with first-order elimination and absorption and lag-time was fitted to the data (ADAPT II). At steady state the average concentration (C_{ss}) was 15.2 ± 6.8 mg/L. The time to reach 90 % of the steady state concentration ($T_{Css\ (90\%)}$) was 11.4 ± 8.6 hours. Body weight, age and body surface area (BSA) were well correlated (p<0.05) with clearance (CL/F) and apparent volume of distribution (V_d/F).
CONCLUSION: The good correlation between serum and saliva concentrations suggests that saliva samples can replace blood samples in assessment of acetaminophen concentrations in children in the postoperative period. There was no evidence of accumulation leading to supratherapeutic concentrations while following this dosing schedule for a mean of 2-3 days. A rectal loading dose of 35 mg/kg, to avoid subtherapeutic concentrations at the beginning of treatment, followed by 25 mg/kg rectally every 6 hours is recommended.

Cardiology

8. The study of cardiovascular risk intervention by pharmacists (SCRIP): a multicenter, randomized trial of the effect of community pharmacist intervention on cholesterol risk management. *Ross T. Tsuyuki, Pharm.D., B.S., M.S.*, Jeffrey A. Johnson, B.S.P., Ph.D., Koon K. Teo, Ph.D., M.B., Scot H. Simpson, Pharm.D., B.S.P., Margaret L. Ackman, Pharm.D., B.S., Rosemarie S. Biggs, B.Pharm., Andrew J. Cave, M.D., M.Cl.Sc., Wei-Ching Chang, Ph.D., Vlad Dzavik, M.D., Karen B. Farris, B.S., Ph.D., Donna Galvin, B.S., William Semchuk, B.S.P., M.S., Pharm.D., Jeff G. Taylor, B.S.P., Ph.D.; University of Alberta, Edmonton, AB, Canada.

Despite strong evidence for the efficacy of cholesterol lowering, there is a deficiency in its real world application.
PURPOSE: To determine the efficacy of pharmacist intervention on cholesterol risk management in patients at high risk for coronary heart disease (CHD) events.
METHODS: Multicenter study of 1000 patients randomized to intervention or usual care. Patients included were those at high risk of vascular events (those with atherosclerotic disease, or diabetes with another risk factor). Intervention patients received education on CHD risk factors, a point-of-care cholesterol test, and, if necessary, referral to their physician. Pharmacists completed and faxed a physician contact form identifying the patient's risk factors and suggestions for assessment/treatment. Patients were contacted after 2, 4, 8, 12 and 16 weeks for educational reinforcement and end point determination. Usual care patients received the brochure and general advice only, with minimal follow up. The primary end point was a composite of measurement of a complete fasting cholesterol panel by the physician, or addition of cholesterol-lowering medication, or modification of previous cholesterol medication.
RESULTS: The external data committee recommended early study termination due to benefit. A total of 675 patients were entered; this preliminary analysis is based upon 565 patients. Average age was 64, and 39% were female. The primary end point was reached in 58% of intervention patients, compared to 30% in usual care (p<0.001). Each component of the primary end point was also significantly improved.
CONCLUSIONS: SCRIP demonstrates the value of community pharmacists in improving the management of cholesterol risk.

9. An economic comparison of amiodarone versus placebo in the prevention of atrial fibrillation after open heart surgery. *Prabashni Reddy, Pharm.D.*, Alisha B. Dunn, Pharm.D., James P. Tsikouris, Pharm.D., C. Michael White, Pharm.D., Satyendra Giri, M.D., Kathy Felton, R.N., Linda-Freeman Bosco, R.N., Jeffrey Kluger, M.D.; University of Connecticut, Storrs, CT; Northeastern University, Boston, MA; Hartford Hospital, Hartford, CT.

PURPOSE: In the randomized, double-blind, placebo-controlled atrial fibrillation suppression trial, oral amiodarone significantly reduced the incidence of atrial fibrillation (AF) by 41% in patients over 60 years undergoing open heart surgery (OHS). The purpose of this analysis was to compare the short-term hospital costs between the amiodarone and placebo groups.
METHODS: The economic analysis was conducted from a hospital perspective. Costs were determined from the time of surgery until hospital discharge. Hospital charges per cost center were obtained from the hospital claims management database. By applying hospital-derived cost-to-charge ratios, charges were converted to costs. Professional fees were not included.
RESULTS: The average total costs per patient were reduced by $552 in the amiodarone group but this did not achieve statistical significance (p=0.63). The cost comparison between the amiodarone and placebo groups is delineated below.

Cost Center	Placebo (n=100)	Amiodarone (n=120)
Board and care	3637 ± 1985	3649 ± 2223
Medical and surgical supplies	3330 ± 2380	2855 ± 1940
Intensive care unit	2505 ± 3132	2404 ± 3487
Operating room	2464 ± 1002	2373 ± 965
Intravenous therapy [a]	1170 ± 1098	1206 ± 1407
Laboratory	789 ± 620	781 ± 703
Pharmacy[b]	667 ± 599	744 ± 1418
Anesthesia	562 ± 201	534 ± 223
Respiratory therapy	439 ± 694	469 ± 843
Cardiac catheterization laboratory	201 ± 573	202 ± 384
Radiology	146 ± 217	144 ± 187
Amiodarone	0 ± 0	23 ± 10[c]
Miscellaneous[d]	215 ± 313	190 ± 432
Total costs	16126 ± 8043	15574 ± 9826

[a] including blood products; [b] excluding amiodarone; [c] p<0.05 versus placebo; [d] includes physical therapy, vascular laboratory, electrocardiogram, electro-encephalogram, nuclear imaging, speech therapy, CT Scan, pulmonary function testing, recovery room, emergency room, gastrointestinal service, hemodialysis

CONCLUSION: Despite reducing AF incidence after OHS, oral amiodarone prophylaxis does not significantly lower short-term hospital costs.

10. Amiodarone increases time to first implantable cardioverter defibrillator therapy. *Sherri L. Alexander, Pharm.D.,* Wafa Y. Dahdal, Pharm.D., William T. Katsiyiannis, M.D., Marye J. Gleva, M.D.; St. Louis College of Pharmacy; Washington University School of Medicine, St. Louis, MO.

PURPOSE: We evaluated the effect of amiodarone treatment on time to first appropriate implantable cardioverter defibrillator (ICD) therapy in patients with ventricular tachycardia/fibrillation (VT/VF).
METHODS: We performed a retrospective study of patients with a left ventricular ejection fraction < 40% who had undergone an ICD implantation between December 1996 and January 2000. Patients were divided based on presence or absence of amiodarone therapy at time of ICD implantation. We defined appropriate ICD therapy as pacing or shock termination of VT/VF. A Cox proportional hazard model was used to compare the time to first ICD therapy between the two groups.
RESULTS: A total of 141 patients were included with a mean follow up of 13.3 months. At ICD implantation, 48 patients (34%) were on amiodarone. Our results demonstrated a significant increase in the time to first appropriate ICD therapy for the amiodarone group. At 1 and 2 years, 86% and 80% of patients on amiodarone were free of ICD therapy vs 71% and 62% of patients not on amiodarone, respectively, ($p<0.0001$).
CONCLUSIONS: ICD therapy is the foundation of current treatment for life-threatening ventricular arrhythmias. Concomitant amiodarone therapy was present in a third of our population. Amiodarone significantly increases time to first ICD therapy at 1 year and this effect persists at 2 years.

11. Increased cardiac sympathetic neurotransmission in cardiac hypertrophy. *Wendell S. Akers, Pharm.D., Ph.D.,* Victoria L. English, B.S., Lisa A. Cassis, Ph.D.; University of Kentucky, Lexington, KY.

HYPOTHESIS: Pressure overload induced by aortic constriction increases norepinephrine (NE) spillover from sympathetic nerve terminals innervating the rat left ventricle.
METHODS: Experiments were performed utilizing a tissue slice system to examine alterations in NE uptake and spillover from rat left ventricle (LV) slices following 10 days of pressure overload induced by abdominal aortic constriction. Kinetic parameters (K_m, V_{max}) for NE uptake into LV slices from sham-operated (SO) and aortic-constricted (AC) rats were determined by incubating slices with increasing concentrations of unlabelled NE and a fixed concentration of *l*-[^{3}H]-NE for 30 minutes. Norepinephrine spillover was examined in LV slices preloaded with *l*-[^{3}H]-NE. The effect of neuronal uptake and presynaptic α_2 receptor inhibition on evoked [^{3}H]-overflow following electrical stimulation was examined by superfusing LV slices from AC and SO rats with Krebs buffer containing desipramine and yohimbine, respectively. The isolated heart preparation was used to examine alterations in β-receptor responsiveness to isoproterenol.
RESULTS: The V_{max} for [^{3}H]-NE uptake was reduced by 46% in LV slices from AC rats. Moreover, evoked [^{3}H]-overflow from LV slices of AC rats was increased by 50% ($p<0.05$) compared to SO rats, which remained evident in the presence of desipramine. Differences in evoked [^{3}H]-overflow between AC and SO rats were augmented in the presence of yohimbine. Additionally, the contractile response to isoproterenol was reduced by 35% ($p<0.05$) in AC rats.
CONCLUSION: These results demonstrate that pressure overload results in increased cardiac sympathetic neurotransmission associated with reduced efficiency of NE uptake, enhanced NE release and β-receptor desensitization.

12. Efficacy and safety of a formulary statin conversion program: prospective validation of the Department of Defense pharmacoeconomic guideline. *Allen J. Taylor, M.D.,* Karen A. Grace, Pharm.D., Jennifer R. Swiecki, Pharm.D., Richard S. Hyatt, M.S., Henry J. Gibbs, B.S., Munazza A. Sheikh, M.D., John Spain, M.A., Pharm.D., Aatif M. Sheikh, Pharm.D., Kent W. Maneval, Pharm.D., David L. Jones, M.D., MPH; Walter Reed Army Medical Center, Washington, D.C.

PURPOSE: There are few data on the safety and efficacy of statin formulary conversion programs. The Department of Defense (DOD) Pharmacoeconomic Center (PEC) recently initiated a DOD system-wide contract for cerivastatin and simvastatin, necessitating conversion of the entire DOD beneficiary population to these agents.
METHODS: Prospective study in 980 volunteer DOD beneficiaries (mean age 68, secondary prevention 41%, diabetes 25%) receiving statin therapy (without concurrent gemfibrozil use). Patients were switched to cerivastatin or simvastatin using a conversion algorithm. Efficacy (lipid values, NCEP goal adherence) and safety (LAE, myositis) were evaluated.
RESULTS: Patients were converted from primarily pravastatin and atorvastatin to cerivastatin (92.8% [0.4 mg/d – 80.6%]). On baseline lipids, 69% of patient were at or below their NCEP target LDL cholesterol. Post-conversion, attainment of NCEP goal increased to 77.5% ($p<0.001$). The mean LDL cholesterol of the cohort decreased from 115 ± 30 to 106 ± 25 ($p<0.001$). HDL cholesterol and triglycerides were not significantly changed. Serious adverse effects occurred in six patients (0.6%; increased LAE, n=1; myositis, n=5). Projected pharmacy cost savings for this conversion were $203 per patient treatment year.
CONCLUSIONS: The empiric DOD PEC statin formulary conversion resulted in greater efficacy of cholesterol reduction at reduced cost. Uncommon, but serious, adverse effects can occur, even in patients formerly tolerant of a statin medication.

13. A community-based, cross-sectional evaluation of patients' achievement of cholesterol targets. *Ross T. Tsuyuki, B.S., Pharm.D., M.S.,* Kari L. Olson, B.S., Pharm.D.; University of Alberta, Edmonton, Alberta, Canada.

Current treatment guidelines recommend titration of hypolipidemic medications based upon the patients' level of risk for coronary heart disease (CHD) events.
PURPOSE: To determine the proportion of patients in the community achieving their target LDL as recommended by the National Cholesterol Education Program (NCEP II) guidelines.
METHODS: Multicenter, prospective, cross-sectional study of patients receiving an HMG-CoA reductase inhibitor, identified through community pharmacies, in Edmonton, Alberta, Canada. Patients with dosage changes within the previous 6 weeks or enrolled in another lipid study were excluded. Researchers conducted clinic visits in pharmacies to assess patients for cardiac risk factors, the use of diet and exercise programs, and concomitant medications and conditions known to affect lipid levels. All patients had a fasting lipid profile performed using a finger-stick test (Cholestech-LDXR).
RESULTS: A total of 404 patients (mean age 65 ± 10 years, 50% female) were enrolled. LDL measurements were evaluable in 365 patients. In 166 patients with established CHD, only 43% achieved their target LDL of 2.6. Of 113 patients with > 2 risk factors, 64% achieved their LDL target, while in the 86 patients with ≤ 2 risk factors, 85% reached their LDL target. Univariate analysis revealed that females were more likely to achieve target LDL than males (OR 3.2, 95% CI 2.0-4.9).
CONCLUSION: Paradoxically, the lowest proportion of patients achieving their target LDL are those at the greatest risk for future CHD events. More effective strategies are necessary to better manage patients, with, or at risk for, CHD.

14. Adequacy of anticoagulation in hospitalized patients with atrial fibrillation. *Tammy J. Bungard, B.S.P., Pharm.D.,* Margaret L. Ackman, B.S., Geotham Ho, Ross T. Tsuyuki, B.S., Pharm.D., M.S.; University of Alberta, Edmonton, AB, Canada.

PURPOSE: To evaluate the adequacy of anticoagulation in patients with atrial fibrillation (AF) presenting to hospital.
METHODS: The medical records of consecutive patients having a most responsible, primary, or secondary discharge diagnosis of AF from a tertiary care hospital in Edmonton, Alberta, Canada, from April 1, 1998 to March 31, 1999, were retrospectively reviewed. Patients were excluded if they were not prescribed warfarin prior to admission, did not have an INR performed, were not at steady state for warfarin, or developed AF as a complication during their hospital stay. Target international normalized ratios (INRs) were defined in accordance with the 5th edition of the American College of Chest Physicians guidelines for antithrombotic therapy.
RESULTS: Of the 1085 AF patients identified, 689 (63.5%) were not taking warfarin upon presentation to hospital, 21 (2.0%) had uninterpretable INRs, and 375 (34.5%) were eligible for further evaluation. Of these, the mean age was 73 years, 56.3% were male, and the majority (68.3%) of patients had nonvalvular AF. Nearly half of the patients (167 patients, 44.5%) had a subtherapeutic INR, 36.5% were therapeutic, and 18.9% were supratherapeutic. Patients presenting to hospital with any thromboembolic event and those presenting with ischemic stroke were significantly more likely to have subtherapeutic INRs ($p=0.00017$ and 0.00007, respectively). Overall, as many as 80% of patients (689 untreated and 167 subtherapeutic) may be inadequately protected from stroke.
CONCLUSION: In addition to the well documented under-utilization of warfarin, this study suggests that even in those patients treated, about half are inadequately treated.

15. Patient-related factors affecting medication adherence in patients with hyperlipidemia. *Ross T. Tsuyuki, B.S., Pharm.D., M.S.,* Tammy J. Bungard, B.S.P., Pharm.D., Marilou Hervas-Malo, M.S.; University of Alberta, Edmonton, AB, Canada.

PURPOSE: To determine patient-reported factors influencing adherence with hypolipidemic medications.
METHODS: This was a cross-sectional telephone survey of patients (identified through community pharmacies) who had been prescribed a hypolipidemic medication within the past 10-24 months. Patients were excluded if they had switched to another pharmacy, were enrolled in a cholesterol study, or were unable to communicate. Adherence was measured as the number of days supplied of medication dispensed to the patient over time. Poorly adherent patients (< 80% days supplied) were asked about specific impediments to medication adherence in a standardized format. Adherent patients (> 80% days supplied) were asked questions relating to their motivation to take their medication.

RESULTS: A total of 190 patients were surveyed (median age 62, 49% females). The median rate of adherence was 94%. Poorly adherent patients indicated that forgetfulness on a usual schedule or on a disrupted schedule strongly or very strongly influenced adherence in 41% and 30% of patients, respectively. In adherent patients, factors strongly or very strongly influencing adherence were: awareness that "lowering cholesterol will reduce complications of heart disease" in 91%, "physician advice" in 75%, and "pharmacist advice" in 21%. On multiple logistic regression, factors associated with good adherence were use of an adherence aid (odds ratio [OR] 3.0) and patient knowledge of drug name (OR 2.5).
CONCLUSION: Forgetfulness appears to be the main impediment to adherence, while physician advice and patients' understanding of the importance of cholesterol-lowering positively influences adherence. The use of adherence aids coupled with reinforcement from physicians may enhance adherence.

16. Itraconazole alters the pharmacokinetics of atorvastatin to a greater extent than either cerivastatin or pravastatin. *Arthur L. Mazzu, Ph.D.*, Kenneth C. Lasseter, M.D., E. Cooper Shamblen, Vipin Agarwal, Ph.D., John Lettieri, Ph.D., Pavur Sundaresen, M.D., Ph.D.; Bayer Corporation; Clinical Pharmacology Associates, Inc., West Haven, CT.

PURPOSE: Myopathy can occur when statins are co-administered with cytochrome P450 (CYP) 3A4 inhibitors. Cerivastatin (CER) is metabolized by CYP3A4 and 2C8, atorvastatin (ATOR) by CYP3A4, and pravastatin (PRA) by less fully defined means. This study examined the effects of itraconazole (ITR), a potent CYP3A4 inhibitor, on the pharmacokinetics (PK) of CER, PRA, and ATOR.
METHODS: In this randomized, open label, three-way crossover, single-dose study, 18 subjects received 0.8 mg CER, 40 mg PRA, or 20 mg ATOR alone (day 1) and in combination with ITR 200 mg (day 10); ITR given on days 6-10. A 2-week washout interval separated each statin period. Pharmacokinetic parameters ($AUC_{0-\infty}$, C_{max}, $t_{1/2}$, and t_{max}) were calculated for days 1 and 10.
RESULTS: Itraconazole increased CER and PRA $AUC_{0-\infty}$ and C_{max} 1.2- to 1.5-fold. Itraconazole co-administration also significantly elevated the $AUC_{0-\infty}$ and C_{max} of ATOR (1.4- to 2.5-fold). Statin $t_{1/2}$ and t_{max} were essentially unaltered when administered with ITR. Expressed as the LS mean ratio ([statin + ITR]/statin alone; [90% CI]), the results are:

PK Parameter	CER	PRA	ATOR
$AUC_{0-\infty}$(µg•hr/L)	1.3* (1.1-1.4)	1.5* (1.1-2.1)	2.5# (2.2-2.9)
C_{max} (µg/L)	1.3* (1.0-1.5)	1.2 (0.9-1.8)	1.4# (1.2-1.6)
$t_{1/2}$ (hr)	1.2* (1.1-1.3)	1.2 (0.9-1.8)	1.3# (1.1-1.6)

*p<0.05 vs statin alone; #p<0.0013 vs statin alone

CONCLUSION: Itraconazole did not cause clinically relevant changes in CER and PRA PK, but increased ATOR $AUC_{0-\infty}$ 2.5-fold. The dual CYP3A4/2C8 metabolism of CER minimizes alterations in its PK when given concomitantly with ITR. The magnitude of the elevation in ATOR PK when given with ITR may warrant caution or avoidance of this combination.

17E. Dobutamine pharmacodynamics. *Larisa M. Humma, Pharm.D.*, Heather E. Richardson, Jannet F. Lewis, M.D., Carl J. Pepine, M.D., Julie A. Johnson, Pharm.D.; University of Florida, Gainesville, FL.

PURPOSE: The objective of this study was to describe dobutamine pharmacodynamics during dobutamine stress echocardiography (DSE) and the impact of β-blocker withdrawal within 24 hours of DSE on heart rate (HR) response to dobutamine.
METHODS: One hundred and twenty-six women participating in the NHLBI-sponsored Women's Ischemic Syndrome Evaluation (WISE) study underwent DSE with dobutamine doses escalating from 5 to 40 µg/kg/minute or to target heart rate or development of ischemic symptoms. Dose response data were modeled with traditional pharmacodynamic models.
RESULTS: Of 95 women not receiving β-blockers prior to DSE, 60 had data described by the sigmoid Emax model; median (range) PD parameter estimates for HR response were: E_o: 68.1 (53-99) bpm; ED_{50}: 13.0 (3.5-28) µg/kg/minute; Emax: 132.6 (87-170) bpm; gamma: 2.9 (1-9.9). Patients taking β-blockers within 24 hours of DSE (n=31) were more likely to exhibit linear (vs sigmoid) dose-responses than those not on β-blockers (61% vs 37%, p<0.05). β-blocker patients also had a smaller increment in left ventricular ejection fraction (10.3 ± 4.3% vs 14.2 ± 9.3%, p<0.05), a slightly higher ED_{50} (median: 17 µg/kg/min) and lower gamma (median: 2.0, p<0.05).
CONCLUSIONS: In the absence of β-blockers, most patients have a plateau in dobutamine response by the 40 µg/kg/min dose rate. Withdrawal of β-blockers ≤ 24 hours before DSE may be inadequate time for elimination of β-blocker effect, requiring larger dobutamine doses to achieve the desired response.
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18. Use of billing records to evaluate costs, reimbursement and length of stay of patients with acute myocardial infarction managed by cardiac intervention with or without GPIIb/IIIa inhibitor therapy. *Vikas Gupta, Pharm.D., BCPS*; Owen Healthcare, Inc., Lombard, IL.

PURPOSE: Current evidence supports primary angioplasty (1°A) plus GPIIb/IIIa inhibitor (GPI) therapy; however, there is a lack of literature describing the financial impact to the institution with GPI therapy. This non-randomized report describes use of billing records to evaluate the financial impact of 1°A ± GPI therapy from an institution perspective.
METHODS: The following patient coding data were obtained from three different institutions for DRG 112 (PCI) and 116 (PCI plus stent procedure) during 1999: total charges, total payment, length of stay (LOS), principle diagnosis/procedure codes, secondary diagnosis/procedure codes, and GPI orders. Patients that underwent 1°A were identified using diagnosis codes 410.00-410.92, except 410.71. Total cost of admission was calculated using Medicare cost to charge ratio (one hospital) or costs from decision support software (two hospitals), where available.
RESULTS: There were 195 patients coded under DRG 112 (26 patients) and DRG 116 (169 patients) of which 143 (73%) received a GPI (125 abciximab, 14 tirofiban, and 2 eptifibatide). Mean LOS (± SD) was 4.34 ± 3.36 days and was not affected by GPI therapy (with GPI 4.36 ± 3.53 days, without GPI 4.26 ± 2.88 days, p=0.83). Mean reimbursement exceeded costs (± SD) by $2557.81 ± $9627.91 and was lower but not statistically significant with GPI use (with GPI $2171.3 ± $9941.28 and without GPI $3600.63 ± $8730.05, p=0.33).
CONCLUSION: Reimbursements exceeded costs in acute myocardial infarction patients by 1°A regardless of GPI use; however, it was lower in patients treated with GPIs. Incorporating such an evaluation with available clinical literature may be valuable in implementing patient treatment strategies.

19. Use of billing records to compare costs, reimbursement and length of stay of patients with non-Q-wave myocardial infarction managed medically or by cardiac intervention. *Vikas Gupta, Pharm.D., BCPS*; Owen Healthcare, Inc., Lombard, IL.

PURPOSE: Current evidence supports that patients with non-Q-wave myocardial infarction (NQWMI) can be managed by medical therapy or by coronary angiography/revascularization (CR). This non-randomized analysis compares the costs, reimbursement and LOS of patients with NQWMI managed by these two strategies.
METHODS: The following patient billing data were obtained from three institutions for DRG 112, 116, 121-123 during 1999: total charges, total payment, LOS, principle diagnosis/procedure codes, secondary diagnosis/procedure codes. Total cost of admission was calculated using Medicare cost to charge ratios (one hospital) or costs obtained from decision support software (two hospitals). Records were manually evaluated to identify patients with NQWMI coded under diagnosis code 410.71.
RESULTS: One hundred eighty six patients with NQWMI were identified, 102 two patients with NQWMI managed medically and 84 patients with NQWMI managed by CR (angioplasty [18], angioplasty plus stent [66]). GPIIb/IIIa inhibitors were given to 21% of patients managed medically and to 73% of patients managed by cardiac intervention. Patients managed by CR showed a significantly lower mean LOS ± SD of 3.8 ± 2.31 vs 6.21 ± 4.05 days with medical management (p=0.000001). Mean reimbursement exceeding costs was significantly higher for patients managed by CR (with CR $2091.22 ± $9283.48, with medical management reimbursement less than costs by $561.63 ± $4259.38, p=0.017).
CONCLUSION: Mean reimbursements significantly exceeded costs in NQWMI patients managed by CR. Also, LOS in patients with NQWMI managed by CR was significantly lower than with medical management. Incorporating such an evaluation with available clinical literature may be valuable in implementing patient treatment strategies.

20. Effectiveness of HMG-CoA reductase inhibitors in modifying lipid profiles in patients with established coronary artery disease. *Craig Williams, Pharm.D.*, Michael Murray, Pharm.D., Cynthia Johnson, M.A.; Purdue University; Indiana University, Indianapolis, IN.

PURPOSE: To determine the observed effectiveness of the HMG-CoA reductase inhibitors (statins) compared to their predicted efficacy in modifying TC, LDL, HDL and TG levels in a county hospital population with established coronary artery disease (CAD).
METHODS: We used an electronic medical record system that integrates data from the pharmacy, laboratory and patient charting information to identify all patients within the system since 1993 with CAD who had had at least two visits to a primary care site with at least one visit since January 1998. Patients were analyzed for presence or absence of cholesterol-lowering therapy and those patients on a statin were further analyzed for dosage used and effectiveness of lipoprotein response within 6 months. An ANOVA was performed on the differences at baseline and end between the agents studied. Predicted efficacy of the observed doses was extrapolated from the dose response curves in the CURVES study (AJC;81:582).
RESULTS: The cohort initially consisted of 5175 patients. Only 1586 (30.6%) patients were treated with any cholesterol-lowering medication, 1582 of whom included a statin agent. Patients were identified who had both a baseline and follow-up lipid panel within 6 months of the start of therapy. Patients on other medications that might affect the lipoprotein profile were

removed. Three hundred seventy-seven patients remained for analysis. The mean baseline lipid profile was (mg/dl): TC: 248 ± 41; LDL: 167 ± 37; HDL: 45 ± 15 and TG: 181 ± 84. Mean daily dose of statin used was: simvastatin 12.9 ± 7.3 mg, atorvastatin: 15.0 ± 8.3 mg and fluvastatin 26.6 ± 9.4 mg. For fluvastatin, atorvastatin and simvastatin, respectively, mean reductions in LDL were 23.4%, 24.5% and 25.5% (p=NS), mean reductions in triglycerides were 6.0%, 11.1% and 13.1% (p=NS) and mean increases in HDL were 2.9%, 3.6% and 6.8% (p=NS). Compared to the predicted efficacy from the CURVES trial, an average of 75% of the expected LDL reduction was actually achieved by the three agents.
CONCLUSION: The effectiveness of the statin agents in practice is different than their efficacy in controlled trails. Similar doses of simvastatin and atorvastatin produce similar reductions in LDL and TG. Although not statistically significant, simvastatin appeared to have a greater effect on increasing HDL than atorvastatin. At approximately two times the daily dose of either simvastatin or atorvastatin, fluvastatin produced a similar reduction in LDL but only half the reduction in triglycerides.

21. Effectiveness of HMG-CoA reductase inhibitors in a county hospital population. *Craig Williams, Pharm.D.*, Michael Murray, Pharm.D., Cynthia Johnson, M.A.; Purdue University; Indiana University, Indianapolis, IN.

PURPOSE: To determine patterns of physician prescribing of HMG-CoA reductase inhibitors (statins) and the clinical effectiveness of these drugs in achieving the National Cholesterol Education Program (NCEP) defined goals for LDL cholesterol reduction.
METHODS: We used an electronic medical record system that integrates data from the pharmacy, laboratory and patient charting information to identify all patients from a county medical center who had received a formulary statin agent between 1993 and July 1999. Data were analyzed for baseline LDL, dose of statin agent used, LDL response within 6 months of the initiation of therapy and percent of patients reaching their NCEP goal LDL. Observed reduction of LDL at the doses used was compared to the predicted efficacy from the CURVES trial (AJC;81:582) for the agents studied. An ANOVA was performed to look for differences in responses of LDL and a chi square test was performed to look for differences in percent reaching NCEP goal.
RESULTS: A total of 3477 patients were identified. Five hundred twenty patients had both a baseline lipid panel and a follow-up panel obtained within 6 months of the start of therapy for analysis. The mean baseline lipid panel with standard deviation was (in mg/dl): TC: 263 ± 44; LDL: 182 ± 40; HDL: 47 ± 15; TG: 171 ± 83. Mean baseline LDL for patients on fluvastatin (184 ± 41) was identical to that for patients on simvastatin (184 ± 40 mg/dl) and higher than that for patients on atorvastatin (173 ± 39 mg/dl; p=0.075 for difference). Mean post-treatment LDL was 139 ± 41 with fluvastatin achieving 156 ± 39 (15.2% reduction), simvastatin achieving 135 ± 38 (26.6% reduction) and atorvastatin achieving 122 ± 42 (29.5% reduction); p=0.0001 for simvastatin vs fluvastatin and p=0.0002 for atorvastatin vs fluvastatin. Only 4.7% of fluvastatin, 11.6% of simvastatin and 15.2% of atorvastatin patients achieved their NCEP treatment goals (p=0.027 for simvastatin vs fluvastatin and p=0.049 for atorvastatin vs fluvastatin, p=NS for atorvastatin vs simvastatin). Mean daily doses of agents used were: 12.2 mg for simvastatin, 13.5 mg for atorvastatin and 22.3 mg for fluvastatin. Compared to the predicted efficacy, an average of 72% of the expected LDL reduction was actually achieved by the three agents.
CONCLUSIONS: Few patients prescribed statin therapy achieve their NCEP goal. The reason appears to be multifactorial including underdosing of statin agents, inappropriate prescriber selection of low vs high potency agents based on patients baseline lipid profiles and the inability of statin agents to achieve in practice the LDL reductions that are observed in controlled trials.

22. Treatment of dyslipidemia in type 2 diabetics: results of a multicenter retrospective study. *William J. Sasiela, Ph.D.*, William Hittel, Pharm.D., Thomas Philpot, Pharm.D.; Parke-Davis, Morris Plains, NJ; Apex Health Outcomes, Atlanta, GA.

PURPOSE: Cardiovascular disease is the leading cause of death in type 2 diabetics and may account for up to 80% of the mortality in these patients. The American Diabetes Association recommends initial and annual lipid screening for all adult diabetics as well as attainment of a low-density lipoprotein (LDL) goal of < 100 mg/dl.
METHODS: We undertook the following study to determine the rate of lipid/LDL screening, the use of pharmacological agents for hyperlipidemia and the achievement of an LDL goal of < 100 mg/dl in type 2 diabetics by retrospective review of patient charts at practices that were part of four large physician networks in the Southeast U.S. Eligible charts were identified by IDC-9 code.
RESULTS: A total of 1938 charts were reviewed. Overall, 1045 (53.9%) of the patients had an LDL value charted in the previous year. Analyzing those patients with charted LDL values, 37.3% achieved their LDL goal. In terms of treatment, 512 of the diabetic patients received nutritional counseling and 438 were receiving of pharmacological therapy for hyperlipidemia. Of those receiving drug therapy, 387 (88.4%) patients were on a statin. Fibrates (13.1%), niacin (0.7%) and resins (0.2%) were also utilized. As would be expected, there was a tendency for a greater proportion of patients on the more efficacious cholesterol-lowering agents to attain their LDL goal.
CONCLUSIONS: These data suggest that there have been improvements in the awareness and achievement of LDL goals in diabetic patients. However, there is still considerable need for more aggressive management of hyperlipidemia in type 2 diabetics.

23. Performance of pharmaceutical companies in an indigent patient assistance program in a cardiology/endocrinology clinic. *Peter A. Dumo, Pharm.D.*, Paul A. Sobotka, M.D.; Wayne State University; Detroit Medical Center, Detroit, MI.

PURPOSE: This study reports on the performance, as measured by turnaround time (TAT) and acceptance rates (AR), of different pharmaceutical patient assistance programs (PAP) petitioned in a cardiology/endocrinology clinic.
METHODS: Date was collected on all on PAP product submission and receipt dates over 6 months. The TAT was calculated by subtracting the product submission date from product receipt date. The value of pharmaceuticals was determined by using average wholesale price. Only companies with three or more submissions were included. Data were analyzed using ANOVA.
RESULTS:

Company	Submissions	Acceptance	TAT (Days)	Value
Searle	13	100%	0 ± 0	539.69
Novartis	3	100%	0 ± 0	667.25
Merck	58	100%	14.4 ± 8.0	16500.07
Smith-Kline Beecham	13	100%	28.0 ± 6.5	7254.96
Hoechst Marion Roussel	13	100%	26.3 ± 9.7	1056.8
DuPont	4	50%	36.3 ± 19.9	159.6
Parke-Davis	7	100%	37.4 ± 10.6	3462.28
Bristol-Myers Squibb	4	75%	38.3 ± 19.9	725.86
Astra-Zeneca	7	100%	46.0 ± 25.6	3456.72
Pfizer	18	100%	49.3 ± 7.7	3641.86
Total	140			37465.09

Searle and Novartis had the fastest TATs (p<0.05 against all). Merck had the second fastest TAT (p<0.05 against all). Merck was the most frequently petitioned company. Acceptance rates of most companies were very high. Searle, Novartis, and Merck used pharmacy benefit organizations (PBO) to facilitate their programs.
CONCLUSIONS: Turnaround times of most PAPs was between 2 weeks and 2 months. The most efficient PAPs were assisted by PBOs.

24. Achieving cholesterol target in a managed care organization: ACTION Trial. *Reza Taheri, Pharm.D.*, James C. Smith, M.D., Susan Cooper, R.Ph., M.S., Robert J. Straka, Pharm.D.; University of Minnesota, Minneapolis, MN; HealthPartners, Bloomington, MN; Regions Hospital, St. Paul, MN.

PURPOSE: To evaluate the effectiveness of a pharmacy-based program targeting patients with coronary heart disease (CHD) who are not at goal low-density lipoprotein (LDL)-cholesterol within staff-model clinics of a large health maintenance organization (HMO).
METHODS: Prospective, controlled trial conducted between May 20, 1999, and February 15, 2000, whereby CHD patients not at goal LDL-cholesterol were identified through an electronic database search in four clinics. Pharmacists worked collaboratively with physicians in two clinics (intervention group) to optimize cholesterol management by vigilantly following nationally accepted guidelines while usual care took place in two matching clinics (non-intervention group). Pharmacists proposed and carried out patient specific plans to optimize cholesterol management after obtaining physicians' and patients' consent. Pharmacists' evaluations and recommendations were communicated to physicians and patients via phone calls, e-mails, and meetings.
RESULTS: A total of 166 CHD patients (M: 118, F: 48, mean [SD] age year: 67 [11]) initially not at goal LDL-C completed the study in the intervention arm. There was a 29% reduction in the average LDL-C compared to baseline (pre-intervention) with a mean (SD) absolute pre-post change in LDL-C of –37 (19.0) mg/dl, p<0.001 (95% CI: -34 to 40 mg/dl). This resulted in the attainment of goal in 122 (73.5%) of the patients with three individuals (1.8%) experiencing elevated liver function tests and one (0.6%) myopathy. Data from the control clinics are not yet available.

Mean (± SD) cholesterol values were:

	Total-C mg/dl	LDL-C mg/dl	HDL-C mg/dl	VLDL mg/dl
Baseline	211 (34)	130 (23)	46 (12)	189 (115)
Post intervention	167 (27)	92 (19)	43 (12)	167 (84)
% Change	-21	-29	-6.5	-12
Absolute pre-post Δ* (95% CI)	-43.5 (-40 to -47)	-37 (-34 to -40)	-3.3 (-2.7 to -3.9)	-21.5 (-13.5 to -29.5)
p value	<0.001	<0.001	<0.001	<0.003

* based on those with both pre- and post- data available; n=157 for LDL-C; n=165 for other cholesterol parameters

CONCLUSION: The implementation of a pharmacy-based initiative to optimize cholesterol management has significantly reduced the average LDL-C value compared to baseline and resulted in the attainment of goal for over 73% of the patients. The result of this approach provides a template for other

institutions to target and pursue patients not at goal LDL-C.

25. Outcomes associated with a change in selection of glycoprotein IIb/IIIa agents in a community hospital setting. *Paul P. Dobesh, Pharm.D., BCPS,* Joy R. Abu-Shanab, Pharm.D., BCPS, Sara L. Schroeder, Pharm.D., BCPS, Jonathan E. Lakamp, Pharm.D., BCPS; St. Louis College of Pharmacy, St. Louis, MO; St. Luke's Hospital, Chesterfield, MO.

PURPOSE: Glycoprotein IIb/IIIa receptor antagonists have been shown in clinical trials to have an impact on the outcomes of death/myocardial infarction (MI). At our institution, tirofiban has largely replaced abciximab in an attempt to decrease costs. This review was undertaken to assess the impact of this change on patient outcomes in the absence of head-to-head trials.
METHODS: Medical records were reviewed and telephone follow ups were conducted on patients receiving tirofiban (n=83) at our facility between February, 1999 and November, 1999. The occurrences of death/MI at 30 days and 6 months post-infusion were recorded. Safety and length of hospitalization (LOH) were also assessed. These data were compared (chi square analysis) with results obtained from a previous review of abciximab (n=83) collected between May, 1997 and November, 1998.
RESULTS: There was no difference in baseline incidence of: 1) cardiovascular risk factors; 2) prior revascularization; 3) prior MI; 4) number of vessels with atherosclerotic disease assessed by angiography; and 5) the number of vessels receiving procedures. Outcomes of death/MI trended to be worse with the use of tirofiban vs abciximab at our institution at 30 days (4.8% abciximab vs 12% tirofiban; p=0.163) and at 6 months (6% abciximab vs 18.1% tirofiban; p=0.032). The incidence of bleeding or mean LOH (4.06 days abciximab vs 4.46 days tirofiban) was not significantly different.
CONCLUSIONS: The economically driven change in medication selection from abciximab to tirofiban may not have been appropriate based on the negative trends seen in this review. To maintain optimal patient outcomes, this change should be re-evaluated.

26E. Evaluation of compliance with National Cholesterol Education Program recommendations for screening and treatment of hyperlipidemia in medical resident primary care training clinics. Deborah S. King, Pharm.D., *Sara L. Noble, Pharm.D.,* Kimberly G. Harkins, M.D., Marion R. Wofford, M.D., MPH, T. Kristopher Harrell, Pharm.D., Leigh Ann Ramsey, Pharm.D., William H. Replogle, Ph.D., and Bill H. Tidwell, Pharm.D.; University of Mississippi Medical Center, Jackson, MS; Pfizer.

PURPOSE: This project evaluated the adequacy of lipid evaluation and treatment as a marker of cardiovascular risk in resident training clinics.
METHODS: A total of 1868 consecutive patients in internal medicine and family medicine resident continuity clinics were screened. After informed consent, patients were interviewed for risk factors; a retrospective chart review was conducted to determine if lipids were measured and if the patients had reached treatment goals as defined by National Cholesterol Education Program (NCEP-ATPH).
RESULTS: Of 358 patients 94 (26%) had a documented cholesterol measurement within the 5 years prior to the clinic visit at which the interview was conducted. A total of 19 (18%) of 158 patients with one risk factor, 40 (24%) of 155 patients with two or more risk factors but no coronary heart disease, and 35 (81%) of 43 patients with coronary heart disease had documented cholesterol evaluation within the last 5 years. Hypertension was the most frequently identified risk factor, with 225 (63%) of patients diagnosed with hypertension. While 74 (21%) of the total 358 patients had documented dyslipidemia, only 44 (59%) of the 74 were on cholesterol-lowering medications. For those patients on cholesterol-lowering medications, 31 (70%) of 44 patients had a low-density lipoprotein (LDL) cholesterol documented. Of all patients with LDL cholesterol documented, only 56% were at their NCEP target goal.
CONCLUSIONS: Identification and treatment of dyslipidemia as a coronary heart disease risk factor is inadequate in medical residency training programs. Strategies for improved detection and treatment of dyslipidemia need emphasis.
Presented at the 15th Scientific Meeting of the American Society of Hypertension, New York, NY, May 2000.

27E. Improvement in blood pressure control through interdisciplinary medication assistance efforts in hypertensive patients with multiple metabolic syndrome. *Deborah S. King, Pharm.D.,* Sharon B. Wyatt, Ph.D., R.N., CANP, Marion R. Wofford, M.D., MPH, T. Kristopher Harrell, Pharm.D., Daniel W. Jones, M.D.; University of Mississippi Medical Center, Jackson, MS.

PURPOSE: This presentation will describe the development of an interdisciplinary medication assistance program and present comparative blood pressure control data for 38 patients 6 months following enrollment.
METHODS: Recognizing finances as a major barrier to effective hypertension control, an interdisciplinary medication assistance program (MAP) was developed to connect needy patients with financial or pharmaceutical company assistance programs. Patients enrolled in the program were evaluated 6 months after entry for changes in average blood pressures, appointment keeping behavior, and markers of disease progression. Average blood pressures (diastolic, systolic [SBP], pulse, mean arterial) were measured and evaluated.
RESULTS: Of the 38 patients evaluated, 21% had controlled blood pressures at study entry. After MAP enrollment, the rate of blood pressure control within the population increased to 53%. Changes in average systolic (155 to 142 mm Hg), diastolic (88 to 83 mm Hg), mean arterial (110 to 102 mm Hg), and pulse (66 to 59 mm Hg) pressures were all significant. Of those with uncontrolled SBP at the initiation of MAP, 71% had a 10 mm Hg or greater improvement in SBP.
CONCLUSIONS: Interdisciplinary medication assistance improves hypertension control and providing medication overcomes one barrier to achieving hypertension control.
Presented at the American Society of Hypertension 15th Scientific Meeting, New York, NY, May 2000.

28. Assessment of lipid-lowering therapy following coronary artery bypass grafting. Ujjaini Khanderia, M.S., Pharm.D., *Tracy V. Faulkner, Pharm.D.,* Kevin A. Townsend, Pharm.D., BCPS, Daniel S. Streetman, Pharm.D.; University of Michigan Health System, Ann Arbor, MI; Pfizer Incorporated, Chelsea, MI.

PURPOSE: To determine the extent to which patients who have undergone a coronary artery bypass graft (CABG) procedure receive lipid-lowering treatment prior to discharge and to compare use in this setting to national recommendations.
METHODS: This was a retrospective chart review of eligible patients who have undergone CABG procedures between June 1, 1998 and May 31, 1999. Data regarding demographics, lipid screening, and lipid-lowering agent use were collected. Descriptive statistics were used to describe the population. Patients were deemed eligible for lipid-lowering therapy according to NCEP criteria, lack of contraindications, and absence of significant interactions. Using chi-squared analysis, the percentage of patients who received lipid-lowering therapy was compared to the percentage that qualified for lipid-lowering therapy. Differences between those who did and those who did not receive lipid-lowering therapy were examined using Student's t-test or chi-squared analysis.
RESULTS: Of 368 eligible patients, 305 patients were included in the final analyses. Low-density lipoprotein values were documented in the charts of only about two-thirds of patients. Nearly 90% of patients qualified for lipid-lowering therapy; however, only 44% actually received lipid-lowering therapy at discharge (90% vs 44%; p=0.001) despite finding that 55% were receiving lipid-lowering therapy at admission and 81% had a history of dyslipidemia.
CONCLUSION: These results are similar to those from other studies in that a minority of post-CABG patients is receiving lipid-lowering therapy. These findings emphasize the need for more aggressive screening and management of dyslipidemia in such patients and call for re-evaluation of institutional guidelines to address this issue.

29. The frequency of epinephrine dosing: effects on return of spontaneous circulation. *Michael R. Brodeur, EMT-CC,* Cynthia A. Sanoski, Pharm.D.; St. John's University; Jamaica, NY.

PURPOSE: Although administration of epinephrine is the standard of care in cardiac arrest, the recommended dose and interval in humans is extrapolated from animal studies. This study was conducted to assess the relationship between epinephrine dosing interval and return of spontaneous circulation (ROSC) in patients suffering cardiac arrest.
METHODS: Prehospital care reports for all patients in cardiac arrest receiving epinephrine from January 1, 1995, to December 31, 1999, were reviewed. Data were obtained from two emergency medical services in Nassau County, NY. Patients' demographic information, initial cardiac rhythm, prehospital course, epinephrine dose, route, and interval were documented. Efficacy was defined as ROSC upon arrival at the emergency department.
RESULTS: Of the 103 patients (63 male, 40 female; mean age 74 ± 14 years) included for analysis, 61% presented in asystole, 34% in ventricular fibrillation, 2% in ventricular tachycardia, and 3% in pulseless electrical activity. A total of 289 epinephrine doses were administered (75% intravenously, 25% endotracheally). Mean epinephrine interval for all patients was 7 ± 4.2 minutes. Return of spontaneous circulation occurred in five (4.9%) patients. No patients receiving endotracheal epinephrine had ROSC. In patients with ROSC, mean epinephrine interval was 5.5 ± 2.3 minutes compared to 7 ± 4.2 minutes in patients without ROSC (p=0.31). Mean epinephrine interval was greater than 5 minutes in 84% of all patients.
CONCLUSIONS: Mean epinephrine interval was outside the accepted standard of care for most of the patients in cardiac arrest. The endotracheal route may not be the optimal method of epinephrine administration during cardiac arrest.

30. Comparison of outcomes in diabetic and nondiabetic patients with acute coronary syndromes treated with tirofiban. *Nina Yousefzadeh, Pharm.D.,* Cynthia A. Sanoski, Pharm.D.; Cedars-Sinai Medical Center, Los Angeles, CA; Philadelphia College of Pharmacy, Philadelphia, PA.

PURPOSE: Diabetes is an independent risk factor for the development of coronary heart disease. While abciximab, a glycoprotein IIb/IIIa (GP IIb/IIIa)

receptor antagonist, has been shown to reduce the incidence of cardiovascular events in diabetics, the effects of other GP IIb/IIIa receptor antagonists in this population is unknown. This study was conducted to evaluate the in-hospital outcomes associated with the use of tirofiban in diabetic and nondiabetic patients with acute coronary syndromes (ACS).
METHODS: Between February 1, 1999 and January 31, 2000, medical records were screened for patients with ACS (i.e., unstable angina or non-Q-wave myocardial infarction (NQWMI)) who received tirofiban for at least 48 hours with heparin and aspirin. Outcomes evaluated included the incidences of death, myocardial infarction, or target vessel revascularization during the patient's hospitalization, and length of stay.
RESULTS: A total of 101 patients (mean age, 66 years; 35 diabetic, 66 nondiabetic) met the inclusion criteria. Upon admission, 52 patients had unstable angina and 49 had a NQWMI. Both groups received tirofiban therapy for approximately 71 hours. Death occurred in two (3%) nondiabetics and none of the diabetics (p=NS). No myocardial infarctions occurred in either group. Target vessel revascularization was performed in 77% and 86% of the diabetics and nondiabetics, respectively (p=NS). The mean length of stay was 9.8 days in the diabetics and 9.4 days in the nondiabetics (p=NS).
CONCLUSIONS: The in-hospital incidences of death, myocardial infarction, and target vessel revascularization in diabetics appear to be similar to those of nondiabetics when tirofiban is used for the treatment of ACS.

31E. Modulation of inward rectifier K+ current in ventricular myocytes by dihydrotestosterone. *Cynthia A Carnes, Pharm.D., Ph.D.*, Margaret Kirian, B.S., Spencer Dech, M.A.; Ohio State University, Columbus, OH.

The inward rectifier potassium current (I_{K1}) is a primary determinant of resting membrane potential in the heart. Ventricular myocytes from adult male New Zealand white rabbits were used to assess the effects of dihydrotestosterone (DHT) on I_{K1}. The nystatin perforated patch whole cell patch clamp technique was used with 100 msec test steps from -140 mV to 0 mV, (holding potential -40 mV). Physiologic (3 nM, n=5) and supraphysiologic (10 nM, n=5) concentrations of DHT were applied in the perfusate after obtaining control recordings. The voltage protocol was repeated every minute and the maximal current density recording was used for analysis. Inward current conductance (mS/cm^2) was determined from the slope of the inward current density-voltage relationship from -140 mV to -100 mV. Outward current density at -60 mV was also determined.

Inward I_{K1} conductance (mean ± SEM)		
Ctrl: 0.529 ± 0.058	3 nM DHT: 0.600 ± 0.064	p=0.018
Ctrl: 0.633 ± 0.121	10 nM DHT: 0.709 ± 0.129	p=0.032

DHT had no effect on outward I_{K1} current or on the reversal potential. DHT increased inward I_{K1} conductance, without changing outward current. This is likely to result in a decrease in ventricular excitability with a reduction in abnormal automaticity, and no change in repolarization.
Presented at the International Society for Heart Research, Louisville, KY, June 16, 2000.

32. Equivalent efficacy and safety of cerivastatin and simvastatin: outcome of mandated statin conversion program at the Cleveland VA Medical Center. *Michael Ganz, M.D.*; Veteran's Administration Medical Center, Cleveland, OH.

PURPOSE: To demonstrate equivalence of efficacy and safety of cerivastatin (CER) to that of simvastatin (SIM) in the context of a SIM-to-CER formulary conversion in the VA Medical Centers of VISN 1, 10, and 13.
METHODS: In this retrospective database analysis of 675 patients meeting selected inclusion criteria (SIM use > 6 months), 172 were switched from SIM to CER as follows: 10 mg to 0.2 mg, 20 mg to 0.3 mg, or 40 mg to 0.4 mg. Patients receiving gemfibrozil were excluded. After 6 weeks, lipid parameters, renal and liver function, and CK were measured. Patients experiencing myalgia or CK/transaminase elevations were discontinued.
RESULTS: Of 172 patients meeting inclusion criteria, 170 patients completed the 6-week study.

Dosage Range (SIM to CER)	n	LDL-C (mg/dl) %Δ	HDL-C (mg/dl) %Δ
10 mg→0.2 mg	33	133.2→128.5	30.1→29.7
	-4.9 ± 0.3%	-1.2 ± 0.2%	
20 mg→0.3 mg	107	135.8→129.1	29.8→30.1
	-2.8 ± 0.2%	+1.0 ± 0.3%	
40 mg →0.4 mg	30	121.3→126.0	30.7→30.2
	+2.0 ± 0.3%	-0.5 ± 0.2%	

*all p>0.05 (NS, paired t-test)

Cerivastatin 0.2, 0.3, and 0.4 mg were equivalent to SIM 10, 20, and 40 mg, respectively, in reducing LDL-C and elevating HDL-C. Two patients receiving CER 0.4 mg were discontinued (inadequate response and muscle ache). The latter patient continued to have symptoms after conversion to SIM, and was withdrawn. The most frequent adverse events were flu-like symptoms, and were similar across groups.
CONCLUSIONS: Cerivastatin produced equivalent changes in LDL-C and HDL-C as SIM with no apparent short-term change in safety, supporting its use in VA statin conversion programs.

33. Long-term (52 week) efficacy and safety of cerivastatin 0.8 mg and 0.4 mg vs pravastatin 40 mg. *Jonathan Isaacsohn, M.D.*, William Insull, Jr., M.D., Peter Kwiterovich, M.D., Patrick Ma, M.D., Ronald Brazg, M.D., Carlos Dujovne, M.D., Michael Shan, Elizabeth Shugrue-Crowley, Steven Ripa, M.D., and Robert Tota, M.D.; Medical Research Services; Lipid Research Clinic, The Methodist Hospital; Johns Hopkins University; Heart Health Institute; Ranier Clinical Research Center; Kansas Foundation for Clinical Pharmacology, Kansas City, KS; Bayer Corporation.

PURPOSE: To compare the long-term efficacy and safety of cerivastatin (CER) 0.8 mg (0.8), CER 0.4 mg (0.4), and pravastatin (PRA) 40 mg.
METHODS: In this 44-week extension of the 8-week placebo-controlled, randomized, double-blind trial, 1170 hypercholesterolemic patients were treated with CER 0.8, CER 0.4, or PRA QD.
RESULTS: Cerivastatin 0.8 reduced low-density lipoprotein (LDL) cholesterol (C), total-C, and triglycerides (TG) to a greater extent than CER 0.4 or PRA. Cerivastatin 0.8 elevated high-density lipoprotein (HDL)-C significantly more than PRA. Cerivastatin 0.8 reduced median TG by 29% in patients having baseline TG 250-400 mg/dl (n=101, mean = 303 mg/dl). Results expressed as %Δ (± SEM) from baseline (mean, mg/dl) to 52-week endpoint (per-protocol) were:

Parameters	PRA 40 (n=171)	CER 0.4 (n=159)	CER 0.8 (n=615)
LDL-C baseline	183	191	190
mean %Δ	-31.5 ± 1.0	-33.6 ± 1	-40.8 ± 0.6*,†
Total-C baseline	266	276	275
mean %Δ	-22.1 ± 0.7	-23.8 ± 0.7	-29.0 ± 0.4*†
TG baseline	172	185	183S
median %Δ	-13.9	-16.8	-22.1
HDL-C baseline	48	48	48
mean %Δ	+7.1 ± 1.0	+8.0 ± 1.0	+9.7 ± 0.6†

* p<0.05 vs CER 0.4; † p<0.05 vs PRA

The most common adverse events (rhinitis, pharyngitis, and arthralgia) and discontinuations were similar between groups. Myalgia occurred in 7-8% in all patients. CK elevations > 5 x ULN occurred in 2.5%, 4.1%, and 4.5% of patients receiving PRA, CER 0.4, and 0.8. CK elevations > 10 x ULN occurred in 2.1% of patients receiving CER 0.8, and 1% experienced symptoms. Repeat transaminase elevations > 3 x ULN were experienced by 0.5% of patients receiving CER.
CONCLUSION: The lipid-lowering effect of CER 0.8 is safely maintained for 52 weeks, demonstrating its use in patients requiring aggressive lipid-lowering therapy.

34. Correlation and clinical assessment of a portable PT/INR monitor in a cardiology ambulatory clinic. *Daniel R. Touchette, Pharm.D.*, Biljana Popovic, B.S., Eric Racine, Pharm.D., Judith C. Andersen, M.D., Michael R. Massanari, M.D., James G. Stevenson, Pharm.D.; Oregon State University, Corvallis, OR; Harper Hospital, Detroit, MI; Detroit Medical Center, Detroit, MI; Wayne State University, Detroit, MI; University of Michigan, Ann Arbor, MI..

PURPOSE: Point of care (POC) prothrombin time (PT) monitors simplify the management of patients requiring warfarin therapy by providing rapid PT/INR results. However, variability in PT/INR measurement can potentially result in complications or unnecessary dose adjustment for patients on warfarin. This study was developed to compare the ProTime® microcoagulation POC monitor, the Detroit Medical Center laboratory (DMC) laboratory, and a reference laboratory (REF) to each other.
METHODS: The INR's of ten healthy volunteers not receiving warfarin and 50 warfarin-treated patients from the DMC Anticoagulation Clinic were determined using the ProTime® microcoagulation POC monitor. Blood samples for these patients were drawn and sent to the DMC and to the REF for INR determination. The POC monitor and the two laboratories were compared for INR correlation and clinical agreement (the frequency that two methods results matched according to the patient's target INR range).
RESULTS: All three systems showed a very high degree of correlation with each other ($r^2 > 0.95$ for all comparisons). A bias was demonstrated between the POC monitor with both the DMC (+ 0.45) and the REF (+ 0.32). The POC monitor agreed 83% of the time compared with DMC and 78% of the time compared with REF. The DMC agreed with the REF 88% of the time (NS). Adjusting for the bias had no significant effect on clinical agreement.
CONCLUSION: The POC monitor displays a high correlation with DMC and REF, despite a slight bias. Clinical agreement is similar between the POC device and between labs. This POC monitor is a reliable method of determining INRs when used in a clinic setting.

35. Community hospital care of the elderly with congestive heart failure in the U.S. *Eric J. Stanek, Pharm.D.*; Center for Advanced Pharmacy Studies; Philadelphia College of Pharmacy; University of the Sciences in Philadelphia; University of Pennsylvania, Philadelphia, PA.

PURPOSE: The U.S. elderly population is expanding, and congestive heart failure (CHF) is the most common discharge diagnosis in these patients. This

retrospective analysis examined the outcomes and economics of CHF in the elderly admitted to U.S. community hospitals.
METHODS: The Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project 3 (HCUP-3) Nationwide Inpatient Sample (NIS) 1997 was accessed using an Internet query tool (HCUPnet). The NIS contained data on 35,406,187 discharges from approximately 1000 community hospitals in 22 states. Aggregate discharge data were extracted for 10 CHF diagnosis codes. The mean (± SD) number of hospital discharges, length of stay (LOS), charges (U.S. $), and discharge status (death or routine) per CHF diagnosis code were compared between non-elderly (NE, age 18-64 years) and elderly patients (E, age ≥ 65 years). Appropriate statistical comparisons were performed using SYSTAT 8.0 (SPSS, Inc, Chicago, IL), with significance set at $p<0.05$.
RESULTS: Total discharges were NE 16, 251, 563 (46%) and E 12, 787, 505 (36%). CHF discharge totals were NE 35, 568 ± 59, 627 vs E 250, 937 ± 366, 180, $p<0.02$. LOS was NE 5.6 ± 0.8 days vs E 6.3 ± 0.6 days, $p<0.05$. Death at discharge was NE 3.2 ± 1.4% vs E 6.7 ± 2.0%, $p<0.001$. Routine discharge was NE 80 ± 3.5% vs E 61 ± 5.5%, $p<0.001$. Hospital charges were NE $13,989 ± 3183 vs E $11,820 ± 1548, $p=0.053$.
CONCLUSION: In U.S. community hospital practice, the elderly with CHF experienced significantly longer hospitalization, greater death rate, and a lower rate of routine discharge vs non-elderly patients. Further research is needed on strategies to prevent hospitalization and improve treatment outcomes in elderly CHF patients.

36. A retrospective analysis of prescribing patterns in patients with systolic heart failure. *Shajuana D. McMillan, Pharm.D.*, Jean M. Nappi, Pharm.D., BCPS; Medical University of South Carolina, Charleston, SC.

PURPOSE: The Advisory Council to Improve Outcomes Nationwide in Heart Failure (ACTION HF) recommends that all patients with stable New York Heart Association (NYHA) class II or III heart failure due to left ventricular systolic dysfunction should receive a β-blocker, unless contraindicated, in addition to an ACE inhibitor and diuretic. This study examined the prescribing patterns of physicians in the treatment of patients with systolic heart failure (ejection fraction ≤ 40%).
METHODS: This was a retrospective chart review of patients, with an ejection fraction ≤ 40%, seen in clinics at the Medical University of South Carolina between August 1, 1999 through December 31, 1999. Patients from each clinic were identified using a database to search all DRG codes with the description heart failure.
RESULTS: A total of 304 patients were identified of which 108 met entrance criteria. Data analysis revealed 87% of patients treated with digoxin, 77% with diuretics, 74% with ACE inhibitors, and 15% with angiotensin receptor blockers. Further analysis showed 51% of patients were treated with a β-blocker. Physicians were less likely to prescribe a β-blocker in patients with asthma or diabetes mellitus. However, of the patients not treated with a β-blocker, 36% lacked a contraindication to therapy.
CONCLUSION: The treatment guidelines established by ACTION HF have been implemented, but improvement is still needed particularly in the use of β-blockers.

37E. Is monocyte tissue factor clinically significant in chronic heart failure? *Kai I. Cheang, Pharm.D.*, Mark A. Munger, Pharm.D., Julie K. Kenney, Pharm.D., Tien M.H. Ng, Pharm.D., Edward M. Gilbert, M.D., Karleen S. Callahan, R.Ph., Ph.D.; University of Utah, Salt Lake City, UT.

PURPOSE: Heart failure patients suffer a high incidence of thromboembolic events, leading to increased morbidity and mortality. A growing body of evidence suggests that thrombotic events are linked to increased monocyte expression of tissue factor (TF), a glycoprotein essential in the initiation of coagulation and thrombus formation. We previously reported 3-fold elevations in monocyte TF procoagulant activity (TF-PCA) in heart failure patients compared to age-matched controls. However, no evidence currently relates whether elevated hypercoagulable markers translate to increased clinical events. This study determined whether elevated TF-PCA is associated with clinical complications in heart failure.
METHODS: Forty-eight New York Heart Association functional class II to IV heart failure subjects were enrolled in this study. TF-PCA was determined by a one-step recalcification assay at baseline. Patients were followed to death or cardiac transplant, and to first clinical event defined as heart failure hospitalization, unstable arrhythmia, acute coronary event, or thromboembolic event.
RESULTS: Patients were followed for a mean of 21 months. When TF-PCA values were divided at the median, the upper 50th percentile demonstrated a trend towards increased mortality ($p=0.06$ by log rank test; absolute number of deaths 10 vs 6) and a significant increase in clinical events ($p=0.04$ by log rank test; absolute number of events 34 vs 19) as compared to the lower 50th percentile. The majority of clinical events were for hospitalizations for acute heart failure.
CONCLUSIONS: Tissue factor appears to be a marker for heart failure disease progression. Further study of hypercoagulable markers in heart failure is warranted.
Presented at the 4th Annual Scientific Meeting of the Heart Failure Society of America, Boca Raton, FL, September 12, 2000.

38. Improved NCEP-goal attainment with cerivastatin: outcome of mandated Department of Defense statin conversion. Maj. Emery Spaar, R.Ph., Karen C. Chung, Pharm.D., M.S., Susan Pitman Lowenthal, M.D., MPH, *Col. Dennis R. Beaudoin, B.S., M.A., BCOP;* Madigan Army Medical Center, Tacoma, WA; Bayer Corporation.

PURPOSE: To determine the effectiveness of the formulary conversion of all statins to either cerivastatin or simvastatin at the Madigan Army Medical Center.
METHODS: This was a retrospective database analysis of patients involved in the conversion. The pre-LDL-cholesterol (LDL-C) level was defined as the most recent measurement prior to conversion; the post LDL-C was the first measurement recorded ≥ 21 days after conversion. Inclusion criteria included cerivastatin use after conversion, pre- and post-LDL-C measurements, gender, and date of birth. RESULTS: Of 1392 converted patients, 89% (1245) were converted to cerivastatin utilizing the Madigan conversion protocol. Of these patients, 451 met all criteria. Patients were converted from fluvastatin (48.6%), atorvastatin (34.8%), pravastatin (11.5%), or > 1 sequential statin (5.1%).

Parameter	Pre-Conversion n (%)	Post-Conversion n (%)	p value
At NCEP goal*	246 (54.5)	335 (74.3)	<0.001
Mean LDL-C (mg/dl)#	107.9	93.78	<0.0001
Mean total-C#	200.0	186.3	<0.0001
Mean HDL-C (mg/dl)#	45.3	50.5	<0.0001
Mean TG (mg/dl)#	181.4	174.4	<0.015

* McNemar chi-square; # paired t-test

In patients receiving statins at any dose, cerivastatin, dosed per protocol, provided additional LDL-C and total-C reductions, and HDL-C elevations, that were statistically significantly greater than pre-conversion statins in secondary prevention patients, and in primary prevention populations who were diabetic, high-risk non-diabetic, and low-risk non-diabetic. Cerivastatin brought more patients to NCEP goal than other statins, including atorvastatin ($p<0.009$).
CONCLUSIONS: Cerivastatin improved important lipid parameters and NCEP goal attainment when compared to pre-conversion statins, supporting its utility in formulary conversion programs.

39E. Increasing dispersion in refractoriness does not alter defibrillation energy requirements. *J. Jason Sims, Pharm.D.*, Allison W. Miller, Pharm.D., Michael R. Ujhelyi, Pharm.D.; University of Georgia; Medical College of Georgia; Augusta VA Medical Center, Augusta, GA.

BACKGROUND: Electrophysiologic mapping studies indicate that post-shock activations occur and propagate arrhythmically regardless of the amount of myocardium directly depolarized by a defibrillation shock. Thus, we hypothesize that the homogeneity of myocardial refractoriness regulates whether post-shock activations propagate arrhythmically and cause failed defibrillation.
METHODS: Twenty-five swine were instrumented with a LAD perfusion catheter placed 10-15 mm past the 2nd diagonal for low-dose regional infusion of d-sotalol 5 mg/hour (n=10), pinacidil 0.15 mg/kg/hour (n=8), or placebo (n=7) to create dispersion in refractoriness (by regionally increasing or decreasing refractoriness) or serve as control. Effective refractory periods (ERP) were measured at five myocardial sites and ERP dispersion was calculated as the maximal difference between the five sites. Biphasic waveform defibrillation energy requirements (DER) values were determined using an up/down algorithm.

	Baseline	d-Sotalol	Baseline	Pinacidil
ERP dispersion (ms)	15 ± 0.8	34 ± 1.1	19 ± 1.8	34 ± 2.5
DER (J)	12 ± 1.2	12 ± 1.4	16 ± 2.1	17 ± 2.1

RESULTS: The table below reports the mean ± SEM for DER values and ERP dispersion at baseline and treatment with regional placebo, d-sotalol or pinacidil. Regional d-sotalol increased ERP in the perfused area by 32 ± 3 ms and regional pinacidil decreased ERP in the perfused region by 26 ± 2.4 ms, which resulted in an increase in ERP dispersion of 127% and 79%, respectively. However, neither regional d-sotalol nor pinacidil changed DER values. Placebo infusion did not alter any electrophysiologic variable.
CONCLUSIONS: Increasing dispersion in refractoriness does not alter DER values regardless of the method by which dispersion is increased. These data suggest that defibrillation efficacy is not primarily dependent on homogeneity of refractoriness. Other electrophysiologic parameters, such as conduction velocity, may be more important regulators of defibrillation efficacy.
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40. Comparison of in-hospital clinical outcomes in patients receiving either eptifibatide or abciximab during percutaneous coronary interventions. *Dawn Bell, Pharm.D.*, Reyaz U. Haque, MD., Ken Jozefczyk, M.S.; Ruby Memorial Hospital; West Virginia University, Morgantown, WV.

PURPOSE: To compare in-hospital clinical outcomes in patients receiving

either eptifibatide (E) or abciximab (A) during percutaneous coronary interventions (PCI).
METHODS: In this observational cohort study, data was abstracted from a central database using ICD-9 codes and chart review was conducted in a randomly selected subset of patients. E was given as a 180 µg/kg bolus dose followed by a 2 µg/kg/minute infusion for 20 hours post-PCI. Outcomes included death, new myocardial infarction and need for transfusion. All nominal data were compared using χ^2 analysis and the Kruskal-Wallis test was used for all other comparisons. All statistical analyses were performed using JMP for the Macintosh.
RESULTS: A total of 520 patients received E and 456, A. There were no significant differences in baseline or angiographic characteristics between groups. Mortality and new MI were similar between groups (9 deaths vs 11 deaths; new MI in 16% vs 29%, E and A, respectively, p>0.05). Length of stay (LOS) was also similar (2.97 vs 3.13 days, E and A, respectively). Transfusion requirements were similar in both groups despite higher activated clotting times (ACT) during PCI in E (median ACT 338 vs 290 seconds in E and A respectively, p<0.0001).
CONCLUSIONS: This study is limited by its small sample size, but is consistent with previous reports of similar in-hospital outcomes in patients receiving either E and A for PCI. Since drug cost per patient for A is three times higher than E, data showing similarity in clinical outcomes is important for pharmacy practice.

Critical Care

41. Fungemia in patients with thermal injury: clinical characteristics, antifungal therapy, and associated outcomes. *David R. Foster, Pharm.D.,* Julie R. Berman, Pharm.D., Jai K. Prasad, M.D.; Detroit Receiving Hospital; Wayne State University, Detroit, MI.

PURPOSE: Invasive candidiasis is associated with high mortality in critical illness, and controversy exists regarding therapy. Our intent was to review clinical characteristics, treatment patterns and outcomes associated with candidiasis in thermal injury.
METHODS: All burn-ICU patients with positive fungal cultures in a 2-year period were identified. Microbiological information, antifungal regimens, and outcomes were collected. Patients were categorized based on fungal cultures as group 1 (candidemia), group 2 (≥ 3 sites, no positive blood cultures) or group 3 (< 3 sites, no positive blood cultures).
RESULTS: Thirty records were reviewed. Mean age and extent of burn were 46.4 ± 19.4 years and 40.1 ± 26.4% TBSA. Eleven cases were group 1, 5 were group 2 and 14 were group 3. All group 1 and group 2, and 50% of group 3 received antifungal therapy (p=0.0065). Of group 1, 90.9% received fluconazole (FLU), compared to 100% of group 2 and 42.9% of group 3 (p=0.70); mean doses (mg/day) were 320 ± 197.5, 240 ± 89.4, and 225 ± 88.0, respectively (p=0.43). Only group 1 (72.7%) received systemic amphotericin B (AMB) (p=0.021); mean dose (mg/day) was 46.9 ± 14.9. When treating candidemia, initial treatment was FLU in 33.3% of cases and AMB in 66.7% of cases (p=0.51). Mortality (p=0.90), clinical improvement (p=0.79), and microbiological failure (p=0.36) were similar in group 1 patients who received AMB and group 1 patients who did not.
CONCLUSIONS: AMB was prescribed exclusively for group 1, while FLU usage and dosage were similar among all groups. We hypothesized that AMB may improve outcomes; however, this was not confirmed. Treatment of group 1 patients was case specific, and therapy with FLU and/or AMB was not always sequential. FLU doses used to treat candidemia may have been suboptimal; ≥ 400 mg/day is currently recommended. This study illustrates a lack of consensus regarding choice of antifungal therapy, and the need to strengthen efforts to ensure appropriate therapy in critically ill patients with candidiasis.

42. Use of alteplase in peripheral arterial occlusions: outcomes and complications. *Anthony T. Gerlach, Pharm.D.,* Kerry K. Pickworth, Pharm.D.; Ohio State University Medical Center, Columbus, OH.

PURPOSE: Due to the urokinase shortage, use of alteplase has increased. The purpose of this study is to report the clinical use and document outcomes of alteplase for treatment of peripheral arterial occlusions (PAO) in a university-based tertiary care setting.
METHODS: All patients receiving alteplase from May 1, to December 31, 1999, for treatment of PAO were identified. Data collected included demographics, dosage, duration of infusion, and bleeding complications. Success was determined angiographically. A major bleed was defined as: a documented cerebrovascular, gastrointestinal or retroperitoneal bleed, use of transfusions, or drop in hemoglobin greater than 2 g/dl with symptoms (i.e., hypotension or hypoxia). Minor bleeds were defined as ecchymosis, epistaxsis, hematoma, hematuria, hemoptysis or petechiae without drop of hemoglobin greater than 2 g/dl. Fisher's exact tests were performed for statistical analysis.
RESULTS: Alteplase was administration to 32 patients for treatment of PAO. All patients received heparin.

	Low Dose < 2 mg/hour	High Dose ≥ 2 mg/hour
n	14	18
Average age (years)	60	58
Average dose (mg/hour)	1.1	2.7
Average total dose (mg)	28.6	59.7
Successful lysis	75%	77%
Total bleeding complications*	23%	61%
Major bleeds*	0	22%
Minor bleeds	23%	39%

* p<0.05

CONCLUSIONS: Use of low-dose alteplase (< 2 mg/hour) resulted in similar efficacy, while significantly decreasing the incidence of major bleeding complications. Studies need to be conducted to determine the effective dose of alteplase for PAO, while minimizing bleeding complications.

43. A randomized, crossover study of duodenal or jejunal compared to nasogastric administration of omeprazole suspension in critically ill patients. *Jeffrey O. Phillips, Pharm.D.,* Keith M. Olsen, Pharm.D., FCCP, Jill A. Rebuck, Pharm.D., Michael H. Metzler, M.D.; University of Missouri-Columbia, Columbia, MO; University of Nebraska Medical Center, Omaha, NE.

PURPOSE: To characterize absorption and pH control of simplified omeprazole suspension (SOS) 2 mg/ml in 8.4% sodium bicarbonate administered via the nasogastric versus jejunal or duodenal route.
METHODS: Nine critically ill surgical patients, NPO, mechanically ventilated were enrolled in this randomized, crossover study. Patients received a single dose 40 mg SOS by nasogastric and either the jejunal or duodenal route. Twenty-four-hour continuous intragastric pH monitoring was performed during the study period. Sequential blood samples were collected over 24 hours to characterize SOS absorption and the pharmacokinetic parameters.
RESULTS: Nasogastric administration of SOS resulted in lower maximum mean ± SD serum concentrations compared to jejunal/duodenal dosing (0.970 ± 0.436 vs 1.833 ± 0.416 µg/ml, p=0.006). SOS absorption was significantly slower when administered via nasogastric tube (108.3 ± 42.0 vs 12.1 ± 7.9 minutes, p<0.001). However, all routes of administration resulted in similar SOS area under the serum concentration-time curves ($AUC_{0-\infty}$; 415.1 ± 291.8 vs 396.7 ± 388.1 µg•hour/ml, p=0.91). Mean intragastric pH values remained above 4 one-hour post SOS administration and remained greater than 4 for the entire 24-hour study (6.32 ± 1.04, 5.57 ± 1.15, nasogastric vs jejunal/duodenal, p=0.015), regardless of administration route.
CONCLUSIONS: In critically ill surgical patients, pharmacokinetic parameters and subsequent pH control following the administration of SOS are similar by the jejunal, nasogastric, or duodenal route. Simplified omeprazole suspension offers an alternative acid control measure when patients are unable to take oral medications, yet have an enteral tube in place.

44. Appropriate use of stress ulcer prophylaxis in a community teaching institution. *Pramodini B. Kale-Pradhan, Pharm.D.,* Kevin C. Dubay B.S., Michael S. Palmer, B.S.; Wayne State University; St. John Hospital and Medical Center, Detroit, MI.

PURPOSE: This prospective observational study examines the appropriate use of stress ulcer prophylaxis (SUP) in a community teaching institution based on the criteria compiled by the American Society of Health System Pharmacists (ASHP).
METHODS: Patients in the surgical intensive care unit (SICU) and non-ICU patients who were prescribed SUP from February 1, to March 31, 2000, were included. Patients with a GI bleed (GIB) within the past year or neurosurgery patients were excluded. The primary outcomes of the study were appropriate use of the SUP and the development of GIB or nosocomial pneumonia (NP). SUP was appropriate if they met either major risk factors (mechanical ventilation > 24 hours, coagulopathy for > 48 hours, Glascow Coma Score ≤ 10, thermal injuries > 35% of their BSA, or partial hepatectomy) or minor risk factors (patients with at least two of the following: ICU stay > 1 week, occult bleeding lasting 6 days, use of high-dose steroids and ICU patients with multiple trauma, transplant patients or hepatic injury).
RESULTS: Seventy-five patients, 44 SICU and 31 non-ICU were included. According to ASHP criteria, 29 of 44 (66%) ICU and 0 of 31 (0%) non-ICU patients received appropriate SUP. However, in 15 of 44 (34%) ICU patients SUP was continued upon transfer out of ICU despite absence of risk factors. Fifteen of 75 (20%) patients were discharged on SUP. No patients developed GIB or NP.

	SICU	Non-ICU
Sex	21 M, 23 F	17 M, 15 F
Mean age (years)	62	63
Discharged with SUP	25%	12.9%
Mean length of SUP therapy (days)	12.6	6.6
Mean length of stay (days)	21	7.5

CONCLUSION: ASHP guidelines for SUP were not followed in 46 of 75 (61%), which present the need for education efforts to ensure optimal management of patients. This may have significant pharmacoeconomic impact.

45. Adverse events associated with propofol therapy: a comparison between the Diprivan® and propofol formulations. *Keith B. Thomasset, Pharm.D.,* Hoan Linh Banh, Pharm.D.; Thomas Jefferson University Hospital, Philadelphia, PA.

PURPOSE: To compare the incidence of adverse reactions associated with the use of two different propofol formulations.
METHODS: A prospective chart review was conducted on all intensive care unit (ICU) patients receiving propofol at Thomas Jefferson University Hospital (TJUH) between October and December 1999. The results were compared to a historic control prospective chart review conducted on all ICU patients receiving Diprivan® at TJUH from June to July 1999. Outcome measures included: decrease in blood pressure, incidence of hypertriglyceridemia, metabolic acidosis and allergic reactions associated with each formulation.
RESULTS: A total of 98 patients were included in the investigation. Of these patients, 48 (49%) received Diprivan®, while the remaining 50 (51%) received propofol. The incidence of decreased blood pressure was higher in the Diprivan® group (31% vs 4%, $p<0.05$). No patients in either group developed metabolic acidosis, or experienced hypertriglyceridemia or allergic reactions.
CONCLUSION: The results reveal a significant difference with respect to the incidence of decreased blood pressure between the two groups. However, no significant difference was observed between Diprivan® and propofol when assessing the incidence of hypertriglyceridemia, metabolic acidosis and allergic reactions. Ethylenediaminetetraacetic acid and metabisulfite, when used as preservatives, were not associated with allergic reactions in the study population.

46E. Reliability of four sedation assessment scales. *Eric T. Wittbrodt, Pharm.D.*, BCPS, Teena Abraham, Pharm.D., Barry D. Fuchs, M.D., Robin McClelland, R.N., John C. Medendorp, R.N., B.S.N., Janet Matthews, R.N.; University of the Sciences in Philadelphia, Philadelphia, PA; Long Island University, Brooklyn, NY; Hahnemann University Hospital, Philadelphia, PA; University of Pennsylvania, Philadelphia, PA.

PURPOSE: Proper assessment of the adequacy of sedation is essential for titration of anxiolytic therapy in agitated critically ill patients. We evaluated the reliability of four sedation assessment scales: Ramsay scale (RAS), visual analog scale (VAS), sedation-agitation scale (SAS), and Hahnemann Sedation Assessment Scale (HSAS), a five-level clinical scoring system which assesses motor activity, ability to follow commands, and level of consciousness.
METHODS: We prospectively assessed the adequacy of continuously infused sedation in adult, critically ill, mechanically ventilated patients. Two pairs of study evaluators simultaneously assessed patients using all four scales without communicating with each other. Intraclass correlation coefficients (r) and κ scores for pairs of evaluators were generated to assess reliability. $R > 0.8$ and $\kappa > 0.5$ were clinically significant.
RESULTS: We evaluated 30 patients admitted to three intensive care units. R values for all evaluators were as follows: 0.85 for HSAS, 0.76 for SAS, 0.75 for RAS, and 0.64 for VAS. For the pair of evaluators with the highest frequency of evaluations, r values were: 0.73 for HSAS, 0.65 for RAS, 0.52 for SAS, and 0.58 for VAS. κ scores were: 0.78 for HSAS ($p<0.001$), 0.80 for RAS ($p<0.001$), and 0.34 for SAS ($p=0.085$). Complete agreement among evaluators occurred in 24/30 patients for HSAS, 10/30 for RAS, 10/30 for SAS, and 2/30 for VAS.
CONCLUSION: HSAS is the most reliable of the scales tested; VAS is the least reliable; SAS and RAS are comparable. HSAS appears to be a reliable scale for the assessment of adequacy of sedation.
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Dermatology

47. Prevalence and treatment of actinic keratosis. *Shilpa S. Mehta, Pharm.D.*, Lester M. Arguelles, M.S., Sanjay K. Gandhi, Ph.D., J. Gregory Boyer, Ph.D.; Pharmacia Corporation, Skokie, IL.

PURPOSE: This study determines the prevalence and treatment of actinic keratosis (AK), a premalignant skin lesion that can progress to non-melanoma skin cancer (NMSC) if untreated, in a privately insured patient population.
METHODS: MarketScan, a national claims database representing 3.5 million lives from 1995-1997, was used to determine the prevalence of AK, comorbidities and treatments associated with AK, and the presence of NMSC in AK patients.
RESULTS: From 1995-1997, the annual prevalence of AK increased from 2.0% to 2.6%, representing a 30% increase. Actinic keratosis was more frequent in males (3.0% vs 1.8%), the South (3.4% vs 2.1%), and older patients. Prevalence rose markedly, beginning at age 50, with highest occurrence at age 70-79 (10.9% in males, 5.9% in females). Malignant skin neoplasms and seborrheic keratoses were the most frequent comorbidities, documented in 4.2% and 3.2% of AK-related visits. Almost all AK treatment was outpatient, with destruction of facial lesions being the most common treatment (62% of all AK-related services). Each year, approximately 5% of AK patients had concurrent NMSC diagnosis.
CONCLUSIONS: The prevalence of AK and NMSC increased 30% over three years, with males, older patients and those in the South at highest risk. Despite the increase, our estimates are lower than those reported in the literature. Reasons may include lack of awareness, underdiagnosis or undertreatment of AK in this population. Pharmacists can educate high-risk patients about AK and strategies to reduce the risk of cancer. Increased awareness will facilitate screening and treatment of AK and help reduce malignancy-related costs.

Drug Delivery

48. Intrapericardial therapeutics: a pharmacokinetic comparison between pericardial and intravenous procainamide delivery. *Michael R. Ujhelyi, Pharm.D.*, Kelly Z. Hadsall, B.S., David Euler, Ph.D., Rahul Mehra, Ph.D.; Medtronic CRM Research; University of Minnesota, Minneapolis MN.

Pericardial delivery (PD) of water-soluble drugs may target atrial myocardium because ventricular tissue diffusion is likely limited by epicardial vasculature uptake. Hence, PD may be able to maximize procainamide (PA) atrial antiarrhythmic efficacy without ventricular proarrhythmia and hypotension. This study assessed pericardial fluid and plasma disposition of pericardial (PD-PA) and intravenous (IV-PA) PA delivery (10 ml) and actions on right atrial and ventricular endocardial effective refractory periods (ERP) in 11 swine treated with PD-PA (n=7) using sequential doses of 0.5, 1 and 2 mg/kg, or IV-PA 2, 8, and 16 mg/kg infusion (n=4) over 10 minutes. PD-PA doses produced high peak PA pericardial fluid levels of 250-900 µg/ml due to a small Vd 0.55 ± 0.07 ml/kg. PD-PA had no pericardial fluid distribution phase, a rapid terminal elimination ($t? 20 \pm 3$ min) suggesting rapid diffusion into coronary vasculature, and undetectable plasma levels. IV-PA doses produced peak plasma PA levels between < 1 to 40 µg/ml similar to literature values. IV-PA produced pericardial fluid PA levels that lagged behind peak plasma levels, but equaled or exceeded trough plasma levels suggesting rapid PA diffusion from coronary vasculature into pericardial fluid. PD-PA prolonged atrial ERP by 20% ($p<0.05$) at 2.0 mg/kg dose but had no effect on ventricular ERP. PA-IV prolonged atrial ERP by 10 and 20% at the 8 and 16 mg/kg doses ($p<0.05$).
CONCLUSION: Procainamide rapidly diffuses into and out of pericardial fluid regardless of delivery route. PA-PD produces very high local concentrations for a brief duration, which only prolongs atrial refractoriness. Pericardial antiarrhythmic drug delivery is a novel method that maximizes atrial pharmacodynamics without ventricular effects.

Education

49. Assessment of e-mail inquiries submitted to an online pharmacist through a consumer Web site and interrater reliability of a data collection tool. *Steven E Porter, Pharm.D.*, Mariela Alvarado Duval, Pharm.D., BCNSP, Laura Flowers, MPH, Antoinette Brooks, M.D., Kevin F Smith, M.D., MPH; eMD.com, Norcross, GA.

PURPOSE: Easy access to the Internet provides consumers with an additional avenue for seeking medical information. The purpose of this study is 1) to summarize profiles from consumers requesting pharmacy related information through an educational Web site; 2) to assess associations between consumer profiles and e-mail content; and 3) to assess the reliability of a data collection form.
METHODS: Consumers asked questions by e-mail to pharmacists through an Internet site. Responses were provided within 1 business day. Information was collected regarding the consumers and their requests. Two pharmacists separately completed the data collection tool for each e-mail to determine its reliability. Statistical analyses, including univariate, bivariate and kappa statistics were performed.
RESULTS: Sixty-eight e-mails, received between January 14, 2000 and June 9, 2000, were reviewed. The average age of the consumers was 39 years (range: 20–79); similar numbers of questions were received from males and females (34 vs 30). Interrater reliability suggested strong agreement between pharmacists for e-mail content categorization ($K = 0.80$, $p<0.001$). Consumers were more likely to indicate hypertension among their medical condition (10%) and sulfa drugs among their allergies (12%). Most consumers requested information about over-the-counter (OTC) medications (27%) and hypertension medications (15%).
CONCLUSION: Internet-based request and delivery is a valuable tool for providing pharmaceutical information. The data collection tool utilized was a reliable means by which to categorize the requests. Consumers use the Internet as an easy, convenient and confidential way to request pharmacy related information, especially for OTC medications.

50. Assessment of e-mail inquiries submitted to an online physician through a consumer Web site. *Mariela Alvarado Duval, Pharm.D., BCNSP*, Antoinette Brooks, M.D., Steven E. Porter, Pharm.D., Laura Flowers, MPH, Kevin F. Smith, M.D., MPH; eMD.com, Norcross, GA.

PURPOSE: Easy Internet access provides consumers with an additional avenue for seeking medical information. The purpose of this study was 1) to summarize the profiles of consumers requesting medical information through an educational Web site; and 2) to assess associations between consumer profiles and e-mail content.
METHODS: Information was collected regarding consumers and their inquiries e-mailed to an online physician. A physician categorized each e-mail, based on the medical content of the question, and provided responses within 1 business day. Univariate and bivariate statistical analyses were performed.
RESULTS: Three hundred fifty e-mails, received between January 14, 2000 and April 26, 2000, were reviewed. A similar number of questions were received from males and females (154 vs 144) and the average age of the consumers was 34 years (range 5 to 80). The most frequent types of questions were dermatological (11%), musculoskeletal (11%), pulmonary (8%) and men's health (6%). Sensitive issues (men's/women's health, and sexually transmitted diseases) represented 15% of the questions. No differences in question content were noted between genders. Questions regarding gastroenterology, men's health, psychiatry, and women's health were more common among consumers less than 40 years of age.
CONCLUSION: The Internet is a valuable tool for providing medical information. Although physicians did not provide diagnosis, they provided information and directed the consumer to a physician when advisable. Consumers use the Internet as an easy, convenient way to request medical information. The consumer may feel more comfortable requesting sensitive information through an indirect route than through a face-to-face encounter.

Endocrinology

51. Improving anti-platelet prophylaxis in high-risk diabetic patients in a rural, primary care clinic. *John J. Faragon, Pharm.D.*, Nathalie Seoldo, Jenny A. Van Amburgh, Pharm.D., Nancy M. Waite, Pharm.D., Eric H. Hobson, Ph.D. Hedy Migden, M.D.; Albany College of Pharmacy, Albany, NY; Northeastern University, Boston, MA; Altamont Internal Medicine and Pediatrics, Altamont, NY.

PURPOSE: The study was designed to 1) identify diabetic patients who were at high risk for cardiovascular disease; 2) identify which patients were taking daily antiplatelet therapy; and 3) examine the impact of an education-focused pharmacist intervention on the percentage of patients receiving antiplatelet prophylaxis.
METHODS: Diabetic patients were identified via database query. Charts were reviewed to determine if the patient was a candidate for antiplatelet (i.e., aspirin, clopidogrel) therapy according to American Diabetes Association criteria and whether the patient was currently taking antiplatelet therapy. An intervention program was developed that included questions to clarify the patient's current use of aspirin-containing products or contraindications to antiplatelet therapy, and counseling information regarding the benefits and risks of antiplatelet therapy. Patients were contacted by the pharmacist during clinic appointments or via telephone. A review at six months examined the percentage of patients using antiplatelet therapy.
RESULTS: Of the 94 diabetic patients identified, 16 (17%) were receiving antiplatelet therapy prior to pharmacist intervention. At the 6-month review, 23 patients had received the education program from a pharmacist. Nineteen patients (82.6%) accepted the pharmacist recommendation and four patients had been lost to follow up. The pharmacist intervention significantly increased the percentage of diabetic patients receiving antiplatelet therapy (36.2%). Other issues identified included the lack of consistent documentation of aspirin use in the patient's charts and the need for a mechanism to contact at-risk patients in a more timely manner.
CONCLUSIONS: The education-focused intervention provided by the pharmacist successfully increased the number of diabetic patients taking antiplatelet therapy.

52E. Atypical antipsychotic agents and glucose metabolism: Bergman's minimal model analysis. *David C. Henderson, M.D.*; Freedom Trail Clinic, Boston, MA.

PURPOSE: Some atypical antipsychotic agents have been linked to diabetic ketoacidosis and adult onset diabetes mellitus in uncontrolled clinical reports. In a cross-sectional study, the effect of the atypical antipsychotic agents, clozapine, olanzapine, and risperidone, on glucose metabolism was examined in schizophrenia subjects.
METHODS: A frequent sampled intravenous glucose tolerance test (FSIVGTT) using Bergman's Minimal Model Analysis (MINMOD), allows for examination of insulin sensitivity (SI) and glucose effectiveness (SG). After fasting overnight, subjects were admitted to the GCRC at Massachusetts General Hospital and underwent a FSIVGTT. Data were analyzed using an analysis of variance comparing the values of the three treatment groups.
RESULTS: Twenty-five subjects completed the study. There were no differences between the three groups in age, race, BMI, fasting glucose, fasting insulin, and insulin 20 minutes post-glucose injection. Significant differences between groups were noted on glucose concentrations 20 minutes post-glucose injection (p=0.02) and SI (p=0.0022). Insulin sensitivity differed significantly between groups comparing clozapine (mean 2.44 ± 2.25 x 10^{-4}•$minute^{-1}$•ml^{-1}) with risperidone (mean 10.45 ± 7.00 x 10^{-4}•$minute^{-1}$•ml^{-1}; p=0.0007) and olanzapine (mean 4.257 ± 2.48 x 10^{-4}•$minute^{-1}$•ml^{-1}) with risperidone (p=0.0051). Controlling for sex, differences between the three groups for SG were not significant (p=0.15), although clozapine (mean 0.015 ± 0.005 $minute^{-1}$) differed from risperidone (mean 0.021 ± 0.006 min^{-1}) (p=0.067) and olanzapine (mean 0.016 ± 0.008 $minute^{-1}$) differed from risperidone (p=0.09) at trend levels.
CONCLUSION: Preliminary results suggest that the three groups differ significantly in insulin sensitivity, with clozapine and olanzapine associated with abnormally low insulin sensitivity. Larger sample sizes are needed to elucidate any effect on SG.
Presented at the Annual Meeting of the NCDEU, Boca Raton, FL, May 30-June 2, 2000.

53. Impact of clinical pharmacy services on outcomes in patients with diabetes mellitus in an urban, multidisciplinary clinic for indigent patients. *Tracy D. Baher, Pharm.D.*, Theresa R. Prosser, Pharm.D., BCPS, Ruth A. Klatt, Pharm.D.; Saint Louis College of Pharmacy, St. Louis, MO.

PURPOSE: 1) Compare outcomes to diabetes quality improvement project (DQIP) measurement set; 2) evaluate impact of clinical pharmacy services; and 3) identify potential patient or system factors if standards were not met.
METHODS: Medical records of adult diabetic patients (n=167) were reviewed in a multidisciplinary, primary care clinic for indigent patients. Microsoft Access was used to evaluate data.
RESULTS: HbA_{1c} was < 8% in 54 % (DQIP standard = 40%) with a mean of 8.9%. HbA_{1c} was obtained ≥ 1x/year in 74% (93%). Blood pressure was checked ≥ 1x/year in 82% (97%). Diastolic blood pressure ≤ 90 mm Hg was documented in 46% (96%). Microalbumin/urine analysis was obtained 1x/year in 68% (31%). Of microalbumin positive patients, 80% were on renal protective agents. Lipid profile was obtained in 64% (52%) and 74% had Tchol < 200 mg/dl or LDL < 130. Eye exams were performed 1x/year in 26% (40%) and foot exam in 25% (74%). Patient factors (e.g., non adherence) appear to be responsible for HbA_{1c} and blood pressure not meeting DQIP standards. System factors (e.g., not performed/documented) appear to be responsible for eye and foot exam variance.
CONCLUSIONS: Areas of clinical pharmacy involvement (e.g., HgA_{1c} at goal, microalbumin, lipid/blood pressure check) were more likely to exceed DQIP standards or variance was attributed to patient factors. In areas without pharmacy involvement, variance was greater and was more likely due to system factors. Causes of patient non-adherence need to be further delineated and enhancing pharmacist involvement may further improve adherence to DQIP standards.

54. Efficacy of hormone replacement therapy on lipid profile and bone mineral density in postmenopausal women: continuous vs sequential treatment. Chang Yun Lee, M.S., *Sukhyang Lee, Pharm.D.*; Sookmyung Women's University, Seoul, Korea.

PURPOSE: Menopausal women experience urogenitory and vasomotor symptoms with increased risk of osteoporosis and cardiovascular diseases, which can be reduced by hormone replacement therapy. However, unopposed estrogen therapy has been associated with an increased risk of endometrial hyperplasia or cancer. The objectives of this study were to assess efficacy and safety of hormone replacement therapy, and compare continuous therapy to sequential therapy. The other objective was to assess the perception of menopause and hormone replacement therapy in Korean menopausal women.
METHODS: In this retrospective study, women were eligible to participate if they were longer than 6 months of menopause, had not started hormone replacement therapy and normal in the mammogram and Papanicolaou smear. Women were excluded if they had history of cardiovascular disease, uncontrolled diabetes mellitus, major organ dysfunction, breast cancer, endometrial cancer, cholesterol level higher than 190 mg/dl or triglyceride level higher than 500 mg/dl. Women were treated with Srogen® (conjugated equine estrogen 0.625 mg tablet) and Provera® (medroxyprogesterone acetate 2.5 mg tablet) for continuous therapy or Cycloprogynova® (Estradiol valerate 2 mg and Norgestrel 0.5 mg complex tablet) for sequential therapy. They were evaluated for menopausal symptoms, lipid profile, bone mineral density, side effect of hormone replacement therapy and their perception of menopause and hormone replacement therapy.
RESULTS: Total 67 patients out of 94 enrollees were included in final analysis (33 in continuous therapy, 34 in sequential therapy). There were significant decreases in total cholesterol (15.04 ± 3.17, p=0.0001), LDL cholesterol (19.72 ± 3.27, p=0.0001), and increase in HDL cholesterol (5.89 ± 1.63, p=0.0001). Bone mineral density increased significantly after treatment (0.02 ± 0.11, p=0.0001). But, there were no significant differences between continuous and sequential therapy. Incidences of flush and urinary frequency were less than 10% in both groups. Menopausal women recognized the necessity of hormone replacement therapy (70%) without exact knowledge of cardiovascular protective effect.
CONCLUSIONS: Hormone replacement therapy was effective in improving

lipid profile, bone mineral density and menopausal symptoms in both continuous and sequential treatments with similar efficacy.

55. Demographic and medication use of the long-term outcomes and sibutramine effectiveness for weight (LOSE Weight) study in a managed care organization. Frances A. Lanty, Pharm.D., BCPS, Erin A. Vogel, Pharm.D., BCPS, Daniel C. Malone, Ph.D., Julie A. Porter, Pharm.D., BCPS, *Marsha A. Raebel, Pharm.D., BCPS*; Kaiser Permanente of Colorado; University of Colorado, Denver, CO; University of Arizona, Tucson, AZ.

PURPOSE: To describe the relationship between medication use and body mass index (BMI) for patients enrolling in a randomized controlled weight management trial.
METHODS: The demographics and medication use of the first 242 patients were evaluated. Demographic data were captured via case report forms. Prescription medications for the year prior to enrollment were identified through pharmacy dispensing records. Medications were classified as obesityrelated by an expert panel consisting of two physicians and three clinical pharmacists. The medications were ranked as probably obesity-related, possibly related or unlikely related. Regression analysis was conducted to determine if BMI could predict obesity-related medication expenditures.
RESULTS: The mean (± SD) age was 46.2 ± 10.0; 85% (205) were female, and mean (± SD) BMI was 38.8 ± 7.2. These patients received 3918 prescriptions, with 676 (17.3%) classified as probably obesity-related. The mean number of prescriptions filled per patient was 16.0 ± 17.5. Total cost of all medications was $170,940. An average of 2.7 ± 5.4 obesity-related medications were filled. The total cost of these medications was $28,730. The regression analysis found that for every 1.0 unit increase in BMI, an increase of $7.32 in obesity-related medication costs was observed (p=0.01). Patients with BMI values > 40 had average obesity-related medication costs of $173 compared to only $48 for patients with BMI values < 33. No relationship was observed between total (obesity and non-obesity) medication expenditures and BMI.
CONCLUSION: There was a positive relationship between BMI and the cost of obesity-related medications. The total cost of medications for obese patients was substantial-over $700 per year per patient.

Gastroenterology

56. Effect of gender on the efficacy of ondansetron and prochlorperazine for the prevention of postoperative nausea and vomiting. *Jack J. Chen, Pharm.D.*, BCPS, David G. Frame, Pharm.D., Western University of Health Sciences, Pomona, CA; Rush-Presbyterian St. Luke's Medical Center, Chicago, IL.

PURPOSE: To describe the effect of gender on the efficacy of ondansetron and prochlorperazine in the prevention of postoperative nausea and vomiting (PONV).
METHODS: Male and female patients at high risk for PONV undergoing total hip or knee replacement procedures were randomized in a double-blinded manner to receive either ondansetron 4 mg intravenously or prochlorperazine 10 mg intramuscularly. Study drug (and dummy saline) was administered immediately upon completion of the surgical procedure. During the subsequent 48 hours, the incidence and severity of PONV was recorded. The Yates-corrected Chi-square test and Fisher's exact test were used for analyses of non-parametric data (e.g., presence of nausea or vomiting, presence of PONV risk factors).
RESULTS: The four study groups consisted of ondansetron-treated males (n=13), prochlorperazine-treated males (n=16), ondansetron-treated females (n=24), and prochlorperazine-treated females (n=25). Baseline demographics (age, height, weight) and the proportion of patients with at least one risk factor for PONV (i.e., history of PONV or obesity) were similar within both gender groups. Overall, the incidence of nausea was greater in the ondansetron group as compared to the prochlorperazine group (81% vs 56%; p=0.02; odds ratio 3.4; 95% CI=1.2-9.4). When analyzed according to gender, the incidence of nausea in ondansetron-treated males and females was similar (77% and 83%, respectively; p=0.64) as was emesis (46% and 50%, respectively; p=0.82). However, in the prochlorperazine group, the incidence of nausea was significantly greater in females as compared to males (76% and 25%, respectively; p=0.001; OR=9.5, 95% CI=2.2-40.8) as was the incidence of emesis (44% and 12%, respectively; p=0.03; OR=5.5, 95% CI=1.1-29.5). The type of surgical anesthesia and postoperative analgesia were similar in all groups.
CONCLUSIONS: The antiemetic response to prochlorperazine is dependent on gender (i.e., greater efficacy in males). The antiemetic response to ondansetron is not affected by gender (i.e., similar efficacy in males and females).

57E. *Helicobacter pylori* treatment in an urban medical center: are the clinical results generalizable? Neil H. Stollman, M.D., *Nicole T. Gordon, Pharm.D.*, Rosanna Moura, M.D., Luigi Frugone, Jose Plaza; Jackson Memorial Hospital; University of Miami, Miami, FL.

PURPOSE: Numerous studies have demonstrated *Helicobacter pylori* (Hp) eradication rates of 80-90%. The generalizability of these results to community practice is unknown. The absence of compliance-enhancing efforts such as counseling, telephone calls and pill counts may compromise the efficacy of these regimens in routine clinical use. The aim of this study was to evaluate the effectiveness of an anti-Hp regimen given as part of standard medical practice in an urban medical center.
METHODS: Patients who were treated for Hp over a 1-year period in the Jackson Memorial Hospital's (JMH) clinics with amoxicillin 1 g, clarithromycin 500 mg and lansoprazole 30 mg (all given twice daily for 14 days) were retrospectively identified. An explanatory letter was sent, telephone contact was made and patients were encouraged to come for an interview and urea breath test (UBT; Meretek UBT®). Patients were instructed to bring any unused medications with them, and to discontinue all antibiotics and anti-secretory agents for 2 weeks before their appointment.
RESULTS: One hundred twenty-five prescriptions for this regimen were identified through the pharmacy database, with Hp positive status confirmed through medical records. Eighty-five patients were able to be contacted by telephone and 41 patients agreed to come in for testing. Hp eradication rate by UBT was 85%. Self-reported compliance (by questionnaire and pill count) was estimated to be adequate in 75% of patients. Age, gender, native language, or language counseled in were not predictive of eradication success.
CONCLUSIONS: Patients treated for Hp in an urban, tri-lingual clinic setting, without the compliance-enhancing measures routinely used in clinical trials still manifested an acceptable level of Hp eradication. This data supports the generalizability of trial results to routine clinical practice.
Presented at the EAHP 5th Congress Meeting, Madrid, Spain, March 2000.

58. Rates of gastrointestinal events in surgical patients. *Connie Chen, Pharm.D.*, Seema Dedhiya, M.S., Lisa Wester, M.S.; Pharmacia, Skokie, IL.

PURPOSE: Determine rates of gastrointestinal (GI) complications among a large group of inpatient surgery patients.
METHODS: Data were obtained from a database, HCIA (Baltimore, MD), containing detailed information from nearly 200 acute-care hospitals and approximately 1.5 million total annual discharges from 1998. All surgical patients were included in the study population. Comparisons were made between cases with and without secondary diagnosis of GI events identified by ICD-9 codes. Significant GI events were categorized as ulcers, hemorrhages, or obstructions.
RESULTS: The average age of patients with GI events was 63 years compared to 47 years in patients without GI events. The percent of female cases with GI events (58%) was similar to patients without GI events (56%). Over 2% of patients experienced a significant GI event during their hospitalization (ulcer, hemorrhage, or obstruction). Gastrointestinal hemorrhage alone comprised 46% of significant GI events. Three percent of patients experienced other GI complications such as dyspepsia, nausea, gastritis, or abdominal pain. Median costs in cases with GI events versus cases without GI events was $5995 versus $3997, respectively. Median length of stay in patients with and without GI events 6 and 3 days, respectively.
CONCLUSION: A significant number of GI events occur during hospitalizations for surgery. Of the cases reporting/experiencing significant GI events, nearly half were due to GI hemorrhage. Total costs and hospital stay were more than 30% greater in patients experiencing any GI event. Risk factors for these resource intensive events have to be identified and managed appropriately.

59. Celecoxib is associated with a lower incidence of serious gastrointestinal toxicity relative to nonsteroidal anti-inflammatory drugs: the celecoxib long-term arthritis safety study. *James. B. Lefkowith, M.D.*, Aimee M. Burr, M.S., William W. Zhao, Ph.D., Clem J. Maurath, M.S., Jeffrey D. Kent, M.D., Kenneth M. Verburg, M.D., Ph.D., George S. Geis, M.D., Ph.D.; Searle, Skokie, IL.

PURPOSE: To determine the incidence of symptomatic ulcers and ulcer complications (perforation, obstruction, bleeding) in arthritis patients receiving the specific COX-2 inhibitor celecoxib at supratherapeutic doses versus therapeutic doses of NSAIDs.
METHODS: This randomized, multicenter, double-blind trial was conducted in 7968 patients receiving celecoxib 400 mg BID (n=3987), ibuprofen 800 mg TID (n=1996), or diclofenac 75 mg BID (n=1985) for ≥ 6 months. Gastrointestinal (GI) outcomes were prospectively defined and adjudicated.
RESULTS: Significantly fewer patients on celecoxib required evaluations for potential GI events relative to NSAIDs (12.6% vs 16% for office evaluations and 2.8% vs 3.7% for consultative evaluations and diagnostic procedures for celecoxib and NSAID groups, respectively; p<0.001). The annualized incidence of symptomatic ulcers and ulcer complications in patients on celecoxib vs NSAIDs was 2.1% vs 3.5% (p=0.023) in the entire cohort and 1.4% vs 2.9% (p=0.017) in patients not on concomitant low-dose aspirin (ASA). For ulcer complications, the incidence rates on celecoxib vs NSAIDs were 0.76% and 1.45% (p=0.092) in the entire cohort and 0.44% and 1.27% (p=0.037) in non-ASA users. Approximately 50% of ulcer complications on NSAIDs occurred within the first 30 days. Celecoxib was safe and better or equally well tolerated compared to NSAIDs with respect to hepatic, renal, and cardiovascular adverse events.

CONCLUSIONS: Celecoxib at supratherapeutic doses was associated with a significantly lower incidence of symptomatic ulcers and ulcer complications and improved general safety and tolerability than therapeutic doses of NSAIDs. Low-dose ASA was an independent cause of GI toxicity. Supported by a grant from G.D. Searle & Co.

60E. Nasogastric lansoprazole or intravenous pantoprazole: which provides better pH control? James W. Freston, M.D., Jorg Taubel, M.D., Nancy L. Lukasik, B.S., Yi-Lin Chiu, Ph.D., *Wei-Jian Pan, Ph.D.*; University of Connecticut; Charterhouse Clinical Research Unit; TAP Holdings Inc.; Abbott Laboratories, Abbott Park, IL.

PURPOSE: To compare the effects on 24-hour intragastric pH following lansoprazole 30 mg QD administered via nasogastric (NG) tube and pantoprazole 40 mg QD administered intravenously (IV).
METHODS: Thirty-six healthy adults received 5-day once daily lansoprazole 30 mg NG and pantoprazole 40 mg IV in a two-way crossover fashion with 14-day washout period between periods. Blood samples for pharmacokinetic evaluation were collected on days 1 and 5, and 24-hour intragastric pH was monitored at baseline and on days 1 and 5 of each period.
RESULTS: Following is a summary of the intragastric pH results.

	Lansoprazole Day 1 (n=32)	Pantoprazole Day 1 (n=33)
Mean 24-hour pH	3.07*	2.76
% of time pH > 3	38.15*	28.19
% of time pH > 4	27.17*	18.96
% of time pH > 5	15.43*	9.77
% of time pH > 6	6.84	5.47
	Day 5 (n=33)	Day 5 (n=33)
Mean 24-hour pH	3.65*	3.45
% of time pH > 3	54.18*	48.67
% of time pH > 4	40.48	36.55
% of time pH > 5	21.76	19.90
% of time pH > 6	10.14	9.91

* $p<0.05$ vs pantoprazole

Lansoprazole bioavailability was not affected when the capsule contents were administered via NG tube.
CONCLUSION: Lansoprazole 30 mg QD (NG) was more effective than pantoprazole 40 mg QD (IV) in elevating intragastric pH on both Days 1 and 5. These data suggest that lansoprazole administration via NG tube is an effective alternative to pantoprazole IV for gastric acid control.
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61E. Simplified lansoprazole suspension or IV pantoprazole: which provides better pH control? J. Tiller, Pharm.D., *Y. Chiu, Ph.D.*, J. Taubel, M.D., J. Griffin, R.N., B. Pilmer, R.N.; TAP Pharmaceutical Products Inc., Lake Forest, IL; Abbott Laboratories, Abbott Park, IL; Charterhouse Clinical Research Unit, London, UK.

PURPOSE: This study compared the acid suppression ability of simplified lansoprazole solution (SLS) to IV pantoprazole (PAN).
METHODS: Thirty-six healthy subjects received 5 days of once-daily doses of SLS (30 mg lansoprazole capsule dissolved in 10 ml of 8.4% sodium bicarbonate) via NG tube or PAN via IV in a randomized two-period crossover fashion. Intragastric (IG) pH was measured for 24 hours on Days 1 and 5 of each crossover period. The effects of pH control were examined over the entire 24-hour dosing period, 0-15 hours (daytime) and 16-24 (nighttime) hours after dosing.
RESULTS: Simplified lansoprazole solution was significantly superior to IV PAN in raising mean pH on both Day 1 (3.13 vs 2.67, $p<0.001$) and on day 5 (3.95 vs 3.61, $p<0.001$). Simplified lansoprazole solution also produced significantly greater percentage of time where IG pH was above 3, 4, and 5 on days 1 and 5 over the 24-hour period. Simplified lansoprazole solution had a faster onset of action, as the mean pH and percentage of time that IG pH was above 3, 4, and 5 were significantly more profound throughout the daytime on day 1 and day 5. Simplified lansoprazole solution remained numerically higher than IV PAN in mean IG pH and percentage of time IG pH was above 3, 4, and 5 for nighttime on both days.
CONCLUSIONS: These data suggest that the simplified lansoprazole solution may provide faster symptom relief and more profound acid suppression than IV pantoprazole.
Presented at the 65th Annual Meeting of the American College of Gastroenterology, New York, NY, October 16-18, 2000.

62E. Rabeprazole vs omeprazole: onset, duration, and magnitude of gastric antisecretory effects. Jerry D. Gardner, M.D., Chatham, NJ, Sheldon Sloan, M.D., *Jay A. Barth, M.D.*; Science for Organizations; Janssen Pharmaceutica, Titusville, NJ; Eisai Inc., Teaneck, NJ.

PURPOSE: Reliable methods are needed to determine the time of maximal action of gastric antisecretory agents to provide physicians with the information necessary to assess treatment.
METHODS: Previously, a randomized, three-way crossover study measured gastric pH hourly for 24 hours in 23 healthy subjects on days 1 and 8 of dosing with placebo, 20 mg rabeprazole (RAB) or 20 mg omeprazole (OME; Aliment Pharmacol Ther 1998;12:1079-89). We used acid concentrations from this study to calculate integrated gastric acidity from which we determined onset, duration, and maximal effects of RAB and OME.
RESULTS: On day 1, inhibition of 24-hour integrated acidity with RAB (61 ± 5%; mean ± SEM) was greater ($p<0.0001$) than that with OME (31 ± 7%). Inhibition with RAB was significantly greater ($p<0.05$) than with OME 8 hours after the first dose. On day 1, median inhibition by RAB was 88% and by OME it was 42% of steady-state inhibition measured on day 8. Onset of inhibition of gastric acidity with RAB (3-4 hours) was similar to that of OME (2-3 hours). RAB and OME produced similar inhibition of acidity at 3 hours. Inhibition with RAB but not OME, continued to increase to a maximum (87% inhibition) at 7 hours. Duration of action of both drugs was at least 24 hours.
CONCLUSIONS: Although RAB has an onset of action that is similar to that of OME, the first-day effect of RAB is twice that of OME. This substantial, sustained first-day effect of RAB will enable physicians to assess its therapeutic actions earlier than agents such as OME that require several days to achieve their full antisecretory effects.
Presented at The American College of Gastroenterology, Phoenix, AZ, October 18, 1999.

63E. Heartburn relief after the first dose of rabeprazole in non-erosive gastroesophageal disease. Philip Miner, M.D., *Sheldon Sloan, M.D.*, Joseph Fillipone, B.A., Leonard Jokubaitis, M.D., Jay Barth, M.D.; Oklahoma Foundation for Digestive Research, University of Oklahoma Health Center, Oklahoma City, OK; Janssen Pharmaceutica, Titusville, NJ; Eisai Inc., Teaneck, NJ.

PURPOSE: In non-erosive gastroesophageal reflux disease (NERD), relief of heartburn and other symptoms with acid suppression is less reliable than in erosive disease. In a study comparing rabeprazole (RAB) 10 and 20 mg tablets once daily with placebo in relieving symptoms in NERD, the response to the first two doses was evaluated.
METHODS: This double-blind trial included patients with endoscopically confirmed NERD who reported at least moderate heartburn during the second week of a 2-week, single-blind, run-in on placebo. Daytime and nighttime heartburn were rated on a 5-point Likert scale from 0 (none) to 4 (severe), with assessments recorded in a diary.
RESULTS: In intent-to-treat analysis (n=199), mean daytime heartburn scores at day 1 were 1.31 for RAB 10 mg and 1.35 for 20 mg, versus 1.91 for placebo ($p<0.001$ for 10 mg, $p\leq0.01$ for 20 mg); day 2 scores were 1.15 for both RAB 10 mg and 20 mg, versus 1.75 for placebo ($p<0.001$ for 10 mg and 20 mg). Mean scores at night 1 were 1.14 for RAB 10 mg and 1.00 for 20 mg, versus 1.64 for placebo ($p\leq0.01$ for 10 mg, $p<0.001$ for 20 mg); night 2 scores were 0.89 for RAB 10 mg, 0.98 for 20 mg, and 1.53 for placebo ($p<0.001$ for 10 mg, $p\leq0.01$ for 20 mg).
CONCLUSION: In NERD, RAB 10 and 20 mg provide significant symptom improvement for both daytime and nighttime heartburn. This fast symptom relief is seen on the first day with the first dose.
Presented at Digestive Disease Week, San Diego, CA, May 21-24, 2000.

64. Physician willingness to discontinue proton pump inhibitors in patients receiving COX-2 inhibitors. *Diane K. Ammerman, Pharm.D.*, Tracy A. Mascari, Pharm.D., Jenene L. Hunkele, Pharm.D., Joshua W. Fredell, Karen M. Epstein; UPMC Heath Plan, Pittsburgh, PA.

PURPOSE: To determine physician consideration of discontinuing proton pump inhibitors (PPI) in patients receiving cyclooxygenase-2 (COX-2) inhibitors.
METHODS: Members in a large managed care organization (MCO) receiving concomitant therapy with a PPI (lansoprazole, omeprazole, rabeprazole) and COX-2 inhibitor (celecoxib, rofecoxib) were identified through pharmacy claims data between January 1, 2000 and April 1, 2000. Physicians were faxed a data collection form requesting the following information: patient demographics, prescribed COX-2 inhibitor and PPI with indications for the use of both, and selection of one of the following actions: 1) Discontinue PPI; 2) Step-down to H-2 antagonist; or, 3) Continue PPI (if selected, physicians were required to justify PPI continuation). Data are presented as numbers of members and corresponding percentages.
RESULTS: Four-hundred sixty-nine members were identified and 204 were excluded due to membership termination or discontinuation of combination therapy. Of the 265 eligible patient forms faxed to physicians, 176 (66.4%) forms were returned by fax. Physicians discontinued PPIs in nine (5.1%) members, stepped-down therapy in nine (5.1%) members, and continued PPIs in 157 (89.22%) members. Physicians justifications for PPI continuation included treatments for one or more of the following: 101 (64.3%) GERD; 38 (24.2%) ulcer prophylaxis; 29 (18.5%) hiatal hernia; 25 (15.9%) esophagitis; 24 (15.3%) ulcer treatment; 2 (1.3%) *H. pylori*; and, 1 (0.6%) hypersecretory condition.
CONCLUSION: COX-2 inhibitors have documentation of a safer gastrointestinal profile than traditional non-steroidal anti-inflammatory drugs; however, physicians in this MCO discontinued PPIs in a small percentage of members using COX-2 inhibitors.

65E. Esomeprazole provides improved acid control vs omeprazole in patients with symptoms of GERD. Tore Lind, Anders Kylebäck, Lars Rydberg, Anette Jonsson, *Tommy Andersson*, Goran Hasselgren, Kerstin Röhss; Kärnsjukhuset, Skövde, Sweden; AstraZeneca LP, Wayne, PA; AstraZeneca R&D Mölndal, Mölndal, Sweden.

PURPOSE: Esomeprazole, a new PPI for the treatment of acid-related disorders, is the first PPI developed as an optical isomer. This study compared the effects of esomeprazole and omeprazole on intragastric acidity in patients with symptoms of GERD.
METHODS: In this double-blind, crossover study, 38 patients with symptoms of GERD underwent three randomized 5-day treatments comprising esomeprazole 40 mg (E40), 20 mg (E20) and omeprazole 20 mg (O20) once daily, with a washout period of ≥ 14 days between treatments. On day 5 of each treatment period, continuous 24-hour intragastric pH and pharmacokinetic variables were measured.
RESULTS: A total of 36 patients (15 males), aged 29-58 (mean 45) years, were evaluable. E40 and E20 maintained intragastric pH > 4 for 6 and 2 hours longer, respectively, than O20 (16.8 and 12.7 hours vs 10.5 hours). Mean 24-hour median intragastric pH for E40 and E20 (4.9 and 4.1, respectively) was higher than that for O20 (3.6; $p<0.001$ and $p<0.01$). Plasma AUC was 2-fold higher for E20 than for O20, while AUC for E40 was five times higher (both $p<0.0001$; Table). Interpatient variability in the proportion of time with intragastric pH > 4 was less marked with E40 and E20 than with O20 (SD 17.8% and 19.7% vs 22.8%). Esomeprazole was well tolerated and the profile and incidence of adverse events was similar across all treatment groups. There were no relevant changes in laboratory variables.

	E40	E20	O20
Mean AUC (MUmol·hour/L)	12.6	4.2	2.3
% of 24-hour with pH >4	69.8**	53.0*	43.7
% of patients with pH >4 for > 12 hours	92	54	44
% of patients with pH >4 for > 16 hours	56	24	14

* $p<0.01$; ** $p<0.001$ vs omeprazole

CONCLUSION: Esomeprazole provides more effective acid control than omeprazole, with less interpatient variability, and may thus offer improved clinical efficacy in patients with acid-related disorders.
Presented at Digestive Disease Week, San Diego, CA, May 21, 2000.

66. P-glycoprotein inhibition results in increased interleukin-8 secretion in caco-2 cells. *Brien L. Neudeck, Pharm.D.*, Jenny M. Loeb, Jessica M. Buck; University of Wisconsin, Madison, WI.

PURPOSE: To evaluate the effects of P-glycoprotein inhibition (Pgp) on interleukin-8 (IL-8) secretion in Caco-2 cells.
METHODS: Confluent Caco-2 cells (P54-61) in 24 well plates or 60 mm^2 dishes were pre-incubated with media (control), or the Pgp inhibitors verapamil (10 or 100 micromol) or tamoxifen (10 or 50 micromol) for 1 hour and then stimulated with IL-1β (3 ng/ml). After 5 hours, the supernatant was collected and assayed for IL-8 using ELISA. Cells were also incubated with each of the inhibitors alone for 6 hours without IL-1 stimulation. Cells in 60 mm^2 dishes underwent identical procedures and the RNA was harvested at the end of the experiment. RT-PCR was performed using published primers for IL-8 and β-actin. All experiments were done in triplicate.
RESULTS: Compared to IL-1β alone, pre-incubation with verapamil 10 and 100 micromol and tamoxifen 50 micromol resulted in significantly increased IL-8 secretion in cells stimulated with IL-1β. Neither inhibitor alone increased IL-8 secretion. Furthermore, the verapamil 100 micromol concentration significantly increased IL-8 expression compared to IL-1β alone as determined by RT-PCR ($p<0.05$).

Condition	IL-8 Concentration (pg/ml)
IL-1 3 ng/ml	91.3 ± 17
IL-1/verapamil 10 micromol	595 ± 7*
IL-1/verapamil 100 micromol	1235 ± 167*
IL-1/tamoxifen 50 micromol	1624 ± 88*

* $p<0.001$

CONCLUSIONS: Inhibition of P-glycoprotein with two pharmacologically diverse inhibitors, led to significant increases in IL-8 secretion in an intestinal epithelial cell line. This was limited to stimulated cells only. These results suggest that the pharmacologic inhibition of P-glycoprotein may trigger a cellular stress response resulting in increased IL-8 production in stimulated cells.

Geriatrics

67. Factors influencing prescribing patterns in the elderly after myocardial infarction. *Robert G. Wahler, Pharm.D.*, Lisanne DiTusa, Pharm.D., Aileen Bown Luzier, Pharm.D.; University at Buffalo; SUNY, Buffalo, NY.

PURPOSE: We evaluated physician prescribing patterns in elderly patients post myocardial infarction (MI) to determine the influence of medical factors on adherence with established guidelines.
METHODS: Medical records of 91 elderly (≥ 70 years old) survivors of MI occurring between January 1, 1998, and December 31, 1998, were reviewed. Patient's demographics, comorbidities, social history, clinical investigations, medical procedures, medication contraindications and specific medication usage were documented prior to MI, upon discharge and during the 12 months following MI. Patients were categorized using the Charlson comorbidity index. Univariate and multi-variate analyses were used to determine which factors predicted use of medications.
RESULTS: The mean age was 77 years (range 70-93) and 48% were females. In patients eligible to receive the specified medication, the percent of patients receiving aspirin increased from 67% to 79%, β-blockers: from 75% to 80%, angiotensin converting enzyme inhibitors: from 49% to 57% upon discharge and at 1 year, respectively ($p<0.05$). Cholesterol was assessed in 64% of patients and 30% attained an low-density lipoprotein < 100 mg/dl upon follow up. Factors significantly associated with adherence to guidelines were male gender, higher comorbidity, lack of revascularization, high medication use and low-ejection fraction.
CONCLUSION: During the 12-month follow-up period, we observed improvement in adherence to guideline recommendations. However, the results indicate that further efforts to improve cholesterol management, the treatment of female patients and patients with low comorbidity are warranted.

68. Pneumococcal vaccination in hospitalized elderly patients: areas for improvement. *Elena Brodetsky, Pharm.D.*, Annie Wong-Beringer, Pharm.D.; Huntington Memorial Hospital, Pasadena, CA; Western University of Health Sciences, Pomona, CA.

PURPOSE: The goal of this study was to identify factors associated with the receipt of pneumococcal vaccine (PV) among hospitalized elderly patients and the role of the pharmacist in advocating its use.
METHODS: Elderly patients (≥ 65 years old) hospitalized during the first 4 days of each month over a 5-month period (n=160) were evaluated in a prospective observational study. Data on patient attitude, knowledge, access to care, health status, and interaction with pharmacists were obtained via direct patient interviews and chart reviews.
RESULTS: Half of the patients had received PV prior to admission. The rate of vaccination was significantly associated with patient awareness of the vaccine, knowledge that pneumonia is a leading killer in elderly, and the belief that vaccination is a good idea. Patients who were cared for by a pulmonologist were more likely to have been vaccinated compared to other specialist and primary care physicians (88% vs 42%, $p<0.0001$). Significantly higher rate of vaccination (59% vs 40%, $p=0.018$) and a trend towards more willingness to receive PV in the pharmacy were noted among those who had received medication consultation by a pharmacist in the past. Additionally, 50% of the non-vaccinated group were willing to receive PV per a pharmacist's recommendation.
CONCLUSIONS: Efforts to increase PV coverage need to be directed towards the elderly with comorbidities other than respiratory conditions and also the non-pulmonologist physicians caring for them. Pharmacists can help by making recommendations during direct patient-pharmacist encounters and becoming certified to administer the vaccine.

69. The management of depression in elderly nursing home residents. *Mary N. Brown, Pharm.D.*, Kate L. Lapane, Ph.D., Andrea F. Luisi, Pharm.D.; University of Rhode Island, Kingston, RI; Brown University, Providence, RI.

PURPOSE: To estimate the prevalence of depression in elderly nursing home residents and describe its pharmacological management.
METHODS: Using a population-based dataset of all 1492 facilities 1992–1996 in five states, we identified 42,901 nursing home residents aged ≥ 65 with a diagnosis of depression based on the Minimum Data Set. The Minimum Data Set provided information regarding clinical conditions and measures of physical and cognitive functioning. We identified patients receiving pharmacologic treatment for depression and grouped antidepressant medications by class: tricyclic antidepressants (TCAs), tetracyclics, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and others. Patients were evaluated based on treatment versus no treatment. Logistic regression revealed predictors of receipt of any antidepressant and if treated, predictors of receipt of an SSRI.
RESULTS: Eleven percent of the nursing home population had a diagnosis of depression, 55% received antidepressant therapy. Overall, 33% of residents were underdosed, with people on TCAs more likely to be underdosed. The oldest-old (odds ratio (OR): 0.93; 95% confidence interval (CI): 0.88 – 0.98), African Americans (OR = 0.83; 95% CI: 0.75 – 0.92), and those with severe cognitive impairment were the least likely to receive an antidepressant (OR = 0.69; 95% CI: 0.64 – 0.75). Among those treated, cardiovascular disease were associated with an increased likelihood of SSRI use. Despite control for co-morbid conditions, women were less likely than men to receive an SSRI (OR = 0.77; 95% CI: 0.72 – 0.82).
CONCLUSIONS: Although depression is a treatable illness, the majority of nursing home residents are inadequately treated. Depression contributes to poor physical health and mortality.

70. Medications considered inappropriate for use in the elderly: assessment of a home health care population. *Laura J. Snider, B.S. Pharm.D.*

candidate, Darren M. Triller, Pharm.D., Robert A. Hamilton, Pharm.D., Carol Furman, M.S.; Albany College of Pharmacy, Albany, NY.

PURPOSE: A well-accepted list of medications considered inappropriate for use in elderly patients has been used to perform medication assessments of geriatrics in various settings, but has not been applied to patients receiving home health care (HHC) services as part of a long-term care (LTC) at home program. To assess prevalence of such medications in LTC patients who do not receive mandatory pharmacist-performed drug regimen reviews, 106 geriatric patients enrolled in a LTC at home program were evaluated.
METHODS: The program accepts patients whose health care needs warrant admission to a residential health facility, but can be managed by an HHC agency's LTC program at home. Patients ≥ 65 years old enrolled in this program were considered for evaluation, and their active medication profiles were assessed.
RESULTS: Patients used numerous chronic medications (9.5 ± 3.9), and 30 patients (28.3%) used at least one listed medication, with four receiving more than one such drug. Inappropriate medications identified most frequently were: propoxyphene (13), antidepressants (6), antihistamines (5), and long-acting benzodiazepines (4). Users were similar to non-users: age (75.9 vs 76.9), gender (80% F vs 66% F), number of non-PRN medications (9.8 vs 9.3) and doses/day (15.4 vs 15.2). Users had more PRN agents listed (p=0.0058).
CONCLUSION: LTC patients in this home program were frequently prescribed inappropriate medications as defined by previous literature. This population of non-institutionalized LTC patients would likely benefit from the drug regimen reviews presently mandated for all institutionalized elderly.

71. Prospective monitoring of adverse drug events in an indigent and homeless geriatric ambulatory population. *Erin Spiker, Pharm.D.,* Ruth Emptage, Pharm.D., Martin R. Giannamore, Pharm.D., Craig Pedersen, Ph.D.; Ohio State University, Columbus, OH.

PURPOSE: To prospectively identify potential adverse drug events (ADEs) in a geriatric ambulatory population through identification of prescribed medications meeting Beers criteria.
METHODS: Medical records of patients ≥ 65 years old who visited the Columbus Neighborhood Health Centers between December 1999 and April 2000, were reviewed by a clinical pharmacist. Medications meeting the Beers criteria were evaluated for identification of most common drug classes, severity potential, and dose or disease state restrictions. The pharmacist left a written recommendation regarding utilization of alternative drugs or doses. Physician acceptance of pharmacy recommendations was also evaluated.
RESULTS: Medical records of 100 patients (31 male), average age 73.1 ± 7.0 years were reviewed. Overall, 34 patients (34.0%) had 47 medications with the potential for causing an ADE. The most commonly identified medication classes were antihistamines (19.1%), narcotic analgesics (17.0%), and β-blockers (17.0%). Eight of these 47 medications (17.0%) had a high severity potential. Identified medications met the following Beers criteria: 40.4% were considered inappropriate for the elderly; 38.3% were considered inappropriate in a specific disease state; 10.6% exceeded maximum dosage guidelines; and 10.6% were considered inappropriate for both the elderly population and the patient's disease state. Seventy-seven percent of pharmacy recommendations were accepted.
CONCLUSIONS: The Beers criteria were a useful tool when reviewing medical records to identify potential ADEs in an indigent ambulatory geriatric population. This study provided an opportunity to increase pharmacist-physician interaction with regard to appropriate geriatric pharmacotherapy. Future directions include ongoing educational efforts to medical staff focusing on the prevention of ADEs in the elderly.

72. Optimizing the use of antithrombotic therapy in elderly patients with atrial fibrillation: a pharmacist-led intervention. *Beata V. Bajorek, B.Pharm.,* Ines Krass, B.Pharm., Susan J. Ogle, Margaret J. Duguid, Gillian M. Shenfield; University of Sydney; Royal North Shore Hospital, Sydney, Australia.

INTRODUCTION: In the investigators previous study it was shown that antithrombotic therapy (ATx), specifically warfarin, continues to be underutilized for stroke prevention in elderly atrial fibrillation (AF) patients, even in the absence of contraindications. Guidelines for the use of ATx in this population are lacking, and while studies have documented the benefits of pharmacist-led anticoagulant monitoring services, few have explored role of the pharmacist in the clinical assessment of patients for such therapy.
PURPOSE: To optimize the use of ATx in elderly AF patients by developing, implementing, and evaluating a pharmacist-led multidisciplinary review process.
METHODS: Algorithms for the systematic assessment of a patients suitability for ATx were developed based on risk factors for both stroke and bleeding. The pharmacist was responsible for 'screening' AF patients, as well as interviewing, educating, liaising, and consulting with patients/care givers and other health professionals, before appropriate ATx was recommended. Recruitment of patients targeted those who were ≥ 65 years of age and who were admitted under the Aged Care or General Medicine specialties.
RESULTS: To date, the review process has been applied to over 130 patients (mean age 87 years) in which there has been a 20% change in the in-hospital prescription of ATx; 80% of these patients received an upgrade to more effective treatment.
CONCLUSIONS: This study may establish an algorithm by which clinical staff may rapidly but comprehensively assess patients to achieve optimal use of ATx. It also demonstrates the beneficial role of the pharmacist in the clinical assessment of patients for such therapy.

73E. Risperidone and 9-hydroxyrisperidone concentrations are not dependent on age or creatinine clearance among elderly subjects. *Robert A. Sweet, M.D.,* Rae Ann Maxwell, R.Ph., Ph.D., Benoit H. Mulsant, M.D., Jules Rosen, M.D., Margaret Kirschner, B.A., Kari B. Kastagno, M.D., Bruce G. Pollock, M.D., Ph.D.; Western Psychiatric Institute and Clinic, Pittsburgh, PA.

OBJECTIVE: Risperidone is extensively metabolized to an active metabolite, 9-hydroxyrisperidone (9-OH) which is dependent on renal clearance. Risperidone and 9-OH clearances are reduced in the elderly when compared with younger subjects.
HYPOTHESIS: Among elderly subjects, risperidone and 9-OH clearance would further decline with increasing age and decreasing creatinine clearance (CrCl).
METHODS: Twenty geriatric inpatients were evaluated in a naturalistic setting with regard to total daily risperidone dose and dosing interval. Baseline CrCl over 8 hours and radioimmunoassay of risperidone and 9-OH steady-state concentrations were determined. Multiple linear regression was used to examine the impact of age, weight, CrCl, total dose, and dosing interval on concentrations of risperidone, 9-OH, their sum, and the ratio of 9-OH:risperidone.
RESULTS: Mean total dose or risperidone was 1.3 ± 0.73 mg. Mean age was 76.4 ± years (range 55-91). Mean CrCl was 55.43 ± 32.8 ml/min/1.73 m^2 (17.0 –141.88 ml/minute/1.73 m^2). Steady-state risperidone and 9-OH concentrations were 4.14 ± 5.3 ng/ml and 9.1 ng/ml, respectively. Concentrations of risperidone, 9-OH, their sum, and 9-OH:risperidone did not correlate with any of the independent variables.
CONCLUSIONS: Among elderly subjects, risperidone and 9-OH clearance does not decline with increasing age of declining CrCl. Accumulation of 9-OH may not be as great as expected.
Presented at the Annual Meeting of the American Psychiatric Association, Chicago, IL, May 13-17, 2000.

74. Case report: possible delirium associated with donepezil in a recently diagnosed dementia patient with rapidly declining cognitive and functional status. *David L. Mace, R.Ph.,* Leonard S. Williams, M.D.; Bay Pines Veterans Administration Medical Center, Tampa, FL.

PURPOSE: The purpose of this case report is to raise awareness of a possible paradoxical effect of drugs to treat Alzheimer's disease and/or depression in some elderly patients.
METHODS: We identified an instance in which paradoxical effects of drug intervention were suspected in clinical practice, and reported the facts of the case.
RESULTS: Within a few weeks of drug treatment with donepezil for Alzheimer's disease and paroxetine for depression, the cognitive and functional status of an elderly female patient paradoxically declined rapidly. The subject became increasingly confused and delusional. She was admitted to the VA Medical Center Geriatric Evaluation and Management Clinic for evaluation, as her spouse caregiver was unable to provide for her constant care needs. Donepezil and paroxetine were discontinued, and the patient improved considerably. The patient was discharged from the hospital to her home.
CONCLUSIONS: Clinicians should be aware of possible paradoxical effects arising from drugs used to treat Alzheimer's disease and depression that are metabolized by the cytochrome P-450 pathway, particularly in the elderly. Additional research on this important topic would be informative.

75E. Lipid changes after conjugated equine estrogens in younger and older postmenopausal women. *Mary Beth O'Connell, Pharm.D., BCPS, FCCP, FSHP,* Ajayi Thomas-Ogunji, Pharm.D.; University of Minnesota, Minneapolis, MN; Pharmerica, Grand Prairie, TX.

PURPOSE: To quantify the effect of estrogens on lipids in older postmenopausal women.
METHODS: Twenty-five nonsmoking postmenopausal women (49-88 years, 13 > 65 years old) completed 6 months of conjugated equine estrogens (CEE; Premarin) 0.625 mg/d. Fasting lipid levels were obtained at baseline (pre) and end of study (post). The clinical laboratory analyzed the lipid samples in batches. Paired and independent t test statistics with SPSS version 8.0 were used.
RESULTS:

Demographics and Lipids (mg/dl)	All	Young	Old
Age (years)	65.8 ± 12.1	55.3 ± 5.5	75.5 ± 7.0*
Weight (kg)	63.9 ± 7.5	63.7 ± 9.4	64.1 ± 5.5
Pre cholesterol	218.4 ± 34.5	210.0 ± 28.9	226.1 ± 38.5

(table continued from previous page)

Demographics and Lipids (mg/dl)	All	Young	Old
Post cholesterol	208.6 ± 37.3	208.9 ± 36.3	208.2 ± 39.7
Pre high-density lipoprotein	55.0 ± 9.7	56.4 ± 7.6	53.8 ± 11.3
Post high-density lipoprotein	63.9 ± 10.2*	63.2 ± 5.4*	64.5 ± 12.9*
Pre low-density lipoprotein	139.8 ± 33.1	130.9 ± 30.9	146.6 ± 34.3
Post low-density lipoprotein	115.4 ± 37.0*	115.9 ± 36.8	115.1 ± 38.5*
Pre triglycerides	115.5 ± 46.1	102.1 ± 26.8	127.9 ± 57.0
Post triglycerides	142.8 ± 45.2*	142.5 ± 29.5*	143.2 ± 57.4
Pre apolipoprotein A-1	138.2 ± 15.5	139.9 ± 11.3	136.7 ± 18.9
Post apolipoprotein A-1	163.0 ± 21.8*	165.3 ± 23.3*	161.0 ± 21.1*

* pre- versus post- within age group comparison; $^{+,*}$ $p \leq 0.05$

No difference between younger versus older women's lipid values for any pre and post pairs. Percent changes for younger and older women were 13% and 22% for HDL, -12% and -21% for LDL, and 45% and 18% for triglycerides, respectively. Postmenopausal age did not correlate with any lipid values.
CONCLUSION: Conjugated equine estrogens produced favorable lipid profiles in both younger and older postmenopausal women.
Presented at the American Geriatric Society Annual Meeting, Nashville, TN, May 20, 2000.

76E. Risk factors for institutionalization in Alzheimer's disease: a brain bank study. Laura Balestreri, M.D., *George Grossberg, M.D.*; St. Louis University Health Sciences Center, St. Louis, MO.

PURPOSE: Alzheimer's disease (AD) affects nearly 4 million older Americans and is a frequent reason for nursing home placement. The purpose of this study was to determine triggers/risk factors for nursing home placement among a cohort of autopsy-confirmed patients with AD.
METHODS: We sent detailed questionnaires, followed by telephone interviews, to primary caregivers of autopsy-confirmed AD patients — inquiring about the reasons they placed their loved ones in nursing homes. Type of caregiver, presence/absence of general/psychiatric symptoms as well as stress levels of caregiver were determined, the latter via a 1-5 point Likert scale, with 1 as mild, 3 as moderate, and 5 as being overwhelming stress at the time of decision to institutionalize.
RESULTS: Twenty-six caregivers completed our survey. Of these, 13 were daughters, 7 wives, 3 husbands, and 3 sons. Twenty-one of 26 patients showed psychotic symptoms at the time of nursing home placement. Of these, 18/26 had delusions (mostly paranoid) and 12 had hallucinations. Wandering was present in 20/26 patients while 20/26 had problems with agitation/aggressivity. Anxiety and mood disturbance were reported in 16/26 and 13/26 patients, respectively. Nineteen of 26 patients had significant sleep problems (mostly day/night confusion), and 19/26 caregivers reported stress levels of 4 or > on the 1-5 Likert scale.
CONCLUSIONS: We conclude that the behavioral and psychological signs and symptoms of dementia, in particular, psychotic symptoms, agitation/aggressivity, and wandering are the major precursors to nursing home admission in AD patients. As well, these symptoms are a major source of caregiver stress.
Presented at the Annual Symposium of the American Medical Directors Association, San Francisco, CA, March 16-20, 2000.

77. Effect of age on monitoring of HMG-CoA reductase inhibitors. *Amy Sayner-Flusche, Pharm.D.,* Carla A. Zeilmann, Pharm.D., BCPS, Tom Meyers, R.Ph.; St. Louis College of Pharmacy; Jefferson Barracks V.A. Medical Center, St. Louis, MO.

PURPOSE: This study investigated the use of the HMG-CoA reductase inhibitors (statins) within the St. Louis Veterans Administration Medical Center to determine 1) if patients are being appropriately monitored for efficacy (LDL measurements) and toxicity (liver function tests [LFTs]); and 2) if differences exist among older (≥ 65) and younger patients.
METHODS: Medical records of 504 patients who received a prescription for lovastatin or simvastatin between January 1, 1999 to December 31, 1999, were reviewed. Patients' ages, type of prevention (primary or secondary), LDL goals, most recent LDL cholesterol, and whether or not LFTs had been performed within the past year were recorded.
RESULTS: Almost 60% of all patients were receiving statin therapy for primary prevention. Older patients were more likely to receive lipid lowering therapy for secondary prevention than younger patients (50.5% vs 26%, $p<0.05$). Forty-one percent of patients were at goal their LDL. However, for the nearly 60% of patients, LDL values were above goal (24.6%) or unknown (32.7%). Percentages of older and younger patients at goal were similar (42.4% vs 43.0%, p=0.712). LFTs were measured in 87% of all patients, with no difference between older and younger patients (87.4% vs 86.9%, p=0.851).
CONCLUSION: The majority of patients are being appropriately monitored for efficacy and toxicity, with no differences among patients 65 years and older and those younger than 65. However, both groups have suboptimal numbers of patients at their goal LDL.

78E. Risperidone in the treatment of negative symptoms in Alzheimer's disease. *Arnaldo E. Negron, M.D.,* William E. Reichman, M.D.; University of Medicine and Dentistry, Piscataway, NJ.

INTRODUCTION: The purpose of this study was to analyze the effectiveness and safety of risperidone in the treatment of clinically significant negative symptoms in Alzheimer's disease (AD) patients.
METHODS: We reviewed the charts of community-residing patients treated in a specialized university-based dementia management clinic and who had the diagnosis of probable AD based on the criteria of the National Institute of Neurological and Communicative Disorder and Stroke and the Alzheimer's Disease and Related Disorders Association. Patients were assessed at baseline and at 12 weeks of treatment. Measures included the Scale for the Assessment of Negative Symptoms in AD (SANS-AD), the Positive and Negative Syndrome Scale (PANSS), the Hamilton Scale for Depression (HAM-D), the Mini-Mental State Exam (MMSE), the Simpson-Angus Extrapyramidal Symptoms Scale (EPS), and the Abnormal Involuntary Movement Scale (AIMS).
RESULTS: Patients (n=50; mean age 79.7 ± 6.0) had moderate cognitive impairment (MMSE score = 12.5 ± 6.90) and were not clinically depressed (HAM-D = 7.9 ± 3.3). After 12 weeks of risperidone treatment (1.3 ± 0.6 mg/d; range, 0.5–3.0 mg), the severity of negative symptoms was significantly reduced. SANS-AD total scores were reduced 22% from baseline (27.8 ± 12.3 to 21.7 ± 13.7, p=0.05). Improvement in negative symptoms appeared to be independent of improvement in positive symptoms (SANS-AD covariate for PANSS-Pos factor, f = 3.1, p=0.08). Conversely, cognitive function (MMSE scores) did not change, and extrapyramidal symptoms did not worsen.
CONCLUSION: Risperidone improved clinically significant negative symptoms without affecting cognitive function or worsening extrapyramidal symptoms in this population of AD patients.
Presented at the Annual Meeting of the NCDEU, Boca Raton, FL, May 30-June 2, 2000.

79. Evaluation of usage patterns of medications for management of glaucoma in two nursing home residents. *Shyam D. Karki, Pharm.D.,* Joshana Karki, Pharm.D., Terrance J. Bellnier, R.Ph., M.P.A., William Patterson, B.S., Rana Masood, M.D.; SUNY, Buffalo, NY; Clifton Spring Hospital and Clinic, Clifton Springs, NY.

PURPOSE: To evaluate the usage patterns of medications for management of glaucoma in two nursing homes.
METHODS: Pharmacy records of all residents on medications for management of glaucoma were reviewed retrospectively to evaluate their use for past six months. Nurses administering glaucoma medications were observed as to their compliance with HCFA guidelines on administration of ophthalmic solutions. Charts were reviewed for physician notes for monitoring glaucoma and intra ocular pressure.
RESULTS: Forty-six (8%) residents in the nursing home A and 14 (13%) residents in the nursing home C were on medications for management of glaucoma. There were 29 (63%) residents in nursing home A and 6 (43%) residents at nursing home C on one medication, 11 (24%) and 7 (50%) on two medications, five (11%) and one (7%) on three medications in nursing homes A and C, respectively. There was no waiting time of more than 1 minute between two different glaucoma medications on the medpass observation. Intraocular pressures were documented on 20 (46%) residents' charts in the nursing home A and none in the nursing home C.
CONCLUSION: Management of glaucoma the nursing home patients had some potential problems; noncompliance with HCFA guideline on ophthalmic medication administration, the usage of multi medications, nonavailability of IOPs and no documentation of the effectiveness of therapy.

80. Stroke prevention with warfarin in a frail elderly population with atrial fibrillation. *Cynthia L. Lackie, Pharm.D.,* Jennifer Pruetz, Kenneth A. Garbarino, M.D.; Kaleida Health, Buffalo, NY; State University of New York at Buffalo, Buffalo, NY.

PURPOSE: We report our experience with a frail, community-dwelling, geriatric population prescribed warfarin for atrial fibrillation and at high risk for stroke.
METHODS: Medical records of 18 patients (median age, 84 years) followed by the Geriatric Ambulatory Program over 2 years, with a target INR of 2.0-3.0 were reviewed. The number and results of INR tests, suspected reasons for sub-optimal response, stroke risk factors, and adverse events were analyzed. Patients were defined as frail if they had of a mini-mental exam (MME) score of ≤ 25, and two or more disabilities on the activities of daily living scale (ADL).
RESULTS: Eighty-three percent (15/18) had ≥ 2 additional stroke risk factors. Fifty-one percent (273/541) of INR responses were therapeutic. Of the sub-optimal responses, 16% (43/268) were thought to be explained by non-compliance, diet, or drug interaction. Of these, 55% (24/43) were due to non-compliance. There were four minor bleeding, and no thromboembolic events. Forty-four percent of the patients were defined as frail and all but one frail patient had caregiver support. The number of INR assessments needed, non-compliance and INR response was not significantly different in the frail subgroup ($p>0.10$).
CONCLUSION: Elderly patients require close monitoring while on warfarin as suboptimal INR results may occur unpredictably and frequently. The presence of frailty in this population did not have a significant impact on any

targeted outcome studied. Therefore, frailty may not be a significant risk factor for treatment with warfarin, if the patient receives caregiver support.

81. Pharmacokinetics of cefuroxime axetil oral suspension in elderly volunteers. *G. Christopher Wood, Pharm.D.*, Mark R. Ling, M.D., Ph.D., Vanessa L. Herring, B.S., Scott D. Hanes, Pharm.D., Bradley A. Boucher, Pharm.D., FCCP; University of Tennessee, Memphis, TN; MedaPhase, Inc., Newman, GA.

PURPOSE: Aging is a factor that may alter drug disposition. This is the first study to describe the pharmacokinetics of cefuroxime axetil oral suspension in elderly volunteers.
METHODS: A single 250 mg dose of cefuroxime axetil suspension was administered orally to 12 healthy, elderly volunteers. Serum samples for cefuroxime analysis were collected at baseline (pre-dose), and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. Serum cefuroxime concentrations were determined using high performance liquid chromatography. Pharmacokinetic parameters were estimated using noncompartmental kinetics.
RESULTS: All 12 patients (9 male, 3 female) successfully completed the study. Demographic results were as follows (means ± standard deviations): age, 71 ± 3.7 years; weight, 77 ± 13 kg; estimated Cl_{Cr} 67 ± 13 ml/min. Composite pharmacokinetic parameters were as follows (means ± standard deviations): C_{max}, 3.38 ± 0.77 µg/ml; $t_{1/2}$, 1.9 ± 0.2 hr; k_{el}, 0.36 ± 0.04 hr^{-1}; CL, 0.22 ± 0.05 ml/minute/kg; $AUC_{0-\infty}$, 15.7 ± 2.6 µg•hour/ml; V, 0.59 ± 0.12 l/kg. Median T_{max} was 3 hours (interquartile range 2-4 hours). Previously published pharmacokinetic studies of a 250 mg dose of cefuroxime axetil oral suspension in younger volunteers (19-40 years) reported C_{max} values of 2.92-3.85 µg/ml and T_{max} values of 2.0-3.63 hours. Similarly, $t_{1/2}$ was 1.36-1.43 hours and AUC_{0-4} was 12.4 - 14.4 µg•hour/ml.
CONCLUSIONS: Cefuroxime axetil oral suspension in elderly volunteers produced C_{max} and T_{max} values similar to those seen in younger volunteers. Half-life and $AUC_{0-\infty}$ were mildly increased and likely due to age-related decreases in CL_{Cr}. No dosage adjustment appears necessary when using cefuroxime axetil oral suspension in the elderly.

82E. A case series of behavioral disturbances associated with dementia treated with trazodone. *C. Rojas-Fernandez, Pharm.D.*, T. White, P.A., T. Nicklaus, M.D.; Texas Tech University HSC, Amarillo, TX.

PURPOSE: To develop treatment strategies for behavioral disturbances associated with dementia (BDD) which have a neurochemical (NC) rationale, implement these in a long term care facility and present preliminary results of an ongoing case series.
METHODS: Treatment strategies were developed based on a literature review of NC correlates of BDD. Incident cases of BDD who required pharmacotherapy were treated according to these strategies and monitored using the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) scale.
RESULTS: To date (program began in January 1999) we have treated seven consecutive residents (mean age 78 ± 9.2 years; three males and four females) with trazodone (doses ranged from 50 to 100 mg per day-mean dose 67 ± 23 mg/day] for various behavioral symptoms, including aggression, anxiety, tearfulness, insomnia, wandering, and hypersexuality. BEHAVE-AD scores improved by ≥ 50% in 5 residents, worsened in one, and did not change in one. Symptoms that improved included insomnia, anxiety, aggression, and tearfulness. One resident was subsequently diagnosed with depression and responded to sertraline. No adverse drug events have been noted thus far. The putative treatment approach will also be described in this presentation.
CONCLUSION: In this open label, unblinded and uncontrolled case series, trazodone appears to be safe and moderately effective in the management of BDD. It is clear that controlled studies are necessary to better define the usefulness of our putative approach to BDD.
Presented at the annual meeting of the American Geriatrics Society, Nashville, TN, May 19, 2000.

83. Dementia with Lewy bodies: response of cognition, hallucinations, function and hypersomnolence to donepezil. *C. Rojas-Fernandez, Pharm.D.*, Loralu Raburn, M.D.; Texas Tech University HSC, Amarillo, TX.

PURPOSE: To describe core features of dementia with Lewy bodies (DLB) in one patient, and report a marked clinical response of DLB symptoms to donepezil.
METHODS: An 86-year-old female recently admitted to a dementia unit of a long-term care facility was assessed and her family interviewed. The resident was diagnosed with DLB, using the consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies. (McKeith IG, et al. Neurology 1996;47:1113-24.]).
RESULTS: The patient presented with a 2-year history of significant cognitive fluctuation, persistent, well-formed visual hallucinations, hypersomnolence and Parkinsonism. The hallucinations were previously treated with risperidone 1 mg BID with modest success, but resulted in excessive Parkinsonism, sedation, and functional impairment and was discontinued. She had previously received diagnoses of Alzheimer's disease and Parkinson's disease (receiving benztropine 1 mg BID and donepezil 5 mg QD) which were revised to DLB. Discontinuation of the benztropine with a subsequent increase of donepezil to 10 mg daily resulted in significant clinical improvement of the cognitive fluctuation, somnolence, hallucinations, function, and cognitive status (much improved as per the clinical global impression scale). She is still stable at 9 months follow up.
CONCLUSION: The patient had core features of DLB which responded clinically to donepezil. Controlled data are needed to further delineate the role of donepezil for patients with DLB.

84E. Suboptimal use of antidepressants in the elderly population of Nova Scotia, Canada. *C. Rojas-Fernandez, Pharm.D.*; Texas Tech University HSC, Amarillo, TX.

PURPOSE/METHODS: Previous research (Wells et al., Gen Hosp Psychiatry 1994;16:4-15) suggests that antidepressants (ADs) are misused in the elderly, often with poor choice of ADs, and suboptimal dosing regimens. The objective of this study is to assess prescribing patterns of ADs in the Nova Scotia (NS) population aged 65 years and older using the provincial administrative drug database.
RESULTS: In 1995-1996, 6448 elderly patients were identified with an AD prescription for depression. The most frequently prescribed ADs were the tertiary tricyclic ADs (TTCAs) amitriptyline (28%) and doxepin (15%). Serotonin uptake inhibitors (SRIs), desipramine or nortriptyline, recommended ADs for the elderly were only prescribed for 31%, 3%, and 1% of the study's elderly patients respectively. Overall, 53% of patients received subtherapeutic doses, 69% with TCAs and 21% with SRIs. By current criteria, 45% of the elderly received ADs which are generally accepted as inappropriate.
CONCLUSIONS: These findings are disturbing, given the toxicity of TTCAs in the elderly, and the availability of alternative agents with more favorable side effect profiles. Furthermore, subtherapeutic dosing diminishes the chances of achieving a remission of depression and preventing future relapse. Reasons for seemingly poor prescribing decisions noted in this study must be explored.
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85. A survey of Texas long-term care facilities to determine the characteristics of medication administration through enteral feeding catheters. *Charles F. Seifert, Pharm.D., FCCP, BCPS*, Barbara A. Johnston, R.N., Ph.D., Carlos Rojas-Fernandez, Pharm.D.; Texas Tech University Health Sciences Center, Lubbock and Amarillo, TX.

PURPOSE/METHODS: To determine the point prevalence and characteristics of medication administration through enteral feeding catheters (EFCs) in the long-term care (LTC) setting, a 62-item, 8-page questionnaire was mailed to the directors of nursing of the 1153 long-term care facilities (LTCFs) registered with the Texas Department of Human Services.
RESULTS: Of the 1153 questionnaires mailed, 147 (12.7%) were returned completed through various stages. Long-term care nurses estimated that 11.6% of their patients received 8.3 doses of medications per day through the EFC. A significantly higher percentage of nurses serving a rural versus an urban area routinely crush enteric coated medications (23.5% vs 8.1%; p=0.023). Those LTC nurses who routinely crush enteric coated and sustained-release dosage forms had a dramatic increase in total catheter obstruction due to medications (18.6% vs 5.0%; p=0.012). Long-term care nurses practicing in facilities serving rural versus urban areas were less likely to have received training in nursing school regarding the proper techniques for administering medications through EFCs (47.5% vs 66.1%; p=0.027). Eleven medications were cited in ≥ 5% of nurses as problem medications which contribute to EFC obstruction. The majority of these medications are available as liquids or should not be crushed.
CONCLUSIONS: Current and new information regarding medication delivery through EFCs should be widely disseminated, particularly in rural LTC settings. Pharmacists should assume a more active role in the education of LTC nurses in the proper techniques for the administration of medications through EFCs, particularly in rural areas.

86. Knowledge of nonsteroidal anti-inflammatory drugs in at-risk elders: effectiveness of individualized patient education. *Stephen M. Setter, Pharm.D., D.V.M.*, Cynthia F. Corbett, Ph.D., B.A. Nursing, Colleen M. Terriff, Pharm.D., Brian J. Gates, Pharm.D., Carol Johns, M.S.N., B.S.N., Lyle Broemeling, Ph.D., David Maccini, M.D., F.A.C.P., Robert Popovian, Pharm.D.; Washington State University; Spokane Digestive Disease Center, Spokane, WA; Pfizer Inc., New York, NY.

PURPOSE: This pilot study compared: 1) patient knowledge of nonsteroidal anti-inflammatory drugs (NSAIDs); and 2) utilization of prescription and OTC NSAIDs between an educational intervention group and a control group.
METHODS: Twenty hospitalized NSAID-consuming elders (> 60 years) at risk for NSAID-induced GI disease were randomly assigned to a control or educational intervention group (n=10 per group). Subjects were assessed for NSAID knowledge, risk factors for NSAID-induced gastropathy and NSAID use during hospitalization and at 1 week and 3 months after discharge. The intervention group received individualized verbal and written information during the 1-week in-home visit and their prescribers were contacted via facsimile when appropriate to recommend strategies to decrease gastropathy risk.

RESULTS: In this high-risk population poor baseline and post-intervention NSAID knowledge existed. Initially, only 50% were able to name their NSAID, with only 10% knowing that NSAIDs could cause upset stomach or ulceration. No significant differences ($p > 0.05$) in NSAID knowledge were found between groups at the 1-week and 3-month assessments. Use of prescription and OTC NSAIDs did not vary during the study period; however, one patient was switched to a potentially safer prescription NSAID (COX-2 selective agent)upon recommendation.
CONCLUSIONS: Preliminary data show there are important NSAID knowledge deficiencies among high-risk elders for NSAID-induced GI disease. These knowledge deficits are not significantly reduced by a one-time educational intervention. More effective educational strategies are therefore needed. Further studies are underway to evaluate the use of a tailored NSAID educational intervention which promotes medication list adoption.

Hematology/Anticoagulation

87. Utilization of anticoagulation in patients with atrial fibrillation at a university hospital. *Deb S. Sherman, Pharm.D.*, Patrick Klem, Pharm.D., J. Mark Ruscin, Pharm.D.; University Hospital; University of Colorado Health Sciences Center, Denver, CO.

PURPOSE: To describe the utilization of warfarin in patients with atrial fibrillation (AF) at a university hospital.
METHODS: A retrospective review of all admissions with a principal or secondary discharge code of AF in calendar year 1998 was conducted. Exclusion criteria were death during hospitalization, isolated AF resolved by discharge, heart transplant, discharge to hospice, admission to the Clinical Research Center, no documented AF, or an unobtainable medical record. The primary outcome was to compare AF patients discharged on warfarin to those not on warfarin utilizing bivariate analysis. Data are reported as mean ± SD.
RESULTS: There were 368 evaluable cases. Patient ages were 69 ± 14 years and 50% of patients were female. Of the 368 admissions, 57% were discharged on warfarin; 25% on aspirin alone. Warfarin was prescribed in 63%, 64%, and 48% of patients < 65, 65-75, and > 75 years, respectively. Of the 157 not discharged on warfarin, 56% had at least one relative contraindication to warfarin. Accounting for contraindications, there was no difference in the percent of anticoagulated patients with respect to age group (76%, 76%, 74%, respectively; p=NS). There were no differences between the anticoagulated and the non-anticoagulated groups regarding age (p=0.3) or gender (p=0.82). Per patient, there were more risk factors for embolism in the anticoagulated group (1.65 ± 1.0 vs 1.08 ± 0.85; p<0.001) and fewer risk factors for bleeding (0.21 ± 0.49 vs 0.79 ± 0.84; p<0.001).
CONCLUSION: At our institution, the majority of AF patients were appropriately discharged on warfarin. Patients not receiving anticoagulation had fewer risk factors for embolism and more risk factors for bleeding.

88. Results of patient and physician satisfaction of a pharmacist-managed anticoagulation clinic in a family medicine center. *Dawn E. Havrda, Pharm.D., BCPS*, Nancy Letassy, Pharm.D., CDE, Hengameh Lavasanifar, Pharm.D., Mark Britton, Pharm.D., CDE; University of Oklahoma, Oklahoma City, OK.

PURPOSE: Surveys were administered to determine patient and referring physician satisfaction of a family medicine pharmacist-managed anticoagulation clinic (AC).
METHODS: Likert statement surveys (1-not satisfied to 5-very satisfied) were developed to measure satisfaction of a pharmacist-managed AC for patients enrolled for > 3 months and referring physicians. All surveys were anonymous. Patients were asked to complete an 18-question survey at conclusion of routine visit, and referring physicians received a 15-question survey on two occasions.
RESULTS: Cronbach α for internal reliability was 0.71 and 0.60 for patient and physician surveys, respectively. Thirty-eight of 52 patients completed the survey with average time in AC of 8.9 months (3-20 months). Average satisfaction scores were 4.47-4.95 for AC with 69.4-97.3% being very satisfied. The lowest satisfaction (mean 4.47, 69.4% very satisfied) was with thinness of blood. Before referral to AC, 70% of patients reported their primary care provider monitored their warfarin (p=0.011 vs other providers); only 26.2% were very satisfied with their control prior to AC (mean 3.10). More patients were very satisfied (84.8%) with their control in AC compared to prior to AC (p<0.0001). No significant difference was found in satisfaction based on time enrolled, INR value at visit, age, or indication. Fourteen of 25 physicians completed the survey, and 78.6-100% were satisfied with AC. The lowest score (mean 4.43, 64.3% very satisfied) was concerning being informed about their patient's anticoagulation.
CONCLUSIONS: Patients and referring physicians have been highly satisfied with a pharmacist-managed AC within a family medicine center.

89. Enoxaparin pharmacokinetics in acutely ill hospitalized patients. *Agneta K. Hurst, Pharm.D.*, Pamela A. Pickens, Pharm.D., Frank C. Chenella, Pharm.D., Roger W. Jelliffe, M.D.; University of Southern California; Los Angeles Country and USC Medical Center, Los Angeles, CA.

PURPOSE: The purpose of this evaluation was to 1) create a pharmacokinetic population model of enoxaparin; and 2) investigate clinical correlates that can be used to predict dosing requirements in hospitalized patients.
METHODS: Forty-eight acutely ill inpatients receiving enoxaparin subcutaneously were studied retrospectively. Enoxaparin doses and plasma factor-Xa inhibition levels were fitted to a linear, 1-compartment absorption model using the USC*NPEM population modeling software. Correlates evaluated were: creatinine clearance (ClCr), age, gender, weight, body mass index (BMI), blood volume, estimated cardiac index (CI), venous thromboembolism (VTE), atrial fibrillation (AF) and congestive heart failure (CHF).
RESULTS: Thirty-seven patients had VTE, 13 AF, 12 CHF. The enoxaparin population medians and coefficients of variation were: Kel = 0.204 hr^{-1} (31%); Vd = 4.5 L (23%); and Ka = 0.218 hr^{-1}(132%). Vd, in liters, for patients with BMI ≥ 30 was not significantly different than in those with BMI < 26, but the Vds in L/kg were significantly different, 0.046 ± 0.009 vs 0.068 ± 0.015 L/kg respectively, p=<0.001. No significant correlations were found between Vd and blood volume, actual body weight or lean body weight. There was no significant correlation between Kel and ClCr, CI, age, gender, CHF or VTE.
CONCLUSION: There is significant variability in enoxaparin pharmacokinetics in acutely ill patients. No reliable clinical correlates were found to predict dosing requirements with precision. Instead of 1 mg/kg without monitoring levels, it can be recommended that acutely ill patients receive an initial 60 mg q12h followed by levels to achieve target concentrations of 0.3-0.8 U/ml.

90E. Comparison of laboratory and bedside activated partial thromboplastin times. Robert L. Begle, M.D., John M. Koerber, B.S.Pharm., *Maureen A. Smythe, Pharm.D.*, Sandra N. Nowak, Pharm.D., Joan C. Mattson, M.D., Sue J. Westley, M.T.; William Beaumont Hospital, Royal Oak, MI; Wayne State University, Detroit, MI.

PURPOSE: The goal was to compare two bedside aPTT devices to a laboratory-based device.
METHODS: The study was conducted in two phases. A single 5 ml blood sample was taken from patients receiving continuous infusion heparin therapy (both phases). In phase I, blood samples from 102 patients were analyzed for aPTT with two bedside devices, (CoaguChek Plus System [CPS] and Thrombolytic Assessment System [TAS]), one lab-based device (MDA-180) and a plasma heparin level (anti-factor Xa). In phase I, a therapeutic range for each device, equivalent to a heparin concentration of 0.3 – 0.7 u/ml, was established. In phase II, samples from another 100 patients were analyzed as above. The purpose of phase II was to compare devices. The strength of the correlation of each bedside device to the laboratory, the bias and limits of agreement and patient care decisions regarding heparin were compared. Heparin dosage adjustment decisions were assessed using the aPTT therapeutic ranges derived in phase I. Decisions agreed when both aPTT results were either therapeutic or non-therapeutic. Correlations, linear regression and Altman-Bland plots were used in the analysis.
RESULTS: Heparin concentration derived ranges were 52-99 seconds (MDA), 64-105 seconds (CPS) and 50-69 seconds (TAS). Correlations between each bedside device and the laboratory-based device were 0.83 (CPS) and 0.77 (TAS). Bias and limits of agreement for CPS: -7.9 seconds (-39.4 to 23.6) and for TAS: +9.8 seconds (-33.3 to 52.9). Biases were different (p<0.001). Decisions guided by the laboratory-based device disagreed with bedside results in 32/98 (33%) patients with CPS and 40/98 (41%) with TAS.
CONCLUSIONS: Results from laboratory and bedside aPTT devices are not interchangeable. The CPS produced higher results relative to the laboratory where the TAS produced lower results. When compared to laboratory-based, bedside devices generate different patient care decisions approximately one-third of the time.
Published in Am J Resp Crit Care Med 2000;161(3):A395.

91. Agreement between point-of-care and laboratory methods for monitoring anticoagulation in hospitalized patients. *Robert A. Reiss, Pharm.D.*, Curtis E. Haas, Pharm.D., Deborah L. Griffis, Pharm.D., Bernadette Porter, M.S.N., Mary Ann Tara, B.S.; Rochester General Hospital, Rochester, NY; University at Buffalo, Buffalo, NY; University of Arizona, Tucson, AZ.

PURPOSE: This study was designed to evaluate agreement between point-of-care (POC) assays and standard hospital (SH) assays for INR and aPTT measurement in hospitalized patients receiving warfarin (W), heparin (H), full-dose enoxaparin (E), or combinations of anticoagulants (W+H, W+E). Congruity in clinical decision-making was also evaluated.
METHODS: Five groups of 30 patients each receiving W, W+H, H, E, or W+E were enrolled. When possible, capillary blood was used for POC INR/aPTT testing, otherwise venous samples were applied. Venous blood was used for all SH INR/aPTT assays. The difference between results was plotted against the average value (Bland-Altman analysis) for each group and across groups. The acceptable 95% limit of agreement was ± 0.4 for INR and ± 10 seconds for aPTT. The assay methods were compared using simple linear regression (SLR). Congruity in clinical decision-making was evaluated using agreement of subtherapeutic, therapeutic, or supratherapeutic interpretation

of POC and SH assays results.
RESULTS: The following tables present 95% limits of agreement for each group and all subjects combined.

INR Results	W (n=30)	W+H (n=30)	W+E (n=30)	All (n=90)
Mean difference	0.14	-0.66	-0.13	-0.23
95% CI	-1.08 to 1.36	-1.9 to 0.58	-0.9 to 0.64	-1.49 to 1.03

aPTT Results:	H (n=30)	W+H (n=30)	E (n=29)	W+E (n=30)	All (n=119)
Mean difference	4.4	9.0	2.1	-5.1	2.6
95% CI	-41.8 to 50.6	-31.9 to 49.9	-14.3 to 18.5	-33.8 to 23.6	-33.6 to 38.8

SLR analysis was also consistent with poor agreement between methods (r^2=0.589 for aPTT results and r^2=0.512 for INR results). For clinical decision-making, INRs agreed 47-93% of the time and aPTTs agreed 67-80% of the time.
CONCLUSION: The POC assay for aPTT and INR agreed poorly with the SH assay in hospitalized patients.

92E. Subcutaneous and oral direct thrombin inhibitors for prophylaxis of deep venous thrombosis and pulmonary embolism after total hip and total knee replacement. *Bengt I. Eriksson, M.D., Ph.D.*, Ann-Christin Arfwidsson, D.D.S., Christine Sareyko Elvander, D.D.S., Peter Kälebo, M.D., Ph.D., Lars Frison, Ph.D., Ulf G. Eriksson, Ph.D., Gunnar Fager, M.D., Ph.D., David Gustafsson, M.D., Ph.D.; Sahlgrenska University Hospital/Östra, Göteborg, Sweden; AstraZeneca R&D, Mölndal, Sweden.

PURPOSE: The early clinical development of melagatran and H 376/95 for the prophylaxis of venous thromboembolism (VTE) following orthopedic surgery (OS) is described. After oral administration, H 376/95 is converted to its active form melagatran (which can be given subcutaneously [SC]).
METHODS: Study I: 66 patients undergoing total hip replacement (THR) received SC melagatran (1.5–6 mg BID) for 8–11 days. Study II: 104 patients undergoing THR or total knee replacement (TKR) received either saline or depot formulation of SC melagatran (2–4 mg BID) for 8–11 days. Study III: 104 patients undergoing THR or TKR received SC melagatran (1–4 mg BID) for 2 days, followed by oral H 376/95 (6–24 mg BID) for 6–9 days, and 33 patients received SC dalteparin (5000 IU QD) for 8–11 days. Deep vein thrombosis (DVT), assessed by bilateral ascending venography, and clinical DVT or pulmonary embolism were assessed as VTE.
RESULTS: Study I: 12% (6/52) of evaluable patients (EPs) had VTE. Major bleeding occurred in three patients at the three highest dose levels. Study II: VTE occurred in 8% (6/77) of EPs. Three patients had bleeding complications. Study III: 21% (16/78) and 19% (5/27) of EPs had VTE with SC melagatran followed by oral H 376/95, and dalteparin, respectively. Three patients given melagatran followed by H 376/95 had bleeding complications, but these were not dose related. Mean bleeding during and after surgery was similar in all groups.
CONCLUSION: H 376/95 and melagatran appear to be promising agents for the prophylaxis of VTE following OS.
Published in Blood 1999;94(Suppl 1):589a.

Herbal Medicine

93. Acute and chronic effects of St. John's wort (*Hypericum perforatum*) on cytochrome P450 3A4 activity in normal volunteers. *Christina E. Hill-Zabala, Pharm.D.*, Michael Golding, M.D., Stanley W. Carson, Pharm.D.; University of North Carolina, Chapel Hill, NC.

PURPOSE: St. John's Wort (SJW) is an herbal product widely used as an antidepressant and is often taken in combination with conventional medications. These include CYP3A4 substrates such as oral contraceptives, cyclosporine, anti-infectives, anti-retrovirals, warfarin, chemotherapeutic agents, and anti-epileptics. The purpose of this study was to examine the acute and chronic herb-drug interaction potential of SJW with Cytochrome P450 3A4 (CYP3A4).
METHODS: Eight normal volunteers were dosed with 600 mg of the standardized LI-160 formulation of SJW (0.3% hypericin) three times daily for 14 days. CYP3A4 activity was assessed at three time points: baseline, after two doses of SJW, and following 14 days of SJW utilizing the erythromycin breath test (ERMBT). Baseline, acute, and chronic ERMBT scores (% ^{14}C in breath/hour) were compared by ANOVA with the paired t-test as the multiple comparison procedure. Statistical significance was declared at $p<0.025$ with the Bonferroni correction for multiple comparisons.
RESULTS: Eight subjects completed the study (four males and four females) with an age of 22.75 ± 4.33 (mean ± SD) years. The mean ERMBT score increased from 3.37 ± 0.98 at baseline to 3.92 ± 0.79 ($p=0.02$) and 5.43 ± 0.83 ($p<0.0001$) following acute and chronic administration of SJW, respectively. This corresponds to a 1.6-fold induction of CYP3A4 following 2 weeks of SJW with a range of 1.35 to 2.42.
CONCLUSIONS: St. John's wort induced CYP3A4 1.6-fold following 14 days of 1800 mg/day SJW. Due to this potent induction, there is a high potential for multiple drug interactions with co-administered CYP3A4 substrates.

94. Characterizing adverse events reported to the California poison control system on herbal remedies and dietary supplements: a pilot study. *Sally Yang, Pharm.D.*, Candy Tsourounis, Pharm.D., Cathi E. Dennehy, Pharm.D.; University of California, San Francisco, San Francisco, CA.

PURPOSE: The purpose of this study was to 1) characterize the population who uses and reports adverse events to the California Poison Control System (CPCS) related to herbal remedies (HR) and dietary supplements (DSs); 2) to assess whether adverse drug reactions (ADRs) occur within the usual recommended dosing; and 3) to describe the nature of adverse events.
METHODS: A retrospective search of HR and DS related calls was conducted between January 1997 and June 1998. Data collection included the demographics of callers, types of exposures, substances involved, amounts ingested and severity of exposures.
RESULTS: Of the total 918 HR and DS calls received, 259 (28.2%) were drug information queries, 599 (65.2%) were exposures, 60 (6.6%) did not qualify. Of these calls, 246 (41%) were for adult exposures, 324 (54%) were for pediatric exposures and 29 (5%) were unknown. The most common products involved were zinc gluconate (37.5%), echinacea (7.6%) and chromium picolinate (6.3%). Nearly 42% of the ADRs occurred when the products were taken within the recommended dose.
CONCLUSION: Nearly 65% of calls reported to the CPCS involved an exposure while 28% involved a drug information query. Approximately 40% of the exposure cases resulted in an ADR. The exposures tended to occur most in pediatric patients. The majority of ADRs, occurred in adults when used within the recommended dosing and tended to be of mild severity.

95. Randomized, double-blind, placebo-controlled study to evaluate the effects of a standardized garlic preparation with hyperlipidemia. *Lisa T. Meade, Pharm.D.*, Colette Fontaine, Pharm.D., Tina W. Dancer, Pharm.D., Anthony J. Verlangieri, Ph.D., Robert D. Hobson, R.Ph., Brendan Ross, M.D., Gordon S. Sacks, Pharm.D.; University of Mississippi Medical Center, Jackson, MS.

PURPOSE: To evaluate the effects of a standardized garlic preparation on lipid parameters, including total cholesterol, triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) in patients with hypercholesterolemia.
METHODS: A randomized, double-blind, placebo-controlled, 20-week study was conducted in patients age 35 to 70 years with a total cholesterol between 200 and 300 mg/dl. Patients were stratified into two groups based on patient age (35-50 and 51-70 years of age). Patients were randomized to receive 10,000 µg of allicin per day or identical placebo. Each tablet contained a total of 2500 µg of allicin. Fasting lipid panels (total cholesterol, triglycerides, LDL and HDL) were measured every 5 weeks for 20 weeks. Data were analyzed using ANOVA with repeated measures and chi-square analysis as appropriate.
RESULTS: Twelve patients received garlic product and 12 received the placebo product. No significant within-group or between-group changes were detected for any lipid parameter in either group. Adverse effects (e.g., itching, headaches, gastrointestinal symptoms) were significantly greater in the garlic group compared with the placebo group (6/12 vs 0/12 patients, $p=0.005$).
CONCLUSIONS: The standardized garlic preparation investigated exhibited no effect on serum lipoproteins in this patient population, but the occurrence of adverse effects was significantly greater in the garlic group. Perhaps with a lower dose (5000 µg allicin/day) and a larger sample size, positive effects of garlic may be observed in future trials of similar design.

96. Attitudes of older Americans toward herbal and dietary supplements. *Jacqueline S. Marinac, Pharm.D.*, Colleen Buchinger, M.D., Lincoln Godfrey, M.D., James Wooten, Pharm.D., Sandra Willsie, D.O.; Truman Medical Center-West; University of Missouri-Kansas City, Kansas City, MO.

PURPOSE: Herbal products and dietary supplements are a billion-dollar industry in the U.S. No information regarding the attitudes of older Americans toward herbal products (HP) and dietary supplements (DS) has been conducted.
METHODS: Two hundred sixty-three Americans over age 60 were recruited from the greater Kansas City metropolitan area. The face-to-face survey consisted of 18 statements either true false or don't know. Subjects were paid $5. Data were tabulated and stratified based upon gender, ethnicity, and highest-grade completed and economic status.
RESULTS: Seventy percent survey were female, 50% white and 49% African American. Eighty-seven percent were under doctor's care. Twenty percent currently take some herbal product. A doctor prescribed it in 14% of the time. Eighty-eight percent felt it was important for their doctor to know what herbal products they are taking. Seventy-eight percent felt herbs offered some health benefit while 36% felt vitamins and nutritional products provide "all the health benefits of real food". Half felt that insurance or Medicare/Medicaid should pay for herbal products. Ninety-one percent felt that older Americans were often the targets of medical quackery. Seventy-two percent want more information about HP, and 45% said they would take a HP if their doctor prescribed it. Twenty-five percent said they would take HP if they "thought it would help me", with 21% stating they "would not take HP".
CONCLUSIONS: The results of this survey demonstrate that 20% of Older Americans are taking herbal products, 86% without doctor's orders. Three-fourths feel than herbs offer some health benefit and want more information with one-half saying they would take it if recommended by their physicians.

97. Herbal product use among older Americans. *Jacqueline S. Marinac Pharm.D.*, Colleen Buchinger M.D., Lincoln Godfrey M.D., James Wooten Pharm.D., Sandra Willsie D.O.; Truman Medical Center-West; University of Missouri-Kansas City, Kansas City, MO.

PURPOSE: The purpose of this study was to survey older Americans regarding use of herbal products (HP). Older Americans are at greater risk of adverse events due to number of concomitant medications and diseases, yet the usage patterns of HP is unknown.
METHODS: Two hundred sixty-three Americans age 60 and over were recruited from the greater Kansas City metropolitan area. The face-to-face surveys were conducted.
RESULTS: Seventy percent surveyed were female, 50% white and 49% African American. Twenty-percent (n=52) were currently taking at least one HP. Of those, 75% female and 73% white (29% of all white surveyed and 11% of all African Americans surveyed [86% female]). Eighty-five percent were at least high school graduates, with half having advanced education, and 75% reported a household income of at least $10,000/year. Eighteen were taking more than one HP. The most commonly used HPs were: glucosamine (14), garlic (9), gingko biloba (8), echinacea (8) herbal/green tea (5), St. John's wort (4), cod liver oil (4), ginseng (3) and saw palmetto (2).
CONCLUSIONS: About 20% of the older population surveyed currently takes at least one HP. All are currently under a doctor's care, yet was doctor prescribed in only seven. White, educated females were most likely to take HP. Health care providers should inquire about HP use in the elderly.

HIV/AIDS

98. The effects of HIV-1 protease inhibitors on the proliferation of placental trophoblasts. *Patty Fan-Havard, Pharm.D.*, Douglas A. Kniss, Ph.D.; Ohio State University, Columbus, OH.

PURPOSE: Highly active antiretroviral therapy (HAART) is now recommended in pregnant HIV-infected women to improve maternal health and further reduce maternal-fetal transmission despite limited clinical and safety studies. The maintenance of fetal well-being and pregnancy is dependent on placental integrity. Currently, there are no published data assessing the cytotoxic effects of HIV-1 protease inhibitors (PIs) on placental trophoblasts (JEG-3). We report here the antiproliferative activity of HIV-1 protease inhibitors, nelfinavir (NFV) and ritonavir (RTV) on JEG-3 cells as part of our ongoing research to study the effects of PIs on the biologic functions of placental trophoblasts.
METHODS: JEG-3 cells were grown in DMEM/F12 medium supplemented with 1 mM sodium pyruvate, 2 mM L-glutamine and 50 mg/ml gentamicin and maintained at 37ºC with 5% CO2 and 95% air. Cells were seeded into 96 well plates (10^4 cells/well) in complete medium. Cells were incubated in serum-free and phenol red-free DMEM/F12 medium containing desired testing concentrations of DHEA, NFV, RTV and NFV/RTV. Cell proliferation was determined using tetrazolium and phenazine methosulfate substrates (MTS) assay and analysis of cell cycle stages was determined by flow cytometry.
RESULTS: We observed a diminished proliferation activity following treatment with NFV (10^{-5}M) and RTV (10^{-5}M) for 48 hours. NFV and RTV alone inhibited cell proliferation by 37% and 10%, respectively, as compared to control. The combined PIs further reduced cell proliferation to 86% (ANOVA with Tukey post-hoc testing, $p<0.001$). Cell cycle analysis using flow cytometry revealed redistribution of cells treated with PIs in different cell cycle stages with a significant increase in the G_0-G_1 phase as compared to control ($p<0.05$).
CONCLUSION: These results suggest antiproliferative effect of PIs on placental trophoblasts with an increase in G_0-G_1 phase. Studies are ongoing to examine the possible mechanisms.

99. Utility of the mean possession ratio in assessing antiretroviral adherence. *Ian R. McNicholl, Pharm.D.*, Rodney H. Lusk, M.D.; Saint Louis College of Pharmacy; John Cochran Veterans Affairs Medical Center; Saint Louis University, St. Louis, MO.

PURPOSE: To evaluate the utility of the mean possession ratio (MPR), an objective measure, in assessing antiretroviral adherence
METHODS: Data were prospectively collected between June 1, 1999 and June 10, 2000, for all active Veterans Affairs (VA) Infectious Diseases clinic patients receiving antiretroviral therapy for at least 3 months. Data collected included demographics, patient/provider reports of adherence, current medications, CD_4 count, viral load and number/dates of refills. The MPR was calculated using number of dosing units dispensed over a 3-6 month period prior to the most recent viral load divided by total number of possible refill days. The MPR was categorized as < 0.7, 0.7-0.79, 0.8-0.89, and 0.9-1.0 where 1.0 represents 100% adherence. Patient interviews were conducted by and refill history verified by the primary investigator.
RESULTS: One hundred and four out of 125 patients (83%) met the inclusion criteria. Mean CD_4 count was 527 ± 400 cells/mm^3 (median 488) with a mean viral load of 32,570 ± 76,380 copies/ml (median 892.5). Median viral load decreased significantly as MPR increased: 42,140 (< 0.7), 14,920 (0.7-0.79), 576.5 (0.8-0.89), and 400 copies/ml (0.9-1.0), $p<0.005$. Percent of patients with an undetectable viral load (< 400 copies/ml) increased as MPR increased: 12.5% (0.7-0.79), 44% (0.8-0.89), and 69% (0.9-1.0), $p<0.0001$. Admissions of non-adherence were 82% (<0.7), 37% (0.7-0.79), 11% (0.8-0.89), and 3.7% (0.9-1.0), $p<0.0001$.
CONCLUSION: MPR provides an objective and valuable measure of antiretroviral adherence inversely correlating with viral load. Its utility may be greatest in clinical settings, as it is easily calculated and monitored.

100. Discrepancy between patient-reported adherence and pharmacist-assessed adherence to antiretroviral therapy in patients with human immunodeficiency virus infection. *Lori D. Esch, Pharm.D.*, Hélène Hardy, Pharm.D., Heather E. Wynn, Pharm.D., Mark J. Shelton, Pharm.D.; University at Buffalo, Erie County Medical Center, Buffalo, NY.

Patient-reported adherence (PRA) can predict virologic outcomes but may overestimate true adherence (ADH). Greater than 95% ADH is required for optimal virologic response but pharmacologic factors, beyond simply taking the correct dose, are critical in ensuring adequate drug exposure.
PURPOSE: To evaluate concordance between PRA and pharmacist-assessed ADH to HIV medications.
METHODS: During regularly scheduled appointments in an HIV adherence clinic, patients were asked a series of routine ADH assessment questions. Patients were asked “Are you compliant?” followed by more specific questions about their ADH. The pharmacist then interviewed the patient, evaluating ADH to prescribed regimens and incorporating knowledge of how the medication should be taken for optimal exposure.
RESULTS: Of the 50 patients evaluated, 41 (82%) reported they were compliant with their regimen; however, 16 of this group (39%) claimed they did not take medications all the time (8), at the right time (7), or with the right food (1). Three (19%) reported missing doses in the previous 48 hours and 7/16 (44%) estimated < 95% ADH with their regimen. After the interview, 18/41 (44%), who had claimed they were compliant were found to be non-adherent for one or more of the following reasons: inadequate spacing with respect to half-life, food or other medications (50%), taking wrong medications or doses (17%), or reported missed doses (67%).
CONCLUSIONS: Patient-reported adherence is only as good as a patient's understanding of true ADH. Understanding drug pharmacology is also required to assess adequate ADH. Pharmacist-assessed ADH plus interview captured more episodes of non-adherence than PRA alone.

101E. Integration of viral dynamics and pharmacokinetics of racemic dOTC in HIV-infected antiretroviral naïve patients. *Patrick .F Smith, Pharm.D.*, Alan Forrest, Pharm.D., John M. Adams, Pharm.D., Craig R. Rayner, Pharm.D., Robin Wood, M.D., Louise Proulx, Ph.D.; SUNY-Buffalo, Buffalo, NY; PRC, Morrisville, NC; Somerset Hospital, South Africa; BioChem Pharma Inc, Canada.

PURPOSE: A novel pharmacokinetics (PK)/pharmacodynamics (PD) modeling approach for a short-term monotherapy (SM) phase I/II study of racemic dOTC, an NRTI.
METHODS: Forty-eight ARV naïve HIV+ men (6 cohorts of 8 patients), normal renal/hepatic function, CD4 > 200, HIVRNA 5-100K; randomized to oral dOTC 400, 600, or 800 mg/d, either q12 or q24h x 7 days. Plasma samples (13 on day one and seven, daily troughs) for chiral assay (HPLC) and HIVRNA (baseline and day 0.5, 1, 1.5, 2, 2.5, 3-8, 21); were obtained and fit by candidate PK/PD models (Adapt II); weighting by 1/variance; model discrimination by AIC. Percentage of Inh (% inhibition of viral replication), %HIV exposure (100[HIVRNA]/baseline), both averaged over 7 days, determined by integration of the fitted PK/PD functions.
RESULTS: HIVRNA is modeled with two compartments: plasma, where HIVRNA is measured and first order elimination occurs, and a tissue compartment, where capacity-limited replication occurs; drug acts to inhibit viral replication. Mean (CV%) %Inh (200q12, 400q24, 300q12, 600q24, 400q12, 800q24, respectively) were: 84(12), 83(12), 89(7), 90(7), 92(3), and 93(3); %HIV were: 43(25), 40(42), 37(31), 33(27), 29(18), 30(26). For both activity measures, daily dose was significant ($p<0.02$), dose interval was not ($p>0.4$).
CONCLUSION: Because viral replication, elimination, and drug PK/PD are modeled as distinct processes, this approach appears more sensitive than comparisons of slopes of HIVRNA decline or log drop from baseline, measures confounded by intrinsic drug-free viral half-life and drug effect. For racemic dOTC in this SM trial: ARV effect increased with daily dose and AUC, and was not a function of peak or time > IC_{50}; we would predict further increases in daily dose would provide only small further increases in activity; it is probable that once daily dosing can be considered in adults.
Presented at the XIII World AIDS Conference, Durbin, South Africa, July, 2000.

102. Health beliefs of patients with HIV requiring hospitalization versus patients in the ambulatory care setting. *Crystal Plasencia, Pharm.D.*, Kathleen K. Graham, Pharm.D., Leanne L. Lai, Ph.D., Alan Shaffer, R.N.; HIV Clinical Research Comprehensive Care Center, Broward General Medical

Center, North Broward Hospital District; Nova Southeastern University, Fort Lauderdale, FL.

PURPOSE: To survey hospitalized and ambulatory patients with HIV/AIDS to determine differences in health beliefs, utilization of health care, and health status which may contribute to hospitalizations.
METHODS: We implemented a 46-question survey composed of demographics, beliefs about HIV and medications, accessibility to health care, and health status. Eligible participants included HIV-positive men and women hospitalized for an AIDS-related event or receiving ambulatory care. We chose random days and times to interview patients in the privacy of the hospital or exam room.
RESULTS: A total of 57 patients were surveyed (27 inpatient and 30 outpatient). Significant differences between hospital versus clinic groups, respectively, include: increased frequency of African Americans (21/27 [77%] vs 18/30 [60%], $p<0.05$) and women (11/27 [42%] vs 9/30 [30%], $p<0.05$), lower CD_4 counts (183 vs 383, $p<0.05$), awareness of viral load and CD_4 counts (15/27 [56%] vs 25/30 [83%], $p<0.05$), frequency of missed doses prior to hospitalization (11/26 [42%] vs 6/29 [21%], $p<0.05$), changes in antiretroviral regimen (20/25 [80%] vs 11/30 [37%], $p<0.05$), prior hospitalizations within the last year (23/27 [85%] vs 14/30 [47%], $p<0.05$), emotional limitations to daily activities most of the time (21/30 [70%] vs 7/26 [27%], $p<0.05$), and desire to have a pharmacist visit them at home to discuss medications (13/25 [52%] vs 7/30 [23%], $p<0.05$).
CONCLUSIONS: Differences in medication knowledge and utilization were found between hospitalized and ambulatory patients with HIV, which may contribute to hospitalizations. We therefore recommend, upon discharge, all patients hospitalized with HIV/AIDS-related events to be enrolled in our medication adherence clinic for counseling and/or psycho-social support services in an effort to reduce future hospitalizations.

103. HIV-1 protease inhibitors diminish de novo biosynthesis of 17β-estradiol and aromatase mRNA expression. *Eunsun Cho, Pharm.D.,* Patty Fan-Havard, Pharm.D., Douglas A. Kniss, Ph.D.; Ohio State University, Columbus, OH.

PURPOSE: Estrogen biosynthesis by placental trophoblasts is critical for fetoplacental development and well-being. Fetal-derived dehydroepiandrostenedione (DHEA) is utilized as a substrate for the production of estrone (E_1), 17β-estradiol (E_2), and estriol (E_3) by cytochrome $P450^{aromatase}$ (CYP19). Inhibitors of HIV-1 protease diminish certain hepatic cytochrome P450 enzymes; thus altering xenobiotic metabolism. We examined whether inhibitors of HIV-1 protease, nelfinavir (NFV), or ritonavir (RTV) could alter the de novo biosynthesis of 17β-E_2 and expression of CYP19 expression using JEG-3 choriocarcinoma cells as a model system of syncytiotrophoblast.
METHODS: JEG-3 cells were grown in DMEM/F12 medium supplemented with 1 mM sodium pyruvate, 2 mM L-glutamine and 50 µg/ml gentamicin and maintained at 37°C with 5% CO_2 and 95% air. Cells were seeded into 24 well plates (2×10^5 cells/well) in complete medium. Cells were incubated in serum-free and phenol red-free DMEM/F12 medium containing desired testing concentrations of DHEA, NFV, RTV and NFV/RTV. Total RNA were extracted as described by Chomcyznski and Sacch, fractionated on denaturing agarose and transferred to nitrocellulose membrane. The membranes were hybridized with digoxinenin-labeled cDNA fragments encoding human CYP19.
RESULTS: We observed a 209-fold increase in 17β-E_2 formation with DHEA alone as compared to medium alone (2.7 vs 564.5 ng/mg protein). NFV (10^{-5}M), RTV (10^{-5}M), and NFV/RTV caused a 24.6%, 31.4% and 64.2% reduction in 17β-E_2 production, respectively, as compared to DHEA alone (ANOVA with Tukey post-hoc testing, $p<0.001$). A decrease in aromatase mRNA expression was observed with NFV (10^{-5}M) and NFV/RTV by Northern blot analysis.
CONCLUSION: These in vitro data suggest that inhibitors of HIV-1 protease alter the biosynthesis of 17β-E_2 and CYP19 mRNA expression. Furthermore, a synergistic reduction in 17β-E_2 was observed following treatment with dual HIV-1 protease inhibitors.

104E. CNS manifestations of paradoxical reaction in HIV+ tuberculosis patients on highly active antiretroviral therapy. Elena S. Hollender, M.D., Masa Narita, M.D., David Ashkin, M.D., Dimeji Akinlabi, P.A., Ningyi Huang, M.D., *Jerry J. Stambaugh, Pharm.D.*, John McFeely; A.G. Holley State Tuberculosis Hospital, University of Miami, Miami, FL.

PURPOSE: We recently reported the phenomenon of paradoxical reaction (PR) in HIV+ patients with tuberculosis (TB) started on highly active antiretroviral therapy (HAART). We now report cases of CNS manifestations of the PR.
METHOD: We conducted a retrospective chart review of all HIV+ patients admitted to our hospital from December 1, 1997 through November 30, 1998. Those with a PR with CNS manifestations were reviewed and compared with those HIV+ without evidence of CNS PR. Cases were analyzed for initial CD_4 and viral loads, CNS lesions and time to onset of symptoms after HAART.
RESULTS: Six of 69 (8.7%) HIV+ patients admitted met the criteria of documented new CNS lesions or worsening CNS lesions after initiation of HAART, in the absence of a response to anti-toxo therapy. Symptoms of headache, weakness, change in mental status, new onset seizures, nausea and vomiting appeared a median of 18 days (range 10-59) in five patients after HAART was initiated. One patient was asymptomatic and lesions found on CT scan for another condition. CT scan or MRI demonstrated lesions in the left frontal area (three patients), cerebellum (two patients), thalamus (two patients), occipital (one patient), and cervical spine (one patient). All showed surrounding edema or mass effect, and all but the asymptomatic patient required corticosteroids. On continued HAART and anti-TB therapy, two patients had complete resolution of lesions, two patients had significant decrease in lesion size and/or number and two have stabilized and continue treatment. Statistical analysis between the CNS patients and control group showed no difference when compared for age, sex or race. Initial median CD_4 was 29.5 (range 22-63) in the CNS group and 69.5 (range 17-711) in the HIV+ control ($p=0.37$). Initial log viral load showed a median of 5.72 (range 5.52-7.08) in the CNS group and 5.16 (range 2.60-6.61) in the control group ($p=0.004$).
CONCLUSION: CNS manifestations occur in a significant number of patients with a PR, and may be potentially life threatening. A high initial viral load and low initial CD_4 appear to be risk factors for CNS PR. Further studies are needed to elucidate this finding.
Presented at the 7th Antiretroviral Conference, San Francisco, CA, March 2000.

105. Macrocytosis associated with nucleoside reverse transcriptase inhibitor therapy is specific to thymidine analogues. *Susan Raber, Pharm.D.,* James Leggett, M.D., Ronald Dworkin, M.D., Sarah Slaughter, M.D., David Gilbert, M.D.; Oregon State University; Providence Medical Center, Portland, OR.

PURPOSE: Macrocytosis has been well documented with the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine (ZDV) and recently reported with stavudine (d4T). Inhibition of DNA polymerase γ and DNA synthesis have been suggested, however, the precise mechanism is unknown. This study was undertaken to evaluate the incidence and characteristics of macrocytosis associated with highly active antiretroviral therapy (HAART).
METHODS: Medical records of 178 HIV patients with clinic visits between July 1999 and March 2000 were reviewed. Patients were included if they had ≥ 1 CBC and were stabilized on a HAART regimen (≥ 16 weeks) or taking no antiretrovirals. Hydroxyurea (HU)-containing regimens were excluded.
RESULTS: One hundred eight patients were included in the final analysis; 48 lacked a CBC, 15 were not on stable regimens, and 7 were taking HU. Regimens containing ZDV or d4T were associated with elevated MCV in nearly all patients, whereas the non-thymidine analogue NRTIs resulted in normal MCV. Patients with MCV < 100 fL on ZDV or d4T had a mean MCV increase of 15 fL (n=4) or documented non-adherence (n=4).

Regimen	N	CD4	MCV	MCV ≥ 100
(cells/mm^3)	(fL)	N (%)		
ZDV-containing	33	439 ± 268	110.1 ± 9.7*†	28 (85)
d4T-containing	54	450 ± 275	107.2 ± 7.7‡	51 (94)
Non-thymidine	7	454 ± 509	89.5 ± 4.2*‡	0
No HAART	14	462 ± 182	88.8 ± 3.5†	0

*$p<0.05$; †$p<0.05$; ‡$p<0.05$; $p<0.05$

CONCLUSION: Macrocytosis is a predictable effect of thymidine analogue NRTIs. MCV may be a surrogate marker for adherence and long-term toxicity. Further investigation of the mechanism is warranted.

Infectious Diseases

106E. Examination of health care resource utilization associated with the treatment of infections caused by susceptible and non-susceptible isolates of *Streptococcus pneumoniae. Donald G. Klepser, MBA,* Michael E. Klepser, Pharm.D., John M. Brooks, Ph.D., Erika J. Ernst, Pharm.D., Daniel J. Diekema, M.D., Holly L. Hoffman, Pharm.D., Essy Mozaffari, Pharm.D., MPH, Joseph Hendrickson, Pharm.D., Gary V. Doern, Ph.D.; University of Iowa , Iowa City, IA; Pharmacia Corporation, Kalamazoo, MI.

BACKGROUND: Although SPN resistance has been well documented, its impact on health care resource utilization (HCRU) has not been established.
METHODS: This retrospective, observational cohort study included hospitalized patients admitted from 1995-98 and treated for a *Streptococcus pneumoniae* (SPN) infection. Data were extracted from medical charts and laboratory, pharmacy, and accounting computer databases. Charge data were collected daily for each patient beginning 7 days prior to day 0 (culture collection date) through 28 days after day 0. Patients were stratified for isolate susceptibility to penicillin (susceptibility [S], MIC ≤ 0.12 µg/ml; non-susceptibility [NS], MIC ≥0.25 µg/ml) and charge data analyzed at aggregate and cost center levels using Wilcoxon Rank Sums.
RESULTS: Two hundred thirty-five patients (S-144, NS-91) met inclusion criteria (blood or respiratory isolate and received ≥ 3 days of anti-SPN antibiotics). Health care resource utilization peaked on day 0 (10% of total) and declined to pre-day 0 levels by day 14. Fifty percent, 12%, 1%, and 8% of

total charge was attributable to room/nursing, pharmacy, antibiotics, and laboratory utilization, respectively. Forty percent of HCRU during the infection window occurred on days 1-7 (intervention window). Median total charges over the infection window (days 2-14) were $19,372.21 and $27,958.70 for S and NS ($p<0.05$). Significant differences were detected between S and NS with respect to total, room, nursing, and pharmacy charges over both infection and intervention windows ($p<0.05$).
CONCLUSIONS: Greatest expenditure of resources occurs within the 7 days following day 0. Non-susceptible SPN results in excess charges of $8582 (95% CI $402; $16,762) over the infection window.
Presented at the 40th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, ON, Canada, September 17-20, 2000.

107. Prospective evaluation of antibiotic rotation in three intensive care units at a tertiary care university hospital. *Steven P. Gelone, Pharm.D.*, Bennett Lorber, M.D., Keith St. John, M.S., Peter Axelrod, M.D., Michael Badelino, M.D., Gerard Criner, M.D.; Temple University; Temple University Hospital; Philadelphia, PA.

PURPOSE: This study evaluated the impact of rotating empiric antibiotic therapy for Gram-negative infections to determine: 1) its practicality, 2) the impact on antibiotic susceptibility, and 3) the clinical and economic outcomes.
METHODS: A 3-year prospective study of monthly changes in empiric antibiotic therapy was conducted in a medical/respiratory intensive care unit (ICU), a surgical/trauma ICU and a ventilator rehabilitation unit. During the first year, baseline data were collected in each unit. A clinical pharmacist rounded daily in each unit and collected data on antibiotic susceptibility, the number of infections and resistant infections, and clinical and economic outcomes. During the second and third years, prospective monthly changes in empiric antibiotic therapy were conducted. Daily rounds by a clinical pharmacist were continued. During this time period, recommendations were made by the pharmacist to optimize antibiotic dosing and to change therapy based on culture and susceptibility information.
RESULTS: Data on antibiotic susceptibility and practicality are currently available. Improved susceptibility has been noted in *K. pneumoniae*, *Enterobacter spp.*, *P. aeruginosa*, *E. coli*, and *E. faecium*. No change has been seen in *S. aureus* or *S. epidermidis*. A decrease in susceptibility to imipenem has been noted in acinetobacter species and *P. aeruginosa*.
CONCLUSIONS: Monthly rotation of empiric antibiotic therapy at a university tertiary care hospital within the ICU setting is very practical. It has resulted in improved antibiotic susceptibility patterns of several different species within the units studied. Its effect on infection rate and clinical/economic outcomes is currently under evaluation.

108. In vitro exposure of human mast cells to amphotericin B: non-IgE mediated effects on histamine release. *Michael D. Schwartz, Pharm.D.*, P. David Rogers, Pharm.D., Stanley W. Chapman, M.D., John D. Cleary, Pharm.D.; University of Mississippi, Jackson, MS.

PURPOSE: Patients receiving amphotericin B (AmB) routinely receive antihistamines as a premedicant in attempt to reduce infusion-related adverse events. Many well-known health care textbooks recommend antihistamine use despite minimal primary literature support. Therefore, our purpose was to evaluate mast cell histamine release secondary to AmB exposure.
METHODS: Human mast cells (HMC-1, Mayo Clinic, peripheral blood of mastocytoma patient) were cultured, suspended in calcium-supplemented phosphate-buffered saline to 1.0×10^6 cells/ml, and then exposed to AmB for 1 hour at concentrations ranging from 0.625 to 5.0 µg/ml. Culture supernatants were collected, diluted 1:100, and assayed for baseline, released, and total histamine using competitive enzyme immunoassay. The experiment was repeated three times and each condition was assayed in duplicate.
RESULTS: Exposure to AmB did not increase detectable histamine above in vitro baseline HMC-1 levels. Exposure actually reduced histamine release but not in statistically significant amounts (Student's t-test, p=0.081). Reductions below HMC-1 baseline were 7.5%, 15%, 32%, and 35% for AmB 0.625, 1.25, 2.5, and 5.0 µg/ml, respectively. An abundance of available histamine was validated by freeze-thawing as well as A23187, a calcium ionophore that was the positive control. This indicated the cells contained approximately three times baseline histamine. Pre-treatment of cells with diphenhydramine 25-50 ng/ml did not alter response to AmB exposure.
CONCLUSIONS: Amphotericin B at clinically achievable concentrations did not induce release of histamine from HMC-1 cells via non-IgE mechanisms. Therefore, routine use of antihistamines as a premedicant prior to infusions of AmB may need to be re-evaluated.

109. To evaluate the impact of usage guidelines on meropenem utilization and resistance patterns in a teaching hospital. *Adnan Gauhar, M.S.*, B.Pharm., Abdul Latif Sheikh, M.S., Arif Rasheed Sarwari, M.D.; University of Bradford, United Kingdom; The Aga Khan University Hospital, Karachi, Pakistan; The Aga Khan University, Karachi, Pakistan.

PURPOSE: To reduce the resistance patterns and promote rational use of meropenem, a carbapenem antibiotic in the hospital formulary. Inpatients microbiological specimen data 1998 of our hospital showed the following resistant pattern with meropenem. Twenty-five percent acinetobacter species, 35% *Pseudomonas aeruginosa*, 12% enterobacter, 7% *Klebsiella pneumoniae*. Utilization data indicated that 45% of the drug was used in general surgery, orthopedics and oncology patients as empirical therapy. The intensive care unit, where the use of meropenem was primarily approved, showed only 18% utilization.
METHODS: A multidisciplinary team was brought together. The team formulated the usage guidelines. The guidelines were approved by the pharmacy and therapeutic committee and then disseminated to the medical staff through a monthly newsletter containing information regarding the pharmacy and therapeutic committee decisions and formulary updates. Senior pharmacist assigned to drug information center was responsible for monitoring of compliance and collecting data.
RESULTS: Hospital inpatients microbiological specimen data of January to June 1999 showed a decrease in resistant pattern of meropenem. Acinetobacter from 25% to 16%, *P. aeruginosa* 35% to 19%, enterobacter 12% to 1%, and *K. pneumoniae* 7% to 0. The empirical utilization of meropenem in general surgery, orthopedics and oncology patients was also decreased from 45% to 22%.
CONCLUSION: Educational strategies have found to be more effective and acceptable to physicians rather than restrictive policies. Effective monitoring of the compliance with the usage guidelines and educating the physician based on the data are effective tools to promote rational use of drug especially antibiotics.

110. Effects of azithromycin exposure on the biofilm formation and overall bactericidal activity against biofilm cells of *Staphylococcus epidermidis*. *S. Lena Kang-Birken, Pharm.D.*; University of the Pacific, Stockton, CA; Cottage Health System, Santa Barbara, CA.

PURPOSE: *S. epidermidis* produces exopolysaccharides, subsequently forming an impenetrable biofilm as defense mechanism. The objectives were to study the effects of azithromycin (A) on biofilm formation in relation to timing of exposure and killing activity of vancomycin (V) and levofloxacin (L) with or without rifampin (R) against biofilm cells.
METHODS: A clinical isolate of methicillin-resistant *S. epidermidis* (MRSE 23) and a reference strain (ATCC 35984) were utilized. Biofilm was formed using an in-vitro model with a cellulose membrane serving as an attachment site. A (3.6 µg/ml) was added after 1 or 10 days of biofilm formation, and kept incubated for 5 additional days.
RESULTS: MIC/MBC of V, L, and R against MRSE 23 and ATCC 35984 were 0.78/0.78, ≤ 0.19/£ 0.19, ≤ 0.19/£ 0.19 µg/ml, and 0.78/1.56, ≤ 0.19/£ 0.19, ≤ 0.19/£ 0.19 µg/ml, respectively. Against MRSE 23, a mild slime producer, there was minimal reduction in biofilm regardless of timing of A exposure. Early exposure significantly eradicated existing slime and prevented formation of biofilm of ATCC 35984, a high slime producer. With early A exposure, individual cells were noted under electron microscope whereas untreated cells were completely covered by slime. Delayed exposure to A was not as effective. In time-kill studies against untreated biofilm cells, R addition to V or L was beneficial, being the most effective regimens. However, 99.9% reduction was not achieved. Against two treated strains, overall activity of V and L improved by one log, and R was antagonistic to both. 99.9% reduction was achieved only with L against treated MRSE 23 (47.4 hour) and with L and L+R against treated ATCC 35984 (36.5 hour and 48.0 hour, respectively).
CONCLUSIONS: A was highly effective in preventing biofilm formation and enhancing the killing activity of V and L, especially against the high-level slime producing strain.

111. Levofloxacin and cefotaxime, alone versus in combination for the treatment of community-acquired pneumonia in hospitalized patients: impact on medical outcomes. *Phil Phung, Pharm.D.*, Teresa Tong, Pharm.D., Michael Gurevitch, M.D., Annie Wong-Beringer, Pharm.D.; Western University of Health Sciences, Pomona, CA; Huntington Memorial Hospital, Pasadena, CA.

PURPOSE: Published guidelines recommend the use of either cefotaxime (MC), levofloxacin (ML) alone or in combination (CB) to treat patients hospitalized with community-acquired pneumonia (CAP). We evaluated the impact of mono- versus combination therapy on in-hospital mortality, medical complications, times to vital sign stability (TS), and length of stay (LOS).
METHODS: Adults admitted for CAP over a 15-month period were screened; 141 patients met study definitions for CAP, received at least 48 hours of study drugs, and had available charts for review. Treatment groups were ML (n=50), MC (n=50), and CB (n=41). Patients were stratified into risk classes using the pneumonia severity index. Sociodemographics, antibiotic therapy, and clinical course were recorded.
RESULTS: Patient groups did not differ in age (mean = 74). Most (76%) patients were in risk classes IV and V; 29% (31/107) received CB. Pneumonia-related death rate was lowest with ML (14%) < MC (18%) < CB (22%). Medical complications were low for all groups; one patient each in CB and MC groups had empyema. TS was shortest in ML (2 days) < CB (3.5) < MC (4) as was the LOS, ML (6 days) < CB (8) < MC (9). Differences between

groups did not reach statistical significance due to small sample size.
CONCLUSION: This preliminary data suggest that monotherapy with levofloxacin may achieve better medical outcomes than either MC or CB in the treatment of severe CAP in hospitalized patients. Further confirmation of our findings and clarification of the observed differences between ML and CB are needed.

112. Efficacy of clarithromycin and azithromycin against *Streptococcus pneumoniae* with various macrolide resistance mechanisms in a neutropenic murine respiratory infection model. *Holly L. Hoffman, Pharm.D.,* Erika J. Ernst, Pharm.D, Michael E. Klepser, Pharm.D., C. Rosemarie Petzold, Gary V. Doern, Ph.D.; University of Iowa, Iowa City, IA.

PURPOSE: We utilized a murine neutropenic lung infection model to determine if the in vivo activity of clarithromycin (CL) or azithromycin (AZ) was influenced by the *Streptococcus pneumoniae* (SPN) macrolide resistance determinants and dose of antimicrobial.
METHODS: Twenty-one resistant SPN strains were studied. Isolates included; ten efflux-mediated resistance (mef A; MICs 0.5-32 µg/ml), four target site mutations (erm B; MICs ≥ 64 µg/ml), five susceptible isolates (MICs ≤ 0.06), and two isolates expressing both mef A and erm B genes (MICs ≥ 32 µg/ml). Swiss-Webster mice were rendered neutropenic with cyclophosphamide, infected via intra-tracheal inoculation and treated via oral lavage for 72 hours starting 12 hours post infection with either CL or AZ at dosages of 4, 40, and 200 mg/kg, BID with CL, QD with AZ. Each cohort contained ten mice. Mortality was assessed at regular intervals for 10 days. Median survival time was calculated using SPSS life tables and survival was compared to untreated control mice using Gehan's generalized Wilcoxon Test.
RESULTS: Survival of mice infected with erm B isolates was comparable to untreated control mice with all three doses of CL and AZ. Among mice infected with mef A strains, a significant reduction in mortality versus untreated controls ($p<0.05$) was noted with the 40 mg/kg dose in 3/10 isolates with CL and 1/10 isolates with AZ. With the 200 mg/kg dose, a significant improvement in survival occurred in 9/10 isolates with CL and 3/10 isolates with AZ ($p<0.05$).
CONCLUSIONS: CL at higher doses, improved survival in mice infected with SPN isolates characterized by mef A-mediated macrolide resistance.

113. Effect of CpG DNA oligodeoxynucleotides and echinacea on the fungicidal activity of amphotericin B in a disseminated murine candidal infection model. *Holly L. Hoffman, Pharm.D.,* Thomas W. Redford, Pharm.D., Michael E. Klepser, Pharm.D., Erika J. Ernst, Pharm.D., Arthur M. Krieg, M.D.; University of Iowa, Iowa City, IA.

PURPOSE: CpG DNA elicits a T-helper 1 (Th-1) type cell mediated immune response via production of proinflammatory cytokines. Echinacea (Ech) is also believed to exert immunomodulatory activity through a Th-1 immune response. In vivo synergistic fungicidal activity has been reported when amphotericin B (AmB) is combined with Th-1 cytokines. We evaluated the impact of adjuvant CpG DNA and Ech on the fungicidal activity of AmB in a murine model.
METHODS: Two infection models were utilized, a non-neutropenic (NN) treatment model and a neutropenic (N) protection model. Groups included: control, CpG, Ech, AmB, Ech plus AmB, and CpG plus AmB. Balb-C mice were infected with *C. albicans* via lateral tail vein injections 5 hours prior to treatment with AmB 1 mg/kg/day x 2 doses. In the NN model, mice were given Ech (130 mg/kg q12h for 72 hours) or CpG (30 µg once) starting 5 hours after infection. Mice were sacrificed at predetermined times and kidneys removed for fungal burden determination. In the N model, CpG, 30 µg, was administered once 72 hours prior to infection and Ech, 130 mg/kg q12h, administered 24 hours prior to infection and continuing 72 hours post infection. Mice in this model were monitored for survival for 10 days.
RESULTS: Among NN mice, no difference in tissue fungal burden were noted with AmB plus CpG or Ech compared to AmB alone. Among N mice, AmB plus CpG or Ech did not improve survival compared to AmB alone.
CONCLUSIONS: In treatment and protection models, AmB plus CpG or Ech failed to demonstrate benefit over AmB alone.

114E. Relationship of valproate treatment to accelerated liver damage in patients with hepatitis C. *Kristin M. Helmboldt, Pharm.D.,* Rex S. Lott, Pharm.D., Karl J. Madaras-Kelly, Pharm.D.; Idaho State University; VA Medical Center, Boise, ID.

PURPOSE: Valproate, a potential hepatotoxin, is commonly prescribed for comorbid mood disorders in patients infected with Hepatitis C virus (HCV). This study evaluated the relationship between valproate use and evidence of accelerated liver damage in HCV positive patients.
METHODS: Retrospective data were reviewed for all Boise VA patients diagnosed HCV positive since January 1992. Patient demographics, ALT/AST values, valproate prescriptions, history of concomitant potentially hepatotoxic medications, and evidence of overt alcohol abuse were evaluated. Potential hepatotoxicity was staged by comparing maximum AST/ALT values against upper limits of normal or against patients' mean elevated baseline AST/ALT: stage 0 (< 1.25X ULN or baseline); stage 1 (1.25-2.5X ULN or baseline); stage 2 (2.6-5X ULN or 2.6-3.5X baseline); stage 3 (5.1-10X ULN or 3.6-5X baseline); and stage 4 (> 10X ULN or > 5X baseline) (JAMA 2000;283:74-80). Statistical analyses included chi square, t-test, and Mann-Whitney U.
RESULTS: Two hundred eighteen evaluable HCV positive patients were identified. Thirty-two were treated with valproate after HCV diagnosis, and 186 never received valproate. Stage 3 or 4 (severe) hepatotoxicity was observed in 6 (19%) and 19 (10%) of the valproate and no valproate groups respectively ($p=0.17$). At time of peak LFT elevations, exposure to other potential hepatotoxins did not differ between the two groups ($p=0.32$).
CONCLUSION: Neither valproate alone nor co-treatment with other potential hepatotoxins appears to accelerate liver damage in HCV positive patients.
Presented at the Western States Conference, Asilomar, CA, May 20, 2000.

115E. Clinical outcomes associated with common antimicrobial regimens for ambulatory acute exacerbations of chronic bronchitis. *Karl J. Madaras-Kelly, Pharm.D.,* Stephanie B. Magdanz, Pharm.D., Christopher K. Johnson, Pharm.D., Sandra G. Jue, Pharm.D., FASHP; Idaho State University., Pocatello, ID; VA Medical Center, Boise, ID.

PURPOSE: Doxycycline or trimethoprim/sulfamethoxazole (doxy/TS) are recommended first-line therapies for ambulatory acute exacerbations of chronic bronchitis (AECOPD) by the Boise VAMC Infectious Diseases Service. The study purpose was to determine if outcome with doxy/TS was equivalent to all comparators in AECOPD.
METHODS: Retrospective analysis of patients with their first AECOPD of the 1999-2000 season was performed. Exclusion criteria were: chronic antibiotics, antibiotics within 14 days prior to AECOPD, lung cancer, pneumonia, or miscoded ICD-9. Demographic, comorbidity, COPD variables, and outcomes data were collected. Failure was defined as an AECOPD-related new prescription, refill, clinic or ED visit, hospitalization, or death within 14 days of initial presentation. Chi square, Fisher's, and Student's t-test were used to compare regimens.
RESULTS: Six hundred eleven patients with COPD ICD-9 codes and antibiotic prescriptions were identified. Three hundred ninety-six patients were excluded: clinically stable no antibiotics for AECOPD (58%), recent/chronic antibiotics (9%), pneumonia (13%), lung cancer (7%), other (13%). Demographic and comorbidities were similar between doxy/TS (n=88) and comparators (n=127) except: comparator recipients had more cardiovascular co-morbidity (61 vs 46%; $p=0.04$) and were frequently O_2 dependent (41 vs 22%; $p=0.01$). Eight (9%) vs 15 (12%) of doxy/TS and comparator recipients experienced failure, respectively ($p=0.52$). Failure was similar when stratified by COPD severity (< 50 FEV 1% pred., O_2 or steroid dependence, smoking status, # AECOPD/year). Four (5%) vs two (2%) were hospitalized upon return visit for doxy/TS and comparators, respectively ($p=0.23$).
CONCLUSION: No differences in failure rates were identified between doxy/TS and comparator antibiotics. A trend toward increased hospitalization for doxy/TS recipients vs. comparators was observed.
Presented at the Annual Meeting of the Western States Residency Conference, Asilomar, CA, May 18-21.

116E. A pharmacodynamic characterization of *Streptococcus pneumoniae* fluoroquinolone efflux resistance utilizing moxifloxacin, sparfloxacin, and levofloxacin. *Karl J. Madaras-Kelly, Pharm.D.,* Christopher K. Daniels, Ph.D., Marisa J. Hegbloom, B.S., Carrie M. Nielson, B.S., Troy J. Kurtz, B.S.; Idaho State University, Pocatello, ID; VA Medical Center, Boise, ID.

PURPOSE: The significance of efflux mediated fluoroquinolone resistance in *Streptococcus pneumoniae* (SP) is unclear. The antimicrobial effect (AME) and selection of resistance for non-efflux and efflux positive SP were compared while simulating pharmacokinetics of moxifloxacin (M), sparfloxacin (S), and levofloxacin (L).
METHODS: A one-compartment model simulated pharmacokinetics against two non-efflux strains (ATCC 49619, 2136), and an efflux mutant (49619E). Duplicate 24 hour experiments were performed at $1x10^8$ CFU/ml. C_{max} (µg/ml) and $T_{1/2}$(hours) were 4.5/12,1.1/16, and 5.7/6 for M, S, and L, respectively. Reserpine (10 µg/ml) was added to select experiments (49619E). E-tests were performed on pre/post experiment strains. Antimicrobial effect was expressed as area-under-the time-concentration-kill-curve (AUKC). ANOVA and Fisher's were used to compare AME and resistance selection.
RESULTS: Mean (± SD) LN AUKC for non-efflux SP were 17.1 (0.1), 18.6 (0.4), and 18.4 (0.4) for M, S, and L, respectively. M AME was significantly ($p<0.05$) greater than (>) S and L, but L = S. Mean (± SD) LN AUKC for 49619E were 17.8 (0.3), 19.7 (0.1), and 20.9 (0.4) for M, S, and L, respectively. Moxifloxacin AME was significantly > S and L, but L = S. AUKC for 49619E were 82, 279, and 1600% > than 49619 for M, S, and L, respectively. AUKC for fluoroquinolone and reserpine vs 49619E were 39, 15, and 24% less than fluoroquinolone alone for M, S, and L, respectively. One of 12 non-efflux vs 4/6 efflux ($p=0.02$) vs 1/6 efflux plus reserpine ($p=0.2$) post-experiment strains exhibited MIC increase.
CONCLUSION: M exhibited > AME vs efflux and non-efflux SP than S or L. Efflux was associated with greater loss of AME for L than S or M. Increased

MIC post-experiment were more common in efflux SP and was decreased with reserpine present.
Presented at the 40th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, ON, Canada, September 17-20, 2000.

117. A 4-year analysis of quinolone-resistant pseudomonas and vancomycin-resistant enterococci in Chicago. *Kevin W. Garey, Pharm.D.*, Mindy R. Neidich, Madhavi Manduru, Pharm.D., Vikas Gupta, Pharm.D., Paul C. Shreckenberger, Ph.D., John P. Quinn, M.D., Larry H. Danziger, Pharm.D.; University of Illinois at Chicago; Owen Healthcare, Inc., Chicago, IL.

BACKGROUND: International and nationwide surveillance sites have been implemented to track antibiotic resistance. However, regional susceptibility patterns in large-urban areas are uncertain. Thus, the purpose of this study was to begin to address this issue by tracking the prevalence of quinolone-resistant pseudomonas (QRP) and vancomycin-resistant enterococci (VRE) from 1995-1998 in the Chicago area.
METHODS: Hospital demographics in the Chicago area were identified using the AHA Guide to Hospitals. The Directors of Pharmacy of each institution were contacted and asked to mail their hospital's antibiograms for the last 5 years. A follow-up cover letter was mailed explaining the study with two follow-up letters mailed to non-responders. Antibiogram data was aggregated to produce antimicrobial susceptibility percentages for the Chicago area.
RESULTS: Fifty-three of the 96 hospitals that were called and utilized antibiograms responded and mailed in antibiogram data from their hospitals (response rate = 55%). Pseudomonas susceptibility decreased over time from 1997 to 1998 for levofloxacin (84% to 62%) and from 1995 to 1998 for ofloxacin (71% to 58%) and ciprofloxacin (74% to 68%). Likewise, enterococcus susceptibility decreased over time for vancomycin from 1995 to 1998 (76% to 66%) and *E. faecium* susceptibilities decreased from 46% to 35% between 1995 and 1998. Multiple linear regression analysis revealed that VRE increased with time ($p=0.055$) and with increasing hospital size ($p<0.001$). Urban vs suburban hospital location had no effect.
CONCLUSION: Regional tracking of antimicrobial susceptibility patterns may help identify increasing resistance over time on a local level.

118. Reduction in the incidence of nosocomial vancomycin-resistant enterococcal infection and its susceptibility by manipulating a hospital formulary from 1996 to 1999. *Vikas Gupta, Pharm.D., BCPS*, Farah Hashemi, M.D., Kelly Johnson, Pharm.D.; Owen Healthcare, Inc., Lombard, IL; St. James Olympia Fields Hospital, Olympia Fields, IL.

PURPOSE: Studies have also shown that decreasing use of vancomycin, third generation cephalosporins and clindamycin can reduce the fecal colonization rates of vancomycin resistant enterococci (VRE). This report demonstrates a reduction in VRE infections and improvement in VRE susceptibilities 3 years after manipulation of the antimicrobial formulary.
METHODS: The susceptibility of VRE isolates on antibiogram, and the occurrence of nosocomial and community acquired VRE infections were evaluated from 1994-1999. Antimicrobial usage was evaluated from 1996 to 1999 on a cost per adjusted patient day (APD) and g/1000 APD or g/100 patient days for third generation cephalosporins, vancomycin, and expanded spectrum agents (i.e., piperacillin/tazobactam, ampicillin/sulbactam, and ticarcillin/clavulanate (Z/U/T)), respectfully. An antimicrobial formulary control program to reduce use of third generation cephalosporins, vancomycin and inappropriate use of all antibiotics was implemented in the 4th quarter of 1996.
RESULTS: The occurrence rate (per 1000 APD) of total, community and nosocomial acquired VRE infection was 0.94, 0.56, 0.38 in 1996 and 1.19, 0.88, 0.31 in 1999, respectively. Antibiogram data shows that the percent of enterococcal isolates resistant to vancomycin decreased from 18% in 1996 to 7% in 1999. During this time period antibiotic costs decreased from $13.39/APD in 1996 to $8.45/APD in 1999. Correspondingly, the utilization of third generation cephalosporins, vancomycin and Z/U/T decreased from 230 g/1000 APD, 100 g/1000 APD, and 115 g/100 APD in 1996 to 113 g/1000 APD, 56 g/1000 APD, and 61 g/100 APD, respectively.
CONCLUSIONS: Development of a comprehensive antimicrobial formulary control process can result in significant decrease in cost and result in improvement in VRE susceptibilities and the occurrence of nosocomial VRE infection.

119. Extended-spectrum β-lactamases: risk factors and outcomes at an urban academic medical center. *Allison E. Einhorn, Pharm.D.*, Melinda M. Neuhauser, Pharm.D., David T. Bearden, Pharm.D., Susan L. Pendland, M.S., Pharm.D.; University of Illinois at Chicago, Chicago, IL.

PURPOSE: Bacterial resistance due to extended-spectrum β-lactamases (ESBLs) is an increasing problem with limited treatment options. The purpose of this study is to identify risk factors and evaluate outcomes in patients infected with ESBL-producing organisms.
METHODS: All cultures with ceftazidime-resistant (presumed ESBLs) *Escherichia coli* or *Klebsiella pneumoniae* from 1/1997-6/2000 were identified from adult patients. Data collected from medical records included demographics, risk factors, antimicrobial therapy, and clinical/microbiological outcomes.
RESULTS: Thirty-three patients were evaluated, yielding 41 cultures (63% *E. coli*, 37% *K. pneumoniae*) consisting of 61% urine, 19% blood, and 20% other. Demographics were (mean ± SD): age 56 ± 15, 14 male/19 female, APACHE II 15 ± 8. Patient location prior to admission was 52% home, 33% nursing home/long-term care, and 12% hospital transfer. Seventy-nine percent of patients had ≥ 2 significant co-morbid conditions (i.e., ESRD, cirrhosis, diabetes). Sixteen of 33 patients had documented antibiotic exposure prior to ESBL isolation. Time to positive ESBL culture was ≤ 48 hours in 55% and > 14 days in 24% of patients. Mean LOS was 18 days (range 0-72). Seventy-six percent of treated patients received monotherapy: 37% fluoroquinolone, 21% trimethoprim/sulfamethoxazole, 16% carbapenems. Clinical outcomes were 18/33 cure/improvement, 2/33 death, and 13/33 indeterminate.
CONCLUSIONS: *E. coli* was the predominant organism isolated, possibly attributable to the high percentage of urinary isolates. An equal number of the patients were admitted from home versus acute/long-term care facilities, with both groups having ≥ 2 significant co-morbidities. There was a dichotomy among time to ESBL isolation (£ 48 hours or > 14 days). Monotherapy was effective in clinically evaluable patients.

120. Influence of methodology, bacterial strains, and multiple healthy volunteers on *Streptococcus pneumoniae*-induced ex vivo TNF-α release. *David T. Bearden, Pharm.D.*, Jennifer L. Prause, B.S., Larry H. Danziger, Pharm.D., Susan L. Pendland, M.S., Pharm.D.; University of Illinois at Chicago, Chicago, IL.

PURPOSE: Cytokines have been correlated with clinical outcomes of infections and response to antimicrobial therapy. Although evaluation of methodology has been performed using gram-negative lipopolysaccharides, limited data are available for testing cytokine response to gram-positive pathogens. The objective of this study was to determine the influence of anticoagulants, bacterial strains, and various volunteers on ex vivo cytokine release.
METHODS: Whole blood was collected from four healthy volunteers and anticoagulated with EDTA or pyrogen-free heparin. Three clinical *S. pneumoniae* strains (penicillin sensitive, intermediate, and resistant) were heat-killed at 60°C for 2 hours and added to whole blood for a final concentration of 10^6 CFU/ml. Blood samples were incubated at 37°C for 24 hours. Plasma was frozen at -70°C for TNF-α quantitation by ELISA. All experiments were performed in duplicate.
RESULTS: TNF-α concentrations were below the limit of detection (< 15 pg/ml) for all EDTA samples. Inter-volunteer variations between heparin samples were 3-fold for resistant (range: 188-7829 pg/ml), 9-fold for sensitive (874-8359 pg/ml), and 41-fold for intermediate (188-7829 pg/ml) strains. Intra-volunteer variability of TNF-α between pneumococcal strains ranged from 1.5 to 7.7-fold. The pneumococcal isolate causing the greatest cytokine release varied among volunteers.
CONCLUSIONS: In contrast to published reports with other stimuli, the use of EDTA completely attenuated the production of TNF-α after *S. pneumoniae* stimulation. Large inter-subject and intra-subject variability was observed, suggesting that further experiments must include multiple bacterial strains and multiple subjects. Further standardization is necessary to firmly establish effects of methodology on cytokine production.

121. In vitro activity of voriconazole and other azoles against candida isolates. *Manjunath P. Pai, Pharm.D.*, Jennifer L. Prause, B.S., Nicole M. Boyea, B.S., Susan L. Pendland, M.S., University of Illinois at Chicago, Chicago, IL.

PURPOSE: Voriconazole is a novel triazole agent reported to be more active than other azoles against candida species. Data on the susceptibility of candida isolates to voriconazole from different geographic regions are limited. Our objective was to compare the MICs of voriconazole, fluconazole, and itraconazole against clinical isolates of candida.
METHODS: Consecutive clinical yeast isolates were obtained from UIC hospital between September and November 1999, and identified using the API-20C system. MICs were performed in duplicate by macrodilution against voriconazole, fluconazole, and itraconazole using the NCCLS M27-A procedure. MICs were defined as the lowest concentration producing 80% growth inhibition at 48 hours.
RESULTS: Seventy-one isolates primarily from urine (66%) and blood (16%), were obtained from 53 patients. The number of isolates, and MIC_{90} (μg/mL) for voriconazole, fluconazole, and itraconazole respectively were: *C. albicans* (n=30, 1, > 128, > 12.8), *C. glabrata* (n=20, 4, > 128, 64), *C. tropicalis* (n=9, > 8, > 128, > 12.8), *C. parapsilosis* (n=5, 0.03, 2, 0.4), *C. famata* (n=5, > 8, > 128, > 12.8), *C. dubiensis* (n=1, 0.03, < 0.25, 0.2), *C. lusitaniae* (n=1, 0.125, 1, 0.4). Voriconazole MICs were lower than the other azoles against all candida isolates. In addition, voriconazole was 32-fold and 3-fold more active than fluconazole and itraconazole respectively. All azoles were less active against *C. glabrata, C. tropicalis*, and *C. famata*. Higher fluconazole and itraconazole MICs correlated with higher voriconazole MICs for all species ($p<0.05$).
CONCLUSIONS: Voriconazole demonstrated greater in vitro activity against all candida isolates compared to the other azoles. MICs of voriconazole were higher in isolates with high fluconazole and itraconazole MICs. Further studies are warranted to determine the efficacy of voriconazole in candida infections.

122. In vitro bactericidal activity of imipenem in combination with amikacin or ciprofloxacin against *Klebsiella pneumoniae* producing extended-spectrum β-lactamases. Sutthiporn Pattharachayakul, Pharm.D., *Melinda M. Neuhauser, Pharm.D.*, Jennifer L. Prause, B.S., Susan L. Pendland, M.S., Pharm.D.; University of Illinois at Chicago, Chicago, IL.

PURPOSE: Carbapenems are the drug of choice for extended-spectrum β-lactamases (ESBL)-producing microorganisms. Combination therapy may produce greater killing and potentially better clinical outcomes. The purpose of this study was to examine the bactericidal activity of imipenem alone and in combination with amikacin or ciprofloxacin.
METHODS: Bactericidal activity (≥ 3 $\log_{10}$ decrease in CFU/ml) was determined using the NCCLS time-kill method. Four clinical isolates of ESBL-producing *K. pneumoniae* were studied. The concentration of each antibiotic tested was 2X MIC. Viable counts were determined at 0, 1, 1.5, 2, 6, 12, and 24 hours.
RESULTS: All isolates were sensitive to imipenem (MICs: 0.06-1 µg/ml) and amikacin (MICs: 1-2 µg/ml); 3 isolates were intermediate to ciprofloxacin (MICs: 1-2 µg/ml). The killing rates were: imipenem/amikacin = amikacin (bactericidal at 1-2 hours) > imipenem/ciprofloxacin (bactericidal at 1.5-6 hours) > ciprofloxacin (bactericidal at 6 hours) = imipenem (bactericidal at 6 hours). One strain demonstrated synergy (≥ 2 $\log_{10}$ decrease in CFU/ml) with imipenem/ciprofloxacin. Additivity (≥ 1 $\log_{10}$ decrease) was seen with imipenem/amikacin in two strains and with imipenem/ciprofloxacin in one strain. No antagonism (≥ 2 $\log_{10}$ increase) was observed.
CONCLUSION: The bactericidal activity of imipenem in combination with amikacin or ciprofloxacin was greater than that of imipenem alone. This was primarily due to the excellent in vitro activity of amikacin and ciprofloxacin. However, the ciprofloxacin concentrations tested may not be clinically achievable throughout the dosing interval. Based on the in vitro data, combination therapy may provide better clinical outcomes than imipenem alone in patients with serious infections due to ESBL-producing organisms.

123. Vancomycin practice patterns and adverse events: OPAT outcomes registry. *Alan D. Tice, M.D., FACP,* Pam A. Hoaglund, R.N., MSN, Barbara Ross Nolet, R.N., M.A., Essy Mozaffari, Pharm.D., MPH, Joseph R. Hendrickson, Pharm.D., BCPS; OPAT Outcomes Registry, Tacoma, WA; Northwest Management Associates, Gig Harbor, WA; Pharmacia Corporation, Kalamazoo, MI.

PURPOSE: The purpose of our study was to identify the practice patterns for outpatient intravenous (IV) vancomycin therapy and the different types of adverse events associated with it.
METHODS: We utilized the U.S. Outpatient Parenteral Antimicrobial Therapy (OPAT) Outcomes Registry to extract the information regarding outpatient IV vancomycin therapy for the period between 1997 and 1999. Twenty-three geographically diverse sites provided outcomes data. Information regarding antibiotic doses, types of IV line, duration of therapy, and adverse events were captured in this registry.
RESULTS: There were 1053 courses of IV vancomycin therapy for 971 patients. Two-thirds of these courses were initiated in the outpatient setting. The mean duration of therapy was 21.5 days. Vancomycin regimens included 1 gram q12h (27.9%) and 1 gram q24h (26.0%). A peripherally inserted central catheter (PICC) was used in 50% of cases and a peripheral catheter in 21%. Adverse events were reported in 119 cases (11%). Of the 1053 courses of IV vancomycin therapy, 6.6% resulted in an early discontinuation of the therapy because of adverse events. In many instances, adverse effects were tolerated because patients lacked alternative antibiotics.
CONCLUSIONS: IV vancomycin-related adverse events require close monitoring; the monitoring has important clinical and economic implications. The availability of a new class of antibiotics may change the practice patterns.

124. Expected cost savings not realized with the addition of oral levofloxacin to the formulary at a tertiary, level I trauma center. *Allycia M. Marie, Pharm.D.*, John W. Devlin, Pharm.D., BCPS, Jeffery X. Barletta, Pharm.D., Peggy S. McKinnon, Pharm.D., Michael J. Rybak, Pharm.D., BCPS, FCCP; Detroit Receiving Hospital, Wayne State University, Detroit, MI.

PURPOSE: Early intravenous-to-oral (IV-to-PO) antibiotic therapy has been advocated based on the availability of potent agents with excellent bioavailability. While evidence demonstrates equivalent efficacy and decreased costs, the impact of these changes has not been well studied in the absence of a formalized pharmacist-directed switch program or in hospitals with a high proportion of critically ill patients. We compared pertinent clinical and economic outcomes before and after the addition of oral levofloxacin (OL) to the formulary at our tertiary, level I trauma center.
METHODS: After the formulary addition of OL, 30 consecutive patients who received OL, were matched based on infection site, APACHE II score, and age with 30 historical controls who received conventional IV antibiotic therapy (CO). Demographics, clinical outcomes and costs were compared between the two groups.
RESULTS: Infection type [intra-abdominal (n=11), skin/ soft tissue (n=10), urinary tract (n=4), pneumonia (n=5)], APACHE II score (8.5 ± 4.1 [OL] vs 7.6 ± 4.6 [CO], p=0.81), clinical (95% [OL] vs 84% [CO], p=0.29) and microbiologic (100% [OL] vs 76% [CO], p=0.12) cure rates did not differ between groups. Neither length of stay (9.5 days [2-58] [OL] vs 8 days [3-24] [CO], p=0.99, median [range]), antibiotic length of stay (8.5 days [2-58] [OL] vs 8 days [3-21] [CO], p=0.42), nor antibiotic cost/patient ($326 [24-2771] [OL], $372 [73-2042] [CO], p=0.19) differed between groups.
CONCLUSIONS: Formulary addition of OL for IV-PO therapy, while not affecting clinical outcomes, did not reduce antibiotic costs nor shorten length of stay at our institution. This may be due to our high patient acuity, the use of inexpensive or appropriately streamlined IV antibiotic regimens, indiscriminate OL prescribing, or lack of inclusion of a formalized, pharmacist-directed IV-PO intervention program.

125. Outpatient reimbursement of intravenous vancomycin therapy. *Peggy S. McKinnon, Pharm.D.*, Essy Mozaffari, Pharm.D., MPH, Joseph R. Hendrickson, Pharm.D., BCPS; Detroit Medical Center; Pharmacia Corporation, Detroit, MI.

PURPOSE: To identify the reimbursement framework for outpatient intravenous (IV) vancomycin therapy for four different payers — managed care organization (MCO), Medicaid, Medicare, and fee-for-service (FFS) — and to quantify the average reimbursements.
METHODS: We conducted a survey of nine home care infusion companies, which were geographically diverse. Actual reimbursement rates for 1 g IV vancomycin given twice daily were solicited from these companies. Our assumptions in computing the reimbursement rates include: 1) an outpatient duration of therapy of seven days; and 2) typically two to three nursing visits for the duration of therapy. Reimbursement of IV vancomycin to home care infusion companies was based on the average wholesale price (AWP). We excluded the cost of IV line placement and vancomycin drug level monitoring.
RESULTS: Managed care organizations typically reimbursed outpatient IV vancomycin therapy based on a pre-negotiated daily per diem rate. Medicaid reimbursed for nursing visits at a predetermined rate and for IV vancomycin and supplies based on AWP. Medicare covered nursing visits only, provided the patient met pre-specified homebound criteria. Fee-for-service reimbursed for each item and service. The average daily reimbursements were: $156 (MCO), $91 (Medicaid), $130 (Medicare – with ~ $80 paid by the patient), and $198 (FFS).
CONCLUSION: The reimbursement framework for outpatient IV vancomycin therapy varies across the different payer types and the daily cost of therapy is substantial, even for Medicaid. These reimbursement rates are an underestimate of total costs because they do not include the cost of IV line placement and vancomycin drug level monitoring.

126. Comparison of monotherapy and combination therapy for *Pseudomonas aeruginosa* bacteremia. *Scott T. Micek, Pharm.D.*, David J. Ritchie, Pharm.D., BCPS, Richard M. Reichley, B.S.; Barnes-Jewish Hospital, St. Louis, MO; St. Louis College of Pharmacy, St. Louis, MO.

PURPOSE: To compare monotherapy and combination therapy of *Pseudomonas aeruginosa* bacteremia with respect to impact on inpatient mortality and time to eradication of bacteremia.
METHODS: Medical records of all patients (n=206) with documented *Pseudomonas aeruginosa* bacteremia admitted to Barnes-Jewish Hospital between January 1, 1997 and September 31, 1999, were reviewed. Antimicrobial regimens, microbiology and laboratory data, APR-DRG severity score, demographics and discharge status were documented.
RESULTS: Antipseudomonal monotherapy was prescribed in 66 patients and included β-lactam (41%), fluoroquinolone (14%), β-lactam then fluoroquinolone (14%), carbapenem (8%), aminoglycoside then β-lactam (8%) and six miscellaneous monotherapies. A total of 140 patients received combination therapy defined as receipt of two or more antipseudomonal antibiotics concomitantly. The most common combinations prescribed were β-lactam/aminoglycoside (61%), fluoroquinolone/aminoglycoside (12%), carbapenem/aminoglycoside (11%), and fluoroquinolone/β-lactam (8%). Although patients treated with combination therapy were more severely ill (median APR-DRG severity score: combination = 4; monotherapy = 3), inpatient mortality did not differ in patients who received monotherapy versus combination therapy (27.3% vs 27.1%, p=NS). Similarly, the median time to eradication of bacteremia did not differ between evaluable patients who received monotherapy (n=37) compared to combination therapy (n=95) (4 vs 3 days; p=NS, 95% CI, 0 to 2.0).
CONCLUSION: Inpatient mortality and time to eradication of bacteremia appeared to be no different with monotherapy and combination therapy for documented *P. aeruginosa* bacteremia.

127. Genome-wide evaluation of differential gene expression in experimental fluconazole resistance in *Saccharomyces cerevisiae*. *P. David Rogers, Pharm.D., M.S.*, Margaret M. Pearson, Pharm.D., Stanley W. Chapman, M.D., Donna C. Sullivan, Ph.D.; University of Mississippi, Jackson, MS.

PURPOSE: Azole antifungal resistance is an emerging problem in immunocompromised patients. The purpose of this study was to identify

genes that are differentially expressed in fluconazole resistant isolates of *Saccharomyces cerevisiae* that might contribute to azole resistance.
METHODS: cDNA microarray analysis was used to compare mRNA populations from isogenic matched sets of fluconazole resistant isolates of *S. cerevisiae*. ATCC strain 9763 was passed in increasing concentrations of fluconazole. Susceptibilities were verified by an outside reference laboratory. Isolates were grown in brain heart infusion broth at 37°C in a shaking incubator to mid-log phase. Total RNA was extracted and $^{[33]}$P dCTP-labeled cDNA probes were prepared by reverse transcription of total RNA primed with oligo-dT. Probes were hybridized overnight with Research Genetics GF100 cDNA microarrays at 42°C. Washed arrays were subjected to phosphorimaging. Data was analyzed using Pathways software. A ≥ 1.8-fold difference in expression was considered significant.
RESULTS: MICs of the two isolates studied were 4 µg/ml and 128 µg/ml. Expression of all 6,144 open reading frames of the yeast genome was evaluated. In resistant isolates, 384 genes were up-regulated and 49 genes were down-regulated. Those up-regulated included genes involved in protein synthesis, amino acid metabolism, small molecule transport, carbohydrate metabolism, lipid/fatty-acid/sterol metabolism, energy generation, and transcription. Those down-regulated included genes involved in protein folding, carbohydrate metabolism, and cell stress.
CONCLUSION: Many genes are differentially expressed in experimental fluconazole resistant isolates of *S. cerevisiae*. Differential expression of these genes may represent novel mechanisms of azole antifungal resistance in this experimental model.

128E. Levofloxacin penetration into cerebrospinal fluid using microdialysis in a rabbit model of pneumococcal meningitis. *Christopher J. Destache, Pharm.D.,* Catherine B. Pakiz, B.S., Cris Larsen, Heather Owens, Pharm.D., Alekha K. Dash, Ph.D.; Creighton University, Omaha, NE.

PURPOSE: This study investigated the penetration of three doses of levofloxacin (LEV) across the blood brain barrier using a microdialysis probe implanted into the cerebrospinal fluid (CSF) in a rabbit pneumococcal meningitis model.
METHODS: The microdialysis probe was implanted into rabbit subarachnoid space using a stereotaxic frame. After 72 hours, 10^4 CFU *S. pneumoniae* serotype 3 in 0.3 ml saline was injected intracisternally and animals were allowed to incubate the organisms for 16-18 hours. Groups of animals (n=5) then received LEV 7, 10.5, or 14 mg/kg IV over 10 minutes. Plasma samples were obtained via ear vein at 0, 0.25, 0.5, 0.75, 1, 2, 4, 6, and 8 hours after LEV infusion. Cerebrospinal fluid microdialysis effluent samples were collected every 0.5 hr for the entire experiment. Plasma and microdialysis effluent samples were analyzed by HPLC. $AUC_{0-\infty}$ in plasma and CSF were computed using the trapezoid rule.
RESULTS: The peak plasma concentrations for the three doses studied were 3.9, 6.4, and 10.3 µg/ml, respectively. There was a significant increase in plasma AUC_{0-8} (29.7 ± 6.3, 49.1 ± 19.1, and 67.6 ± 8.9 µg•hr/ml [p<0.005]). Peak CSF concentrations were 3.8, 5.7, and 8.6 µg/ml and occurred at 0-0.5 hours after the administration of the dose. The $AUC_{CSF(0-8)}$ were significantly higher as the dose increased (7 mg/kg 15.8 ± 6.6; 10.5 mg/kg 37.3 ± 7.8; and 14 mg/kg 46.4 ± 20.9 µg•hr/ml; p<0.03). Penetration of LEV averaged 53% for the 7 mg/kg dosage group, 76% for the 10.5 mg/kg, and 86% for the 14 mg/kg groups, respectively.
CONCLUSIONS: Our results demonstrate that LEV penetration into the CSF increases with increasing doses.
Presented at the American Association of Pharmaceutical Scientists Meeting, November 1999.

129. A prospective, multicenter study comparing clinical, microbiologic, and economic outcomes between methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* infections. *Sujata M. Bhavnani, Pharm.D.,* Alan Forrest, Pharm.D., Jenna L. Sunderlin, B.S., Christopher C. Battaglia, B.S., Rupal N. Panchal, B.S., Jerome J. Schentag, Pharm.D., National Nosocomial Resistance Surveillance Group; Millard Fillmore Hospital/Kaleida Health, Buffalo, NY.

PURPOSE: To compare clinical, microbiologic, and economic outcomes between patients with nosocomial-acquired methicillin-resistant *Staphylococcus aureus (*MRSA) and methicillin-susceptible *Staphylococcus aureus* (MSSA) infections.
METHODS: Inpatients with SA pneumonia (PN), superficial (SI) or deep (DI) surgical, or bloodstream infections (BI) from U.S. hospitals were followed until infection resolution. Methicillin-resistant *Staphylococcus aureus* and MSSA groups were evaluated for differences in comorbidities, and clinical and microbiologic outcome (Fisher's exact test), antibiotic-related length of hospital stay (ABX LOS) in days (Wilcoxon rank sum), and time to clinical success (TCLIN) and duration of antibiotic treatment (TTX) in days (Kaplan-Meier).
RESULTS: Fifty cases were collected from 13 hospitals. Primary infection types were (%): PN (66); SI (4.0), DI (12) and BI (18). MRSA (n=31) and MSSA (n=19) differed by median age (77 vs 53 years, p<0.001) and comorbidities (%): respiratory illness (84 vs 40, p=0.002), vascular insufficiency (52 vs 20, p=0.04), and expected survival > 5 years (10% vs 59%, p<0.001). Groups did not differ by probability of successful clinical or microbiologic outcome (89% vs 70%, p=0.1), by total hospital ABX LOS, or by mortality (p>0.2). Mean TCLIN differed between MRSA and MSSA (24 vs 17, p=0.05) with a borderline difference for mean TTX (27 vs 22, p=0.09). Primary therapeutic agents used (%) for MRSA were vancomycin (97) and trimethoprim/sulfamethoxazole (3); and for MSSA, anti-staphylococcal β-lactams (74), vancomycin (10), and other (16).
CONCLUSIONS: The longer TCLIN observed for patients with MRSA infections may have resulted from differences in age and comorbidities, MRSA being more difficult to eradicate than MSSA, or differences in pharmacodynamics of agents used.

130. Early predictors of outcome in patients with *Staphylococcus aureus* lower respiratory tract infections. *Pamela A. Moise, Pharm.D.,* Alan Forrest, Pharm.D., Mary C. Birmingham, Pharm.D., Jerome J. Schentag, Pharm.D.; The Clinical Pharmacokinetics Laboratory; Millard Fillmore Hospital; SUNY-Buffalo, Buffalo, NY.

PURPOSE: Clinical factors predictive of response to *Staphylococcus aureus* (SA) lower respiratory tract infections (LRTIs) were investigated.
METHODS: All patients treated with antibiotics for a documented SA LRTI during a 1-year period at our institution were retrospectively reviewed. Tree-based modeling (CART) was performed for two analyses: probability of clinical and microbiological (micro) success. Independent variables were: age, sex, weight, creatinine clearance, baseline APACHE II score, baseline ventilator status, hospital days prior to occurrence, organism (MSSA or MRSA), and $AUIC_{24}$ of the antimicrobial agents for SA. Changes in pneumonia score (consisting of ten clinical parameters) from baseline in two groups (clinical success and failure) were compared using Kruskal-Wallis ANOVA.
RESULTS: The 108 cases had a median age of 74 (range 32-93) years; 54% were male. Fifty-eight percent of cases evaluable for CART were considered clinical treatment successes. Patients with MRSA and an $AUIC_{24}$ > 345 had 73% clinical success, while patients with and $AUIC_{24}$ ≤ 345 had 7% clinical success. Fifty-five percent of cases evaluable for CART had a micro success. Patients with MRSA and an $AUIC_{24}$ > 428 had 58% eradication, while patients with an $AUIC_{24}$ ≤ 428 had 17% eradication. Median change in pneumonia score from baseline for days 2-16 differed significantly (p<0.05) on all days except 2, 13, and 14. A ≥ 4 point decrease in score by day three correlated with 83% success.
CONCLUSION: The results of this study suggest that both $AUIC_{24}$ and pneumonia scoring play an important role as early predictors of response of SA LRTIs to antibiotic therapy.

131. Antibiotics decrease neutrophil phagocytosis. *Daniel P. Healy, Pharm.D.,* Chris E. Clendening, B.S., Alice N. Neely, Ph.D., Ian Alan Holder, Ph.D., George F. Babcock, Ph.D.; University of Cincinnati; Shriners Hospitals for Children, Cincinnati, OH.

BACKGROUND: We have previously shown that antibiotic exposure can increase neutrophil (PMN) CD11b adhesion molecule expression and PMN apoptosis.
PURPOSE: To evaluate the effect of antibiotic exposure on PMN phagocytosis.
METHODS: Using a whole blood in vitro assay, 12 antibiotics from all major classes were added at concentrations representing peak serum levels. After a 1-hour incubation, FITC-labeled *Escherichia coli* were added, followed by RBC lysis and flow cytometric analysis of PMNs (n=10,000 cells per treatment) to determine % PMNs undergoing phagocytosis and relative number of bacteria phagocytosed per PMN. Data are mean ± SEM (range) for three replicate experiments.
RESULTS: All tested antibiotics resulted in consistent, but modest decreases in the % of PMNs phagocytosing *E. coli* (-12.8% ± 7.25%, range -2 % to -32%; all antibiotics combined vs control p<0.05). Nafcillin resulted in the largest decrease; however, the large number of antibiotics tested prevented demonstration of significant differences from other agents. Antibiotic exposure also resulted in a decrease of 31.5% ± 7.57 % (-11.0% to -42.1%) in the number of bacteria phagocytosed per PMN cell. All except aztreonam decreased versus untreated control cells; p<0.05). There were no differences detected among agents.
CONCLUSION: Brief in vitro antibiotic exposure using clinically relevant concentrations resulted in modest decreases in the percentage of PMNs undergoing phagocytosis, but a larger decrease in the number of bacteria phagocytosed per PMN cell. These in vitro antibiotic effects are currently being evaluated in healthy volunteers and infected patients.

132. Determining the optimal dosing of trimethoprim/sulfamethoxazole against vancomycin-intermediate *Staphylococcus aureus*. *Sandy J. Close, B.S.,* Cory G. Garvin, Pharm.D., Steven J. Martin, Pharm.D.; University of Toledo, Toledo, OH.

PURPOSE: Vancomycin-intermediate *Staphylococcus aureus* (VISA) poses a significant challenge to successful antimicrobial treatment. We have shown that trimethoprim/sulfamethoxazole (T/S) has activity against VISA strains both by MIC and time kill testing. Optimal clinical dosing of T/S is unknown.

Doses of 8-15 mg T/kg/day have been suggested, divided in q6h or q12h intervals. To determine the optimal dosing/schedule for T/S against VISA, we evaluated an 8 mg/kg/day dose of T/S vs VISA (14379) divided either q6h or q12h in a two-compartment in vitro pharmacodynamic model of infection.
METHODS: Drug was added to the central compartment to simulated peak T/S concentrations at steady state; q12h (3/57 µg/ml), q6h (2.5/46.5 µg/ml). The model provided a 9.6 hour $T_{1/2}$. Bacteria were added (1.5×10^5 CFU/ml) to the peripheral compartment at baseline, and aliquots for colony count and drug concentrations were sampled from each compartment at various intervals over 24 hours. The model was performed in duplicate.
RESULTS: Neither dosing regimen was bactericidal at 24 hours. A decrease in CFU/ml was not observed for either regimen until at least 4 hours into the dosing interval. The q12h regimen killed bacteria at twice the rate of the q6h regimen. This difference in bactericidal effect was not evident until 4 hours.
CONCLUSION: The pharmacodynamics of T/S are not well characterized. We observed faster bacterial killing with higher peak concentrations, suggesting that T/S killing may be related to concentration. Further work is now ongoing to study these dosing regimens for longer durations (48-72 hours) and at higher daily doses (15 mg/kg).

133. Antibiotic use in a family practice setting. *Susan Karakashian, B.Sc.Phm.,* Zafar Hussain, M.D. FRCPC, Anne Marie Bombassaro, Pharm.D.; London Health Sciences Centre, London, Ontario, Canada.

PURPOSE: To determine the antibiotics prescribed for infections addressed in the 1997 Ontario Anti-infective Guidelines for Community-Acquired Infections (AIG) and adherence of initial therapy to first-, second-, or third-line recommendations prior to undertaking an educational strategy for prescribers. Secondary objectives included an assessment of the infection outcomes and the antibiotic complication rate associated with adherent and non-adherent regimens.
METHODS: A prescriber blinded, concurrent review of consecutive prescriptions at a university-affiliated family practice clinic between February 1, and March 31, 2000. Patients prescribed an oral antibiotic for a diagnosis addressed in the AIG were enrolled into the study. Patients were followed for repeat health care contact (HCC) over a 6-week period.
RESULTS: Oral antibiotics accounted for 6% of prescriptions screened (182/3110) and represented the third most commonly prescribed class of prescription drugs. A total of 144 patients were enrolled. Amoxicillin and trimethoprim-sulfamethoxazole accounted for approximately 50% of their treatment courses. Prescribed antibiotics adhered to first-, second-, or third-line AIG recommendations in 94% (135/144) of initial treatment courses. Overall adherence, represented by the factors of drug, dose, frequency and duration, was 72% (103/144). Of the 97 patients with repeat HCC no difference in infection outcome was observed, but a higher incidence of adverse effects (33% vs 7%, $p<0.05$) was associated with receipt of nonadherent versus adherent therapy respectively.
CONCLUSION: An educational strategy aimed at dosing, duration of therapy and adverse effects rather than antibiotic selection would be most valuable for prescribers at this family practice clinic.

134. Assessment of patients with community-acquired pneumonia admitted to a health system using the pneumonia outcomes research team risk stratification system. *Staci Pacetti, Pharm.D.,* Bennett Lorber, M.D., Steven P. Gelone, Pharm.D.; Temple University; Temple University Health System; Philadelphia, PA.

PURPOSE: This study evaluated patients diagnosed with community-acquired pneumonia (CAP) admitted throughout our health system to determine 1) the severity of illness; 2) the appropriateness of admission based on the pneumonia outcomes research team (PORT) scheme; and 3) to identify areas in the care process requiring improvement.
METHODS: Medical records from 700 patients with CAP admitted to one of four hospitals between January 1999, and March 2000, were reviewed. Patient demographics, antibiotic therapy, time to oral conversion, and length of stay were recorded. Pneumonia outcomes research team scores were calculated for all patients.
RESULTS: Based on the PORT criteria, 37% of patients were admitted unnecessarily across the health system (PORT scores of I or II). Antibiotic prescribing varied from institution to institution, with one hospital utilizing a fluoroquinolone in 95% of patients, while others used a more diverse group of therapies. The average time to oral conversion was 3.9 days (range 3.4-5 days) even though the average time to first oral medication was 1.3 days. The majority of patients (65%) were not switched to oral therapy until the time of discharge. The mean length of stay was 5.3 days (range 4.6-6 days).
CONCLUSION: A significant proportion of patients admitted to the health system for CAP can likely be treated as outpatients. The majority of those admitted can have therapy changed to the oral route significantly earlier in their hospital stay. Use of the PORT scoring system in the emergency departments and more active pharmacy intervention are planned to address these issues.

135. The effect of formulary conversion from ceftazidime to cefepime on in vitro sensitivities of Gram-negative organisms. *Matthew E. Levison, M.D.,* Joseph Hayburn, R.N., Alan Evangelista, Ph.D., Kimberly Walters, Pharm.D.; Medical College of Pennsylvania Hahnemann University, Philadelphia, PA; Dura Pharmaceuticals, San Diego, CA.

PURPOSE: Nosocomial infections due to antibiotic-resistant Gram-negative organisms are of increasing concern to health care professionals. Formulary conversion from ceftazidime (TAZ) to cefepime (PIM) for broad-spectrum therapy is reported to improve susceptibility patterns in patient isolates. PIM, a fourth-generation cephalosporin, has demonstrated stability in the presence of β-lactamases and in vitro activity against TAZ-resistant organisms. A pilot study was performed to measure the effects of formulary conversion to PIM on susceptibility patterns for three prevalent Gram-negative organisms in nosocomial infections: *Enterobacter cloacae, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*.
METHODS: Susceptibilities of the three organisms were recorded for the 3-month period prior to conversion (January through March). The next 3-month period was the conversion period, and susceptibilities were again recorded for the 3-month period (July through September) after the conversion. Testing was performed using the Vitek system.
RESULTS: Documented susceptibilities (% S) of the 3 organisms to PIM and TAZ for the 3-month period (January through March) prior to and the 3-month period (July through September) after conversion to PIM are presented:

Pathogen	Drug %S (n)	3 Months Prior %S (n)	3 Months After
E. cloacae	PIM	ND	100 (29)
	TAZ	63 (32)	83 (29)
K. pneumoniae	PIM	ND	98 (59)
	TAZ	96 (74)	98 (59)
P. aeruginosa	PIM	ND	89 (96)
	TAZ	90 (95)	90 (96)

%S = percent susceptibility; n = number of isolates; ND = not documented

CONCLUSION: Formulary conversion from TAZ to PIM was associated with improved susceptibility to TAZ for *E cloacae* isolates. *K pneumoniae* and *P aeruginosa* susceptibilities to either antimicrobial did not decrease after the conversion. A multicenter investigation of this conversion may be warranted.

136E. Vancomycin-resistant and vancomycin-sensitive enterococcal bacteremia: effect on patient outcomes. *Eric T. Wittbrodt, Pharm.D.,* BCPS, Michael J. Cawley, Pharm.D., Teena Abraham, Pharm.D.; University of the Sciences in Philadelphia; Philadelphia, PA; Long Island University, Brooklyn, NY.

PURPOSE: Enterococcal infections are a persistent threat to the recovery of critically ill patients. We evaluated the effect of vancomycin-resistance on the outcomes of critically ill patients with Enterococcal bacteremia.
METHODS: We retrospectively evaluated six patients with documented blood cultures positive for vancomycin-resistant enterococcus (VRE) paired with six patients with documented vancomycin-sensitive enterococcus (VSE). Patients' prior antibiotic use, APACHE II score, and in-hospital course were documented. Continuous data were analyzed using Mann Whitney U test; nominal data were analyzed using Fisher's exact test.
RESULTS: The use of antibiotics within 1 week prior to the positive blood culture was similar between groups (5/6 patients for VRE vs 4/6 patients for VSE, $p>0.05$). The number of intensive care unit (ICU) days did not differ significantly between groups (12.7 days for VRE vs 10.0 days for VSE, $p>0.05$) nor did days on mechanical ventilation (12.3 days for VRE vs 10.0 days for VSE, $p>0.05$). APACHE II scores on the date of positive blood culture were not significantly different (19.5 for VRE vs 18.8 for VSE, $p>0.05$). In addition, mortality was equal in both groups (2/6 patients, $p>0.05$).
CONCLUSION: Vancomycin resistance did not significantly alter patient outcomes or length of ICU stay in patients with enterococcal bacteremia when compared with patients who had vancomycin-sensitive strains of the organism. Severity of illness and prior antibiotic use did not appear to affect the incidence of vancomycin resistance.
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137E. Comparative pharmacodynamics of gatifloxacin, moxifloxacin, and levofloxacin vs common respiratory tract pathogens at various levels of renal function. *Lawrence V. Friedrich, Pharm.D.,* Hilary D. Mandler, Pharm.D.; Bristol-Myers Squibb, Princeton, NJ.

PURPOSE: The 24-hour AUC/MIC, the pharmacodynamic (PD) parameter most often associated with therapeutic outcome for fluoroquinolones (FQ) can vary over the range of creatinine clearances (CrCL), especially for FQ that are primarily renally eliminated. To accurately compare these agents, one should compare PD across the range of CrCL. We assessed the impact of different levels of renal function on PD profiles of FQ.
METHODS: AUCs were estimated for a range of CrCL (10-100 ml/minute, 10 ml/minute increments) based on manufacturers' recommended daily doses at each CrCL and published relationships between CrCL and drug clearance, assuming a 70 kg patient and corrected for protein binding

(gatifloxacin [GAT] 20%, moxifloxacin [MOX] 50%, levofloxacin [LEV] 30%). The weighted geometric mean MIC90 for *S. pneumoniae* (SPN), *H. influenzae* (HFLU), and *M. catarrhalis* (MCAT) were calculated from studies published between 1997-99. Differences in AUC/MICs were assessed using ANOVA.
RESULTS: The MIC90 µg/ml (# isolates) for SPN, HFLU, and MCAT were GAT 0.49 (3625), 0.02 (3083), 0.02 (1437), MOX 0.22 (7053), 0.03 (7828), 0.06 (3856), LEV 1.56 (22338), 0.04 (4759), 0.13 (2575), respectively. Mean (range) free AUC/MIC90 for SPN were GAT 90 (54-156), MOX 103, LEV 30 (22-43); for HFLU: GAT 2748 (1668-4774), MOX 719, LEV 1102 (852-1679), for MCAT: GAT 2587 (1570-4493), MOX 383, LEV 373 (266-525). For SPN, LEV AUC/MIC was significantly less than both GAT and MOX ($p<0.0001$). The difference between GAT and MOX was not significantly different. AUC/MIC > 30 were only achieved in 50% for LEV and in 100% for GAT and MOX at all CrCL evaluated. For HFLU and MCAT, GAT AUC/MIC was significantly higher than both MOX and LEV ($p<0.0001$). Differences between MOX and LEV were not significant. AUC/MIC > 100 were achieved for all agents for both organisms.
CONCLUSIONS: Based on this analysis, these FQ achieve AUC/MIC well in excess of those desired for HFLU and MCAT. For SPN, the PD of GAT and MOX are similar and superior to LEV. While the optimal AUC/MIC for therapy of SPN infections remains controversial, it may be prudent to select the safest FQ that provides the highest AUC/MIC to maximize clinical outcome and minimize the emergence of resistance.
Presented at the 38th Annual IDSA Meeting, New Orleans, LA, September 7-10, 2000.

138E. Differences in fluoroquinolone pharmacodynamics against recent isolates of 20 different bacterial species. *Charles R. Bonapace, Pharm.D.*, Kurt R. Lorenz, Pharm.D., John G. Fowler, John A. Bosso, Pharm.D., Roger L. White, Pharm.D.; Medical University of South Carolina, Charleston, SC.

BACKGROUND: Pharmacodynamics (PD) parameters associated with efficacy of fluoroquinolones (FQs) are AUC/MIC and maximum serum concentration/MIC (C_{max}/MIC).
METHODS: Pharmacokinetic (PK) parameters obtained from peer-reviewed publications were used to simulate unbound serum concentration-time profiles (70 kg adult) for IV and PO ciprofloxacin (C), gatifloxacin (G) levofloxacin (L), and PO moxifloxacin (M). Using all manufacturer-recommended non-UTI regimens, simulations were performed at creatinine clearances (CrCl) of 100, 75, 50, 25, and 5 ml/minute (64 regimens) using published CrCl/drug clearance relationships and AUCs were calculated. The same dose/PK values were used throughout for M, which requires no renal dosage adjustments. MIC_{90} values were obtained from North American studies published from 1998-2000 for 7 Gram-positive and 10 Gram-negative organisms (~28,000 isolates). Weighted geometric means were used to calculate AUC/MIC for each drug/organism. AUC/MIC ≥ 30 and ≥ 100 were considered acceptable for Gram+ and Gram- organisms, respectively. C_{max}/MIC ≥ 10 was considered acceptable for all bacteria. Tests for significant differences among drugs and among differing CrCl were performed by ANOVA.
RESULTS: No FQ produced acceptable AUC/MIC at any level of CrCl for all organisms. Rank order of FQ producing the highest % of acceptable AUC/MIC varied from one CrCl category to the next although, in general the highest percentage of acceptable values were with G (≥ 67%) and the lowest were with low-dose IV C (≤ 35%). Similar results were produced when considering C_{max}/MIC. Overall AUC/MIC was significantly greater with L and G than with C and M ($p<0.0001$).
CONCLUSION: One should consider the variability in PD profiles among FQs and common pathogens and their variance with renal function when selecting agents for empirical therapy.
Presented at the 40th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, ON, Canada, September 17-20, 2000.

139. Effect of impaired renal function on fluoroquinolone pharmacodynamics against streptococci. *Charles R. Bonapace, Pharm.D.*, Kurt R. Lorenz, Pharm.D., John A. Bosso, Pharm.D., Roger L. White, Pharm.D.; Medical University of South Carolina, Charleston, SC.

BACKGROUND: AUC/MIC, a pharmacodynamics (PD) parameter associated with therapeutic outcome, may be expected to vary with altered renal function (RF) for those fluoroquinolone (FQ) significantly eliminated by the kidneys.
METHODS: We constructed four 1000-patient populations representing different RF (creatinine clearance: CrCl) distributions (e.g., mostly normal RF, mostly poor RF, etc), assessed our own institution's distribution, and determined PD for IV and PO ciprofloxacin (C), levofloxacin (L), gatifloxacin (G), and PO moxifloxacin (M). AUCs were derived from manufacturers' recommended dosing for varying RF and published CrCl/drug clearance relationships (unbound concentrations; 70 kg patient). MICs used were derived from cumulative analysis of the 1998-2000 literature (weighted geometric mean MIC_{90}) for both *S. pneumoniae* and *S. pyogenes.* AUC/MIC for each organism/FQ pair was multiplied by a weighting factor relating number of patients at each RF level within the various populations. Differences in AUC/MIC for each FQ based on CrCl distribution were tested for significance using ANOVA. Qualitatively, the number of AUC/MICs ≥ 30 for each renal distribution population were determined and tested for significant differences by ANOVA.
RESULTS: Among all FQ, highest AUC/MICs occurred in the population with an approximately normal distribution of CrCl. For *Streptococcus pneumoniae*, manufacturers' recommendations for dosing produced acceptable AUC/MICs at all CrCl for all FQ except C. With *S. pyogenes*, the results were more variable (several between-drug significant differences across all RF distributions; $p<0.0001$) with only IV and PO G and PO M producing acceptable AUC/MICs at all CrCl.
CONCLUSION: Such variation in PD may have therapeutic implications for some of these FQ when following recommended dosing for patients with renal impairment.

140E. Cost of therapy with fluoroquinolones in patient populations with various distributions of renal function. *Charles R. Bonapace, Pharm.D.*, Kurt R. Lorenz, Pharm.D., John A. Bosso, Pharm.D., Roger L. White, Pharm.D.; Medical University of South Carolina, Charleston, SC.

BACKGROUND: For three renally eliminated fluoroquinolones (FQs), each manufacturer has recommended dosing for impaired renal function (RF). The cost implications of utilizing these recommendations may be important depending on the distribution of various levels of RF within a patient population.
METHODS: We constructed four 1000-patient populations representing different RF distributions (e.g., mostly normal RF, mostly poor RF, etc.), determined our own institution's distribution, and determined the cost of therapy for IV and PO ciprofloxacin (C), levofloxacin (L), gatifloxacin (G), and PO moxifloxacin (M; not renally eliminated, included for contrast) for a 10-day course of therapy with doses indicated for community-acquired pneumonia. Costs included average wholesale prices and IV dose preparation/administration costs when applicable. Costs were multiplied by a weighting factor relating numbers of patients at each RF level within the various populations and the results were then totaled for each FQ. Differences in costs for each renal function distribution were examined for significant differences, with each drug, by ANOVA.
RESULTS: Within drug comparisons for the various population RF distributions revealed dramatic differences in costs for IV L (> $54K between populations skewed toward high and low RF, $p=0.0601$) and IV G (> $48K between populations skewed toward high and low RF, $p=0.17$). Among the FQ, differences in costs were greatest between IV L and IV G (L < G; ~$100K) among all distributions of renal function ($p\leq0.0016$). Differences among the FQ were much smaller (< $20K) when considering oral regimens regardless of RF mix in the population.
CONCLUSION: It may be appropriate to consider the distribution of RF within a given patient population and its effects on costs of therapy with FQ when making formulary decisions.
Presented at the 40th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, ON, Canada, September 17-20, 2000.

141. Quantitative assessment of relationships between antibiotic use and susceptibility of Gram-negative aerobes over an eight-year period. *Charles R. Bonapace, Pharm.D.*, Kurt R. Lorenz, Pharm.D., John G. Fowler, John A. Bosso, Pharm.D., Roger L. White, Pharm.D.; Medical University of South Carolina, Charleston, SC.

BACKGROUND: Relationships between antibiotic use and bacterial susceptibility (S) rates should be thoroughly characterized at a given institution so that antibiotic utilization and formulary decisions can be optimized.
METHODS: We collected antibiotic usage (dose, number of daily doses, length of therapy) and susceptibility data (% S/intermediate[I]/resistant[R] for all non-urine isolates) from adult patients throughout our institution between January 1992, and December 1999. Data were collected on a quarterly basis and annual totals calculated. Patient days/year was recorded and used to normalize drug usage data. Nineteen antibiotics were studied and included β-lactams (BL), aminoglycosides (AG), fluoroquinolones (FQ) and other various classes (e.g., TMP/SMX). Gram-negative bacteria considered included *A. baumannii*, *E. coli*, *E. aerogenes*, *E. cloacae*, *P. mirabilis*, *P. aeruginosa*, *S. marcescens*, *K. pneumoniae*. Linear regression was used to assess the relationship between drug usage and % S. Only relationships with % S ≥ 70 during the study interval and $r^2 \geq 0.5$ were assessed.
RESULTS: There were 19 relationships that met the criteria. Of these, 15 relationships had a negative slope; 87% with increasing drug usage/decreasing % S, and 13% with decreasing drug usage/increasing % S. These findings suggest a strong relationship between amount of antibiotic used and S of some organisms. Negative slopes were most often found with *A. baumannii* and *K. pneumoniae* and least often found with *E. aerogenes*. The rank order of negative slopes by drug class (out of the possible number of slopes) was: FQ (24%), TMP/SMX (14%), BL (10%), and AG (8%).
CONCLUSION: This quantitative assessment of drug use/S relationships in our institution revealed important differences in the association of some drug classes with resistance.

142E. Differences in fluoroquinolone MICs between Europe and North America against 16 bacterial species. *Charles R. Bonapace, Pharm.D.*, Kurt R. Lorenz, Pharm.D., John A. Bosso, Pharm.D., Roger L. White, Pharm.D.; Medical University of South Carolina, Charleston, SC.

BACKGROUND: Important differences in bacterial susceptibility to fluoroquinolones (FQs) may vary geographically.
METHODS: MIC_{50} and MIC_{90}s for eight FQs (ciprofloxacin, clinafloxacin, gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin, ofloxacin, and trovafloxacin) against 16 bacterial species (5 Gm+ and 11 Gm-) using a database of studies published from 1997-99 were evaluated. Then, the weighted (on number of isolates) geometric mean MIC_{50} and MIC_{90} were calculated and used for further analyses. To assess differences in MICs, the ratio of the MIC_{50} and MIC_{90} between EU and NA was calculated for each drug/organism combination.
RESULTS: Overall, 105 drug/organism combinations were evaluated (approximately 10,000 isolates). At least 4x higher MIC_{90}s were found in 15% of cases in North America (NA) while the same was true for 24% from EU. For some specific combinations, MICs tended to be higher in Europe (EU), up to 17x and 67x for MIC_{50} and MIC_{90} respectively. When higher for NA, differences were up to 7x and 36x higher for MIC_{50} and MIC_{90}. MIC_{90}s were higher in NA than EU for *A. baumanii, Acinetobacter spp*., and *E. cloacae*, with median differences of 24, 9, and 8x, respectively. MIC_{90}s were higher in EU for *E. aerogenes, E. coli, P. aeruginosa,* and *S. marcescens*, with median differences of 8, 11, 17, and 8x, respectively. These findings were consistent among the FQs (approximately 80%) studied.
CONCLUSIONS: This analysis of recently published literature from NA and EU found large differences for several important pathogens. Differences often involved yet to be marketed FQs, suggesting common resistance mechanisms. Such regional differences in MICs should be kept in mind when utilizing published susceptibility data in antimicrobial decision-making.
Presented at the 100th General Meeting of the American Society for Microbiology, 2000.

143E. Quantitation of increasing resistance to fluoroquinolones in North America, Europe and Asia, 1982-2000. *Charles R. Bonapace, Pharm.D.*, Kurt R. Lorenz, Pharm.D., John A. Bosso, Pharm.D., Roger L. White, Pharm.D.; Medical University of South Carolina, Charleston, SC.

BACKGROUND: Rate and extent of change of decreases in bacterial susceptibility (S) are largely unknown. Further, such assessments may be more readily made with MICs rather than categorical data.
METHODS: We assessed S trends for 8 fluoroquinolones (FQ; ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, ofloxacin, sitafloxacin, trovafloxacin) using studies published from 1982-2000. Using ≥ 3 studies and ≥ 3 years of data, linear regression of log- MIC_{50} and MIC_{90} was performed for each organism/drug combination.
RESULTS: Literature was evaluated for trends with 8 FQ and 70 organisms. Final analysis involved 152,406 isolates. Positive slopes from the regression analysis, indicating increasing MICs over time, were detected in 57%, 71%, and 76% of possible instances for North America (NA), Europe (E) and Asia (AS). In a subset of data reflecting steepest + slopes ≥ 0.5), the median increase in MIC_{90} over time was 32-fold. Gram-negative (GN) aerobes were associated with the most positive slopes (74% of possible instances) and Gram-positive (GP) anaerobic cocci with the least (20%). Slopes of ≥ 0.5 were more often associated with GN aerobes (13 of 23 cases). With FQ, the steepest positive slopes were detected in the 1990s, usually with newer agents. Of the GP organisms evaluated, the highest slope was observed with *S. aureus* and ciprofloxacin while with GN organisms the highest slope was with *P. aeruginosa* and trovafloxacin.
CONCLUSIONS: We detected increases in MIC_{50} and MIC_{90} of FQ over time against numerous pathogens. Increases were greatest for drugs that have been used for the longest period of time; the steepest slopes often involved newer agents and occurred in the decade of the 90s, suggesting either inherent differences in these newer FQ or a cumulative effect of FQ use over time on susceptibility.
Presented at the 40th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, ON, Canada, September 17-20, 2000.

144. Changes in candida species causing candidemia from 1995 to 1999. David S. Burgess, Pharm.D., *K. Michelle Crawford, Pharm.D.,* James S. Lewis II, Pharm.D., Gavin R. Corcoran, M.D.; University of Texas at Austin, Austin, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX.

PURPOSE: Recently, candida has risen to the fourth leading cause of bloodstream infections, and is associated with a much higher mortality rate than bacterial bloodstream infections. Therefore, the purposes of this study were to evaluate the possible change in incidence and epidemiology of fungemia in a tertiary teaching hospital to help rationalize empiric therapy.
METHODS: All hospitalized patients with candida isolated from blood cultures between January 1995 and December 1999, were identified from microbiology department records. Patient identifier, date the culture was obtained, and organism were recorded. Subsequent strains isolated from the same patient were excluded, unless the species differed. Hospital census data were obtained from the financial department to determine the rate of bloodstream infections.
RESULTS: One hundred thirty-eight candida bloodstream infections were identified, with the following distribution of species: *C. albicans* (47%) ,*C. tropicalis* (21%), *C. parapsilosis* (15%), *C. glabrata* (11%), *C. krusei* (4%), and *C. lusitaniae* (2%). From 1995 to 1999, the incidence of candidemia increased steadily from 1.6 to 4.1/10,000 patient days. During the study period, bloodstream infections due to *C. albicans* increased by 50% while those due to non-albicans species increased by 400%. *C. albicans* remained the most common isolate for each year of the study. However, the proportion of candidemias due to *C. albicans* declined steadily from 62% in 1995 to 37.5% in 1999 while *C. parapsilosis* and *C. glabrata* increased by 800% and 900%, respectively.
CONCLUSION: During the study period, the incidence of candida bloodstream infections increased. The change in species identified showed the greatest rise in *C. parapsilosis* and *C. glabrata*, with a significant and proportionate decline in *C. albicans*. These data may influence empiric antifungal treatment in our institution.

145. Piperacillin/tazobactam serum inhibitory and bactericidal activity: intermittent bolus versus continuous infusion. David S. Burgess, Pharm.D., *Travis W. Waldrep, Pharm.D.*; University of Texas at Austin, Austin, TX; University of Texas Health Science Center at San Antonio, San Antonio, TX.

PURPOSE: To compare the inhibitory and bactericidal activity of piperacillin/tazobactam (Pip/Tazo) when administered as intermittent bolus vs continuous infusion (CI).
METHODS: Twelve normal healthy volunteers (eight male, four female) received each of the following regimens with at least a 1-week washout period: Pip/Tazo 3.375 g q6h for four doses, 6.75 g CI and 13.5 g CI over 24 hours. Blood samples were obtained at 19, 21, and 24 hours to perform SIT and SBT for each regimen against five clinical isolates of *K. pneumoniae* and *P. aeruginosa*. These times represent the peak, midpoint, and trough concentration for the intermittent bolus and the steady state serum concentration for the continuous infusion regimens. MICs, SITs, and SBTs were determined by NCCLS guidelines. Inhibitory and bactericidal titers at each time point were determined by assigning an ordinal number to each reciprocal titer (e.g., < 1:2, 0; 1:2, 1, 1:512, 10). These ordinal numbers were determined for each organism, regimen, and sampling time and rounded to the nearest whole number. Values were then reconverted to the corresponding reciprocal inhibitory or bactericidal titer. Differences were determined by analysis of variance (ANOVA). A p value < 0.05 was considered statistically significant.
RESULTS: *K. pneumoniae* and *P. aeruginosa* MICs ranged from 2–32 µg/ml and 4–64 µg/ml, respectively.

	K. pneumoniae		*P. aeruginosa*	
Regimen	Mean 24 hour SIT (SBT)	% 24 hour SIT ≥ 1:2	Mean 24 hour SIT (SBT)	% 24 hour SIT ≥ 1:2
3.375 g q6h	1:2 (< 1:2)	92%	1:2 (< 1:2)	52%
6.75 g CI	1:4 (1:2)	96%	1:2 (< 1:2)	76%
13.5 g CI	1:8 (1:4)	100%	1:4 (< 1:2)	87%

For *P. aeruginosa*, a statistical difference existed among the regimens for % of patients with 24-hour SITs ≥ 1:2 (p=0.0147).
CONCLUSION: No differences existed among the Pip/Tazo regimens against *K. pneumoniae*. However, both continuous infusion regimens provided a higher percentage of patients with 24-hour SITs ≥ 1:2 than intermittent bolus against *P. aeruginosa*.

146. The impact atypical organism coverage has on mortality in hospitalized-community acquired pneumonia patients. *Jim Koeller, M.S.*, Mike Johnsrud, Ph.D.; University of Texas at Austin; University of Texas Health Science Center at San Antonio, TX.

PURPOSE: This study evaluated the effects initial IV antibiotic selection that includes coverage for atypical organisms had on survival in hospitalized patients with presumed community-acquired pneumonia (CAP).
METHODS: A retrospective patient chart review was carried out utilizing a two-page automated data capture form, on hospitalized patients presumed CAP from 124 community hospitals from across the U.S. between January 1998, and December 1999. The database contains 5231 evaluable patients. We selectively compared third-generation cephalosporin therapy alone to third-generation cephalosporin plus macrolide and to a newer fluoroquinolone (levofloxacin) looking at their impact on survival (controlling for age and disease).
RESULTS: We identified 713 patients who had received only third-generation cephalosporin therapy, 723 patients who had received third-generation cephalosporin plus macrolide therapy, and 249 patients who had received levofloxacin alone. After controlling for age and acuity of illness differences between the groups, logistic regression analysis failed to detect a significant difference in mortality between third-generation cephalosporin and third-generation cephalosporin plus macrolide (Wald p=0.823) and between third-generation cephalosporin and levofloxacin (Wald p=0.725).

CONCLUSION: In this relatively large pneumonia data base from community hospitals across the U.S., treatment with third-generation cephalosporins plus a macrolide or levofloxacin did not appear to confer a survival advantage in hospitalized patients with presumed CAP when compared to third-generation cephalosporin use alone.

147. The effect of formulary conversion from ceftazidime to cefepime on in vitro susceptibilities of *Enterobacter cloacae* isolates. *Paul M. Southern, M.D.*, Kimberly Walters, Pharm.D.; University of Texas Southwestern Medical Center, Dallas, TX; Dura Pharmaceuticals, San Diego, CA.

PURPOSE: Antibiotic resistance in Gram-negative organisms is of increasing concern to health care professionals. Previous reports state that replacing ceftazidime with cefepime for broad-spectrum therapy increases susceptibility of enterobacter isolates. Cefepime, a fourth-generation cephalosporin, has demonstrated in vitro activity against ceftazidime-resistant organisms as well as stability in the presence of inducible β-lactamases. In addition, acquired resistance to cefepime is not expected in Gram-negative organisms because two distinct mutation steps may be needed. A pilot study was performed to measure the effects of a hospital-wide formulary conversion from ceftazidime to cefepime on susceptibility patterns for *Enterobacter cloacae*, a prevalent Gram-negative pathogen in nosocomial infections.
METHODS: Formulary conversion to cefepime was defined as cefepime usage ≥ 80% of ceftazidime usage. Susceptibilities of *E. cloacae* isolates to ceftazidime were measured each month for 3 months before formulary conversion (M–3 through M–1) and also measured to both agents for 9 months after conversion (M–1 through M–9). The MicroScan Walkaway system (Dade Diagnostic Inc.) was used to assess susceptibility.
RESULTS: Documented susceptibilities of *E. cloacae* to ceftazidime and cefepime during M–3, M–6, and M–9 were as follows:

Percentage of *E. cloacae* Susceptible

	(No. Tested)	
Month	Ceftazidime	Cefepime
M–3	71 (86)	ND
M–6	83 (24)	96 (24)
M–9	83 (23)	100 (23)

ND=not documented

CONCLUSION: Formulary conversion from ceftazidime to cefepime was associated with improved susceptibility to ceftazidime for *E. cloacae* isolates after 6 and 9 months of cefepime use, while susceptibility to cefepime remained high. A large, multicenter investigation of this conversion may be warranted.

148. Variability in antibiotic use in U.S. hospitals: analysis of the MediMedia Information Technology database. Jennifer M. Clarke, *Roula B. Qaqish, Pharm.D.*, Susan Dennis, Ronald E. Polk, Pharm.D.; Virginia Commonwealth University/Medical College of Virginia Campus, Richmond, VA; MediMedia Information Technologies, North Wales, PA.

PURPOSE: There is a presumed quantitative relationship between hospital antibiotic (ABU) and bacterial resistance, but there are little supporting data. In part this reflects difficulty in obtaining ABU data from multiple hospitals. We have an alliance with MediMedia Information Technology (MMIT), a company that records dispensed drug data at participating hospitals. The objective was to evaluate the correlation between ABU and bed size (as a severity of illness surrogate).
METHODS: ABU in 15 hospitals was obtained from MMIT database and expressed as defined daily dose (DDD) per 1000 patient days (PD) for 1999 and 2000.
RESULTS: Bed size ranged from 186 to 907.

Antibiotics	Mean ABU ± SD (DDD/1000 PD)	Median ABU (Range)
Vancomycin	44 ± 35	28 (9-131)
Antistaphylococcal penicillins	20 ± 20	9.0 (3-61)
Antifungals (amphotericins, azoles, triazoles)	20 ± 16	14 (6-52)
Potent β-lactams (3^{rd}ceph, imipenem, aztreonam)	179 ± 154	154 (35-598)
Aminoglycosides	77 ± 35	35 (17-263)
Fluoroquinolones	121 ± 131	131 (41-187)
Penicillin/β-lactamase inhibitors	64 ± 59	41 (1-228)

There was a 14-fold range in vancomycin use, and 5.9-fold range in total ABU (range = 190-1127). There was no correlation between bed size and total ABU (r^2=0.029). ABU is skewed right, except for fluoroquinolones. Use of potent β-lactams and aminoglycosides was correlated (r^2=0.46), but not use of potent β-lactams and quinolones (r^2=0.12) or antifungal drugs (r^2=0.00).
CONCLUSION: There is wide variability in ABU unrelated to bed size. A few hospitals account for a disproportional amount of ABU. The MMIT database is suited for epidemiologic investigations of variability in antibiotic use in U.S. hospitals.

149. Susceptibility patterns of select Gram-negative organisms after a formulary switch from ceftazidime to cefepime. *Lori L. Hamm, Pharm.D.*, David F. Volles, Pharm.D., Robert G. Sawyer, M.D., Kevin C. Hazen, Ph.D.; University of Virginia Health System, Charlottesville, VA.

PURPOSE: This study documented changes in susceptibility patterns of Gram-negative organisms, including *Pseudomonas aeruginosa*, *Enterobacter aerogenes*, *Acinetobacter calcoaceticus*, and *Serratia marcescens*, from surgical patients, after a formulary switch from ceftazidime to cefepime.
METHODS: Culture and susceptibility results generated by our VITEK automated system between August 1996 and August 1999, 1 year before and 2 years after the formulary switch, were reviewed. Percent susceptible and median minimum inhibitory concentration (MIC) values were evaluated. Pseudomonas results from different culture sites were also evaluated. Duplicate isolates with the same MIC value and culture site were excluded.
RESULTS: A total of 957 samples from 489 patients were included. Susceptibility results for the 2-year period after the formulary switch favored ceftazidime over cefepime for pseudomonas (79% vs 52% susceptible; n=485) and acinetobacter (65% vs 29% susceptible; n=140). In contrast, cefepime demonstrated greater susceptibility with enterobacter isolates compared with ceftazidime (95% vs 69% susceptible; n=208). Ceftazidime and cefepime had comparable susceptibilities with serratia (100% vs 98% susceptible; n=124). Pseudomonas susceptibility to ceftazidime increased during the 2-year period after formulary removal (71% before vs 79 % after). Pseudomonas susceptibility results from different culture sites followed a similar trend as the overall results.
CONCLUSION: Susceptibility to cefepime and ceftazidime is organism specific; therefore, it may be appropriate to include both cefepime and ceftazidime on the formulary. In addition, instituting an antibiotic rotation policy may be beneficial. Monitoring susceptibility patterns following formulary changes is vital for identifying resistance development.

150. Unreliability of an antimicrobial order sheet-based review system in monitoring anti-infective therapy. *Jeannie D. Chan, Pharm.D.*, Kimberly Botwin, Pharm.D., B. Joseph Guglielmo, Pharm.D.; University of California at San Francisco, San Francisco, CA.

PURPOSE: Antimicrobial order sheets (AOSs) are widely utilized to improve appropriateness of anti-infective prescribing. The medical center requests prescribers to provide indication for use (surgical prophylaxis [SP], empiric therapy [EMP] and documented infection [DI]) on the AOS. The objectives were to assess provision of patient demographics, verification of prescriber-selected indication with that documented in the medical record, and utilization of microbiology results.
METHODS: Retrospective analysis of 600 randomly selected AOS (150 SP, 150 EMP, 150 DI, 150 with no indication [NI] provided) was performed. Computerized medical records were reviewed to verify true indication, microbiology results, and demographics.
RESULTS: Indication for use was selected in only 80% of AOS. Allergy history and weight was provided in 82% and 39% of cases, respectively. Large discrepancies were observed between selected and verified indication, particularly with DI (50%) and EMP (37%). In those instances with discrepancies, the most common verified indication was determined to be SP. When NI occurred, 62 (41%) were intended for SP, 45 (30%) EMP, 7 (5%) DI, 13 (9%) febrile neutropenia, and 23 (15%) opportunistic infection prophylaxis. Microbiological cultures were obtained 79% of the time before initiation of anti-infectives. Empiric therapy was streamlined to the documented pathogen in 42% of the cases when positive cultures were isolated. Similarly, EMP was changed only 39% of the time in those patients with negative cultures.
CONCLUSION: The lack of correlation between prescriber-selected and verified indications, inconsistent reporting of allergies and weight, and minimal streamlining calls into question the validity of an antimicrobial system solely centered upon AOS.

Nephrology

151. Safety of cisapride therapy in hemodialysis patients. *A. Scott Mathis, Pharm.D.*, Constantinos Costeas, M.D., Joseph Barone, Pharm.D.; Rutgers University, Saint Barnabas Medical Center, Livingston, NJ.

PURPOSE: Cisapride is used, yet is contraindicated in patients with endstage renal disease and gastrointestinal motility disorders. Ventricular arrhythmias (VAs) have been associated with both cisapride and hemodialysis (HD). However, reports are conflicting regarding the safety of cisapride in HD patients. We undertook this study to characterize the safety of cisapride in HD patients, evaluating QT intervals (QTI) and QT dispersion (QTD).
METHODS: Baseline and steady-state electrocardiograms (ECG) were retrospectively selected for calendar year 1999 for each patient receiving cisapride if ECGs demonstrated sinus rhythm, potassium was ≥ 3.5 mEq/dl, and there were no pharmacokinetic drug interactions. QTIs were measured by two investigators, and QTD were calculated ($QT_{max} - QT_{min}$). Averages between investigator measures (± SD) are presented for each value, and are evaluated using student's t-test.
RESULTS: Thirty-one HD patients received cisapride. Seventeen failed to meet entry criteria, and none had pharmacokinetic drug interactions. In

included patients (six male/eight female), heart rates were 86.71 (± 20.87 BPM) at baseline, and 86.57 (± 14.23 BPM) during treatment (p=NS). Serum potassium was 4.97 (± 1.2 mEq/dl) at baseline, and 4.94 (± 0.76 mEq/dl) during treatment (p=NS). The average baseline QT_{max}/QT_{min} intervals were 391.07 (± 42.43 ms)/330.71 (± 40.94 ms). Treatment QT_{max}/QT_{min} were 391.43 (± 38.2 ms)/343.93 (± 35.69 ms) (p=NS, both). QTD at baseline was 60.36 (± 17.59 ms), and during treatment, was 47.5 (± 19.59 ms) (p=0.074). No VAs were observed during at least 160 days [range 2-830] of cisapride exposure. Two patients died during this study, both 4 days after discontinuing cisapride, due to other causes.
CONCLUSIONS: Cisapride did not significantly increase the QT_{max} or QTD in patients undergoing HD. Cisapride was safe in this population with stable potassium level and no pharmacokinetic interactions.

152. Changing to subcutaneous administration of erythropoietin in a county-funded hemodialysis unit. *Michael Knauss, Pharm.D.*, Ted Walton, Pharm.D., BCPS, Edwin J. Macon, M.D.; Grady Health System, Atlanta, GA.

PURPOSE: Past studies have indicated that subcutaneous administration of erythropoietin reduces dose requirements by approximately one-third versus intravenous administration in hemodialysis patients. The objective of this study was to determine if an overall dose requirement reduction would result when Grady Health System hemodialysis patients were switched from intravenous to subcutaneous administration of erythropoietin while maintaining a stable hematocrit.
METHODS: The trial was a non-randomized, unblinded, concurrent study involving 27 chronic hemodialysis patients. After 3 months of data collection on intravenous therapy, all patients were converted to subcutaneous administration and were followed for an additional 3 months. Computer records and the patient dialysis chart were used to collect laboratory data and demographic information.
RESULTS: Fifteen of the initial 27 patients completed the study. Patients were excluded from the study due to the following: eight transferred to another facility, three were hospitalized, and one refused subcutaneous administration. The conversion from intravenous to subcutaneous administration resulted in a 46% reduction in weekly erythropoietin dose requirement (14,340 units for intravenous versus 6667 units for subcutaneous, $p<0.00001$). The hematocrit remained stable after conversion as well (36.5% for intravenous versus 37.3% for subcutaneous, $p>0.5$), with 80% (12/15) of patients in the intravenous phase and 100% (15/15) of patients in the subcutaneous phase maintaining a hematocrit > 33%. The dose reduction appreciated in this study would result in a yearly erythropoietin cost savings of approximately $49,000 for the 15 patients in this study.
CONCLUSIONS: Subcutaneous administration of erythropoietin is an effective method to maintain a stable hematocrit. In addition, dose reductions are possible with this route of administration, potentially resulting in significant cost savings.

153. The effects of nandrolone decanoate on nutritional parameters in hemodialysis patients. *Amy Barton Pai, Pharm.D.*, Celia Chretien, R.N., Alan H. Lau, Pharm.D.; University of Illinois at Chicago, Chicago, IL.

PURPOSE: Malnutrition with hypoalbuminemia is an independent predictor of mortality in end-stage renal disease patients. Anabolic steroids reduce protein catabolism and therefore may improve nutritional parameters. This study was undertaken to determine the effects of the anabolic steroid nandrolone decanoate on the nutritional status of hemodialysis patients. Secondary endpoints were to examine the effects of androgen therapy on hematocrit and erythropoietin (EPO) dose.
METHODS: Charts of chronic hemodialysis patients who received nandrolone decanoate for greater than 30 days were reviewed. Data collected included: demographics, dose, frequency, duration of treatment and cumulative dose of nandrolone. Baseline albumin, transferrin, dry weight, phosphorous, creatinine, hematocrit and erythropoietin dose were obtained for comparison to values after treatment.
RESULTS: Of the nine patients evaluated (mean ± SD age 55 ± 28 years, 4/9 male), two patients received nandrolone doses of 25 mg intramuscularly every week, while the remainder received 100 mg every 2 weeks. The mean ± SD duration of treatment was 96 ± 43 days, with a mean ± SD cumulative dose of 656 ± 371 mg. The mean ± SD baseline albumin was 2.9 ± 0.6 mg/dl which increased to 3.3 ± 0.4 mg/dl after treatment ($p<0.05$). Dry weight increased from a mean ± SD of 64.4 ± 11.7 kg to 66 ± 10.9 kg after nandrolone therapy ($p<0.05$). Hematocrit at baseline was 28.2 ± 4.5% and increased to 33.2 ± 5.1% ($p<0.05$) without significant changes in EPO dose.
CONCLUSIONS: Nandrolone significantly improved markers of nutritional status. This therapy may also enhance the hematopoietic effects of EPO.

154E. Economic evaluation of benazepril versus placebo in the treatment of patients with chronic renal insufficiency in the U.S.: a Markov model analysis based on clinical study data. *Arnold Seto, Pharm.D., M.S.*, Thomas J. Hogan, MBA; Churchill Health Economics, Secaucus, NJ.

PURPOSE: Chronic renal insufficiency (CRI) is associated with significant health and economic consequences. Angiotensin-converting enzyme inhibitors have been shown to favorably affect progression of renal disease. Our objective was to conduct an economic evaluation in the U.S. of benazepril versus controls in treatment of patients with CRI.
METHODS: We designed a Markov model to evaluate economic consequences of benazepril versus placebo, based on clinical data obtained from a 3-year trial and 3.6-year extension study in which the clinical effects of standard hypertension management plus benazepril therapy were compared to those of hypertension management alone. Costs associated with patient health outcome states were obtained from available sources.
RESULTS: After year 1, benazepril therapy is more cost-effective than control treatment. In years 2, 3, and 4, mean per-patient treatment costs are roughly $4000 per-patient less for benazepril patients than controls. In years 5, 6, and 7 of analysis, benazepril therapy yields both lower costs and higher quality-adjusted survival than controls. Patients in the benazepril arm cost between $10,000 to $13,000 less per patient than those in the control group, and in addition enjoyed a greater mean per-patient quality adjusted survival.
CONCLUSION: Benazepril is cost-effective therapy in the treatment of CRI of various causes, relative to placebo control. Over 7 years, total care costs for those in the benazepril arm are $10,000 to $13,000 per patient lower than for controls, while quality-adjusted survival is greater.
Presented at the 33rd Annual Meeting of the American Society of Nephrology, Toronto, ON, Canada, October 14, 2000.

155E. Effects of supplemental enteral nutrition on nutritional status and quality of life in ESRD patients receiving hemodialysis. Niyati A. Shah M.S., *Bruce A. Mueller, Pharm.D.*, Joseph Thomas Ph.D., Michael A. Kraus M.D., Meri Kay Scott Ph.D.; Purdue University; Indiana University, Indianapolis, IN.

BACKGROUND: Nutritional status and quality of life (QOL) in hemodialysis (HD) patients remain suboptimal despite numerous interventions.
PURPOSE: To quantify the effects of supplemental enteral nutrition on serum albumin and QOL in end stage renal disease (ESRD) patients receiving HD.
METHODS: Forty-four subjects received one can of Nepro® (Ross) with each thrice-weekly HD session for 3 months. Forty-four subjects served as a control. Serum albumin was measured at baseline and monthly. The Kidney Disease QOL questionnaire was used for QOL assessment at baseline and end of study. Repeated measures ANOVA was used to analyze changes between groups.
RESULTS: The change in albumin was significantly greater over the 3-month period within the Nepro® group (baseline 3.68 ± 0.33 to 3.75 ± 0.40 g/dl at 3 months) versus control subjects group (baseline 3.93 ± 0.34 to 3.81 ± 0.37 g/dl at 3 months; $p<0.05$). However, out of eight generic and 11 disease-specific QOL domains, role-physical and role-emotional were the only domains significantly influenced by the intervention (both $p<0.05$; repeated measures ANOVA with covariate analyses).
CONCLUSION: This simple nutritional intervention significantly improved serum albumin compared to a control population, but appeared to have little effect on overall QOL over a 3-month period.
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156. Tolerability and efficacy of intravenous ferric sodium gluconate complex (Ferrlecit®) in iron dextran-allergic hemodialysis patients. *Naomi V. Dahl, Pharm.D.*, Neeta B. Omara, Pharm.D., BCPS; UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ; DCI-Robert Wood Johnson Dialysis Center, North Brunswick, NJ.

PURPOSE: Iron deficiency is common in hemodialysis patients. Due to ongoing iron losses, oral therapy is ineffective, so iron dextran-allergic patients represent a unique problem. A new parenteral preparation, ferric sodium gluconate complex (FeGC), is considered safer than iron dextran (FeD), but the extent of cross-reactivity with FeD is unknown. We retrospectively evaluated the efficacy and safety of intravenous FeGC in FeD-allergic hemodialysis patients.
METHODS: Patients with FeD allergies documented on their medical record who received FeGC between November 1999, and June 2000, at two outpatient hemodialysis units were included. Medical records were reviewed for demographics, FeD prior reactions, other allergies, and adverse effects during and after FeGC administration, laboratory values and erythropoeitin dose.
RESULTS: Nine patients (13-87 years, mean 55.8) were studied. Iron dextran reactions included rash, hypotension, chest pains, and anaphylaxis requiring intubation. Six patients had multiple drug allergies. All had transferrin saturation values < 20% and ferritin < 200 ng/ml. Patients received 118 doses (2-24) of 125 mg FeGC IVP over 10 minutes (n=66), or IV infusion over 1 hour (n=52). Patients were not pretreated with antihistamines or steroids. No patients experienced allergic-type reactions to FeGC. One patient developed diarrhea. All patients experienced an improvement in iron indices (mean saturation 10.2% to 16.8%, ferritin 72 to 215 ng/ml), and significant increase in hemoglobin (mean 9.6 to 12.2 g/dl, $p<0.005$), and decrease in erythropoietin dose (mean 13,300 to 8200 units TIW, $p<0.05$).
CONCLUSION: Intravenous FeGC appears effective and safe in hemodialysis patients with documented allergy to FeD and should be considered a viable therapeutic option in these patients.

157E. Safety of an investigational phosphate binder (lanthanum carbonate) in hemodialysis patients. *Melanie S. Joy, Pharm.D.,* Gerald A. Hladik, M.D., William F. Finn, M.D., L. Garrett, J. Godwin, R. Schmidt, D. Wombolt, V. Richards, W. Smith, C. Galphin, M. Moore, R. Moore, III; University of North Carolina, Chapel Hill, NC.

The safety and tolerability of lanthanum carbonate was assessed in 145 ESRD patients enrolled in a phase II, dose-ranging, placebo-controlled study. After a 1- to 3-week washout period, patients were randomized to either placebo (n=32) or lanthanum carbonate (n=113) in lanthanum doses of 225, 675, 1350, or 2250 mg in divided doses with meals for 6 weeks followed by a 2-week washout phase. Standard safety assessments were employed. In addition, whole blood lanthanum concentrations were measured by atomic absorption spectroscopy. Patients were removed from the study if iPTH increased > 500 pg/ml from baseline, if serum PO_4 levels increased to > 10 mg/dl, or if the PO_4 ¥ Ca^{++} product was > 80 mg^2/dl^2. Study termination points and adverse events are summarized as follows:

	Placebo	Lanthanum
PO_4 x Ca^{++} > 80 mg^2/dl^2	34% (n=11)	12% (n=14)
PO_4 > 10 mg/dl	6% (n=2)	4% (n=4)
PTH > 500 pg/ml	0% (n=0)	1% (n=1)
Adverse effects	9% (n=3)	8% (n=9)
Death	0% (n=0)	1% (n=1)

The adverse effects leading to early termination were not considered to be drug related. Causality (possibly or probably related) of reported adverse events showed more gastrointestinal complaints consisting of nausea (11%), vomiting (8%), and abdominal pain (6%) in patients randomized to lanthanum carbonate versus placebo (3%, 3%, and 0%, respectively). For patients completing the study, blood lanthanum levels (ng/ml ± SD) at the end-of-treatment were: 0.10 ± 0.23 (placebo); 0.23 ± 0.23 (225 mg); 0.80 ± 1.18 (675 mg); 0.48 ± 0.43 (1350 mg); and 1.16 ± 1.91 (2250 mg). Lanthanum carbonate was well tolerated. While there was a slight increase in gastrointestinal complaints, no serious adverse events were considered to be drug related. Early study termination was greatest in the placebo group as a result of PO_4 x Ca^{++} products > 80 mg^2/dl^2.
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158E. Results of a randomized dose-ranging, placebo-controlled study of lanthanum carbonate for reduction of serum phosphate in chronic renal failure patients receiving hemodialysis. William F. Finn, M.D., *Melanie S. Joy, Pharm.D.,* Gerald A. Hladik, M.D., L. Garrett, J. Godwin, R. Schmidt, D. Wombolt, V. Richards, W. Smith, C. Galphin, M. Moore, R. Moore, III; University of North Carolina, Chapel Hill, NC.

Lanthanum in the form of its carbonate salt is a highly effective phosphate (PO_4) binder. Because the carbonate and phosphate salts are extremely water insoluble, lanthanum is relatively unavailable for absorption, suggesting that lanthanum carbonate may be useful in the treatment of hyperphosphatemia in ESRD patients. One hundred ninety-six patients > age 18 on hemodialysis for at least 6 months with a URR ≥ 0.65 entered a 1- to 3-week placebo washout period off all PO_4 lowering agents. One hundred forty-five patients fulfilled randomization criteria (serum PO_4 level ≥ 5.6 mg/dl). Five groups were treated for up to 6 weeks with either placebo or lanthanum carbonate in lanthanum doses of 225, 675, 1350, or 2250 mg given daily in divided doses with meals. Withdrawal occurred for serum PO_4 > 10 or < 2.0 mg/dl, for a PO_4 x Ca^{++} product > 80 mg^2/dl^2, or for a PTH level increase > 500 pg/ml. The intent-to-treat analysis showed significant dose-related reductions in serum PO_4 (mg/dl ± SD) at lanthanum doses of 675, 1350 and 2250 mg.

Dose	Week 0	Week 3	Week 6	Post Rx
Placebo	7.2 ± 1.4	7.5 ± 1.6	7.0 ± 1.4	7.5 ± 1.7
225 mg	6.6 ± 1.1	7.0 ± 1.4	7.0 ± 1.4	7.2 ± 1.8
675 mg	7.3 ± 1.4	6.3 ± 1.2 [a,b]	6.8 ± 1.2	8.3 ± 1.8
1350 mg	6.8 ± 1.4	6.0 ± 1.9 [a,b]	5.5 ± 1.2 [a,b]	7.0 ± 1.5
2250 mg	7.4 ± 1.2	5.8 ± 1.5 [a,b]	6.0 ± 2.3 [a]	7.9 ± 1.8

[a]p<0.05 vs week 0; [b]p<0.05 vs placebo.

For patients eligible for per-protocol analysis, differences in PO_4 among the five groups were highly significant (ANOVA; p<0.0001). The end of treatment reductions in serum PO_4 (Dunnett's test) compared to placebo were significant for the 1350 mg (-1.92 mg/dl) and 2250 mg doses (-2.17 mg/dl). Drug compliance was 91.2 ± 11.6%. Lanthanum carbonate is an effective and well-tolerated agent for the treatment of hyperphosphatemia in patients with ESRD.
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Neurology

159E. Physician specialty and variation in cost of status epilepticus treatment at an urban medical center. *Denise H. Rhoney, Pharm.D.,* Allison L. Somerville, Pharm.D., William M. Coplin, M.D.; Wayne State University; Detroit Receiving Hospital, Detroit, MI.

PURPOSE: Our objective was to describe the cost of status epilepticus (SE) at our urban medical center from an institutional perspective, and to study cost variation among admitting physician specialties.
METHODS: We reviewed adult patients admitted between July 1996 and August 1998. Data collection included demographics, diagnostic tests, SE treatments, and outcomes. Institutional cost information was obtained from a cost accounting system.
RESULTS: Of 96 patient charts reviewed, 69 had cost information available. Common etiologies of SE included: medication noncompliance (31%), toxic/metabolic (24%), and acute brain injury (16%). The median total cost (TC) and total variable cost (TVC) per year was $16,000 and $6000, respectively. The neurology service had a higher TVC ($8600), which is primarily reflected in the ICU and pharmacy costs. Independent predictors of both TC and TVC included: history of seizure disorder, etiology of SE, in-hospital complications, premorbidly prescribed AED, number of agents prescribed to treat SE, and length of stay (LOS) (p<0.05). The median ICU and hospital LOSs were 4 and 8 days, respectively. There was a trend for patients who were admitted to the neurology services to have longer ICU stay (p=0.06). Independent predictors of LOS included: history of seizure disorder, in-hospital complications, unresolved SE, time from onset of SE to receive treatment, number of agents prescribed to treat SE, and premorbidly prescribed antiepileptic drugs (p<0.05).
CONCLUSION: Pre-existing seizure disorders, pre-morbid AED prescription, and in-hospital complications are important predictors of TC. Admission to the neurology service resulted in higher costs and LOS which could not be explained by severity of illness. Both public and health care provider SE education may provide a significant avenue for cost-reduction of SE treatment at our institution.
Published in Crit Care Med 2000;27:89.

161. Beneficial effect of rivastigmine on behavioral symptoms in patients with dementia (Alzheimer's disease or dementia with Lewy bodies). *Barbara Koumaras,* Ana Cicin-Sain, M.D., Jacquiline Danyluk, Pharm.D., Ravi Anand, M.D., Richard Hartman, Ph.D., Jeffrey Cummings, M.D., Ian McKeith, M.D.; Novartis Pharmaceuticals Corporation, East Hanover, NJ; University of California, Los Angeles, CA; Institute for the Health of the Elderly, Newcastle upon Tyne, UK.

PURPOSE: To assess the effect of rivastigmine on behavioral symptoms in patients with Alzheimer's disease (AD) and in those with dementia with Lewy bodies (DLB).
METHODS: An open-label, multicenter study was conducted in nursing home residents with AD (n=173) who were treated with rivastigmine 3 to 12 mg/day. The Neuropsychiatric Inventory-Nursing Home version (NPI-NH) was used to assess changes in behavioral symptoms after 26 and 52 weeks of treatment. A double-blind, international study was conducted in patients with DLB (n=120) who received rivastigmine 3 to 12 mg/day or placebo. The subtotal score of four key items of the Neuropsychiatric Inventory (NPI-4) was used to assess behavioral changes over 26 weeks.
RESULTS: In nursing home AD patients who exhibited behavioral symptoms at baseline (n=92), a mean reduction of 18% from baseline on total NPI-NH score was observed after 26 weeks and approximately 50% of patients had a 30% reduction in score. Furthermore, after 52 weeks of treatment, the following symptoms were significantly improved from baseline (p<0.05): irritability, anxiety, aberrant motor behavior, delusions, disinhibition, hallucinations, night-time behavior, and appetite. A reduction in psychotropic medication usage was also noted. In patients with DLB, a significant difference on the NPI-4 was observed in the rivastigmine group compared with the placebo group.
CONCLUSION: Beneficial effects of rivastigmine on behavioral symptoms in patients with AD and in those with DLB may reduce the requirement for additional drug therapy. Additionally, patients with DLB are unusually sensitive to antipsychotics, and rivastigmine offers another treatment option for these patients.

162. Extremely high-dose requirements of valproic acid in a pediatric patient with intractable seizures. *Kathryn A. O'Hara, R.N.,* Lawrence D. Morton, M.D., Nicole Meloche, R.N., William R. Garnett, Pharm.D.; Virginia Commonwealth University, Richmond, VA.

PURPOSE: The purpose of this case report is to describe a pediatric patient with intractable seizures who needed extremely high doses of valproic acid (VPA).
METHODS: A 3-year-4-month-old male, with a weight of 11.4 kg, was transferred from an outlying hospital after 51 days with intractable seizures. On admission, medications were topiramate, lamotrigine, lorazepam, VPA, ranitidine, L-carnitine, amoxicillin, albuterol, beclomethasone dipropionate and ipratropium bromide. Levels of VPA were subtherapeutic (< 25 mg/L) with doses of 25 mg/kg every 6 hours (88 mg/kg/day). Bolus doses of IV VPA ranged from 90 mg/kg/day to 263 mg/kg/day with levels ranging from 26 mg/L to 104 mg/L, with a mean average of 52 mg/L. A continuous infusion of IV VPA was begun at a rate of 50 mg/hour and seizure activity stopped. The blood level was 71 mg/L.
RESULTS: An attempt to convert the subject to oral doses of VPA (sprinkles and syrup) was unsuccessful, because the VPA level decreased to 39 mg/L

with the recurrence of seizure activity. Continuous infusion of VPA was re-started but at a rate of 80 mg/hour. With seizure control achieved, an upper GI was performed and demonstrated rapid transmit time from the small bowel to the colon. Valproic acid was started at 1200 mg/day, but was increased to 4875 mg/day (428 mg/kg/day) to maintain a constant level of 65 mg/L. The patient was discharged on VPA 3375 mg/day (296 mg/kg/day), gabapentin 500 mg/day (44 mg/kg/day), potassium chloride, ferrous sulfate, ranitidine and L-carnitine.
CONCLUSION: The case illustrates the need to monitor patient response and to not be limited by usual doses.

163E. Baseline antihypertensive medication use in the African American antiplatelet stroke prevention study. Romy Mavumkal, Pharm.D., *Kiranpal S. Sangha, Pharm.D.*, Sue Leurgans, Ph.D., Elena Hung, M.S., Hesham Hassaballa, M.D., Chung Y. Hsu, M.D., Ph.D., Daniel Woo, M.D., John Choi, M.D., Philip B. Gorelick, M.D., the African American Antiplatelet Stroke Prevention Study Investigators; University of Cincinnati, University Hospital, Cincinnati, OH; Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL; Washington University School of Medicine, St. Louis, MO; Walter Reed Army Medical Center, Washington, D.C.

PURPOSE: The African American Antiplatelet Stroke Prevention Study (AAASPS) is a double-blind, multicenter randomized trial comparing ticlopidine and aspirin in preventing vascular events in African Americans (AA) with recent ischemic stroke. Cardiovascular risk factor control is carried out by the patient's primary care physicians. We analyzed the utilization of baseline antihypertensive medications in the AAASPS patient population as related to JNC VI recommendations.
METHODS: Baseline medication forms from the database frozen on June 30, 1999, were analyzed. This included 1087 patients, with a total of 5138 medication records. Each medication was categorized based on the classification systems from the AAASPS case report form codes and American Hospital Formulary Service. Odds ratios (ORs) were determined for patient subgroups.
RESULTS: Of 1087 patients, 917 (84%) had hypertension and the antihypertensive utilization rates were determined from this population: calcium channel blockers 46%, angiotensin converting enzyme inhibitors 41%, diuretics 35%, β-blockers 17%, and others 18%. In addition, 30% of AAASPS patients were on some combination of diuretics and other agents. Patients with a history of diabetes were twice as likely to be on ACE inhibitors than patients without a history of diabetes (54% versus 32%, OR = 2.4; $p<0.0001$). Patients with a history of cardiac disease were more likely to be on a BB (34% versus 13%, OR = 3.4; $p<0.0001$), CCB (54% versus 44% OR = 1.5; $p=0.02$) or other anti-hypertensives (45% versus 21%, OR = 3.0; $p<0.0001$) than patients without a history of cardiac disease.
CONCLUSIONS: Baseline therapy of patients with hypertension are consistent with JNC VI recommendations for the treatment of hypertension in AAs.
Presented at 25th International Stroke Conference, New Orleans, LA, February 10-12, 2000.

Oncology

164. Comparison of the safety and efficacy of outpatient-based histamine dihydrochloride plus interleukin-2 therapy versus interleukin-2 alone in metastatic melanoma. *Mary Kay Penic, Pharm.D.*; Home Medical of America, San Diego, CA.

PURPOSE: Histamine protects T-cells and NK cells from inhibition by monocyte- and macrophage-derived reactive oxygen metabolites and synergizes with cytokines (interleukin-2, interferon-α2b) in preclinical models. Animal and phase II study results suggest an important immune-modulating adjuvant role for histamine.
METHODS: A multicenter, randomized, open-label, phase-III study was conducted in 305 patients with metastatic melanoma. Each treatment cycle consisted of IL-2 (9 MIU/m^2, days 1 and 2, weeks 1 and 3; 2 MIU/m^2, days 1-5, weeks 2 and 4), ± histamine (1 mg, days 1-5, weeks 1-4), followed by a 2-week rest for ≤ 8 cycles. All injections were given subcutaneous, BID. Exclusion criteria included prior IL-2 therapy, and compromised cardiovascular, pulmonary or renal function. A primary end point was overall survival prospectively applied to the overall intent-to-treat (ITT) and liver metastases (ITT-LM) populations. Pharmacists prepared all doses. Most patients were taught to self-administer both agents at home.
RESULTS:

Population	n	Survival (months) Histamine + IL-2	IL-2 Alone	p=(Log Rank)
ITT	305	9.1	8.2	>0.05
ITT-LM	129	9.4	5.1	=0.004*

* statistically significant

Histamine-related side effects (SE) included: flushing, hypotension, tachycardia, headache, rash, mucosal congestion, pain/itching at the injection site and metallic taste, usually resolving spontaneously ≤ 60 minutes. Histamine SE could be minimized or eliminated by slowing the injection rate and/or by dose reduction. Severe SE incidence was ≤ 10%.
CONCLUSIONS: The combination of histamine with IL-2 significantly improves survival over IL-2 alone in MM patients with liver metastasis. The combined therapy provided in an out patient setting was well tolerated.

165. Development of neutralizing antibodies to DT-GM during a phase I study in patients with relapsed/refractory acute myeloid leukemia. *Tony E. Willoughby*, Philip D. Hall, Pharm.D., Arthur E. Frankel, M.D.; Medical University of South Carolina, Charleston, SC; Wake Forest University, Winston-Salem, NC.

We have initiated a phase I clinical trial of a fusion toxin (DT-GM) consisting of the catalytic and translocation subunits of diphtheria toxin (DT) linked to human granulocyte-macrophage colony stimulating factor (GM) for the treatment of relapsed/refractory acute myeloid leukemia (AML).
PURPOSE: The purpose of this study was 1) to determine if the phase I patients would have pre-existing neutralizing antibodies due to immunizations against diphtheria; and 2) if the DT subunit antigenicity would trigger the further development of neutralizing antibodies upon treatment.
METHODS: To date, 24 patients with relapsed/refractory AML have been treated with DT-GM. Patients received 1, 2, 3, 4, or 5 µg/kg/day doses for 5 days. Serum samples were taken prior to therapy and on days 15, 30, and 60 after course one. Five patients underwent a second course of therapy; serum sample collection followed the same schedule. Four patients expired before a post-therapy sample was obtained, and two patients have not reached day 30. Antibody neutralization capacity was assessed via an in vitro bioassay to inhibit DT-GM utilizing HL60 cells. Samples with titers ≥ 1:8 were considered positive if the diluted serum completely neutralized DT-GM.
RESULTS: None of the 24 patients displayed pre-existing neutralizing antibodies against DT-GM. To date, only 6 of 18 patients developed neutralizing antibodies after course one (titer range 1:8 – 1:1024). Five patients received a second course of therapy. Two patients that had previously displayed neutralizing antibodies after course one remained positive after the second course of therapy. One of the three patients who was negative for neutralizing antibodies after course one developed neutralizing antibodies after the second course of treatment (titer of 1:2048).
CONCLUSIONS: The majority of these patients receiving a single course of therapy do not develop neutralizing antibodies. Updated results will be presented at the meeting. Future work will correlate these results with the individual's pharmacokinetics of DT-GM, and ultimately clinical outcome.

166. Assessment of the pharmacokinetics of gemtuzumab ozogamicin in pediatric patients with relapsed acute myelogenous leukemia. *James A. Dowell, Ph.D.*, S. Peter King, Ph.D., Hank Liu, Ph.D., Mark S. Berger, M.D., Joan M. Korth-Bradley, Pharm.D., Ph.D.; Wyeth-Ayerst Research, Radnor, PA.

PURPOSE: To assess the pharmacokinetics of gemtuzumab ozogamicin in pediatric patients with relapsed acute myelogenous leukemia (AML).
METHODS: Gemtuzumab ozogamicin (Mylotarg™) is a recently approved antibody-targeted chemotherapeutic agent. It consists of a monoclonal antibody directed against CD_{33} (hP67.6) linked to a cytotoxic agent, N-acetyl-gamma calicheamicin DMH. The pharmacokinetic parameters from five CD_{33}-positive pediatric patients with relapsed AML (aged 2-14 years; two males/three females) who received two 6 mg/m^2 doses by IV infusion were determined. Plasma samples were assayed for hP67.6 and calicheamicin derivatives (total and unconjugated) by ELISA and pharmacokinetic parameters were determined by non-compartmental methods. Comparisons were made with adult AML patients who received 9 mg/m^2.
RESULTS: The hP67.6 pharmacokinetic parameters for the first dose period (children and adults) are shown in the table.

	C_{max} (mg/L)	$t_{1/2}$ (hour)	AUC (mg•hour/L)	CL (L/hour)	V_{ss} (L)
Pediatric (n=5)					
Mean	1.42	51.6	48.5	0.296	16.3
SD	0.92	25.0	43.0	0.248	10.7
(Mean/BSA [m^2])	-	-	-	(0.254)	(13.1)
Adult (n=141)					
Mean	3.09	66.5	132.3	0.353	20.6
SD	2.27	36.8	136.3	0.551	20.2

The concentration-time profiles of calicheamicin paralleled hP67.6. Decreased drug clearance was observed after the second dose in both children and adults, which is believed to be due to the reduction in CD_{33}-binding sites due to destruction of blasts by chemotherapy.
CONCLUSION: The pharmacokinetics of gemtuzumab ozogamicin were assessed in five pediatric patients with AML receiving 6 mg/m^2. The drug clearance and $t_{1/2}$ were similar between pediatric and adult patients.

167. Impact of low-dose acyclovir prophylaxis on *Herpes simplex* virus in leukemic patients. *R.A. Abo-Zena,* D.L. Capozzi, M. Kalaycio; Cleveland Clinic Foundation, Cleveland, OH.

PURPOSE: Approximately 80% of *Herpes simplex* virus (HSV) seropositive

patients undergoing induction chemotherapy for leukemia will reactivate HSV. It is for this reason that appropriate prophylaxis is critical in this population. At the Cleveland Clinic Foundation, the oral prophylactic dose of acyclovir was reduced from 800 mg to 400 mg twice daily. The purpose of this study was to evaluate the efficacy of this lower dose regimen as prophylaxis for HSV.
METHODS: Leukemic patients were identified from July 1994 to December 1998. A retrospective chart review was completed to evaluate the HSV prophylactic regimens in these patients. Records were reviewed to determine the dose of acyclovir used as prophylaxis and whether or not the patients developed HSV disease, defined as a positive HSV culture.
RESULTS: Eighty-two patients were identified that received HSV prophylaxis with acyclovir. There were 45 instances where these patients were prophylaxed with 400 mg twice daily by mouth and 44 instances where patients were prophylaxed with 800 mg twice daily. Seven of these patients received both prophylactic regimens at different times in their therapy. There were no cases of HSV reactivation in either of the treatment groups.
CONCLUSION: The results reveal that there has been no increase in rates of HSV reactivation since the reduction of acyclovir dose. It appears that the 400 mg twice daily oral dose of acyclovir is as effective as the 800 mg dose and is more cost effective. Future analyses may be required to determine the lowest possible effective dose of acyclovir for prophylaxis.

168. Oral dolasetron 100 mg plus dexamethasone 20 mg, intravenous or oral, is effective in preventing nausea and vomiting in patients receiving multiple treatments of highly emetogenic chemotherapy. *Samy A. Ayoub, Pharm.D.*, Rakesh Ojha, M.D., Arnold D. Rubin, M.D.; St. Joseph's Hospital and Medical Center, Paterson, NJ.

PURPOSE: Two large controlled trials showed oral dolasetron (DOL) 100 mg, without concurrent dexamethasone (DEX), effective in preventing chemotherapy-induced nausea and vomiting (CINV). Chemotherapy in these trials was classified as moderately emetogenic based on the primary agent only. Koeller et al's reanalysis (Pharmacotherapy 1998;18:1147) showed that half the patients randomized to 100 mg oral DOL in these trials received Hesketh level 5 chemotherapy. Our analysis sought to confirm the efficacy of oral DOL 100 mg plus DEX 20 mg for use in our pharmacy as preferred therapy for preventing CINV related to highly emetogenic chemotherapy.
METHODS: Patients receiving level 4 or 5 chemotherapy were included in this trial. Patients received 100 mg oral DOL plus DEX 20 mg (oral or IV) ≤ 1 hour before chemotherapy and were monitored for 24 hours. Patients were classified as a successful responder (no vomiting or nausea), a partial responder (nausea only or 1 vomiting episode that did not delay therapy), or a treatment failure (> 1 vomiting episode). Prochlorperazine was used as rescue medication.
RESULTS: Twenty-six patients (17 females; 9 males) underwent 37 chemotherapy treatments (25 female; 12 male). Successful responses were observed in 70% (26/37) of treatments; partial responses in 24% (9/37) of treatments. Two patients were treatment failures.
CONCLUSION: Our results support the findings of the Koeller reanalysis and show that oral DOL 100 mg plus DEX 20 mg is effective in preventing CINV in patients receiving multiple courses of highly emetogenic chemotherapy and is now preferred therapy for this indication in our institution.

169E. Transarterial chemoembolization in patients with unresectable diffuse versus focal hepatocellular carcinoma. *Shi-Hui Pan, Pharm.D.*, Allen Hoffman, M.D., Linda Sher, M.D., Sergio Rojter, M.D., Richard Lopez, M.D.; St. Vincent Medical Center, Los Angeles, CA.

Hepatocellular Carcinoma (HCC) varies in histology and growth patterns which may affect response to treatment and survival. We prospectively compared the clinical outcomes of transarterial chemoembolization (TACE) in patients with unresectable, diffuse vs focal HCC.
METHODS: From 9/95 to 12/99, 77 TACE treatments (Txs) were performed in 38 patients with focal HCC and 18 in 15 patients with diffuse HCC. Transarterial chemoembolization consisted of an infusion of a mixture of doxorubicin, cisplatin, and mitomycin followed by selective embolization. Clinical and biochemical effects were monitored at regular interval. Childs-Pugh classification (C-P Class), length of hospital stay (LOS), readmission, α-fetoprotein (AFP) response, complications, and mean survival were analyzed.
RESULTS: Mean follow-up was 744 (30-1480) days. Fourteen patients in diffuse group and 30 patients in focal group had cirrhosis (p=0.4). Mean tumor size in the focal group was 7 cm and 24 patients had > 1 tumor. Twelve patients with diffuse tumors had a mean AFP level of 29,931 vs 3439 ng/ml for 25 patients with focal tumors (p<0.01). The AFP response was greater with focal tumors: 76% of patients had a mean decrease of 76% in AFP 1 month following treatment. This decrease was sustained over time with additional TACE. All nine readmits in the diffuse group were due to complications of cirrhosis. In the focal group seven of eight readmits were due to complications of the procedures. The actual 1-year survival was 0% (0/14) in the diffuse group vs 65% (15/23) in the focal group. The results of TACE in these two groups are shown below:

Data in mean ± SD	P Class (A and B)	LOS (days)	Readmits (No./Txs)	AFP Response	Survival (days)
Diffuse HCC n=15	11/14 (79%)	2.6 ± 1.9 (50%)	9/18 (25%)	3/12	104 ± 76
Focal HCC n=38	30/30 (100%)	1.7 ± 1.0 (10%)	8/77 (76%)	19/25	372 ± 226
p value	<0.05	<0.01	<0.01	<0.01	0.01

CONCLUSIONS: In patients with diffuse HCC, TACE results in significant morbidity and does not impact survival. However, TACE is well tolerated in patients with focal HCC and may provide a survival benefit.
Presented at the Annual Meeting of the Digestive Disease Week, May 2000.

170E. Clinical significance of NAD(P)H: quinone oxidoreductase 1 C609T polymorphism in patients with disseminated peritoneal cancer receiving intraperitoneal mitomycin C. *Ronald A. Fleming, Pharm.D.*, Jeffrey Drees, M.D., Brian W. Loggie, M.D., Greg B. Russell, M.S., Kim R. Geisinger, M.D., Reba T. Morris, M.S., Debbie Sachs, B.S., Richard P. McQuellon, Ph.D.; Wake Forest University, Winston-Salem, NC.

PURPOSE: NAD(P)H: quinone oxidoreductase 1 (NQO1) is important in the activation of mitomycin C. The purpose of our study was to determine the effect of the NQO1 exon 6 C609T polymorphism on tumor NQO1 activity and overall survival in patients with peritoneal cancer administered mitomycin C.
METHODS: Patients with disseminated peritoneal cancer of gastrointestinal or other origin were eligible. After surgical debulking, patients received a 2-hour heated (40.5°C) intraperitoneal perfusion with mitomycin C (40 mg). NQO1 activity was determined in tumor tissue obtained at surgery and patients were genotyped for the C609T polymorphism using a PCR-RFLP method.
RESULTS: Of the 117 patients genotyped for the NQO1 C609T polymorphism, 67% were wild-type (WT), 31% were heterozygous (HE), and 2% were homozygous mutant (HM). The mean tumor NQO1 activities in WT (n=14) and HE (n=5) patients were 794 ± 603 and 70 ± 133 nmol/minute/mg protein respectively (p=0.006). Significant differences in survival between WT vs HE/HM genotypes were noted in optimally debulked patients (R0/R1) (43.6 months, median not yet reached vs 23 months, respectively, p=0.037) and in patients with peritoneal carcinomatosis of colonic origin (18.2, n=26 vs 11.5 months, n=12, respectively, p=0.050).
CONCLUSION: These data indicate that the NQO1 C609T polymorphism results in significantly reduced tumor NQO1 activity and reduced overall survival in subsets of patients receiving intraperitoneal hyperthermic mitomycin C therapy.
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171. Stability of mycophenolate mofetil for intravenous infusion. *Victoria J. Lee, Pharm.D.*, Timothy Synold, Pharm.D., Marvin Chow, Pharm.D.; City of Hope National Medical Center, Duarte, CA.

PURPOSE: Bone marrow transplantation (BMT) protocols use mycophenolate mofetil (MMF) for prophylaxis and treatment of graft-versus-host disease (GVHD). MMF is packaged as 500 mg vials and dosed at 500 mg or 1000 mg for patients receiving allogeneic cardiac and renal transplants. Doses for BMT patients are calculated based on mg/kg/day basis. The manufacturer reports a stability of 6 hours after reconstitution and dilution. MMF requires a minimum of 2 hours for infusion. This presents a problem for pharmacy in terms of cost and efficiency. The objective of this study was to determine the stability of mycophenolate mofetil for intravenous infusion after reconstitution and dilution to 6 mg/ml following product labeling instructions.
METHODS: Reversed-phase HPLC using a C18 column was utilized for determination of MMF. The mobile phase, with a flow rate of 1.5 ml/minute, consisted of 42% acetonitrile and 20 mM phosphoric acid buffered to a pH of 5.0. UV detector was set at 254 nm. Samples were collected and analyzed at 0, 1, 4.5, 6, 22.5, 24, 29, and 48 hours following preparation and storage at room temperature and ambient light.
RESULTS: MMF concentrations were measured and found to have no significant change over 48 hours. The mean concentration at 1 hour was 100.4% and at 48 hours was 101.3%.
CONCLUSION: MMF is routinely used off label for prophylaxis and treatment of GVHD in BMT patients. This study demonstrates that MMF is stable up to 48 hours after reconstitution and dilution at room temperature and ambient light.

172E. A phase I pharmacokinetic and pharmacodynamic study of high-dose topotecan in combination with ifosfamide/mesna and etoposide followed by autologous stem cell rescue in refractory malignancies. *James S. Partyka, Pharm.D.*, A.N. Hernandez, K.K. Fields, M.D., S. C. Goldstein, M.D., W.L. Trudeau, B.L. Maddox, R.N., R.K. Keller, Ph.D., R.M. Lush, Ph.D., and D.M. Sullivan, M.D.; H. Lee Moffitt Cancer Center, Tampa, FL.

The dose-escalation and pharmacokinetic/pharmacodynamic (PK/PD) analyses of a topoisomerase I (topo) inhibitor in combination with an alkylating agent and a topo II inhibitor were investigated. The drugs were

sequenced as: ifosfamide (IFOS) → topotecan (TPT) → VP-16. Plasma TPT levels were measured on the first and third day of administration and PK parameters calculated by model independent methods using WinNonlin™ software (Scientific Consulting). Forty-five patients were treated with 8 dose levels of TPT (10 to 85 mg/m^2 total dose). PK analyses of total TPT and lactone (HPLC) show a harmonic mean $t_{1/2}$ of 2.9 hours and 2.6 hours, median clearance of 14.0 L/h/m^2 and 30.4 L/h/m^2, and a median V_{dss} of 52.9 L/m^2 and 88.3 L/m^2, respectively. Median peak TPT concentrations (lactone) and AUC have ranged from 0.179 µM/0.24 µM•h (level 1) to 1.88 µM / 2.44 µM•h (level 8). Through dose level 5 (36 mg/m^2 total), TPT (total and lactone) has demonstrated linear and non-saturating PK. There were no differences observed between the first day and third day of administration. NHL patients demonstrated a significantly lower median TPT clearance of 12.4 L/h/m^2 (total, $p<0.039$) and a higher median AUC of 2.414 µM•h ($p<0.135$) compared to other patients. A linear regression model demonstrated a significant correlation between days of grade 3 or 4 mucositis and TPT systemic exposure (lactone AUC, $p<0.0001$). For time to platelet recovery (platelets > 50,000/uL, untransfused) a Cox's proportional hazards model demonstrated two significant risk factors: number of CD34+ cells/Kg infused ($p<0.0001$) and TPT systemic exposure (lactone AUC, $p<0.0190$).
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173E. Phase I trial of fusion toxin DTGM containing human GM-CSF fused to truncated diphtheria toxin in adults with relapsed or refractory acute myelogenous leukemia. *Philip D. Hall, Pharm.D.,* Dianna S. Howard, M.D., Gordon L. Phillips, M.D., Robert J. Kreitmen, M.D., Arthur E. Frankel, M.D.; Medical University of South Carolina, Charleston, SC; University of Kentucky, Lexington, KY; National Cancer Institute, Bethesda, MD; Wake Forest University, Winston-Salem, NC.

Although remission is inducible in the majority of patients with acute myelogenous leukemia (AML), only 25-35% of patients experience long-term disease-free survival even with aggressive post-remission therapy. The granulocyte-macrophage colony-stimulating factor receptor (GM-CSFR) is expressed on leukemic cells in 80% of the cases, but not on normal early hematopoietic progenitors. To target GM-CSFR, we have produced a fusion toxin consisting of the catalytic and translocation domains of diphtheria toxin (residues 1-388) fused to human GM-CSF, DT-GM. To determine if DTGM would be safe and effective in humans, we initiated a phase I trial in patients with relapsed or refractory AML. Sixteen patients, median age of 58 years (24-82), were treated with five daily 15-minute infusions of 1, 2, 3, or 4 µg/kg/day of DTGM. Twelve of the 16 patients were refractory, the remaining 4 patients were in first or greater relapse. Cytogenetic analyses were available in all but four patients. Multiple karyotypic abnormalities were observed in 9 of 12 patients; none associated with good risk. No patients have withdrawn early from the study for any adverse event. The majority of patients have experienced only grade one or two non-hematologic toxicity (common toxicity criteria, 2.0, NIH/NCI). A systemic inflammatory response syndrome (SIRS) characterized by transient fever, transaminasemia, third-spacing of body fluids, and elevations of interleukin-1 receptor antagonist and interleukin-6 was observed in four of six patients treated at 2 µg/kg/day. One patient experienced transient grade three vascular leak syndrome, but fully recovered within 7 days. SIRS was successfully prevented in six of seven patients subsequently treated at the 3 and 4 µg/kg/day dose levels using steroids. A transient grade four elevation of creatinine kinase (CK) in one patient treated at the 4 µg/kg/day dose level has been the only grade four non-hematologic toxicity. Transient complete or > 90% reductions in circulating blasts were documented in 8 of 13 evaluable patients. Additional patients are being enrolled to determine the maximum tolerated dose, and whether responses can be achieved with higher dose levels.
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Pediatrics

174. Frequency, causality and preventability of adverse drug events in pediatric patients. *Mary E. Temple, Pharm.D.,* Milap Nahata, Pharm.D., Julie C. Miller, Pharm.D.; Ohio State University; Children's Hospital, Columbus, OH.

PURPOSE: To evaluate the frequency, severity, causality, and preventability of adverse drug events (ADEs) in pediatric patients.
METHODS: Patient demographics, documented allergies, suspected drug and AHFS drug classification, dosage regimens, patient outcomes, and length of hospital stay (LOS) were obtained from medical records. ADEs were categorized by severity, type, causality, and preventability. Analysis was conducted by Chi-square and Wilcoxon rank sum tests.
RESULTS: During 1994-99, 565 ADEs were reported. Narcotic analgesics, anticonvulsants, and cephalosporin antibiotics were the most frequently implicated drug classes. Over one-half of the ADEs resulted in treatment intervention and/or temporary patient discomfort, and of these, 73% required drug therapy. Sixty-five percent of the ADEs were unexpected, 18.2% were from drug overdose, 15.6% were from an exaggerated effect of the drug, and 1.9% involved a drug interaction. Causality was classified as definite (43.7%), probable (50.1%) or possible (6.2%). Twenty-five percent of the reported ADEs were preventable and occurred most commonly during ordering (42.6%) and administration (31.2%). The most common error in both stages was a wrong dose. Increased length of hospital stay due to ADEs as compared to national geometric LOS accounted for about $2.3 million in hospital costs.
CONCLUSIONS: Adverse drug events resulted in treatment intervention in > 50% of patients. Preventable ADEs were most common with anticonvulsants and occurred at the ordering and administration stages. Our data should be useful in developing targeted programs to prevent ADEs and reduce associated costs in pediatric patients.

175. Antiepileptic hypersensitivity syndrome in children: 10-year experience. *Olga Bessmertny, Pharm.D.,* Randy C. Hatton, Pharm.D., Regino P. González-Peralta, M.D.; Shands Hospital and Section of Hepatobiliary Diseases; University of Florida, Gainesville, FL

PURPOSE: Antiepileptic hypersensitivity syndrome (AHS) is an idiosyncratic reaction to aromatic anticonvulsants that can result in severe multi-organ dysfunction and death. While these agents are frequently used to treat childhood neurologic diseases, little is known about AHS in children. Our aim was to assess the clinical features and outcome of childhood AHS.
METHODS: Children with suspected AHS (fever, rash, lymphadenopathy or liver dysfunction) were identified via a computerized adverse drug event reporting system. Medical charts of children with suspected AHS were reviewed.
RESULTS: Fourteen of 36 children met criteria for AHS (mean age 10.4 years; males:females, 8:6; Caucasian:African-American:biracial, 10:3:1). Seven patients were receiving phenytoin, six carbamazepine, and four phenobarbital alone or in combination. The average time from exposure to development of symptoms was 23 days. In addition to rash and fever (present in all by definition), other features of AHS were lymphocytosis (71.4%), elevated sedimentation rate (64.3%), elevated aminotransferases (64.3%), lymphadenopathy (50%), eosinophilia (42.8%), coagulopathy (42.8%), leukocytosis (35.7%), leukopenia (35.7%), hyperbilirubinemia (35.7%), nephritis (7.1%.) All children recovered except one, who died from complications of liver failure. Clinical outcome was similar between children who received systemic steroid therapy (n=5) and those who did not. Offending antiepileptics were discontinued in all patients; four children were switched to another aromatic anticonvulsant.
CONCLUSIONS: AHS can be fatal in children if not promptly recognized. Fever, rash, and hepatotoxicity should serve as presumptive evidence for AHS requiring immediate discontinuation of an offending anticonvulsant. Health care workers should be aware of significant cross-reactivity among aromatic anticonvulsants.

176. Risperidone in children with significant conduct problems and sub-average intellectual functioning. *Robert L. Findling, M.D.,* Michael G. Aman, M.D.; University of Cleveland Hospital, Cleveland, OH; Ohio State University, The Nisonger Center, Columbus, OH.

INTRODUCTION: The benefit of risperidone for severe conduct disorder in children with sub-average intellectual functioning was documented in a previous multi-center randomized, placebo-controlled study of short duration (6 weeks).
OBJECTIVE: To assess the long-term safety and efficacy of risperidone for conduct disorders in children with sub-average intellectual functioning.
METHODS: A 48-week, open-label study was conducted in 107 patients, between 5 and 12 years old, with sub-average intellectual functioning who had conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified, who had previously completed at least 2 weeks of the 6-week, double-blind, placebo-controlled, randomized study.
RESULTS: All patients received open-label risperidone at doses between 0.02 and 0.06 mg/kg/day. Statistically significant improvements over the double-blind, randomized study baseline occurred for on the primary efficacy variable—the conduct problem subscale of the Nisonger Child Behavior Rating Form (N-CBRF)—and in all other N-CBRF subscales as well, after 48 weeks. The three most common adverse events were somnolence, headache, and rhinitis.
CONCLUSION: Risperidone has a good overall risk-benefit profile and is effective for the long-term treatment of conduct disorder, disruptive behavior disorder and oppositional defiant disorder in children with sub-average intellectual functioning.

177. Use of intravenous nicardipine during hypertensive emergencies in critically ill pediatric patients. *Varsha Bhatt-Mehta, Pharm.D., FCCP,* Burgunda Sweet, Pharm.D., Christine Gadzinski; University of Michigan, Ann Arbor, MI.

PURPOSE: Nicardipine (N) is the first dihydropyridine calcium channel antagonist used intravenously (IV). It has been used effectively in adults with hypertensive emergencies (HE). Data on the safe and effective use in children are lacking. This study evaluated the safety and efficacy of IV N by continuous infusion in children with HE defined as systolic blood pressure (SBP) equal to or greater than 95th percentile for age. The goal of the study

was to identify the N dose that resulted in a 10% decrease in baseline SBP. A secondary objective was to evaluate the effect of IV N on diastolic blood pressure (DBP).
METHODS: Medical records of all pediatric patients 0-18 years of age, who were prescribed IV N between 6/96 and 12/98, were reviewed. Forty-one patients were identified. Thirty-two actually received the drug and were included in the study. Data collected included relevant hemodynamic, demographic and laboratory test information as well as N infusion-related data. Patients were divided into two groups for data analysis. Group A (GA) received N as sole treatment for HE and group B (GB) received N with other antihypertensive agents. Data were analyzed for time to reach goal SBP, IV N dose at goal SBP, and percentage of change in DBP at goal.
RESULTS: Ten patients (seven in GA and three in GB) did not respond to IV N. The results of the remaining 22 patients are presented as Mean ± SD in the table.

	Group A n=10	Group B n=12
Age (years)	6.48 ± 5.23	9.28 ± 7.18
Weight (kg)	23.56 ± 13.53	33.54 ± 25.33
Dose at goal(µg/kg/min)	1.07 ± 1.04	2.03 ± 1.39
Time to meet goal (hours)	9.4 ± 8.5	13.42 ± 14.30
Total infusion time (hours)	23.6 ± 18	73.33 ± 71.62
% change SBP at hoal	17.9 ± 9.5	14.08 ± 3.48
% change DBP at goal	17.8 ± 8.3	6.91 ± 11.1

CONCLUSION: IV N was safe and effective in the treatment of HE. No change in heart rate or any other adverse events were noted. The dose, time to meet to goal SBP, and total infusion time were lower in GA compared with GB indicating more malignant hypertension in the latter group.

178. Gastrostomy tube placement to improve adherence to therapy in HIV-infected children. *Mary E. Temple, Pharm.D.*, Katalin Koranyi, M.D., Michael Brady, M.D., Milap Nahata, Pharm.D.; Children's Hospital, Columbus, OH.

PURPOSE: Evaluate gastrostomy tube (G-tube) use in HIV-infected children experiencing difficulty with antiretroviral administration.
METHODS: A G-tube was inserted for antiretroviral medication administration in HIV-infected children experiencing difficulty with drug administration. Demographic data, weight, height, RNA load, CD_4 count, and quality of life (QOL) was assessed prior to and for 6 months following G-tube placement. The number of pills or volume of medication received by each patient was recorded. Wilcoxin rank sum test was used to determine the change in viral RNA load or CD_4 count.
RESULTS: Six HIV-infected children had G-tube placement. The average age at G-tube placement was 6.3 years. Children took an average of six medications, ten pills (range 1-28) and 11 ml (range 0.5-34 ml) of liquid medicine per day. Their QOL prior to G-tube placement was poor in all cases. Overall, average weight and height increased 19% and 7%, respectively. Viral load prior to G-tube placement ranged from undetectable to 691,430 copies/ml. After G-tube placement, the viral load was significantly reduced and ranged from undetectable to 2900 copies/mL. The parents reported full adherence to medication regimens, and rated their QOL as good to excellent after G-tube placement was done in their children. The G-tube was well tolerated by all six children. One child developed an abdominal wall abscess adjacent to the G-tube site.
CONCLUSIONS: The G-tube for administering medications improved patient adherence, QOL, and decreased viral RNA loads. Gastrostomy tubes are an option in children who experience difficulties with antiretroviral administration when other methods to improve adherence have failed.

179. Determination of an appropriate once-daily tobramycin dose for pediatric bone marrow transplant patients. *L. Lee Dupuis, M.S.Pharm., FCSHP*, Anna Taddio, B.S.Pharm., Ph.D., Lillian Sung, B.A., M.D., FRCPC, Mohammed Abdolell, B.S., M.S., Upton Allen, M.D., FRCPC, John Doyle M.D., FRCPC; Hospital for Sick Children, Toronto, Ontario, Canada.

PURPOSE: This study sought to determine the once-daily (OD) tobramycin (T) dose requirements of children undergoing bone marrow transplant (BMT).
METHODS: Parameters of T disposition were determined using a pre-existing database of children with febrile neutropenia secondary to antineoplastic agents. Data were fitted to a 1-compartment, 30-minute infusion model (WinNonLin 1.0). Mean disposition parameters were calculated and stratified by age, by diagnosis, and by transplant. These parameters were used to simulate the dose required by BMT patients to achieve a peak T concentration (C_{max}) of 22.5 mg/L and a time that the T concentration was < 1 mg/mL (TFI) of ≥ 4 hours.
RESULTS: Data from 112 febrile neutropenic episodes were included in the database. Twenty-three episodes occurred subsequent to BMT.

Patient Age (years)	n	Mean k_e ($hour^{-1}$) (95% confidence limits)	Mean Vd (L/kg) (95% confidence limits)
1 to < 5	47	0.332 (0.31 - 0.35)	0.299 (0.27 - 0.33)
5 to < 12	43	0.328 (0.31 - 0.35)	0.237 (0.20 - 0.27)
≥ 12	22	0.323 (0.30 - 0.34)	0.186 (0.15 - 0.22)

Children ≥ 12 years had a lower mean Vd compared to children 1 to < 5 years old, whereas mean k_e was unaffected by age. Simulation indicated that ODT doses of 9, 8, and 7 mg/kg/day would achieve the target parameters in most children undergoing BMT aged 1 to < 5, 5 to < 12, and ≥ 12 years, respectively. The mean simulated TFI ranged from 11.9 to 14.4 hours.
CONCLUSIONS: Under simulated conditions, ODT doses of 7 to 9 mg/kg/day achieved the target parameters in pediatric BMT patients. These guidelines require prospective clinical evaluation.

180. The safety and antiviral effect of protease inhibitors in HIV-infected pediatric patients. Mary E. Temple, Pharm.D., Katalin I. Koranyi, M.D., *Milap C. Nahata, Pharm.D.*; Ohio State University and Children's Hospital, Columbus, OH.

PURPOSE: Determine the safety and antiviral effect of protease inhibitors (PIs) in HIV-infected pediatric patients.
METHODS: The demographics, dosage regimens, genotype data, compliance, viral RNA and CD_4 counts, adverse drug events (ADEs), and laboratory tests were evaluated over 3 years. Chi Square, ANOVA, repeated measures and paired t tests were used to analyze the data.
RESULTS: Twenty-one pediatric patients (age 3 months to 15 years) were enrolled. The average daily doses for ritonavir (n=12) was 26 mg/kg, nelfinavir (n=16) 94 mg/kg, indinavir (n=5) 49 mg/kg, and saquinavir (n=4) 43 mg/kg. Five patients developed resistance to an existing PI. Overall compliance was 70%. Baseline log RNA counts were significantly higher than average follow-up RNA counts during 3-36 months in patients taking ritonavir ($p<0.001$) and nelfinavir ($p<0.001$). Sample size was insufficient for indinavir or saquinavir. Sixty ADEs occurred and diarrhea was the most common. Patients with ADEs required increased monitoring in 55%, and treatment intervention in 43% of the cases. Ritonavir was associated with the most ADEs (28), followed by nelfinavir (16), indinavir (11), and saquinavir (5). A significant increase between baseline and follow-up cholesterol levels was found with ritonavir ($p=0.02$), and nelfinavir ($p=0.001$) and for serum creatinine ($p=0.02$) and triglycerides ($p=0.02$) with ritonavir. Follow-up triglycerides were significantly higher than baseline for indinavir ($p=0.003$).
CONCLUSION: Nelfinavir and ritonavir were effective in decreasing viral loads and improving CD_4 counts. Ritonavir caused more ADEs than other PIs. Different PIs were associated with different laboratory abnormalities.

181E. Effects of intravenous erythromycin on gallbladder contractility in preterm neonates. *Irving Steinberg, Pharm.D.*, Katrina Tesmer, M.D., Manuel Durand, M.D., Frank R. Sinatra, M.D.; University of Southern California, Los Angeles, CA.

PURPOSE: TPN-associated cholestasis is thought, in part, to be due to a lack of recirculation of bile acids in non-enterally fed newborns. Erythromycin (ERY) has been demonstrated to enhance gastric and gallbladder (GB) emptying at low doses due to its motilin receptor stimulation. In this pilot study, we examined the existence and magnitude of GB contractility, and the ERY dose-effect relationship in preterm neonates.
METHODS: Parenterally fed, premature neonates (n=30) 26-37 weeks gestational age (GA) were evenly randomized to receive either saline, 1 mg/kg or 4 mg/kg intravenous ERY by short intravenous infusion. Measurements of GB volume (GB) were performed by ultrasound at baseline and 0, 30, 60, 90, and 120 minutes after infusion. GB was calculated using the biplane ellipsoid formula. Percent differences from baseline were calculated for each timed measurement, and means, medians and ranges were summarized for each group. Kruskal-Wallis and Mann-Whitney U-tests were used for group comparison; ANOVA $p<0.1$ was used to further explore between-group comparisons.
RESULTS: GA (30.9 ± 2.3 weeks) and birthweight (BW = 1509 ± 320 g) did not differ among the groups. Baseline GB ranged 7-14 fold within the groups. Decreases in GB were seen for the 1 mg/kg group at 0, 30 and 60 minutes in seven, six, and six patients, respectively, with five at each time-point having a ≥ 20% decrease from baseline. Only one patient in the 4 mg/kg had a ≥ 20% decrease in GB group at these time-points. At 30 minutes, differences in percent change from baseline between the 1 mg/kg (-19.7 ± 37.3) and saline (15.3 ± 39.4; $p=0.041$) groups, and between the 1 mg/kg and 4 mg/kg (11.7 ± 30.0; $p=0.059$) groups were observed (ANOVA $p=0.088$). Additionally, significant positive correlations were found between %GB differences and BW in the 4 mg/kg group at 0 ($r=0.707$), 30 ($r=0.895$), and 60 minutes ($r=0.798$) post-dose; no other significant correlations were observed.
CONCLUSION: Similar to observations in adults, ERY causes GB contractility in premature neonates, but only at lower doses. At higher doses, cholinergic responses distal to the GB may dominate, causing increases in GB; these responses, but not the motilin-agonist effect, were associated with BW. Further studies are required to better define the ontogeny of motilin and cholinergic gastrointestinal responses to erythromycin in neonates.
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182. Drug-related problems in pediatrics: an Australian perspective. *Kylie L. Easton-Carter, B.Pharm., Bpharm.Sci(Hons).*, Colin B. Chapman, Ph.D., Jo-anne E. Brien, Pharm.D.; Victorian College of Pharmacy, Monash University, Melbourne, Australia; University of Sydney and St Vincent's Hospital, Sydney, Australia.

PURPOSE: To determine the frequency and preventability of emergency department (ED) attendances and hospital admissions associated with drug-related problems (DRPs) at the Royal Children's Hospital (RCH), Melbourne, a tertiary referral pediatric teaching hospital in Australia.
METHODS: All unplanned medical patients attending the RCH ED over an 11-week period of data collection or admitted to hospital over a separate 20-week period were considered for inclusion. The investigator and the attending medical practitioner or clinical pharmacist screened eligible patients. A multidisciplinary panel reviewed collated data and causality, preventability and clinical significance classifications, according to prospectively determined criteria, were established for each case.
RESULTS: Of the 7956 eligible patients attending the ED during data collection, 244 fulfilled study criteria. The frequency of ED attendances associated with DRPs was 3.07%. Preventability was assessed for 170 of the 244 cases as per the study protocol. Eighty-nine cases (52%) were determined to be preventable. Of the 2745 eligible patients admitted to hospital during data collection, 121 fulfilled study criteria. The frequency of hospital admissions associated with DRPs was 4.41%. Preventability was assessed for 75 of the 121 cases as per the study protocol. Thirty-five cases (46.7%) were deemed preventable. The drugs involved were different from those reported in DRP studies in adults.
CONCLUSIONS: In this study a high percentage of ED attendances and hospital admissions were preventable. Prevention strategies developed from adult populations may not be applicable in pediatrics.

Pharmacoeconomics/Managed Care/ Health Services Research

183. Economic evaluation of the study of cardiovascular risk intervention by pharmacists (SCRIP). *Scot H. Simpson, Pharm.D.,* Jeffrey A. Johnson, Ph.D., Ross T. Tsuyuki, Pharm.D., M.S.; University of Alberta, Edmonton, Canada.

BACKGROUND: The study of cardiovascular risk intervention by pharmacists (SCRIP) was a randomized trial conducted in over 44 western Canadian community pharmacies. The main study was designed to evaluate the efficacy of an intervention program by community pharmacists, working in collaboration with patients at high risk of cardiovascular disease and their family physicians, to improve management of cholesterol risk.
PURPOSE: To identify the added costs for providing this intervention program in view of its effectiveness.
METHODS: Cost and consequence analyses were used to characterize the value of this health care program. Change in Framingham Risk score for the intervention group from baseline to final follow up was used to measure effectiveness. Resource utilization data (physician visits, cholesterol panels, and new cholesterol-lowering medications) were collected during follow-up visits and through a patient questionnaire. Economic perspectives of a government-funded health care system and the pharmacy manager were used.
RESULTS: Data reported here are based on an interim analysis of 565/675 patients enrolled. Main study terminated early for benefit. In the intervention group, 10-year risk of cardiovascular disease, estimated by the Framingham Risk score, decreased from 17.4% to 16.5% (p=0.001) over the four-month follow-up period. There were also significant reductions in total cholesterol (5.02 ± 1.02 to 4.87 ± 0.89; p=0.013) and systolic blood pressure (140 ± 18 to 138 ± 18; p=0.039). The incremental cost to a government payer to provide the intervention was $6.08 per patient and to the pharmacy manager was $21.76 per patient.
CONCLUSION: Based on this interim analysis, the pharmacist intervention program in SCRIP significantly reduced cardiovascular risk during the four-month follow-up period. The incremental cost for providing this program appeared to be minimal.

184. Cost effective management of cholesterol in patients with cardiovascular disease. *Lisanne DiTusa, Pharm.D.,* Aileen B. Luzier, Pharm.D., Mara Poulakos, Pharm.D., Marc Reinhardt, Brian Snyder, M.D.; University at Buffalo; SUNY; Promedicus Health Group, Buffalo, NY.

PURPOSE: To determine the clinical and economic impact of a pharmacy-based cholesterol management program.
METHODS: From January 1999, to December 1999, we enrolled patients with documented cardiovascular disease in a pharmacy-based cholesterol management program at our managed care facility. A similar group of randomly selected patients who were receiving usual care during the same time period served as the comparator group. The following were collected for both patient groups: patient demographics, co-morbidities, fasting lipid profiles (FLP), cholesterol medication and cost of cholesterol medication. Cholesterol management was assessed at initial enrollment (baseline) and during a 12-month follow-up period. Chi-square and Kruskal-Wallis tests were used to compare the groups with respect to proper evaluation of cholesterol, the number of patients who reached low-density lipoprotein cholesterol target, cost of therapy and appropriateness of follow-up monitoring.
RESULTS: Overall, there were 300 patients enrolled in the program and 100 patients receiving usual care, mean age 68 and 71 years, respectively. Cholesterol management improved significantly in program patients as described in the following table:

	Baseline		Follow-up	
	Program	Usual Care	Program	Usual Care
FLP monitoring	51%	63%	97%	49%*
Treated with medication	60%	43%	72%	51%
At LDL cholesterol target	43%	35%	61%	45%*

*$p<0.05$ for program versus usual care

A greater increase in mean drug costs was observed with usual care; $2 and $6 per patient per month for program and usual care patients, respectively.
CONCLUSION: The pharmacy-based cholesterol management program resulted in substantial improvement in the management of cholesterol with minimal increase in drug costs.

185. Telehealth attainment of lipid goals through automated workflow technology. *Mary Bloome, R.Ph.,* Rick Saier, M.D., Tom Bronken, M.D., Barbara Zarowitz, Pharm.D., FCCP, BCPS; Henry Ford Health System, Detroit, MI.

PURPOSE: An opportunity exists to increase the percentage of coronary artery disease (CAD) patients reaching their target low-density lipoprotein (LDL)-cholesterol goal.
METHODS: A pharmacist-run lipid clinic was established to identify, educate, monitor and manage patients with the diagnosis of CAD, on drug therapy, and having two consecutive LDL-cholesterol values not at goal. Under delegated authority, pharmacists order laboratory tests and titrate medications to ensure achievement of LDL-cholesterol goals. Patients are counseled on lifestyle modifications, with emphasis on adherence to drug therapy and detection and management of medication side effects. Most of the patient interaction occurs by telephone. Automated workflow technology was developed as an integrated component of the electronic medical record. The program notifies the pharmacist of laboratory results or lack of laboratory compliance, identifies patients for enrollment, uploads clinic progress notes into the medical record, and creates patient letters based on test results or scheduled laboratory tests.
RESULTS: Following 1 year of lipid clinic operation, 72.7% of enrolled CAD patients (n=479) have achieved or are within 10 points of their LDL-cholesterol goal compared to 31% at baseline. Both physician satisfaction and patient demand have increased. Pharmacist efficiency has increased to enable management of 575 patients, up from 250 during a program pilot in 1997.
CONCLUSIONS: Establishment of a telehealth lipid clinic, supported through workflow technology, was successful in increasing the percent of CAD patients achieving their LDL-cholesterol goal significantly above national averages of 18-24%.

186. Evaluation of a pharmacist-managed erythropoietin program at Kaiser Permanente. *Rita L. Hui, Pharm.D., M.S.,* James Chan, Pharm.D., Ph.D., Leonie Wohl, B.Pharm.; Kaiser Foundations Hospitals, Oakland, CA.; Kaiser Permanente Medical Center, South San Francisco, CA.

PURPOSE: The purpose of this study is to assess the clinical and economic impact of a pharmacist-managed erythropoietin clinic compared to usual care using a retrospective cost consequence analysis.
METHOD: Pre-dialysis patients receiving erythropoietin therapy managed by a pharmacist were compared to a matching group of patients on erythropoietin therapy managed the usual way. The matching group was based on age, gender, cause of anemia, baseline creatinine, hematocrit and transferin saturation. They were selected at a 5:1 ratio to minimize systematic error. Outcomes measures included maintenance of hematocrit > 32%, time before dialysis, mortality, anemia-related hospitalizations, anemia-related laboratory utilization, transfusions, erythropoietin and iron costs, office visits, urgent care visits, emergency department visits, and overall costs. Doctor visits, drug costs, and overall costs were adjusted for age, gender, prior utilization, and comorbidities. The follow-up time was 9 months. Time before dialysis was analyzed using Cox proportional hazard model.
RESULTS: There were 155 pharmacist-managed patients and 785 in the matching group. A significantly greater proportion of study patients had a hematocrit > 32% at 3 months (51% vs 37%, p<0.001) and at 6 months (39% vs 30%, p=0.03). They also had fewer office visits (p<0.001) but no difference in other outcomes measures. There was a trend toward a longer time before dialysis in study patients (Hazard ratio = 0.71, p=0.052).
CONCLUSION: Erythropoietin patients managed by pharmacists have better mean hematocrits, fewer offices visits and may have a longer time before dialysis compared to those managed by usual care. No differences in drug costs and overall costs were found.

187. Utilization of antipsychotic medications in the treatment of schizophrenia in a managed care population. *Michael B. Nichol, Ph.D.,* Ann S. M. Harada, MPH, Jason P. Jones, M.S., Jeffrey S. McCombs, Ph.D., Amy Grogg, Pharm.D., Alex Gilderman, Pharm.D., Jerome V. Vaccaro, M.D.; Pharmaceutical Economics and Policy, USC, Los Angeles, CA; Janssen Pharmaceutica, West Trenton, NJ; Prescription Solutions, Costa Mesa, CA; PacifiCare Behavioral Health, Inc., Van Nuys, CA.

PURPOSE: The purpose of this study was to document the treatment experience of patients with schizophrenia in a managed care population.
METHODS: This study utilized an administrative claims database from PacifiCare Health Systems and PacifiCare Behavioral Health, Inc. Claims from January 1, 1995 to September 1, 1999, for California, Texas, Oklahoma, Washington and Oregon were evaluated with an intent-to-treat analysis. Only adults with a schizophrenia diagnosis made within ± 6 months of treatment start, prescription treatment starting after 1995, ≥ 6 months prior eligibility, and no antipsychotic use in the 120 days before treatment start (washout period) were included.
RESULTS: Only 27 (2%) of the 1096 patients qualifying for this analysis, initiated treatment using ≥ 2 antipsychotics simultaneously. Of the 1069 initiating monotherapy, 624 (58%) began therapy on a conventional medication, while 445 (42%) started on an atypical medication. Patients starting on a conventional medication were 52% more likely to be switched to an atypical agent after 1 year than those initiating on an atypical being switched to a conventional agent (p=0.011). No difference was found in time to discontinuation by antipsychotic type (p=0.518). Roughly 50% in both groups had discontinued antipsychotic medication use by the first 100 days; 70% by 365 days.
CONCLUSION: Antipsychotic medication discontinuation rates increase rapidly in the first year of treatment regardless of the type of antipsychotic initiated. The more recent availability of several newer atypical medications and an increasing difference between the rates of switches from conventional to atypical as opposed to atypical to conventional may be confounding the discontinuation intent-to-treat analysis.

188. Medication information needs assessment of patients. *Reem Haj, B.S.Phm.*, Tom Chin, Pharm.D.; Heart and InnerCity Health Programs, St. Michael's Hospital; University of Toronto, Toronto, Ontario.

A general hospital survey indicated our patients were dissatisfied with health care information received in the hospital. Given the importance of medication information and that patients have different perceptions of what information is important, we evaluated the medication information needs of patients.
This was a prospective study consisting of survey development, pilot and study phases, conducted over a 14-week period. The survey tool utilized a five-point Likert scale to obtain opinion on 51 items regarding medication information needs. All eligible patients discharged from two medicine and two cardiology in-patient units were requested to complete the survey. Descriptive statistics were used to summarize the data.
A total of 415 surveys were distributed with 204 returns (49%), of which 115 were analysed as 89 were refusals. Average age of patients was 64 ± 14 years; 59% respondents were male. Forty-nine percent of patients reported being discharged on one to four medications. Patients ranked (out of five) highly the importance of the following components of medication information: purpose (4.77), benefits (4.67), side effects (4.63) drug interactions (4.62) and risks of not taking (4.52). They identified the need to learn more about medications, especially risks of drug interactions and non-compliance. Most preferred choice for receiving information was verbal and written, with Internet, hotline or videos ranked lower. Although pharmacists documented interaction with > 60% of patients, only 40% patients recalled they had interactions during their stay.
Patients reinforced the importance of the five areas of medication information which should be emphasized during counselling. Verbal and written information remains the main vehicle for communication for this patient group. Pharmacists need to promote their role and visibility to patients.

189E. Algorithm for the treatment of hypertension: what determines its utilization? *Shimuna Yosselson-Superstine, Pharm.D., MPH, BCPS*; Tel Aviv University, Israel.

An attempt was made to associate the characteristics of physicians and patients with the use of the guidelines for the treatment of hypertension.
Two hundred four hypertensive patients treated by 25 different physicians were interviewed on three separated occasions about different aspects of medical care received upon their last visit to their doctor. The questions focused on utilization of services drug therapy and the content of physician-patient encounter. The characteristics of the physicians correlated with the above aspects of medical care were sex, age, country of birth and study of medicine, and length of practice. The most prescribed hypertensive agents in descending order were β-blockers, diuretics, calcium channel blockers and angiotensin converting enzyme inhibitors. No antihypertensive drugs were prescribed to 20% of the patients. Non pharmacologic therapy was more prevalent in patients whose doctors were males, who studied medicine in a western country. Diet was more frequently recommended by female physicians while physical activity was more frequently recommended by male physicians. Drug information and instructions were given more by the young doctors, while drug compliance was more frequent than expected among patients whose doctors were older and from east Europe.
Presented at the Annual Meeting of the Israeli Society of Clinical Pharmacy and Biopharmacy, June 7, 2000.

190E. Comparative effects of carvedilol and metoprolol on the health economic outcomes in patients with chronic heart failure. *Aileen Luzier, Pharm.D.*, Laura A. Antell, MBA, MPH, Li-Ling Chang, Ph.D., M.S., Jianwei Xuan, Ph.D., M.S., David A. Roth, M.D., M.S.; University of Buffalo, Buffalo, NY; SmithKline Beecham, Health Economics and Outcomes Research, Collegeville, PA.

PURPOSE: Both selective and nonselective β-blockers have shown favorable effects in individual heart failure (HF) trials but whether large comparative studies will demonstrate any advantage of agents with multiple receptor blockade, over single receptor blockade, will be unknown for at least another year; therefore, a retrospective, reimbursement claims analysis was conducted to compare the health and economic outcomes in HF patients receiving metoprolol, a selective β_1-receptor inhibitor, or carvedilol, which inhibits β_1-, β_2-, and α_1-adrenergic receptors.
METHODS: Clinical and economic data were extracted for patients with a HF diagnosis in a carvedilol or metoprolol group for 6 months after the index date, using claims submitted to six plans between June 1997 and 1998. Differences between groups were tested with Chi square and Wilcoxon rank sum tests. Stepwise logistic regression was used to measure the influence of baseline variables on medical and total costs. A modified Charleson's index was used to assess comorbidity.
RESULTS: Claims from 139 carvedilol and 106 metoprolol patients showed that carvedilol patients experienced significantly fewer hospitalizations (36% vs 51%; p=0.005) and emergency room visits (24% vs 42%; p=0.0018); filled significantly more prescriptions for carvedilol than metoprolol (mean: 5.2 vs 4.4; p=0.0018); reported significantly higher pharmacy costs (mean: $1677 vs $1322; p<0.001) but significantly lower medical (mean: $6424 vs $13,153; p<0.0001); hospitalization (mean: $4563 vs $10,685; p=0.0046) and total (mean: $8100 vs $14,475; p=0.0249) costs.
CONCLUSION: A retrospective reimbursement claims analysis suggests that carvedilol, which inhibits β_1-, β_2-, and α_1-adrenergic receptors, may offer clinical and economic benefits over metoprolol, a selective β_1-receptor inhibitor.
Presented at the 2000 Educational Conference of the Academy of Managed Care Pharmacy, San Diego, CA, October 4-7, 2000.

191. Clinical and economic outcomes of antihypertensive drug therapy in a managed care organization. *T. Jeffrey White, Pharm.D., M.S.*, Eunice Y. Chang, Ph.D.; Prescription Solutions, Costa Mesa, CA.

PURPOSE: The purpose of this study is to determine the relationship between antihypertensive medication compliance and hypertension-related events (e.g., myocardial infarction, stroke, and aneurysm).
METHODS: Pharmacy and medical databases from a large managed care organization were analyzed. Patients were included if they were newly diagnosed with hypertension. Clinical and economic outcomes were assessed over a 3-year period. A medication possession ratio (MPR) was calculated as a measure of compliance.
RESULTS: There were 2902 patients identified for the study cohort and 2223 (77%) received antihypertensive therapy. The mean age was 65.8 (SD = 9.8) and 55.9% were female. For patients who received antihypertensive therapy, the mean MPR was 0.77 (SD = 0.27). After controlling for confounding variables such as age, gender, previous health care costs, and previous hypertension-related events, the adjusted total costs over the follow-up period for MPRs of 0-0.5, 0.5-0.9, and > 0.9 were $16,680, $22,592, and $18,892, respectively (p<0.001). Patients with a MPR of 0.5-0.9 were more likely to experience a hypertension-related event compared to patients with a MPR of > 0.9 (OR = 1.58, 95% CI = 1.12, 2.22). Patients not maintained on one drug class for greater than 70% of their therapy were more likely to experience a hypertension-related event (p=0.003) and incur higher total costs (p=0.008).
CONCLUSIONS: In this population, patients who were more than 90% compliant had lower total health care costs and fewer hypertension-related events compared to those who were 50-90% compliant. Clinical and economic outcomes were dependent on the drug class.

192E. Shorter hospital length of stay for coronary angioplasty patients who receive abciximab versus eptifibatide or tirofiban. Maureen J. Lage, Ph.D., Beth L. Barber, Ph.D., Joel Scherer, M.D., *Patrick McCollam, Pharm.D.*; Miami University, Miami, FL; Lilly Research Laboratories, Eli Lilly & Co., Indianapolis, IN.

OBJECTIVES: The purpose of this study is to examine the effect of treatment with abciximab versus eptifibatide or tirofiban during angioplasty on hospital length of stay (LOS).
METHODS: Hospital billing data for PTCAs performed over a 1-year period (July 1998 to June 1999) was obtained from HCIA's clinical pathways database. Data were collected for all patient discharges whose records indicated use of abciximab, eptifibatide, or tirofiban. Results are reported for 6637 patients. Multivariate analysis was used to control for a wide range of factors (patient demographics, insurance, health conditions, admission and discharge information, as well as hospital characteristics) which may influence LOS. Estimation was conducted via a two-stage sample selection model. The first stage of the analysis utilizes a probit regression to determine the factors associated with the likelihood of receiving abciximab. In the second stage of the analysis, a negative binomial model is estimated for

patients' LOS, while controlling for unobserved factors that are correlated with the patients' likelihood of receiving abciximab.
RESULTS: The average LOS for PTCA patients was 3.48 days. After controlling for high-risk indications and selection bias, PTCA patients who were given abciximab had a significantly shorter LOS than patients who were administered eptifibatide (0.981 fewer days ± 0.243) or patients who were administered tirofiban (0.934 fewer days ± 0.251).
CONCLUSIONS: Results of this study indicate that there are potential cost off-sets for hospitals that administer abciximab versus eptifibatide or tirofiban, given the significantly shorter LOS associated with patients who received abciximab.
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193. Reductions in productivity loss following oral sumatriptan during a migraine attack. *W. Jacqueline Kwong, Pharm.D.*; University of North Carolina at Chapel Hill, Chapel Hill, NC; Glaxo Wellcome Inc., Research Triangle Park, NC.

OBJECTIVE: To estimate the effect of oral sumatriptan versus usual non-triptan therapy on productivity loss reported by migraine sufferers during a migraine attack.
METHODS: Diary data recorded by 251 subjects participating in an open-label, clinical trial conducted in 21 centers across the U.S. were analyzed using random effects generalized least squares regression analysis. Subjects used their usual non-triptan therapy to treat migraine attacks for 2 months, and sumatriptan 100 mg to treat migraine attacks for the following 4 months. Data from 6803 treated migraine days were available for analysis. Overall productivity loss was estimated on a treated migraine day basis using a summary measure to aggregate time missed from work and non-work activities, as well as reduced effectiveness while working with migraine symptoms. Subject demographics, baseline pain severity, and the need for rescue medication were controlled for in the model.
RESULTS: As compared with usual non-triptan therapy, oral sumatriptan significantly reduced overall productivity loss by 0.94 hours per treated migraine day ($p<0.001$). Treating migraine when the pain was mild and moderate further decreased overall productivity loss by an additional 2.35 hours and 1.54 hours, respectively ($p<0.001$). The use of rescue medication within 2 hours and 4 hours was associated with increases in overall productivity loss of 0.53 and 1.70 hours, respectively, ($p<0.001$).
CONCLUSION: The results confirmed previous findings that oral sumatriptan significantly reduced productivity loss as compared to usual non-triptan therapy, and suggested that treating a migraine early before it progressed to severe pain reduced productivity loss.

194. Dalteparin versus enoxaparin for the treatment of deep vein thrombosis: a cost-effectiveness decision model. *Lori C. Dupree, Pharm.D.*, Donald F. Brophy, Pharm.D., BCPS, Michael A. Crouch, Pharm.D., BCPS, David A. Holdford, Ph.D.; Virginia Commonwealth University-MCV Campus, Richmond, VA.

PURPOSE: To compare the cost-effectiveness of dalteparin to enoxaparin for the treatment of deep venous thrombosis (DVT).
METHODS: From an institutional perspective, a decision-analysis model was constructed to assess the costs and consequences of DVT treatment with dalteparin (200 IU/kg subcutaneously daily x 5 days) compared to enoxaparin (1 mg/kg subcutaneously twice-daily x 5 days) for the treatment of DVT. The model incorporated safety and efficacy data from published clinical trials of similar design and duration. Treatment and adverse event costs were based on flat-fee, diagnosis-related group (DRG) reimbursement data; drug costs were based on average wholesale price (AWP). The primary outcome measure was the total cost of therapy per successful DVT treatment with either agent. A two-way sensitivity analysis was conducted on the efficacy and adverse event rates to assess their robustness to change.
RESULTS: Safety and efficacy rates are similar for dalteparin and enoxaparin, while dalteparin's AWP is relatively less expensive. Based on these values, dalteparin appears to be more cost-effective than enoxaparin for the successful treatment of DVT ($7425 vs $7752, respectively). When the two-way sensitivity analysis decreased dalteparin's efficacy by 4%, and increased its adverse event rate to that of enoxaparin, there was equivalent cost-effectiveness between regimens.
CONCLUSION: The decision-analysis model suggests that dalteparin is the more cost-effective agent for the treatment of DVT, with an estimated savings of $327 per patient. This is due principally to its lower acquisition cost.

195. Net cost analysis of aprotinin in patients undergoing coronary artery bypass graft surgery. *Santanu K. Datta, MBA*, Joseph Lipscomb, Ph.D., Gregory Samsa, Ph.D., Thomas Yuran, Pharm.D.; National Cancer Institute; Bayer Corporation; Duke Center for Clinical Health Policy Research, Durham, NC.

PURPOSE: The purpose of our research was to assess the tradeoff between the cost of aprotinin and the cost saving benefits that it may provide to coronary artery bypass graft (CABG) patients from a hospital's perspective.
METHODS: Multivariable regression modeling was conducted using clinical, resource utilization and cost data on 2481 patients who received CABGs at Duke University Medical Center between July 1993 and October 1997, to estimate unit costs of resources utilized and incremental costs of complications experienced during the admission for CABG. These resource utilization and complication costs were combined with clinical and resource utilization costs of patients who participated in five clinical trials for aprotinin.
RESULTS: In 1995 dollars, the incremental costs of complications were estimated to be $831 for reoperations, $351 for strokes and $960 for acute myocardial infarctions. For primary CABG patients, the total peri-operative cost was estimated to be $23,621 for those who received a full dose of aprotinin, $24,778 for those who received a half dose of aprotinin and $23,495 for placebo. For repeat CABG patients, the peri-operative costs were $27,576 for full-dose, $27,989 for half-dose and $29,777 for placebo.
CONCLUSIONS: The use of aprotinin among repeat CABG patients is cost saving ($2201 for full-dose aprotinin and $1788 for half-dose aprotinin). Among primary CABG patients, all but $126 of the cost of full-dose aprotinin is recouped through decreased resource utilization, whereas half-dose aprotinin is associated with $1283 of increased resource utilization. Hospitals must be aware of the clinical and economic relationship between CABG surgery and aprotinin dose.

196. Cost-minimization analysis of early, elective cardioversion guided by transesophageal echocardiography followed by early hospital discharge for the acute management of atrial fibrillation. *Robert J. DiDomenico, Pharm.D.*, Joel Fain, Ph.D., Jerry L. Bauman, Pharm.D., FCCP; University of Illinois at Chicago, Chicago, IL; Pharmacia, Peapack, NJ.

PURPOSE: Early cardioversion of atrial fibrillation (AF) guided by transesophageal echocardiography (TEE) has been shown to be safe and effective and may facilitate early hospital discharge. Therefore, we performed a cost-minimization analysis comparing a more aggressive treatment strategy that utilizes TEE-guided cardioversion and early hospital discharge with conventional therapy for acute AF.
METHODS: A computer-based decision model was developed to compare aggressive management of AF (TEE-guided cardioversion, 23 hour observation, and outpatient anticoagulation with dalteparin) with conventional therapy (hospital admission for rate control and anticoagulation followed by readmission for elective cardioversion). A cost-minimization analysis was then performed to compare the overall total costs for each treatment strategy from the perspective of a third party payer. Univariate and multivariate sensitivity analyses were performed on all economic variables, event probabilities (rates of cardioversion, incidence of complications) and other model-specific variables.
RESULTS: Aggressive management of AF was associated with a cost savings of $1546 compared to conventional therapy ($2816 vs 4362, respectively). Total costs in the aggressively managed cohort were less than conventional therapy in all univariate sensitivity analyses. The cost savings associated with the aggressive approach were lost when the cost of TEE was increased, daily hospital bed costs were decreased, and when LOS for AF in patients managed conventionally was decreased. Rates of cardioversion and complications were similar in both groups.
CONCLUSION: This analysis suggests that an aggressive treatment strategy for AF that employs TEE-guided cardioversion and early hospital discharge reduces the overall costs compared to conventional therapy secondary to abbreviated hospital stays.

197. The clinical and economical assessment of alteplase versus urokinase in peripheral arterial occlusion. *Krista A. Piekos, Pharm.D.*, Raymond Farmer, Pharm.D., Daniel Croteau, M.D., Barbara Purdon, R.N., Monty Harvill, M.D., Scott Sturza, M.D., Clifford Crabtree, R.Ph., MBA, Eric Racine, Pharm.D.; Harper Hospital, Detroit Medical Center, Detroit, MI.

PURPOSE: The unavailability of urokinase forced our institution to adopt a new protocol, using alteplase for treating patients with peripheral arterial occlusions (PAO). This study analyzed outcomes data for patients who received alteplase as an alternative to urokinase, by comparing 1) cost of thrombolytic therapy; and 2) outcomes data between the groups.
METHODS: A retrospective review of medical records for patients who received urokinase for PAO in 1998 was preformed. Patients receiving alteplase for PAO were prospectively followed. Cost of thrombolytic therapy, total hospital length of stay (LOS), ICU LOS, success rates, and adverse events were documented.
RESULTS: To date, 25 urokinase cases, and 19 alteplase cases have been reviewed. Institution of this protocol revealed significant cost savings when using alteplase, as compared to urokinase ($6207 per case for UK vs $811 for alteplase, $p<0.001$). There was no difference in total LOS between the groups (9.28d vs 9.3d, $p=0.99$). There was trend toward a shorter ICU LOS in the alteplase group; however, it did not reach statistical significance (3.7d vs 2.75d, $p=0.12$). This could potentially be attributed to a significantly shorter infusion time required with alteplase (37 hours for UK vs 19 hours for alteplase, $p<0.001$). Successful thrombolysis was achieved in 14/25 (56%) UK patients, and 13/19 (68%) alteplase patients ($p=0.40$). Bleeding events were similar (5 vs 6, $p=0.41$). One event was classified as a major bleed.
CONCLUSIONS: Alteplase may be a safe, efficacious, and economical alternative to urokinase for treating patients with PAO.

197A. Comparison of preoperative skin preparation products. *Edward P. Armstrong, Pharm.D.*, Kristin L. Patrick, Pharm.D., Brian L. Erstad, Pharm.D.; University of Arizona, Tucson, AZ.

PURPOSE: The purpose of this study was to compare the user satisfaction and cost (using cost minimization analysis) of four preoperative skin preparation products based on the products' application, drying and removal times.
METHODS: After obtaining IRB approval, a total of 25 operating room personnel and 25 patient volunteers were recruited to participate in this study. Each of the operating room personnel was paired with one of the patient volunteers. Investigators then recorded the application, drying and removal times of the four skin preparation products. Operating room personnel who applied the products were then asked to complete a user satisfaction survey. Application and drying times, along with product costs, were used for the cost minimization analysis.
RESULTS: The application and drying times were longest ($p<0.05$) with the povidone iodine paint and scrub product and shortest ($p<0.05$) with a povidone iodine/alcohol product (Prevail™). Removal times were variable between and within groups with statistically significant differences found between various combinations of products. The questionnaire results revealed povidone iodine paint and scrub had the highest rating based on overall user satisfaction. Cost minimization analysis revealed that although the quicker drying, alcohol-containing products had lower overall costs, the savings may not outweigh the safety risks (i.e., operating room fires) associated with their use.
CONCLUSIONS: Despite povidone iodine having slightly longer application and drying times, it was the most favored product among operating room personnel. Cost differences favored the alcohol-containing products but the safety of these products remains a concern.

Pharmacoepidemiology

198. Acute coronary syndrome management in 45 U.S. hospitals. *Francesca Venturini, Pharm.D., M.S.*, Alan Hopefl, Pharm.D., Kathleen A. Johnson, Pharm.D., Ph.D.; Farmacia Interna, Policlinico G.B. Rossi, Verona, Italy; Amerinet, St. Louis, MO; University of Southern California, Los Angeles, CA.

PURPOSE: In the past few years, rapid progress has been made in the management of patients with acute coronary syndrome (ACS), and some new recommendations have emerged regarding the use of troponin as a diagnostic and prognostic tool, the use of low-molecular weight heparin, and of the new class of antiplatelet agents in addition to aspirin. The objective is to compare past treatment patterns with the new recommendations on ACS patients management.
METHODS: The study was a multi-center survey carried out in 45 U.S. hospitals belonging to the Amerinet network during the period of November 16, 1998 to March 1, 1999. Data were prospectively collected by clinical pharmacists on consecutive patients with a diagnosis of either unstable angina or non-Q-wave myocardial infarction at admission, during the hospital stay or at discharge.
RESULTS: In the participating hospitals (36 community and 9 teaching) 1178 patients were recruited (41.2% female, mean age 68.7 years). Troponin level as a diagnostic tool was performed in 815 patients (69.2%), with a lower rate in small hospitals (bed size < 100). Only 12.1% (n=142) of the patients received low-molecular weight heparin, vs 60.4% (n=712) who received unfractionated heparin, with a significant difference between community and teaching hospitals (10.3% vs 20.5%). Aspirin was administered to 83.9% (n=988), while new antiplatelet agents (e.g., platelet glycoprotein IIb/IIIa), were used in 7.7% (n=91) patients (5.8% community hospitals vs 17% teaching hospitals, $p<0.001$).
CONCLUSIONS: The new recommendations on the management of ACS were already in use in hospitals prior to guideline publication. Practice consistent with the guidelines was higher in teaching rather than community hospitals.

199E. Does aspirin attenuate the effect of ACE inhibitors on health outcomes of very old patients with heart failure? *Anne L. Hume, Pharm.D.*, Marilyn M. Barbour, Pharm.D., Kate L. Lapane, Ph.D.; University of Rhode Island, Kingston, RI; Brown University, Providence, RI.

PURPOSE: Many older individuals with congestive heart failure (CHF) have concomitant ischemic heart disease requiring an antiplatelet agent. Concerns have emerged about the potential for a significant interaction between ACE inhibitors and aspirin. We sought to evaluate the extent to which concomitant use of aspirin attenuates the beneficial effect of ACE inhibitors among patients with CHF living in long-term care.
METHODS: Using the Systematic Assessment of Geriatric drug use via Epidemiology (SAGE) database, we identified 13,024 residents with CHF who were taking an ACE inhibitor. We considered aspirin use to be any standing order for aspirin. Sixteen percent of the sample received aspirin. We evaluated the effect of aspirin on 1-year mortality and decline in physical functioning using Cox proportional hazards models to simultaneously adjust for potential confounders.
RESULTS: Fifty percent of residents were over 85 years of age. Over half of the patients taking ACE inhibitors users were receiving captopril. Sociodemographics, measures of severity of illness, comorbid conditions and concomitant medication use did not vary substantially by aspirin use. No excess rate of death (adjusted relative rate [RR]: 1.00; 95% confidence interval [CI] 0.92-1.08), hospitalization (RR: 0.99; 95% CI: 0.93-1.05), or decline in physical functioning (RR: 0.99; 95% CI: 0.90-1.10) occurred among aspirin users. Stratified analyses by presence of ischemic heart disease revealed similar patterns.
CONCLUSIONS: In a cohort of very old CHF patients living in long-term care facilities, we found that treatment with aspirin did not negatively affect outcomes.
Presented at ISPE, Barcelona, Spain, August 22, 2000.

200. Retrospective cohort study: multivariate linear regression model to measure the association between age and symptoms in patients with community-acquired pneumonia. *Ru-Ming Fan, Pharm.D., MPH*; Brookdale University Hospital and Medical Center, Brooklyn, NY.

PURPOSE: The purpose of this study is to evaluate the association between age and the presenting symptoms in patients with community-acquired pneumonia. Advanced age has become a well-recognized risk factor in patients with pneumonia. It may also be associated with reduced symptoms reporting, raising the possibility that diagnosis and treatment may be delayed in older patients.
METHOD: A retrospective cohort study was conducted at the Brookdale University Hospital and Medical Center from January 1, 1997 to September 30, 1999. A total of 884 cases were sampled if patients were older than 18 years with clinical and radiographic evidence of pneumonia. The presence of four respiratory symptoms (cough, dyspnea, sputum production, and pleuritic chest pain) and ten nonrespiratory symptoms (fatigue, fever, chills, anorexia, nausea, vomiting, sore throat, diarrhea, abdominal pain, and tachypnea) were recorded. Patients were categorized into four groups and univariate tests were based on an analysis for trend across age groups. For the presence of symptoms, signs, and most patient characteristics, the Mantel-Haenszel chi-square test for trend was used. For the ordinal variables, a nonparametric test was used to test for trend across age group. A multivariate linear regression analysis was performed to assess the association between age group and total symptoms for the patients, separately, controlling for patient comorbid illness and severity of illness at presentation.
RESULTS: The 884 eligible study patients were categorized into four age groups: 18 through 44 years (39%), 45 through 64 years (21%), 65 through 74 years (22%), and 75 years or older (18%). For 12 out of 14 symptoms, there were significant decreases in prevalence with increase age ($p<0.05$). In a multivariate linear regression analysis, controlling for patients' comorbidity and severity of illness at presentation, older age remained associated with less symptoms ($p<0.001$).
CONCLUSIONS: Respiratory and nonrespiratory symptoms are less commonly reported by older patients with community-acquired pneumonia, even after controlling for the increased comorbidity and illness severity in these older patients. Recognition of this phenomenon by clinicians and patients is essential given the increased mortality in elderly patients with community-acquired pneumonia.

201. A population-based cohort study of drug utilization patterns in diabetics receiving oral hypoglycemic agents. *Jenifer Wogen, M.S.*, Jennifer Kim, Pharm.D., Jennifer Sung, Pharm.D., James B. Roehm, M.S., MBA, Stephen J. Boccuzzi, Ph.D.; Institute for Effectiveness Research L.L.C., Merck-Medco Managed Care L.L.C., A Merck Company, Bridgewater, NJ; Novartis Pharmaceuticals, Inc., East Hanover, NJ.

PURPOSE: To characterize oral hypoglycemic agent (OHA) utilization patterns in a cohort of newly-treated OHA patients using continuously benefit-eligible members from the Merck-Medco Managed Care pharmacy claims database during the period of February 1997 through July 1999 (n=15.1 M).
METHODS: This retrospective study included patients initiating OHA between August 1, 1997 through July 31, 1998 (n=111,625). The follow-up period for each patient was at least 12 months. Assessment of drug utilization patterns included switching, therapy augmentation, persistence and compliance.
RESULTS: Mean age of the study cohort was 65.6 years; 44% were female. Monotherapy new starts included sulfonlyureas (61%), metformin (22%), troglitazone (16%), and α-glucosidase inhibitors (1%). Overall, 14% who initiated OHA monotherapy switched from their initial agent to another OHA, with a mean time to switch of 286 days. Twenty-five percent of patients initiated on monotherapy added a second agent; percentage of therapy augmentation by initial agent was similar between agents. Across initial monotherapy agents, time to therapy augmentation averaged 194 days (range 130-241). Only 11.8%, 9.8%, and 8.2% had no drug therapy modification or disruption during the first 12 months of therapy for glipizide (extended release), glyburide and metformin patients respectively. Persistence was relatively low at 12 months post-therapy initiation, ranging from 66% for sulfonylureas to 34% for α-glucosidase inhibitors. Monotherapy compliance

was highest in sulfonylureas (79%) and metformin (77%).
CONCLUSIONS: Results indicate that, in a real-world setting, patients receiving OHA therapy have suboptimal persistence and frequent therapy augmentation. Opportunity exists to optimize drug therapy to ensure effective dosing and duration, thereby improving drug effectiveness for long-term glycemic control.

202. Concomitant use of other medications that may interact with HMG-CoA-reductase inhibitors (statins) in the cytochrome P450 system. *Daniel M. Huse, M.A.,* Mason W. Russell, MAPE, Jennifer C.Y. Sung, Pharm.D., M.S., Douglas Gause, M.S., Dr.PH; ICSL Healthcare Research, Burlington, MA; Novartis Pharmaceuticals, East Hanover, NJ.

PURPOSE: Most statins (atorvastatin, cerivastatin, lovastatin, and simvastatin) are metabolized by cytochrome P450 isoenzyme (CYP) 3A4 while fluvastatin is predominantly metabolized by CYP 2C9. Since statins are often involved in polypharmacy, the rate of concomitant use of statins with other medications that may interact with them in the CYP system was examined, as well as the occurrence of adverse events.
METHODS: Health care claims data from a northeastern U.S. managed care organization was utilized to identify patients who received prescriptions for statins during 1996-1998. Instances where these persons simultaneously received prescriptions for other drugs metabolized by the same CYP isoenzyme were considered "co-prescriptions." Occurrences of adverse events were identified based on ICD-9 diagnosis codes recorded on medical claims. Patients on pravastatin, which does not undergo hepatic metabolism, were excluded from the analysis.
RESULTS: Fluvastatin was used by 1488 patients and statins metabolized by CYP 3A4 were used by 3590 patients, including 3504 on atorvastatin, 2 on cerivastatin, 30 on lovastatin, and 54 on simvastatin. Compared to statins metabolized by CYP 3A4, significantly fewer patients in the fluvastatin group had any co-prescriptions (35.5% vs 64.0%; $p<0.001$; unadjusted odds ratio = 0.30; $p<0.001$). When adjusted for age, gender, number of other medications, and duration of statin therapy, the relative risk of co-prescription in the fluvastatin group declined further (adjusted odds ratio = 0.19; $p<0.0001$). Adverse event rates did not differ significantly among statin groups.
CONCLUSION: In view of the prevalence of polypharmacy and potential drug-drug interactions, more judicious selection of statins is warranted.

Pharmacogenomics

203. Effects of β-adrenoceptor polymorphisms on resting hemodynamics and dobutamine response in humans. *Brian J. Puckett, Pharm.D.,* Larisa M. Humma, Pharm.D., Beatrice L. Lejeune, Pharmacist, Jannet F. Lewis, M.D., Carl J. Pepine, M.D., Julie A. Johnson, Pharm.D.; University of Florida, Gainesville, FL.

PURPOSE: There are common polymorphisms at β_1-adrenoceptor (β_1-AR) gene codons 49 and 389 and β_2-adrenoceptor (β_2-AR) gene codons $^{-}$19, 16, and 27. Presented are data from a pilot study in which we sought to determine if β_1- and/or β_2-AR polymorphisms affect resting hemodynamics and/or response to dobutamine in humans.
METHODS: Fifty-nine women not on β-blockers who participated in the NHLBI-sponsored Women's Ischemic Syndrome Evaluation (WISE) study underwent dobutamine stress echocardiography (DSE) by standard protocol. Hemodynamics were determined after 30 minutes of rest and after 5 minutes at each dobutamine infusion rate. β_1- and β_2-AR genotypes were determined by PCR and RFLP.
RESULTS: β_1-AR Arg389 homozygotes exhibited higher resting heart rates versus Gly389 carriers (75 ± 11 vs 66 ± 10 bpm, $p<0.05$) and slightly higher BPs (SBP 149 ± 19 vs 141 ± 26 mm Hg, $p=0.16$; DBP 82 ± 11 vs 77 ± 11 mm Hg, $p=0.09$, respectively). No associations between β_1-AR codon 49 or β_2-AR genotypes and resting hemodynamics were observed. Due to genotype distributions, we had limited power to detect differences in dobutamine response. However, the following trends were observed: greater increases in SBP response for Gly389 cohort, Ser49 homozygotes, Gly16 homozygotes, and Arg -19 cohort; greater decrease in DBP response for Arg16 cohort; and greater increase in HR response for Gly16 homozygotes. As an example, mean SBP response by codon 49 genotype is given (5 µg/kg/minute: 11 vs 14; 10 µg/kg/minute: 15 vs 24; 20 µg/kg/minute: 8 vs 24; Arg49 homozygotes and Gly49 cohort, respectively).
CONCLUSIONS: Higher resting hemodynamics among Arg389 homozygotes suggest these patients experience greater catecholamine-mediated effects; this may have important implications with respect to β-blocker response. Our data also suggests that β_1- and β_2-AR genotypes may influence responses to dobutamine. Full characterization of dobutamine pharmacogenetics in an adequately powered, prospective study is ongoing in our laboratory.

204. Amphotericin B-induced differential expression of genes encoding immunomodulatory proteins in human T- and B-lymphocytes detected by cDNA microarray. *P. David Rogers, Pharm.D., M.S.,* Margaret M. Pearson, Pharm.D., Stanley W. Chapman, M.D., Donna C. Sullivan, Ph.D., John D. Cleary, Pharm.D.; University of Mississippi, Jackson, MS.

PURPOSE: Amphotericin B (AmB) has been shown to modulate the function of human lymphocytes and to induce the expression of genes encoding cytokines in human monocytes. The purpose of this study was to identify genes that encode immunomodulatory proteins that are differentially expressed in human T- and B-lymphocytes in vitro in response to AmB.
METHODS: Jurkat T-cells and Raji B-cells were grown in supplemented medium at 37°C and 5% CO_2 at 10^6 cells/ml in the presence or absence of 5 µg/mL AmB for 2 or 24 hours. Total RNA was extracted and $^{[33]}$P dCTP-labeled cDNA probes were prepared by reverse transcription of total RNA primed with oligo-dT. Probes were hybridized overnight with Research Genetics GF211 cDNA microarrays at 42°C. Washed arrays were subjected to phosphorimaging. Data was analyzed using Pathways software. A ≥ 1.8-fold difference in expression was considered significant.
RESULTS: Expression of 4324 genes was evaluated. In Jurkat T-cells, 334 and 28 genes were up-regulated and 6 and 340 genes were down-regulated after exposure to AmB for 2 and 24 hours, respectively. In Raji B-cells, 5 and 87 genes were up-regulated and 662 and 127 genes were down-regulated after exposure to AmB for 2 and 24 hours, respectively. These included genes encoding cytokines, cytokine receptors, chemokines, and proteins involved in antigen presentation, complement function, and cell adhesion.
CONCLUSION: AmB alters in vitro expression of many genes encoding immunomodulatory proteins in human T- and B-lymphocytes. Such effects may be involved in the toxicity and immunomodulatory properties of this agent.

205. Amphotericin B-induced differential gene expression in human epithelial kidney cells. *Kimberly L. Davis, Pharm.D.,* P. David Rogers, Pharm.D., M.S., Brenda A. Chapman, B.S., John D. Cleary, Pharm.D., Stanley W. Chapman, M.D.; University of Mississippi Medical Center, Jackson, MS.

PURPOSE: The purpose of this study was to expose human epithelial kidney cells (HK-2) in vitro to amphotericin B and evaluate differential gene expression in relation to the toxicities associated with its use.
METHODS: Human epithelial kidney cells (HK-2; 1×10^7 cells) were grown and equilibrated in supplemental medium at 37°C and 5% CO_2. Cells were exposed to either amphotericin B 5 µg/ml or media alone for 6 hours. Total RNA was isolated using TRIZOL reagent and ^{33}P dCTP-labeled cDNA probes were prepared by reverse transcription of total RNA primed with oligo-dT. Probes were then hybridized overnight with Research Genetics GF211 Named Genes Human Genefilter cDNA microarrays at 42°C. Washed arrays were exposed to a phosphor screen for 48 hours and radioactivity correlating with gene expression intensity was quantified using a Molecular Dynamics Storm PhosphorImager at a resolution of 50 microns. Data were analyzed using the Research Genetics Pathways software. A ≥ 2-fold difference in expression was considered significant.
RESULTS: Of the 4324 genes evaluated, 36 genes were up-regulated and 82 genes were down-regulated after exposure to amphotericin B for 6 hours. Up-regulated genes included IL-8, adrenomedullin, CYP21, squalene epoxidase, TNFSF9, and amphiregulin. Down-regulated genes included the high mobility group protein isoform I-C, EEF2, EIF2S2, and TPI1.
CONCLUSION: Amphotericin B induces in vitro differential expression of a myriad of genes in human epithelial kidney cells. Many of these gene expression responses represent putative mechanisms by which amphotericin B may cause its toxicities.

206. β_1- and β_2-adrenergic receptor polymorphisms and diurnal blood pressure variation. *Larisa M. Humma, Pharm.D.,* Nhi B. Nguyen, Pharm.D., Margaret R. Wallace, Ph.D., William G. Farmerie, Ph.D., Julie A. Johnson, Pharm.D.; University of Florida, Gainesville, FL.

PURPOSE: Morbidity and mortality are greater among hypertensive nondippers, whose nighttime BPs decline < 10%, than dippers. There are common polymorphisms at β_1-adrenergic receptor (β_1AR) gene codons 49 and 389 and β_2-adrenoceptor (β_2AR) gene codons $^{-}$19, 16, and 27. The objective was to determine the association between β_1AR and β_2AR genotypes and dipper status.
METHODS: Thirty-eight hypertensives, withdrawn from antihypertensive medications for ≥ 2 weeks, underwent 24-hour ambulatory BP monitoring. Nondippers and dippers were those with < 10% and ≥ 10% decline in nighttime SBP, respectively. β_1AR and β_2AR genotypes were determined by PCR and RFLP. β_2AR haplotypes were determined by T-vector cloning with sequencing.
RESULTS: Mean ± SD nighttime SBP declines were 15 ± 4% in dippers (n=17) and 3.6 ± 6% in nondippers (n=21). Three β_2AR haplotypes were revealed: Arg^{-}19/Gly16/Glu27 (RGE), Cys^{-}19/Gly16/Gln27 (CGQ), and Cys^{-}19/Arg16/Gln27 (CRQ). The RGE haplotype frequency was 0.18 for dippers and 0.40 for nondippers ($p<0.05$). The odds ratio for being a nondipper with the RGE haplotype was 3.2 (95% CI: 1.1-9.3). The CGQ haplotype frequency was 0.38 in dippers and 0.14 in nondippers ($p<0.05$). The RGE/RGE genotype occurred only in nondippers (n=3), the CGQ/CGQ genotype occurred only in dippers (n=4), and the CRQ/CRQ genotype was equally distributed between groups. There were no significant differences in β_1AR allele frequencies at codons 49 (0.87/0.13 vs 0.81/0.19) or 389 (0.59/0.41 vs 0.56/0.44) between dippers and nondippers, respectively.

CONCLUSION: The β_2AR RGE haplotype associated with the nondipper phenotype; the CGQ haplotype associated with the dipper phenotype. We conclude the β_2AR, but not the β_1AR, plays an important regulatory role in determining nocturnal BP decline.

207E. Pharmacogenomic effects of a polymorphism in the 5′ promoter region of CYP3A4 in stable kidney transplant recipients. *Janet L. Karlix, Pharm.D.*, Joseph R. Walker, Pharm.D., Heather A. Myers, B.S., Clara F. Johary, B.S.R.R.T., R.C.P., William G. Farmerie, Ph.D., Alan I. Reed, M.D., John R. Silkensen, M.D., Willem J. Van der Werf, M.D., Alan W. Hemming, M.D., Janet M. Crabtree, M.D., Titte R. Srinivas, M.D., Pamela R. Patton, P.A., and Richard J. Howard, M.D., Ph.D.; Interdisciplinary Center for Biotech Research; University of Florida, Gainesville, FL.

BACKGROUND: CYP3A4 is the most important drug metabolism enzyme in the transplant population because it metabolizes cyclosporine (CyA), tacrolimus, and sirolimus. Up to 40-fold interindividual differences have been reported in the activity of CYP3A4. Recently, a substitution mutation [A→G] in the 5′ promotor region in the gene encoding CYP3A4 has been described. The frequency of the variant allele (G) has been reported to be 3.6% in Caucasian-Americans, 54.6% in African-Americans, and 0.0% in Asian-Americans. There are conflicting reports on the clinical significance of this alternate form of CYP3A4 [CYP3A4*1B]. We hypothesized that presence or absence of CYP3A4*1B would explain the large variability in CyA dose and thus CYP3A4 activity.
PURPOSE: To determine the role of CYP3A4*1B on CyA requirements in stable kidney transplant recipients.
METHODS: All kidney transplant recipients with extremely low (< 1.8 mg/kg/day) and extremely high (> 4.2 mg/kg/day) Neoral® maintenance doses were invited to participate. Genomic DNA was isolated from whole blood, and genotype was determined via RFLP.
RESULTS: This pilot study included 48 kidney transplant recipients who were greater than 6 months post transplant and whose Neoral® dose was stable for at least 4 weeks prior to enrollment and who were on no drugs known to interact with cyclosporine. In the African-American cohort, the frequency of the variant allele (G) was 75.0% in the high CyA dose group (n=10) and 71.4% in the low dose group (n=7). Also, in the Caucasian-American cohort, the variant occurred in 4.8% of the high CyA dose group (n=21) and 5.0% in the low-dose group (n=10).
CONCLUSION: The frequency of the variant enzyme (CYP3A4*1B) did not differ between CyA dose strata in either racial cohort. It is unlikely that the recently identified polymorphism in CYP3A4 contributes to the large interpatient variability in CYP3A4 activity and CyA requirements exhibited by stable renal transplant recipients.
Presented at Transplant 2000 Meeting, American Society of Transplantation, Chicago, IL, May 2000.

Pharmacokinetics/Pharmacodynamics/ Pharmacometrics/Drug Metabolism

208. The effect of interleukin-6 on the hepatic metabolism of itraconazole and its metabolite hydroxyitraconazole. *Paul O. Gubbins, Pharm.D.*, Russell B. Melchert, Ph.D., Scott A. McConnell, Pharm.D., Amy H. Franks, Scott R. Penzak, Pharm.D., Bill J. Gurley, Ph.D.; University of Arkansas for Medical Sciences, Little Rock, AR; Mercer University, Atlanta GA.

PURPOSE: To determine in vitro, what effects, if any, the cytokine interleukin-6 (IL-6) has on hepatic cytochrome P450 (CYP)-mediated itraconazole (ITZ) metabolism using primary human hepatocytes (PHH).
HYPOTHESIS: IL-6 directly inhibits hepatic CYP-mediated ITZ metabolism and thereby decreases hydroxyitraconazole (OHITZ) formation.
METHODS: Six-well plates containing PHH cultures from male donors age 18-60, who had not received any CYP substrates, inducers or inhibitors, were obtained from a national supplier. All cells were exposed to ITZ 500 ng/ml (I), and the effects of 120 µg/ml cimetidine (I+CIM), 50 ng/ml human IL-6 (I+IL6) and 50 ng/ml IL-6 receptor antagonist (I+IL6+RA) were studied for 2, 4, 8 and 12 hours. Intracellular (IC) ITZ and OHITZ concentrations were measured using HPLC and normalized to IC protein. Groups were compared using the Kruskal-Wallis ANOVA, ($p<0.05$)* and corresponding Z test for multiple comparisons to pinpoint which groups differ ($p<0.02$)**.
RESULTS: PHH cultures from 5 donors (mean age 42 [± 15]) were studied:

	Mean ICITZ Concentrations (ng/mg protein)				Mean ICOHITZ Concentrations (ng/mg protein)			
Group	I	I+CIM	I+IL6	I+IL6+RA	I	I+CIM*	I+IL6*	I+IL6+RA*
Time (hour)								
2	348.4	361.0	323.6	391.9	45.3	40.0	60.1	62.6
4	221.9	281.9	259.6	324.8	54.6	19.2**	74.9**	70.9**
8	132.3	257.4	165.3	203.0	51.6	26.2	76.8	80.2
12	183.7	225.1	189.7	238.5	55.1	30.3**	76.2	96.0**

* $p<0.05$; ** $p<0.02$

CONCLUSIONS: The PHH cultures metabolized ITZ. Cimetidine somewhat inhibited OHITZ formation. IL-6 did not inhibit OHITZ formation. IL-6 may inhibit subsequent CYP-mediated metabolism of OHITZ.

209. Racial differences in disposition of cyclosporine between African-American and Caucasian healthy volunteers. *David I. Min, Pharm.D., M.S.*, Miyoung Lee, M.S., Yi-Min Ku, M.S., Pharm.D., Michael Flanigan, M.D.; University of Iowa, Iowa City, IA; University of Nebraska, Lincoln, NE.

PURPOSE: To determine the effects of race on cyclosporine (CsA) pharmacokinetics in 22 (11 Caucasian [C], 11 African-American [AA]) healthy subjects.
METHODS: Each subject received two doses of CsA, one oral form (5 mg/kg) and one IV (1.5 mg/kg). Seventeen blood samples were collected for CsA during a 24-hour period, which were analyzed by a high-performance liquid chromatography method.
RESULTS: Compared with C, the peak concentration (Cmax) of oral CsA in AA subjects was significantly lower [1220 ± 329 ng/ml (AA) vs 2053 ± 366 ng/ml (C), $p<0.0001$], and area under the time-curve (AUC) was smaller [5896 ± 1330 ng•hour/ml (AA) vs 8772 ± 1668 ng•hour/ml (C), $p=0.0002$]. In addition, AUC of IV CsA was smaller in AAs compared to that of C [5456 ± 1054 ng•hour/ml (AA) vs 6800 ± 906 ng•hour/ml (C), $p=0.007$]. The clearance (CL) of AAs was significantly faster than that of C [20.0 ± 4.5 L/hour (AA) vs 16.3 ± 1.9 L/hour (C), $p=0.027$]. The mean absolute bioavailability of CsA in AA was significantly lower compared to C [32.8 ± 6.6% (AA) vs 39.3 ± 7.1% (C), $p=0.049$]. However, time to peak concentration (Tmax), mean absorption time (MAT) or mean residence time (MRT) of CsA was not significantly different between AA and C subjects.
CONCLUSIONS: Disposition of CsA in AA subjects is significantly different from that in C subjects, which may partly explain the racial differences in outcomes of organ transplantation.

210. Pharmacokinetics of intranasal hydromorphone in healthy subjects. *Daniel P. Wermeling, Pharm.D.*, Anita C. Rudy, Ph.D., Sanford M. Archer, M.D., Mary K. Rayens, Ph.D., Michael Jay, Ph.D.; University of Kentucky, Lexington, KY.

PURPOSE: To evaluate the pharmacokinetics (PK) and bioavailability of 2 mg hydromorphone (HM) HCl via intravenous (IV) and intranasal (IN) routes of administration. We recently developed an IN form of HM HCl (10 mg/ml) using a buffered aqueous solution and a commercially available single-dose metered spray pump.
METHODS: Healthy male subjects (n=9 nonsmokers) were given 2 mg doses of HM HCL by IV and IN routes in a randomized, crossover study. Blood samples were serially taken from 0 to 16 hours. HM in plasma was determined by LC/MS/MS. Noncompartmental analysis was used to estimate PK parameters.
RESULTS: Mean (%CV) are given except for $t_{1/2}$ where median (range) is given for two routes of administration.

Parameter	IV	IN
Cmax (pg/ml)	15547 (39)	3438 (17)
Tmax (hour)	0.094 (30)	0.305 (27)
AUC_{0-t} (pg·hr/ml)	9899 (10)	6188 (25)
$AUC_{0-\infty}$ (pg·hr/ml)	10393 (12)	6681 (24)
γ_z (hr^{-1})	0.170 (40)	0.248 (92)
$t_{1/2}$ (hr)	4.07(2.4-8.1)	4.17 (2.3-9.2)
F (%)	assume 100%	64 (19)

CONCLUSIONS: HM HCl was well absorbed after IN administration with bioavailability of 64%. No nasal pathology was seen. This study demonstrates that IN HM HCl has potential for commercial use as an alternative route of HM HCl delivery. This work was supported by Inhalation Technology, Inc.

211. Limitations of current once-daily aminoglycoside dosing methods compared to a proposed individualized extended-interval dosing method. Susan R. Raber, Pharm.D., *Sandra B. Earle, Pharm.D.*; Oregon State University, Portland, OR.

PURPOSE: Current methods of once-daily aminoglycoside dosing (ODA), developed to optimize C_{max}/MIC and provide a drug-free interval, lack patient individualization of AUC_{0-24}, dosing interval (τ) and T < MIC. An individualized extended-interval dosing (IEID) method is proposed which optimizes each of the parameters for efficacy and safety.
METHODS: Population k_e and V_d values and an MIC of 1 mg/L were used to calculate dose and τ necessary to achieve the best C_{max}/MIC and AUC_{0-24} without excessive T < MIC for creatinine clearances 30-125 ml/minute. Each of the parameters were also calculated for the Hartford (HART) and Sandford Guide (SG) dosing recommendations. Group-wise comparison was by one-way ANOVA and Tukey test.
RESULTS:

Method	Dose (mg/kg)	τ (hour)	AUC_{0-24} (mg•hour/L)	C_{max}/MIC	%τ<MIC
IEID	2.8-5.6	q12-24	85 ± 25.2‡	11.8 ± 4.5*	34.1 ± 13.7§
SG	2.5-5.1	q24	66.9 ± 13.6*	13.7 ± 1.8†	48.6 ± 20.5§
HART	7.0	q24-36	109.6 ± 34.6*‡	22.2 ± 1.0*†	43.3±18.6

*$p<0.001$; ‡$p=0.011$; †$p<0.001$; §$p=0.035$

CONCLUSIONS: Weaknesses exist in the current ODA methods. The HART method subjects patients to significantly higher drug exposure, increasing potential for toxicity. The SG method results in concentrations below the MIC for nearly half the dosing interval, possibly allowing for bacterial regrowth. The current methods fix either dose or interval. Varying both dose and dosing interval individualizes therapy without sacrificing simplicity.

212. Pharmacokinetics and pharmacodynamics of subcutaneously administered anti-CD11a (hu1124) in psoriasis subjects. *Russell L. Dedrick, Ph.D.,* Robert Bauer, Ph.D., David Bohmann, Patricia Walicke, M.D., Marvin R. Garovoy, M.D.; XOMA (US) LLC, Berkeley, CA; Genentech, San Francisco, CA.

PURPOSE: Anti-CD11a is a humanized monoclonal antibody that inhibits the binding of leukocyte function-associated antigen-1 (LFA-1) to intercellular adhesion molecules (ICAMs), a critical event for both T-cell trafficking and activation. In previous studies, intravenous (IV) infusion of anti-CD11a significantly improved psoriasis symptoms. This study evaluated the pharmacokinetics, pharmacodynamics, efficacy and safety of drug administered subcutaneously (SC).
METHODS: In this open-label study, subjects with moderate to severe plaque psoriasis received eight weekly injections of anti-CD11a SC at doses from 0.5 to 2 mg/kg. Pharmacokinetics and pharmacodynamics (WBC, lymphocyte subpopulations and CD11a expression and saturation) were assessed before, during and for 7 weeks after treatment. Clinical safety and efficacy were also monitored.
RESULTS: Peak plasma levels of anti-CD11a occurred 1-3 days after SC injection. Mean peak levels increased from 3.4 to 18.1 µg/ml as doses increased from 0.5 to 2.0 mg/kg. Mean trough levels increased from 1.7 to 9.6 µg/ml. Anti-CD11a was detectable in the plasma for 10-58 days after the final dose. Overall bioavailability was 35% compared to IV. CD11a expression on circulating T-cells decreased about 75% and available anti-CD11a binding sites decreased more than 90% at all dose levels. Lymphocyte counts increased approximately 2-fold. CD11a expression and lymphocyte counts returned to pretreatment levels after drug clearance. SC administration produced similar improvements in psoriasis symptoms with fewer acute post-dose adverse events than IV.
CONCLUSIONS: Despite decreased bioavailability compared to IV, SC anti-CD11a had similar pharmacodynamic effects and improvement in psoriasis symptoms with fewer acute post-dose adverse events.

213. The factors affecting the phenytoin-free fraction in serum and their correlation in Korean patients. Ji Young Lee, R.Ph., *Kie Ho Sohn, Ph.D.*, Okkyung Suh, Pharm.D., Kyung Eob Choi, Pharm.D.; Samsung Medical Center, Seoul, Korea.

PURPOSE: To assess the factors affecting free fraction of phenytoin in serum and the performance of currently available equations used to predict normalized total phenytoin concentrations and to identify more appropriate equation for Korean patients.
METHODS: Patients in Samsung Medical Center, a 1400-bed teaching hospital, with both total and free phenytoin concentrations measured were enrolled retrospectively. Total of 227 patients were enrolled. Correlation between free fraction of phenytoin and various factors was assessed. Predictive performance of the equations was evaluated using bias (mean prediction error [MPE]) and precision (root mean squared error [RMSE]).
RESULTS: Free fraction of phenytoin correlated well with all factors (r^2=0.51). However, only albumin and concurrent medication showed significant correlation ($p<0.05$). Normoalbuminemia patients exhibited a weak correlation (r^2=0.16) and hypoalbuminemia patients exhibited a strong correlation (r^2=0.69) between free fraction and the factors. The age also had shown a significant correlation with free fraction in hypoalbuminemia patients. Bias and precision of the equations predicting normalized total phenytoin concentrations were as follows: the Sheiner-Tozer equation (MPE = 2.1, RMSE = 5.82), the revised Winter-Tozer equation (MPE = -0.74, RMSE = 5.09), the new equation using affinity constant of 0.24 (MPE = -0.26, RMSE = 5.07).
CONCLUSIONS: There was high correlation between free fraction of phenytoin and the factors affecting protein binding such as albumin and concurrent medication. In addition, the age had a significant impact on free fraction in hypoalbuminemia patients. The equation with affinity constant of 0.24 had smaller bias than 0.20 or 0.25 in Korean patients. However, it needs to be reassessed in a larger study.

214. The pharmacokinetics, metabolism and elimination of H 376/95, a novel, direct thrombin inhibitor, in healthy male subjects, after oral and intravenous administration. Ulf Eriksson, Ph.D., Ann Cathrine Liljenvald, D.D.S., Gunnar Fager, M.D., Ph.D., *Anneli Thuresson, M.S.,* Margareth Gabrielsson; AstraZeneca R&D Molndal, Sweden.

PURPOSE: To evaluate the pharmacokinetics, metabolism and elimination of H 376/95 (a novel, oral, direct thrombin inhibitor) in healthy subjects.
METHODS: This was an open-label, sequential, non-randomized study, in which five healthy, male, Caucasian subjects received a single oral dose of 50 mg ^{14}C-labeled H 376/95, followed 20 days later by a single IV dose of 10 mg unlabelled H 376/95. Blood, urine and feces samples were taken before and for 7 days after oral administration. Blood and urine samples were also collected before and up to 12 hours and 24 hours, respectively, after IV administration.
RESULTS: After oral and IV administration, H 376/95 was converted rapidly to melagatran, its active form and the major circulating metabolite (C_{max} = 0.355 micromole/L and 0.148 micromole/L, t_{max} = 1.85 hours and 1.25 hours following oral and IV administration, respectively). Melagatran was also the major metabolite in urine and feces, although H 376/95 and two intermediary metabolites, H 338/57 and H 415/04, were also present in small quantities in plasma and urine. The elimination half-life of melagatran was 3.64 ± 0.70 hours and 4.29 ± 0.53 hours following oral and IV administration, respectively. The bioavailability of melagatran after oral administration of H 376/95 was 43.1% of that after IV administration. Approximately 70% of the oral dose of H 376/95 was excreted in feces with a further 25% in urine.
CONCLUSIONS: Following oral dosing with H 376/95, melagatran was the principal metabolite found in plasma, urine and feces, and its bioavailability was approximately half that observed following IV administration.

215E. The pharmacokinetics of melagatran, the active form of the oral, direct thrombin inhibitor H 376/95, in healthy male subjects. *A. Thuresson, M.S.,* U.G. Eriksson, Ph.D., L. Johansson, M.S., K. Taure, B.S., L. Frison, Ph.D., U. Bredberg, Ph.D., D. Gustafsson, M.D., Ph.D.; AstraZeneca R&D Mölndal, Sweden.

PURPOSE: To evaluate the pharmacokinetics of melagatran (the active form of the oral, direct thrombin inhibitor, H 376/95) in healthy male subjects following melagatran (IV, SC and oral) and H 376/95 (oral) administration.
METHODS: Study I: ascending single doses of melagatran given IV (1.7–82 µg/kg) and po (0.02–3.3 mg/kg; n=2–4/dose level). Study II: tritium-labeled melagatran given IV (2.3 mg) and orally (110 mg; n=13). Study III: melagatran given SC (0.1–5 mg; n=4/dose level). Study IV: ascending single doses of H 376/95 given PO (1–98 mg; n=5/dose level). Melagatran plasma concentrations were determined in all studies.
RESULTS: Following IV administration melagatran had a relatively low plasma clearance (1.8 ml/minute/kg), small volume of distribution (0.22 L/kg) and short half-life (1.7 hours). SC administration of melagatran resulted in complete bioavailability ($F_{melagatran}$) with maximum plasma levels ~0.5 hours post-dosing and the same mean half-life as with IV administration. Plasma levels increased linearly with dose and inter-individual variability was low after both IV and SC administration. Oral administration of melagatran produced a mean $F_{melagatran}$ of 5.8% (± 2.3%) with a tendency to be dose-dependent. Oral administration of H 376/95 produced an $F_{melagatran}$ of ~20% that was dose independent with low variability across the range of concentrations studied and a mean half-life of 3 hours. H 376/95 and melagatran were well tolerated at all doses regardless of administration route.
CONCLUSION: The pharmacokinetics of melagatran after IV and SC dosing and after oral dosing with H 376/95 were predictable and reproducible.
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216. Determination of sildenafil citrate in plasma by high-performance liquid chromatography and effect of grapefruit juice on sildenafil pharmacokinetics in a single elderly male subject. *Miyoung Lee, M.S.,* David I. Min, M.S., Pharm.D.; University of Iowa, Iowa City, IA.

PURPOSE: Determination of sildenafil in plasma has not been easily available in public because a special sample pretreatment system was required according to previous method by Cooper et al. Therefore, this study was designed to establish the simple and reliable assay method, which can be routinely employed in laboratories using high-performance liquid chromatography (HPLC) with liquid extraction. In addition, effect of grapefruit juice on sildenafil pharmacokinetics was examined in a single elderly male subject.
METHODS and RESULTS: Sodium hydroxide (0.01N) and diethylether were used for liquid-liquid extraction, achieving more than 85% of recovery for sildenafil and internal standard. The isocratic HPLC mobile phase was employed, consisting of acetonitrile (32%) and potassium phosphate buffer (500 mmol/L, 68%) at a flow rate of 0.7 ml/minute. The peaks of sildenafil and internal standard were identified with an UV detector measuring at 230 nm and detection limit was 10 ng/ml as sildenafil salt form. In addition, it was found that grapefruit juice increased the Cmax of sildenafil by 42% (1067.7 ng/ml to 1517.0 ng/ml) although AUC was not significantly altered (4082.9 ng•hour/ml to 4171.9 ng•hour/ml) by grapefruit juice.
CONCLUSIONS: Sildenafil could be determined routinely in a reliable and simple way using HPLC with liquid extraction. Grapefruit juice appears to increase the Cmax of sildenafil by 42% without significant AUC change. However, a further study with appropriate number of subjects is recommended before assuming the effect of grapefruit juice on sildenafil pharmacokinetics since this result was obtained from only one subject.

217. Bioavailability of intradialytically administered vancomycin during CAHP hemodialysis. *Aroonrut Lucksiri, Pharm.D.,* Meri Kay Scott, Ph.D., Bruce A. Mueller, Pharm.D., FCCP, Kevin M. Sowinski, Pharm.D.; Purdue University, Indianapolis, IN.

PURPOSE: Vancomycin is often administered during the last hour of hemodialysis because it was not removed significantly by older dialyzers, but newer high-permeability dialyzers may remove vancomycin. The purpose of this study was to determine the intradialytic bioavailability (F) of vancomycin when administered during the last hour of hemodialysis with high-efficiency CAHP210 hemodialyzers.
METHODS: Eight subjects (2 female/6 male) with ESRD received intravenous vancomycin 15 mg/kg after their regular hemodialysis session. Serum samples for the determination of vancomycin concentrations were obtained serially for 44 hours. After a 3-week washout, the study was repeated with the vancomycin infused during the last hour of their regular hemodialysis session using a CAHP210. Vancomycin concentrations were determined by EMIT. Differential equations describing a two-compartment open pharmacokinetic model were fitted to the serum concentration time data using ADAPT II. The model was simultaneously fitted to the data from both vancomycin doses. A two-sided paired t-test was used to determine if F significantly differed from 1.
RESULTS: Subjects were (mean ± SD) 53 ± 12 years old and weighed 70.8 ± 17.4 kg. Pharmacokinetic parameter estimates appear below.

V_c (L/kg)	V_p (L/kg)	V_{ss} (L/kg)	Cl_s (ml/minute)	Cl_{dist} (ml/minute)	F; p value
0.10 ± 0.03	0.38 ± 0.10	0.48 ± 0.12	8.6 ± 1.9	241 ± 102	0.82 ± 0.15; p=0.012

V_c, V_p, V_{ss} are volume of distribution in the central and peripheral compartments and at steady-state, respectively; Cl_s and Cl_{dist} are systemic and distribution clearance, respectively
CONCLUSION: Vancomycin administered during the last hour of CAHP210 dialysis results in 18% less vancomycin reaching the systemic circulation than when administered post-dialysis. This F is similar to that reported for other high-efficiency cellulosic hemodialyzers.

218. Characterization of once-daily aminoglycoside pharmacokinetics in the critically ill: suggestions for clinical monitoring. Heath R. Jennings, Pharm.D., Kenneth E. Record, Pharm.D., Paul A. Kearney, M.D., *George A. Davis, Pharm.D.*; University of Kentucky Chandler Medical Center, Lexington, KY.

PURPOSE: Studies demonstrating prolonged drug distribution following once-daily aminoglycoside (ODA) dosing in healthy volunteers have suggested that current recommendations for patient monitoring may be inappropriate. To our knowledge, no study has evaluated this controversy in patients. The purpose of this study was to characterize ODA pharmacokinetics (PKs) and validate a monitoring strategy for critically ill patients.
METHODS: Following 30-minute gentamicin infusions (7 mg/kg/day), 20 serum samples were collected from 13 trauma surgery patients. Elimination rate (k_e), half-life ($t_{1/2}$), volume of distribution (V_d), time of complete distribution (t_d), area under the curve (AUC), and estimated 24-hour-trough concentration (C_{24h}) were calculated using WinNonlin (WNL). Two methods of PK analysis were also utilized and compared to WNL parameters for accuracy: method-1 used two serum concentrations collected at 0.5h and 10h post-infusion; method-2 used 4-hour and 12-hour post-infusion concentrations. Statistical analysis included one-way ANOVA with Dunnett's test.
RESULTS: Mean dose = 7.0 ± 0.1 mg/kg and t_d = 3.5h.

	WNL*	Method -1*	Method -2*
k_e (h^{-1})	0.15 ± 0.05	0.24 ± 0.05^y	0.15 ± 0.05
$t_{1/2}$ (h)	5.4 ± 2.1	3.1 ± 0.9^y	5.0 ± 1.7
V_d (L/kg)	0.55 ± 0.12	0.37 ± 0.11^y	0.55 ± 0.12
C_{24h} (mg/L)	0.57 ± 0.46	0.19 ± 0.23^y	0.56 ± 0.47
AUC (mg/L•hour)	86.6 ± 26.1	89.5 ± 26.2	67.7 ± 26.1

* mean ± standard deviation; ^{y}p value < 0.05 vs WNL

CONCLUSIONS: ODA distribution in the critically ill is not complete until ~3.5h following a 30-minute infusion. Further, Method-2 was more accurate for estimation of PK parameters. At our institution, we recommend that two serum concentrations, collected 4 and 12 hours post-infusion, be used to adjust ODA dosing intervals.

219. Lack of effect of St. John's wort on carbamazepine pharmacokinetics in healthy volunteers. *Aaron H. Burstein, Pharm.D.*, Ralph L. Horton, AAS, Timothy J. Dunn, M.D., Raul M. Alfaro, M.S., Stephen C. Piscitelli, Pharm.D., William Theodore, M.D.; Epilepsy Research Branch, NINDS; National Institutes of Health, Bethesda, MD.

PURPOSE: St. John's wort (SJW) has been shown to reduce plasma concentrations of the CYP3A4 substrates indinavir and cyclosporine. The present study was conducted to determine the effect of SJW on carbamazepine (CBZ) pharmacokinetics (PKs) under conditions of CBZ autoinduction.
METHODS: Eight normal, healthy volunteers (5 M, ages 24-43 years) received CBZ 100 mg BID x 3 days then 200 mg BID x 3 days followed by 400 mg qAM x 14 days. Blood samples were collected prior to and 1, 2, 4, 6, 8, 10, 12 and 24 hours following the dose on day 21. SJW 300 mg (0.3% hypericin standardized tablet) three times daily with meals was then taken with CBZ for 14 days. On day 35 blood sampling was repeated as described above. Plasma samples were analyzed for CBZ and CBZ epoxide (CBZe) by HPLC (LLQ: CBZ 50 ng/ml , CBZe 100 ng/ml). CBZ and CBZe PKs were determined using noncompartmental methods. Comparison of PK values before and after SJW was performed using a Student's paired t-test.
RESULTS: Carbamazepine PKs (mean ± SD) before and after SJW were:

	C_{max} (mg/L)	C_{24} (mg/L)	T_{max} (hour)	AUC_{0-24} (mg•hour/L)	CL/F (L/hour)	AUC_{0-24} Ratio CBZe/CBZ
Before SJW	7.2 ± 1	4.8 ± 0.5	6 ± 2.4	142.4 ± 12.9	2.83 ± 0.26	0.26 ± 0.04
After SJW	7.6 ± 1.3	4.3 ± 0.8	5.8 ± 2.7	143.8 ± 27.2	2.87 ± 0.56	0.32 ± 0.09

No statistically significant differences were found. Additionally, no differences (before vs after) in CBZe C_{max} (2 ± 0.5 vs 2.1 ± 0.4 mg/L), C_{24} (1.3 ± 0.29 vs 1.4 ± 0.3 mg/L) or AUC_{0-24} (37.5 ± 7.4 vs 42 ± 10.3 mg•hour/L) were seen.
CONCLUSIONS: The results suggest that the potential for interaction of SJW with CBZ is minimal. Treatment with SJW for 14 days appears to be incapable of further inducing the clearance of a previously induced medication.

220E. A comparison of the pharmacokinetics and in vivo bioaffinity of DigiTab® versus Digibind®. *Michael R. Ujhelyi, Pharm.D.*, Suzzane Ward, Pharm.D., Lena Sjostrom, PhD. Protherics Inc, Nashville, TN; University of Georgia College of Pharmacy, Augusta GA.

The in vivo digoxin binding affinity and normal pharmacokinetic values of dioxin immune Fab are unknown. Healthy subjects (n=16) were randomized to one of the two digoxin-immune Fab products, DigiTAb® or Digibind® to compare the in vivo digoxin binding affinity and pharmacokinetic disposition. Each subject received 1 mg of intravenous digoxin over 5 minutes followed 2 hours later by 76 mg of either DigiTAb or Digibind. Both Fab products reduced free digoxin serum concentrations to below assay detection with equal ability. Consequently, total digoxin serum concentrations increased approximately 10-fold. Peak total digoxin serum concentrations post-Fab dosing were similar to the pre-Fab peak digoxin concentration for both Fab products (45 ± 14 and 44 ± 11 for DigiTAb, pre and post, respectively; 50 ± 17 and 41 ± 9 for Digibind, pre and post, respectively) indicating in vivo equimolar binding affinity. While bioaffinity for digoxin was equal between groups, total digoxin AUC (5.6 ± 1.9 vs 10.8 ± 2.8 ng/ml/hour/kg, $p<0.05$) and digoxin immune Fab AUC (0.57 ± 0.17 vs 0.85 ± 0.21 µg/ml/hour/kg, $p<0.05$) were lower in the DigiTAb group compared to the Digibind group, respectively. Hence, systemic total digoxin (0.59 ± 0.16 vs 0.31 ± 0.06 ml/minute/kg, $p<0.05$) and Fab clearance (0.43 ± 0.06 vs 0.3 ± 0.06 ml/minute/kg, $p<0.05$) were greater in the DigiTAb treated group vs Digibind group, respectively. The faster systemic clearance of DigiTAb was explained by a higher renal clearance. In conclusion, equimolar doses of both DigiTAb and Digibind completely bind digoxin in vivo. The ability of digoxin immune Fab to bind to digoxin is not affected by the systemic disposition of the Fab product.
Presented at the Society of Critical Care Medicine, Orlando FL, February 2000.

221E. Inhibitory effect of methanolic solution of St. John's wort (*Hypericum perforatum*) on cytochrome P450 3A4 activity in human liver microsomes. Stanley W. Carson, Pharm.D., *Christina E. Hill-Zabala, Pharm.D.*, Sarah H. Roberts, Pharm.D., Roy L. Hawke, Ph.D.; University of North Carolina, Chapel Hill, NC.

PURPOSE: St. John's Wort (SJW) extract is extensively utilized as an herbal antidepressant and is often used in conjunction with conventional medications. St. John's Wort contains hypericin, flavonoids, and quercetin that potentially may interact with cytochromes. Therefore, the potential for an herb-drug interaction was investigated in human liver microsomes.
METHODS: Methanolic solutions of SJW from commercially available capsules and pure hypericin were initially compared for effects on 3A4 mediated 6β hydroxytestosterone formation. St. John's Wort extract concentrations were expressed as fluorescence units of hypericin (HFU).
RESULTS: The IC_{50} was 0.6 HFU (0.7 µM) for SJW. In contrast, no effect for hypericin up to 4.04 HFU was found. The mechanism of inhibition was studied at 25 to 1000 µM of testosterone. Michaelis-Menten plots showed the V_{max} of the control was reduced from 1835 to 1412 and 533 pmol/mg/minute at 0.0944 and 0.446 HFU (0.125 and 0.625 MU M) of SJW. The apparent Km increased from 69 µM to 171 µM by 0.446 HFU SJW. An initial attempt at fractionation revealed an aqueous fraction contained potent inhibitory activity similar to the SJW.
CONCLUSIONS: In conclusion, SJW methanolic solution exhibited potent, but not competitive, inhibition of CYP 3A4 activity in human liver microsomes with inhibitory activity retained in a polar fraction but not in hypericin.
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222E. Altered hepatic cytochrome P450 3A4 activity following surgical stress. *Curtis E. Haas, Pharm.D.*, David C. Kaufman, M.D., Carolyn Jones, M.D., William Reiss, Pharm.D., Aaron Burstein, Pharm.D.; University at Buffalo, Buffalo, NY; University of Rochester, Strong Memorial Hospital, Rochester, NY; University of Maryland, College Park, MD.

PURPOSE: This study was designed to evaluate the effect of surgical stress on

changes in CYP3A4 activity following three different surgical procedures involving varying degrees of inflammatory response.
METHODS: Sixteen patients undergoing the following procedures completed the study: abdominal aortic aneurysm repair (n=5, A), colectomy (n=6, C) and peripheral vascular surgery (n=5, P). CYP 3A4 activity was measured using the ^{14}C-erythromycin breath test (ERMBT) performed pre-op, then 24, 48 and 72 hours post-op. Correlates of surgical stress, including plasma TNFα, IL-1β, and IL-6 concentrations, intra-op fluids, OR times, and estimated blood loss (EBL), were collected. Data are reported as mean ± SEM. ANOVA with Tukey's was used for statistical comparisons.
RESULTS: The P group had the least surgical stress and the smallest decrease in CYP3A4 activity (Table). The A and C groups had a greater suppression of CYP 3A4 activity. TNFα and IL-1β plasma concentrations were undetectable. One C patient with an atypical inflammatory response was excluded from the ANOVA and is listed separately in the table. Log Peak IL-6 concentrations correlated with the maximum decrease in ERMBT (Max dERMBT) results (r^2=0.351, p=0.024) supporting a relationship between the degree of inflammatory response and decrease in CYP3A4 activity.

Group	OR Time (minutes)	EBL (ml)	OR Fluids (L)	Peak IL-6 (pg/ml)	Max dERMBT (%)
A	228 ± 30*	1280 ± 301*†	8.7 ± 0.9*†	275.2 ± 34.0	65.9 ± 7.3*
C	174 ± 22	370 ± 124	3.7 ± 0.4	283.0 ± 79.8*	60.7 ± 7.7*
P	110 ± 26	140 ± 98	1.4 ± 0.4	85.8 ± 25.6	33.2 ± 4.2
Atyp. C	113	100	2.1	37	7.5

* p≤0.05 compared to P; † p≤0.05 compared to C

CONCLUSION: Surgical stress was associated with substantial reductions in CYP 3A4 activity by 48 to 72 hours post-op, and the magnitude of this reduction appeared to be influenced by the amount of surgical stress and resulting inflammatory response experienced by the patient.
Published in Crit Care Med 1999;27, No. 12 (Suppl):A145.

223E. Pharmacokinetics and effect on pentagastrin stimulated peak acid output of omeprazole and its two optical isomers, S-omeprazole/ esomeprazole and R-omeprazole. *Tommy Andersson*, Eva Bredberg, Maria Sunzel, Madeleine Antonsson, Lars Weidolf; AstraZeneca LP, Wayne, PA; AstraZeneca R&D Mölndal, Mölndal, Sweden.

PURPOSE: Omeprazole (O) is mainly metabolized by cytochrome P450 (CYP) 2C19, which forms hydroxyomeprazole. The sulphone is formed by CYP3A4. Omeprazole is administered as a racemic mixture of its two optical isomers, Esomeprazole (E) and R-omeprazole (R-O). The aim of this study was to investigate whether the metabolism of the optical isomers is different from each other.
METHODS: Samples from three livers were used for human liver microsomal studies, and four healthy males were used for in vivo pharmacokinetics (PK) and pharmacodynamics (PD) studies. The subjects were given O, E, or R-O, 15 mg QD over 7 days, in a randomized, three-way crossover design. The PK was studied on days 1 and 7. Peak acid output (PAO) was measured on days 0 and 7.
RESULTS: In vitro studies demonstrated that E was less hydroxylated (CYP2C19 mediated reaction) than R-O and that the total intrinsic clearance for E was lower than for R-O. The in vivo studies demonstrated that the mean AUC on day 7 was almost 2x greater for E and approximately 0.5x for R-O, both as compared with O. This resulted in a more pronounced effect on PAO for E than for O and R-O (91% vs 65 and 25% inhibition, respectively.)
CONCLUSION: The almost 2-fold higher AUC for E than for O resulted in a more pronounced gastric acid inhibitory effect for this optical isomer.
Presented at Digestive Disease Week, San Diego, CA, May 21, 2000.

224E. Pharmacokinetics and dose-response relationship of esomeprazole. *Tommy Andersson*, Kerstin Rohss, Mohammed Hassen-Alin, and Eva Bredberg; AstraZeneca LP, Wayne, PA; AstraZeneca R&D Mölndal, Mölndal, Sweden.

PURPOSE: The two optical isomers of omeprazole (O) have a differential metabolism resulting in an almost 2x greater AUC for esomeprazole (E), the S-isomer of O, than for O after equivalent doses. This leads to a more pronounced inhibitory effect on gastric acid secretion with E.
METHODS: Twelve healthy *H. pylori*-negative males completed this randomized, four-way crossover study. Each 5-day treatment period was separated by a 2-week washout. Either 5, 10, or 20 mg E solution or 20 mg O capsule was administered QD. The effect on pentagastrin stimulated peak acid output (PAO) as well as the pharmacokinetics (PK) were studied on days 1 and 5 in each period.
RESULTS: For E 10 and 20 mg the AUC increased 55 and 134%, respectively, from day 1 to day 5 and for O 20 mg the AUC increased 62%. The AUC for E 20 mg was 70% higher than for O at steady state. PAO was inversely correlated to AUC. The mean effect on PAO on day 1 was 15, 29, and 46% for E 5, 10, and 20 mg, respectively. Corresponding figures on day 5 were 28, 62, and 90%, respectively. The inhibition by O 20 mg was 35% on day 1 and 79% on day 5.
CONCLUSION: Repeated administration of E 20 mg resulted in a greater inhibition of acid secretion as compared with O 20 mg (90% vs 79%), because of the 70% higher AUC. Less intersubject variability was demonstrated for E.
Presented at Digestive Disease Week, San Diego, CA, May 21, 2000.

225E. A population pharmacokinetic analysis of gemtuzumab ozogamicin: a new antibody-chemotherapeutic agent. *James A. Dowell, Ph.D.*, S. Peter King, Ph.D., Hank Liu, Ph.D., Mark S. Berger, M.D., Joan M. Korth-Bradley, Pharm.D., Ph.D.; Wyeth-Ayerst Research, Radnor, PA.

A population pharmacokinetic (PPK) analysis of gemtuzumab ozogamicin (GZ, gemtuzumab zogamicin, CMA-676), a novel antibody-chemotherapeutic conjugate, was performed using pharmacokinetic data from 142 relapsed acute myelogenous leukemia (AML) patients. GZ is a novel chemotherapeutic agent that consists of an engineered human antiCD_{33} antibody (hP67.6) linked to a potent cytotoxic agent, N-acetyl-gamma calicheamicin DMH, with a bifunctional AcBut linker. The NONMEM PPK software was used to develop and estimate a model for hP67.6 plasma concentrations and to determine the possible influence of patient demography. The majority of patients in the analysis received GZ as a 2-hour IV infusion of 9 mg/m^2, the therapeutically intended dose for AML. Most patients received two administrations of GZ with doses separated by at least 14 days. The successfully developed PPK model, shown below, consisted of a two-compartment structure with interindividual errors on CL (CV=87%) and V_1 (CV=63%). The concentrations of hP67.6 were observed to increase after the second dose compared to the first, presumably due to changes in disease burden. A proportional term (ΔCL) was used to empirically describe these changes in the pharmacokinetics.

	CL (L/h)	V_1 (L)	Q (L/h)	V_2 (L)	ΔCL
Estimate	0.106	7.05	0.0436	9.97	0.777

There were no observed relationships between patient demographic variables tested and the PPK parameters.
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226. Design, pharmacokinetic, and pharmacodynamic evaluation of novel soft mydriatic agents. *Fenglei Huang, Ph.D.*, Gene Browne, Ph.D., Whei-Mei Wu, Ph.D., Attila Juhasz, Ph.D., Nicholas Bodor, Ph.D.; University of Florida, Gainesville, FL.

PURPOSE: Design and PK/PD evaluation of novel safer and short-acting mydriatic agents based on soft drug approach. (A soft drug is a biologically active, therapeutically useful chemical compound [drug] characterized by a predictable and controllable in vivo destruction [metabolism] to nontoxic moieties after achieving its therapeutic role.)
METHODS: Novel soft mydriatics based on the existing muscarinic receptor subtype selective agents were designed. Four compounds were synthesized and further characterized by receptor binding. Mydriatic studies were carried out on the soft mydriatic agents, atropine, and tropicamide. Eqi-effective doses of the mydriatic agents were instilled into one of the rabbit eyes while the opposite eye was instilled only normal saline as control. The pupil dilation was recorded as mydriatic response. The protective effect against carbachol induced bradycardia of atropine and soft mydriatics were also evaluated on rats with ECG to assess duration of the side effects of these agents. In vitro (biotransformation) and in vivo pharmacokinetic studies (iv bolus) of the compounds were carried out in rats.
RESULTS: The receptor binding studies demonstrated that the novel soft mydriatics were potent anticholinergic agents (pK = 7.5~ 9.0) with subtype selectivity ($M_{3,mydriatic}/M_{2,cardiac}$). After unilateral administrated, the mydriatic recovery time was found to be significantly lower with the rabbits treated with soft mydriatics compared to that of atropine and tropicamide. Significant dilation of the untreated (control) eyes was observed only with atropine and tropicamide, indicating the soft mydriatic agent lacking of systemic toxicity. The duration of the cardiac (side) effects of soft mydriatic agents (15 to 20 min) was much shorter than that of atropine (at least 60 min). The in vitro and in vivo PK studies showed that the soft mydriatic agents were rapidly hydrolyzed into the inactive metabolites once they entered systemic circulation.
CONCLUSIONS: Compared with atropine and tropicamide, the novel soft mydriatics were safer and short-acting agents.

227. A first-pass compartmental model to assess the linearity and bioavailability of verapamil enantiomers in young and elderly patients. *Jean F. Marier, M.S.*, Darrell R. Abernethy, M.D., Ph.D., Irving W. Wainer, Ph.D., Murray P. Ducharme, Pharm.D.; University of Montreal, Phoenix International Life Sciences, Quebec, Canada; Georgetown University, Washington, D.C.

PURPOSE: To provide new insights on the pharmacokinetic (PK) of verapamil and norverapamil enantiomers after single and multiple administrations in young and elderly patients.
METHODS: Fifteen young and 15 elderly patients received 40 mg of IV verapamil on day 1 and 80 mg of IR verapamil TID on days 2-6. Blood samples were collected over 24 hours on days 1 and 6. Verapamil and norverapamil enantiomers were assayed in plasma using stereoselective HPLC. PK parameters were calculated with ADAPT-II®. Quality of fit was assessed by AIC, visual inspection and R^2. Multiple first-pass compartmental models were tested.

RESULTS: Plasma concentrations were fitted using a linear 3-compartmental model with first-pass effect. A 2-compartment model did not fit the data properly, and was suggesting nonlinear PK. Mean results are presented below:

	Young		Elderly	
	R-Verapamil	S-Verapamil	R-Verapamil	S-Verapamil
Cl (nmol/hour)	30.3	58.8	24.0	43.1
V_c (L)	48.7	65.0	64.4	85.5
V_{ss} (L)	462.9	663.7	494.5	652.3
$t_{1/2}$ (hour)	30.5	23.8	28.9	21.0
F%	86.2	41.9	87.0	41.2

	Young		Elderly	
	R-Norverapamil	S-Norverapamil	R-Norverapamil	S-Norverapamil
Cl (nmol/hour)	8.3	9.8	5.9	8.8
V_c (L)	23.5	45.9	12.2	53.0
V_{ss} (L)	67.2	198.0	61.9	98.0
$t_{1/2}$ (hour)	21.6	11.3	29.1	23.6

CONCLUSIONS: Contrary to what has been reported before, verapamil displays linear PK after multiple administrations. In agreement with previous report, population differences are seen in clearance values. Our model succeeded in describing the PKs of verapamil and norverapamil enantiomers. We propose to use this model to monitor and to optimizes therapy in the population.

228. Evaluation of in vivo cocaine metabolism by hepatic carboxylesterase. *Robert B. Parker, Pharm.D.,* Naomi M. Gades, D.V.M., Timothy D. Mnadrell, D.V.M., S. Casey Laizure, Pharm.D.; University of Tennessee, Memphis, TN.

PURPOSE: Numerous reports suggest that cocaine (C) elimination occurs via spontaneous hydrolysis to benzoylecgonine (BE). However, recent in vitro studies indicate formation of BE by hepatic carboxylesterase plays an important role in the metabolism of C, but no in vivo studies have corroborated this finding. The purpose of this study is to evaluate the effect of hepatic carboxylesterase on in vivo C metabolism by comparing the pharmacokinetics of intravenous (IV) and oral C.
METHODS: This study was conducted in animals that were part of ongoing studies of the interaction between cocaine and ethanol. Five adult, conditioned mongrel dogs received 3 mg/kg IV cocaine and 4 mg/kg oral cocaine on different study days separated by at least 48 hours. Blood was collected at various times before and after drug administration for HPLC analysis of C and BE concentrations. Standard non-compartmental methods were used to determine C and BE pharmacokinetic parameters. Data are presented as mean ± SD.
RESULTS: Pharmacokinetic parameters are summarized in the table below.

	IV Cocaine	Oral Cocaine
CL (l/minute)	1.0 ± 0.2*	5.6 ± 1.8
C $AUC_{0-\infty}$ (μg•min/L)	62483 ± 11567*	14980 ± 4710
$t_{1/2}$ (minute)	74.9 ± 16.7	85.2 ± 6.6
Bioavailability		0.18 ± 0.05
BE $AUC_{0-\infty}$ (μg•min/L)	268050 ± 91295*	171867 ± 45484
AUC BE/AUC C	4.19 ± 0.70*	11.9 ± 3.4

*p<0.05 compared to oral cocaine by paired t-test

CONCLUSIONS: 1) The increased AUC BE/AUC C ratio for oral versus IV cocaine suggests hepatic carboxylesterase-mediated first-pass metabolism of cocaine; and 2) hepatic metabolism appears to play a significant role in cocaine elimination.

229. Single-dose and multiple-dose pharmacokinetics of interferon ALPHA-2b in chronic hepatitis C patients. *Jeong M. Park, M.S., Pharm.D.,* Anne M. Larson, M.D., Robert L. Carithers, Jr., M.D., Paul Glue, M.D., Ph.D., Mary F. Hebert, Pharm.D.; University of Washington, Seattle, WA; Schering-Plough Research Institute, Kenilworth, NJ.

PURPOSE: To evaluate single-dose and multiple-dose interferon α-2b (IFN) pharmacokinetics and to assess the dose-linearity in chronic hepatitis C patients.
METHODS: Chronic hepatitis C patients (n=18; age, 29-52 years; body weight, 54.2-118.6 kg) were randomized into four dose groups: subcutaneous IFN 1.5, 3, 5 and 10 million units daily (MU/day) for 6 weeks. Serial blood samples were collected over 24 hours on day 1 and week 6. Serum IFN levels were measured by an electrochemiluminescence immunoassay. Pharmacokinetic parameters were estimated using standard non-compartmental techniques and comparisons were made using analysis of variance.
RESULTS: All AUC_{0-24}'s were greater at week 6 than on day 1 (data not shown). AUC_{0-24} at week 6 increased proportionally with increasing dose (body weight-normalized). At week 6, apparent subcutaneous clearance and apparent subcutaneous steady-state volume of distribution were not different across the dosages. Week 6 pharmacokinetic parameter estimates were reported in the table as mean ± SD.

Dose (MU/day)	1.5 n = 3	3 n = 4	5 n = 5	10 n = 6	p value
AUC_{0-24} (IU hr/ml) (normalized to 70 kg patient)	230 ± 71	482 ± 83	751 ± 227	1772 ± 353	
CL/F (ml/hr/kg)	98.8 ± 28.2	91.0 ± 15.8	103.1 ± 34.0	83.1 ± 14.9	0.56
V_{ss}/F (L/kg)	2.32 ± 1.87	1.24 ± 0.27	1.55 ± 0.23	2.17 ± 1.47	0.66

CONCLUSION: Multiple-dose IFN (subcutaneous, 1.5–10 MU/day) appears to exhibit linear pharmacokinetics in chronic hepatitis C patients.

Pharmacy Practice

230E. Evaluation and follow up patients by the pharmacist in an outpatient setting. *Geneviève Béliveau, B.Pharm.*, Julie Méthot, M.S., Isabelle Taillon, M.S., Jean-Pierre Grégoire, MPH, Ph.D.; Laval Hospital, Laval University, Ste-Foy, PQ, Canada.

PURPOSE: Since February 1998, Laval Hospital pharmacists have implemented an outpatient anticoagulation clinic. The objective of the clinic were to reach therapeutic INR, stabilise patient and transfer them to their physician within a two-week period. This report describe patient's characteristics, warfarin indications, INR therapeutics reaching time, the amount of time the patient spent with the pharmacist, adverse side effects, vitamin K use, rehospitalisation rate and the presence of drug interaction.
METHODS: A retrospective chart review was performed on all patients admitted to the anticoagulation clinic during January 1, 1999 to December 31, 1999. Exclusion criteria were patients anticoagulated with acenocoumarol (Sintrom®), patients on chronic treatment with warfarin or patients admitted for a brief period follow up (≤ 3 days). One patient record out of two was used to select a probabilistic sample consisting of 107 patients.
RESULTS: The age of the population was 65 ± 13 years (mean ± SD). The indication for anticoagulation was primarily auricular fibrillation (56%) followed by venous thrombosis (31%). Mean INR therapeutic reaching time was 5.2 ± 2 days. Mean patients following time by the pharmacist was 10.1 ± 4.7 days. Twelve patients had adverse side effects. One patient had major bleeding, six had minor bleedings and six patients had non specific warfarin adverse reactions. None of these reactions required vitamin K use nor transfusion. Few patients have been rehospitalized (6/107). Twenty-nine patients (27.3%) took one or more potential interacting drug with warfarin.
CONCLUSION: These results demonstrated that patients followed by pharmacists in an outpatient setting is safe and efficient since therapeutic INR was reached quickly and few side effects and rehospitalizations occurred.
Presented at the CCS Annual Meeting, Vancouver, Canada, October 2000.

231. Outcomes evaluation of pharmacist-managed diabetes mellitus patients under a collaborative drug therapy agreement. *Jaime Ponce Anaya, Pharm.D.,* José O. Rivera, Pharm.D., Raymond W. Hammond, Pharm.D., BCPS, FCCP, Victor Anchondo, R.Ph., CDE, José Luna, Jr., M.D.; Cooperative Pharmacy Program, Austin and El Paso, TX; University of Houston, Houston, TX; R.E. Thomason General Hospital, El Paso, TX.

PURPOSE: This study is an outcome evaluation of patients with diabetes mellitus (DM), whose drug therapy was managed by pharmacists under a collaborative drug therapy agreement (CDTA).
METHODS: This study is a prospective evaluation of DM patients referred by a physician to a pharmacist for drug therapy management between June 1, 1999 and March 1, 2000. The pharmacists developed and used a CDTA that was approved by the Texas State Board of Pharmacy (TSBP), and signed by participating physicians. The outcome indicators evaluated for pre- and post-pharmacists interventions were as follows: Primary end points – HgA_{1c} and LDL values; secondary end points – microalbuminuria, ER visits, hospital admissions, and medications used. A paired t-test analysis was performed on pre- and post-values to determine statistical significance.
RESULTS: A total of 116 patients were enrolled in the study. Eighty-seven patients had a diagnosis of type II DM, nine patients type I DM, and 20 patients did not have a definitive diagnosis as to type upon referral to the pharmacist. Fifty-nine patients were females and 57 were males. The mean age was 57.5 years (SD=11.9) with a range of 28 to 77 years of age. The mean number of days patients were treated by a pharmacist was 115 days (SD=57.7). Where pre- and post-values were available, the primary endpoints of the study indicated a mean reduction in HgA_{1c} of 0.85 (p=0.001, n=66) and a mean reduction in LDL of 11.97 mg/dl (p=0.046, n=29). The patients' mean values for HgA1c dropped from 8.09% to 7.24%. There was no significant change in microalbuminuria (p=0.368, n=18). The number of ER visits and hospital admissions were lower for the pharmacist-managed group (14 vs 6 and 6 vs 3) during the time period studied. Second generation sulfonylureas and metformin were the most common agents used in both groups but at different percentages (51.5% and 24.2% vs 42.7% and 33.3%).
CONCLUSIONS: In our study, pharmacist interventions, under a CDTA resulted in significant improvement in HgA_{1c} and LDL values in patients with DM. These are two of the most important goals of diabetes therapy.

232. Survey on the professional image of pharmacists to the public in Taiwan. Tzu-Han Wu, M.S., *Hsiang-Yin Chen, M.S., Pharm.D.,* Shing-Mei Hsu-

Lee, B.S., You-Mei Lin, B.S., Li-Hua Huang, M.S.; Taipei Municipal Wang Fang Hospital; Taipei Medical College, Taipei, Taiwan.

PURPOSE: A survey was conducted to investigate the barriers to pharmaceutical care in Taiwan. Three years after amending law related to separation of pharmacy practice from medicine, professional image of pharmacists and pattern of general public to seek for medical help have not been improved significantly. Recognizing the impediment is essential to develop the realistic policies to elaborate pharmacy practice in Taiwan.
METHODS: Questionnaire included ten questions related to current status of pharmacy practice in Taiwan was constructed by the pharmacists in the Taipei Municipal Wang-Fang Hospital (TMWFH). One hundred patients were randomly invited to fill out the questionnaire from the waiting area of outpatient pharmacy at the TMWFH.
RESULTS: Eighty-two percent of patients still preferred to have prescription filled in hospitals or clinics directly, 16% of patients preferred in community pharmacy. While having drug-related problems, 61% would ask hospital pharmacists and 15% would ask community pharmacists. Only 53% of patients felt very satisfied with pharmacist consultation most of the time; 41% sometimes felt satisfied and 4% frequently felt unsatisfied. If pharmacists inform medication having some very rare side effects, more than half patients admitted that their willingness to take the medicine would decrease; only 8% would not change their willingness. Upon prescription dispensed, 45% would ask the actions of medication; and 55% would not ask at all.
CONCLUSIONS: Results from this survey clearly demonstrated that improving the professional image and knowledge of community pharmacists, and educating the public about the general and basic concepts of drug usage are eminent approaches to improve current pharmacy practice in Taiwan.

Psychiatry

233E. Cognitive effects of risperidone and olanzapine in patients with schizophrenia or schizoaffective disorder. *Philip D. Harvey, M.D.*; Mt. Sinai School of Medicine, New York, NY.

BACKGROUND: Novel antipsychotic medications have been reported to enhance cognition in patients with schizophrenia, in contrast to the negligible effects of conventional medications. In this study, the relative cognitive enhancing effects of risperidone and olanzapine, the two most commonly used of the newer medications, were compared.
METHODS: Three hundred seventy-seven outpatients with schizophrenia or schizoaffective disorder were randomized to 8 weeks of double-blind treatment with 2-6 mg/day of risperidone or 5-20 mg/day of olanzapine. The patients were rated with assessments of clinical symptoms and side effects (reported separately) and with a cognitive functioning battery examining secondary and working memory, vigilance, visuomotor speed, executive functioning, and verbal fluency.
RESULTS: Statistically significant improvements over baseline functioning with risperidone and olanzapine were found for spatial working memory, Trail-making A and B, Wisconsin Card Sorting Test categories, total errors and perseverative errors, phonological fluency and category fluency, CPT performance and California Verbal Learning Test learning, recall and recognition. There were no statistically significant differences between the two medications in the extent of cognitive enhancement on any of the measures.
IMPLICATIONS: Wide ranging improvements in cognitive functioning were detected, encompassing nearly all cognitive functions known to predict functional outcome. There were no differences between medications in group mean or proportionate improvement rates. When these analyses were repeated considering the effects of anticholinergic medications, results were still statistically significant and no effects of anticholinergic medication were statistically significant. These data are likely to be representative because they were obtained using current dosing standards, and the dropout rate for the study was low. A previous report of olanzapine superiority was not confirmed.
Presented at the Winter Workshop in Schizophrenia, Davos, Switzerland, February 5-11, 2000.

234E. Long-term cognitive effects of risperidone treatment in schizophrenia. *Philip D. Harvey, M.D.*; Mt. Sinai School of Medicine, New York, NY.

BACKGROUND: Cognitive enhancement has been demonstrated with novel antipsychotic medications. The duration of these studies has been quite short and there is no information available about the long-term cognitive-enhancing effects of these medications.
METHODS: Three hundred sixty-seven clinically stable community-dwelling patients with schizophrenia were randomized to 1 year's treatment with risperidone or haloperidol. The patients were examined at 16 and 52 weeks after baseline with assessment of clinical symptoms and cognitive functioning. Rates of relapse were also examined.
RESULTS: One hundred twenty-one subjects completed the 52-week protocol, while 25% of the risperidone patients and 40% of the haloperidol patients relapsed ($p<0.01$). Total learning on the California Verbal Learning Test was the one aspect of cognitive functioning that was significantly enhanced by treatment with risperidone at both 16 and 52 weeks ($p<0.05$). At 52 weeks, 45% of the patients treated with risperidone improved by more than 0.5 SD on this index of learning efficiency, resulting in their having scores in the clinically normal range at the end of the study.
IMPLICATIONS: In addition to preventing relapse in stable patients with more efficiency than haloperidol, risperidone improved memory performance as well. This improvement was clinically as well as statistically significant, indicating that risperidone treatment improves certain aspects of cognitive functioning even in patients who are selected for the absence of notable clinical symptoms.
Presented at the Winter Workshop in Schizophrenia, Davos, Switzerland, February 5-11, 2000.

235E. Weight gain in schizophrenic patients treated with atypical antipsychotics. *John A. Noviasky, Pharm.D.*, Shyam D. Karki, Pharm.D., M.A., FASCP, Terence Bellnier, B.S., MPA, FASCP; United Memorial Medical Center, Batavia NY; Monroe Community Hospital, Rochester, NY; Rochester Psychiatric Center, Rochester, NY.

PURPOSE: This study evaluates risk variables associated with weight gain which has been reported as a side effect of the atypical antipsychotics. In addition, effects of nutrition counseling on weight change was determined.
METHODS: Chart review was conducted on 274 patients exposed to atypical antipsychotics. Demographic data as well as weight data were collected for 6 months before and after initiation of study drug.
RESULTS: Weight changes seen are as follows: risperidone (n=107) had weight loss at –4.0 (SD = 8.7, $p<0.001$) pounds and quetiapine (n=12) had negligible effect at 0.4 (SD = 15.6, $p=0.93$) pounds, olanzapine (n=66) and clozapine (n=19) had weight increase at 3.1 (SD = 13.9, $p=0.07$) and 5.4 (SD = 8.1, $p<0.01$) pounds, respectively. When groups were broken down into male vs female and below and above maximal ideal body weight, statistical analysis revealed no significant difference between groups, although some trends were noted. Patients on olanzapine who received nutrition counseling (n=49) gained 4.0 pounds ($p=0.10$) compared to group without counseling (n=18) who gained 7.5 pounds ($p=0.05$). Multiple linear regression showed that age was important in olanzapine group ($p<0.05$) and percent above mean ideal body weight (MIBW) was important in the risperidone group ($p<0.05$). The clozapine and quetiapine groups showed no significant linear relationship to age, medication dosage, or percent above MIBW.
CONCLUSION: These results indicate that demographic variables such as age or percent above MIBW may impact on atypical antipsychotic induced weight gain. However, the association was not consistent and was not seen in clozapine or quetiapine groups. Nutrition counseling reduced weight gain and should be considered as a non-invasive intervention for patients begun on this class of medications.
Presented at the Annual Meeting of the New York State Council of Health-System Pharmacists, Bolton Landing, NY, May 2000.

236. Lack of effect of grapefruit juice and ketoconazole on the pharmacokinetics of clozapine and its major metabolites in schizophrenic patients. *Hiral D. Desai, Pharm.D.*, Michael W. Jann, Pharm.D., FCCP, BCPP, Hsien-Yuan Lane, M.D., Y.W. Francis Lam, Pharm.D., Hui-Ching Liu, M.D., Wen-Ho Chang, M.D.; Mercer University Southern School of Pharmacy, Atlanta, GA; Graduate Institute of Life Sciences, National Defense Medical Center; Hung-Tzu Psychiatric Hospital; Taipei City Psychiatric Center, Taipei, Taiwan; UTHSCSA, San Antonio, TX.

PURPOSE: The purpose of the study was to measure the effect of grapefruit juice and ketoconazole on the pharmacokinetics of clozapine and its major metabolites in schizophrenic patients.
METHODS: Five nonsmoking schizophrenic male patients received clozapine 50 mg as a single dose. All patients were co-administered 250 ml of water (control), double-strength grapefruit juice, and 400 mg of ketoconazole orally for 7 days with a washout period of at least 1 week between co-administrations. Blood samples were drawn over a 48-hour period. Plasma levels of clozapine, norclozapine, and clozapine N-oxide were analyzed by HPLC and pharmacokinetic parameters were determined. Statistical analysis was performed by ANOVA and significance was defined as $p<0.05$.
RESULTS: Pharmacokinetic parameters of clozapine were as follows:

Parameters	Water	Grapefruit Juice	Ketoconazole
T_{max} (hour)	2.4	2.7	3.4
C_{max} (ng/ml)	203.5	240.76	110.14*
$T_{1/2}$ (hour)	15.78	19.38	28.68
AUC (ng•minute/ml)	2810.24	3148.64	1989.8
CL (L/hour)	19.02	17.62	21.03

* $p=0.077$

The co-administration of ketoconazole, compared to water, significantly decreased the C_{max} of norclozapine (40.7 ng/ml vs 20.4 ng/ml; $p=0.02$) and clozapine N-oxide (33.0 ng/ml vs 15.3 ng/ml; $p=0.008$). Ketoconazole significantly decreased the AUC of clozapine N-oxide (403.9 ng•minute/ml vs 208.1 ng•minute/ml; $p=0.01$) without modifying the clozapine N-

oxide/clozapine ratio (0.144 vs 0.104; p=0.16). Grapefruit juice did not significantly effect any pharmacokinetic parameters of norclozapine or clozapine N-oxide.
CONCLUSION: Significant inhibitory effects of grapefruit juice and ketoconazole were not found upon clozapine disposition. These results can be partially explained by the abundance of hepatic CYP 3A4 versus 1A2. More importantly, in vitro models show that the Km and V_{max} for CYP 1A2 is at least ten-fold and three-fold greater than compared to CYP 3A4, respectively. Clinically relevant drug-drug interactions under in vivo conditions are mediated by Km and V_{max} parameters of CYP metabolic pathways.

237E. Switching clozapine formulations results in pharmacokinetic and pharmacodynamic differences. *L. Ereshefsky*, Y.W.F. Lam, G.B. Toney, D. Dugan, C. Gonzales, D. Velligan; University of Texas Health Science Center San Antonio; GCRC, South Texas Veterans Healthcare System; Clinical Research Unit, San Antonio State Hospital, San Antonio, TX.

PURPOSE: To investigate whether pharmacokinetic (PK) differences exist between brand and generic formulations of clozapine and whether these are reflected in cognitive pharmacodynamic (PD) measures.
METHODS: Twenty-one patients stabilized on Clozaril® (≥ 3 months of treatment) participated in the prospective, randomized (blinded rater and laboratory), crossover study. All subjects underwent a 2-week run-in period with long-term Clozaril®, before receiving a 2-week treatment each of clozapine (Zenith-Goldline) and Clozaril® (Norvartis). PK parameters were determined at the end of the 2-week treatment period (AUC day). PD measurements included Digit Symbol Substitution Test (DSST) and cognitive changes (as measured by Overall Cog Z, an overall index of cognitive functioning calculated from the Z scores of a neurocognitive test battery). The PD parameters were assessed at 0, 1, and 4 hours after clozapine dosing on both AUC days.
RESULTS: The difference in the dose normalized ln C_{max}, was statistically different between Clozaril® and generic clozapine, but the ln AUC_{0-12} and ln C_{min}, were not. The change in concentration (C_{max} - C_0) as a result of the morning dose on the AUC day, was significantly different between the two formulations. In addition, regression analysis showed a significant correlation between the AM dose (range: 100 to 400 mg) and the change in concentration (r=0.493, p=0.023) for Clozaril®, but not for clozapine (r=0.012, p=0.959). DSST and Overall Cog Z were different between the two formulations at 1 hour post dose administration, possibly reflecting the significant differences in C_{max}.

Dose Normalized PK Parameters	Clozaril® LS Mean (SD)	Clozapine LS Mean (SD)	p Value and 90% CI Ratio
ln C_{max} (ng/ml)	0.61 (0.12)	0.45 (0.12)	0.002
	0.78, 0.92		
ln AUC	2.72 (0.13)	2.63 (0.13)	0.066
	0.85, 0.99		
ln C_{min} (ng/ml)	-0.17 (0.15)	-0.23 (0.15)	0.354
	0.85, 1.05		
Parameters	Mean (SD)	Mean (SD)	
ΔC (C_{max} - C_0; ng/ml)	363.80 (164.84)	260.80 (189.03)	0.006
DSST	32.24 (3.17)	35.00 (3.17)	0.025
Overall Cog Z at 1 hour	0.00 (0.12)	0.10 (0.12)	0.042

CONCLUSION: The small numeric difference in mean AUC between the two formulations, does not reflect the systematic bias observed for lower plasma concentrations for clozapine than Clozaril®, as reflected by the AUC CI ratio < 1. In addition, the absolute changes in drug concentration after the AM dose and the correlation between these two variables suggest a significant difference in the amount of drug absorbed between formulations. PK parameters are reflected in PD measures such as DSST and Overall Cog Z scores.
Presented at the 3rd Annual Meeting College of Psychiatric and Neurologic Pharmacists, Washington D.C., April 2000.

238. Paroxetine effects on psychological and sympathetic responses during public speaking. *Michael Golding, M.D.*, Michael Kotlyar, Pharm.D., James C. Garbutt, M.D., Joseph Guzzo, M.D., Eric Sontz, M.D., Alan Hinderliter, M.D., Donald W. Graff, Pharm.D., Stanley W. Carson, Pharm.D.; John Umstead Hospital, Butner, NC; University of North Carolina at Chapel Hill, Chapel Hill, NC; University of Minnesota, Minneapolis, MN.

PURPOSE: Increased sympathetically mediated cardiovascular responses to mental stress tasks in patients with coronary artery disease (CAD) have been found to predict subsequent adverse cardiovascular events and death. Although selective serotonin reuptake inhibitors (SSRIs) have been shown to decrease cardiovascular reactivity to mental stress tasks in patents with psychiatric disease, no such data are available for those with no psychiatric diagnoses. This pilot investigation assessed whether administration of paroxetine alters cardiovascular reactivity in psychiatrically healthy patients with a history of CAD.
METHODS: This double-blind, placebo-controlled pilot study enrolled five psychiatrically healthy subjects with a history of coronary artery bypass grafting or balloon angioplasty. Each subject delivered an impromptu public speech prior to and after receiving a month of either 10 mg paroxetine once daily (n=3) or placebo (n=2). Measurements of psychological distress, blood pressure, heart rate, and plasma norepinephrine concentrations during the speeches were compared between subjects randomized to the two study groups.
RESULTS: Relative to placebo, subjects receiving paroxetine reported less psychological distress and exhibited decreased average plasma norepinephrine concentrations (221 vs 312 ng/ml), systolic blood pressure (149 vs 156 mmHg), diastolic blood pressure (79 vs 87 mmHg) and heart rate (59 vs 67 bpm) during their speech after paroxetine. No such decreases were found in placebo treated subjects.
CONCLUSIONS: This pilot investigation suggests that paroxetine may decrease psychological and physiological responsivity to mental stress in patients with a history of CAD.

239. Coronary heart disease risk factor characterization of patients co-prescribed atypical antipsychotics and lipid-lowering agents. *Charles F. Caley, Pharm.D.*, Chandra K. Cooper, B.S., R.Ph.; University of Connecticut, Storrs, CT; Institute of Living, Hartford, CT.

PURPOSE: Numerous reports indicate that atypical antipsychotics may be associated with increases in serum triglycerides, weight and serum glucose which can contribute to coronary heart disease development. Coronary heart disease (CHD) risk factors were characterized in patients co-prescribed an atypical antipsychotic and lipid-lowering treatment.
METHODS: A computer search of hospital records between January 1994 and April 1999, identified inpatients who had lipid-lowering and atypical antipsychotic treatments co-prescribed. Medical records were reviewed retrospectively for demographics, psychiatric/medical diagnoses, medications, weight, total/LDL/HDL cholesterol, serum triglyceride and serum glucose values.
RESULTS: Eighty-four of 1,992 (4%) patients were co-prescribed a lipid-lowering agent with an atypical antipsychotic. Our sample (37 M/47 F) had a mean age of 59 ± 14.39 years; the most common psychiatric diagnoses were: schizoaffective disorder (25%), major depression (21%), schizophrenia (17%), dementia (14%), and bipolar disorder (12%). Risperidone and olanzapine were used most commonly for antipsychotic treatment, and HMG Co-A reductase inhibitors were used most frequently for lipid treatment. Forty-eight percent of our patient sample had ≥ 3 CHD risk factors. Most common risk factors overall included: LDL greater than target (49%), hypertension (43%), cigarette smoker (39%), and diabetes (37%). Additional results will be presented.
CONCLUSION: This study indicates that multiple CHD risk factors exist in patients co-prescribed atypical antipsychotic and lipid-lowering treatment. Our data also illustrates that CHD risk factor awareness is important and that a complete understanding of how atypical antipsychotics affect CHD risk factors is needed.

Pulmonary

240E. Interleukin-1β protects A549 lung epithelial cells from apoptosis. *Kristin R. Coulter, Ph.D.*, Daren L. Knoell, Pharm.D.; Ohio State University, Columbus, OH.

Lung epithelial cells constitutively express the Fas receptor on their surface. Therefore, Fas-mediated apoptosis may be critical in epithelial cell remodeling in the lung. This work investigates the effects of interleukin-1β (IL-1β), a relevant pro-inflammatory cytokine in lung disease, on Fas-mediated apoptosis and epithelial cell survival. A549 cells were treated with IL-1β and/or IFN-γ prior to the addition of a Fas-crosslinking antibody (FasAb). Cells were then stained to detect cytoplasmic and nuclear apoptotic events using a monoclonal antibody specific for caspase-cleaved cytokeratin 18 and DAPI, respectively. Cells staining for both caspase-cleaved cytokeratin 18 and condensed nuclei/chromatin were identified as apoptotic. Treatment with IL-1β before FasAb lead to a significantly lower relative incidence of apoptosis than treatment with IFN-γ and FasAb alone or in combination (IL-1β + FasAb, 3.4%; IFN-γ, 83%; IFN-γ + Fas Ab, 100%; IL-1β + IFN-γ + Fas Ab, 7.2%). FACS analysis revealed that IFN-γ increases Fas surface expression whereas, IL-1β does not. Western analysis revealed that IL-1β completely prevents activation of caspase-8 and induces the expression of the anti-apoptotic factor Bcl-X_L. Finally, protection from Fas-mediated death via IL-1β was in part PI 3-K dependent since pretreatment with the PI 3-K inhibitor, LY294002, increased the incidence of apoptosis in IL-1β/FasAb treated cells. This demonstrates that IL-1β may function as a survival factor in lung epithelial cells by preventing Fas-mediated death. Overall, this establishes a critical link between inflammation and parenchymal cell remodeling in the lower airway microenvironment. HL56336-01 (DLK) and F32 HL09991-01 (KRC).
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241. Do children with asthma take oral montelukast more consistently than inhaled fluticasone? *Parul Patel*, Alan Hutson, Ph.D., James Sherman, M.D.,

Sarah Chesrown, M.D., Ph.D., Leslie Hendeles, Pharm.D.; University of Florida, Gainesville, FL.

PURPOSE: To test the hypothesis that adherence with montelukast (M), a once-daily tablet, would be greater than with fluticasone propionate (FP), a twice-daily metered dose inhaler.
METHODS: We obtained prescription records of 166 children with persistent asthma, median (range) age of 7.7 (1.7-21) year who were prescribed M alone (n=54), FP alone (n=48) or the combination (n=69). In younger children, FP was administered through a chamber/mask. Patients who received free samples were excluded. Refill histories were obtained from pharmacies identified by caretakers (n=140) or from Medicaid when caretakers could not be contacted (n=26). Maximum possible adherence was calculated as (#doses refilled) / (#doses prescribed) x 100 for a median (range) observation period of 203 (84-365) days for M and 314 (97-365) days for FP. Bootstrapping techniques were used to calculate 95% CIs while Spearman was used for rank correlations.
RESULTS: Median (95% CI) adherence was 59% (48%, 65%) for M and 44% (35%, 50%) for FP. The overall median difference between M and FP, accounting for paired data, was 16% (2%, 30%) which was statistically significant. Adherence was not significantly correlated with age or length of observation period. In the combination group, there was a weak correlation between adherence to M and FP (r=0.34, p=0.004). Patients taking monotherapy were not significantly more adherent than those taking the combination.
CONCLUSIONS: Adherence to both drugs was suboptimal. However, these data indicate that children are likely to take M more consistently than FP. Whether this translates into better asthma control requires further study.

Rheumatology

242. Safety and efficacy of etanercept in the juvenile rheumatoid arthritis. *Renee F. Robinson, Pharm.D.*, Milap C. Nahata, Pharm.D., Robert Rennebohm, M.D., Gloria Higgins, M.D.; Children's Hospital; Ohio State University, Columbus, OH.

PURPOSE: The aim of this study was to demonstrate the safety and efficacy of etanercept in the treatment of juvenile rheumatoid arthritis (JRA).
METHODS: All JRA patients (n=23) who received etanercept in rheumatology clinic over a 14-month period were evaluated. Patient demographics, type of arthritis, dosing regimens, family history, measures of joint function, and laboratory parameters were obtained for each patient. A survey including questions noted in the CHAQ, JFAR and PedsQL scales were administered to patients and parents to assess physical and emotional function, pain, adverse events and quality of life on each clinic visit.
RESULTS: The mean dose was 0.4 mg/kg/dose (maximum of 25 mg/dose) in patients with polyarticular (16 patients) and systemic arthritis (7 patients). Patient and parent assessment of overall function scores from baseline to last clinic visit (scale 0 to 10, 0 = best) were significantly improved (-4.6 ± 2.3, p=0.00). However, the differences were not significant between patients with polyarticular and systemic arthritis (p=0.07). Frequency and duration of pain decreased (-4.0 ± 2.2, p = 0.00) and the energy level increased (p=0.00) with etanercept therapy. Joint function, laboratory parameters and overall abilities of patients improved with therapy. Patient concerns with long-term health declined and school absence due to disease (-0.7 ± 1.2, p=0.01), was decreased.
CONCLUSIONS: Etanercept was effective in improving patient joint function. It appears to significantly improve physical and emotional function, and quality of life of patients with JRA.

Substance Abuse/Toxicology

243. Outcome variations between psychiatric and non-psychiatric patients in an outpatient smoking cessation program. *Deepa Dronamraju, Pharm.D.*, Susan R. Winkler, Pharm.D., BCPS, Julia L. Seabolt, Pharm.D., BCPP; University of Illinois at Chicago, Chicago, IL.

PURPOSE: This research evaluated psychiatric and non-psychiatric patients enrolled in a smoking cessation clinic in order to determine what differences exist in severity of smoking, quit rate and methods used to quit.
METHODS: A retrospective chart review of subjects enrolled in the University of Illinois at Chicago Medical Center smoking cessation clinic from January 1997, to April 1999, was performed. The information extracted from each subject was as follows: number of cigarettes smoked per year, Fagerstrom score, diagnosis of a current or past mental illness, whether they quit smoking or not, length of smoking cessation, if successful, methods used to quit, and number of group sessions attended.
RESULTS: Psychiatric patients had an average Fagerstrom score higher than non-psychiatric patients (5.63 vs 4.5). Psychiatric patients averaged more in-person visits compared with non-psychiatric patients (7.0 vs 3.2). A correlation between the number of visits attended and the quit rate was shown for the psychiatric patients, but not for the non-psychiatric patients. The majority of psychiatric patients successfully quit by the cold turkey method (3/6, 50%). In non-psychiatric patients the most successful method for quitting smoking was self-taper (5/13, 38.5%), followed by using a nicotine replacement patch (4/13, 30.8%).
CONCLUSIONS: Psychiatric patients appear to develop more severe nicotine dependence when compared to non-psychiatric patients. Psychiatric patients seemed to benefit from more in-person contact in order to quit; however, this was the not the case for non-psychiatric patients. In addition, there appears to be a difference in the successful quit methods between the two populations.

244. Management of alcohol withdrawal using the clinical institute withdrawal assessment for alcohol scale. *Kam Capoccia, Pharm.D.*, Stacy Cambell-Bright, Pharm.D., BCPS, Toyin Tofade, M.S., Pharm.D., BCPS; University of North Carolina Hospitals, Chapel Hill, NC.

PURPOSE: This study used the Clinical Institute Withdrawal Assessment (CIWA) for Alcohol Scale to prevent the progression and complications of alcohol withdrawal (AW).
METHODS: Patients admitted to the medicine or respiratory intensive care unit or the critical care step down unit who demonstrated any signs or symptoms of AW were assessed using the CIWA Scale. The patients' medical and social histories were documented along with the complete management of the AW. The use of restraints and the rates of aspiration pneumonia, seizures, delirium tremens and over-sedation were also documented. A retrospective chart review was performed to compare the management of AW in this patient population prior to the use of the CIWA Scale. Intention-to-treat analysis, Wilcoxan Rank Sum and Fisher's Exact Test were used to analyze the data.
RESULTS: Nineteen patients were assessed using the CIWA Scale and 24 patients were identified retrospectively. There was no difference in the amount of benzodiazepines used among the two groups but the number of PRN doses and the number of patients who were over-sedated was significantly less in the CIWA group ($p<0.05$). The use and length of time in restraints were significantly less in those patients assessed by the CIWA Scale ($p<0.05$). The rates of complications did not differ among the two groups.
CONCLUSION: An assessment tool used to individualize treatment of AW allows for safer and smoother management of these patients. Due to the small number of patients the protocol will be reinstated in these units to collect more data.

245. Elimination of inadvertent methotrexate overdose using continuous venovenous hemodiafiltration. *Martha G. Slot, R.Ph., Wendy L. Thomas, Pharm.D.*, Adam T. Wolfe, M.D., Jean Deans, M.D., Robert F. Johnson, M.D., Jeffrey L. Wilt, M.D.; Spectrum Health-East Campus, Grand Rapids, MI.

A 77-year-old Caucasian male receiving chronic hemodialysis presented after inadvertent methotrexate administration with shock and pancytopenia. He had been recently transferred to a rehabilitation center; while there, the patient inadvertently received nine doses of oral methotrexate in 5 days (22.5 mg total). An initial methotrexate serum level returned as 0.36 uM, and the patient was started on leucovorin and folic acid. Methotrexate is cytotoxic at concentrations greater than 0.05 uM. Toxicity appears to be
related more to the duration of exposure to methotrexate than to the actual dose or maximum concentration obtained. Hemodialysis was not possible secondary to the patient's hemodynamic compromise.
Instead, continuous venovenous hemodiafiltration (CVVHDF) was instituted for renal replacement as well as to attempt clearance of serum methotrexate levels. The predominant route of methotrexate elimination is renal excretion through glomerular filtration. Daily serum methotrexate levels were obtained along with methotrexate levels in the dialysate fluid. On CVVHDF the kinetic parameters for methotrexate included: $k_{el}=0.0288^{-1}$ and $T_{1/2}$ of 24 hours.
In our patient, serum levels of methotrexate rapidly decreased to a level of 0.06 uM. CVVHDF was effective in clearing toxic concentrations of methotrexate from this patient. CVVHDF was chosen to avoid the hemodynamic instability and because systemic clearance of methotrexate has been disputed using conventional hemodialysis. We propose CVVHDF may be used to remove undesired methotrexate in human subjects, particularly in those with renal disease and/or shock.

Transplantation/Immunology

246. Impact of mycophenolate therapy on recurrent rejection in kidney transplant patients. *Eva M. Vasquez, Pharm.D.*, Raymond Pollak, M.B., Enrico Benedetti, M.D.; University of Illinois at Chicago, Chicago, IL.

Approximately one-third of kidney transplant patients, who have a rejection (REJ) episode, experience recurrent rejection. The purpose of this study was to assess the efficacy of mycophenolate mofetil (MMF) in reducing the occurrence of recurrent REJ following an initial REJ episode in kidney transplant patients during the first year following transplant. The active study group consisted of 42 kidney transplant patients who were prospectively placed on Mycophenolate mofetil following treatment of their initial REJ episode to prevent recurrent REJ. Mycophenolate mofetil 1-2 g/day was given.

Doses were adjusted based on tolerance; MMF was to be continued for at least 6 months. The control group consisted of 122 consecutive kidney transplant patients who had received standard anti-REJ therapy without the addition of MMF. Anti-REJ therapy for both groups consisted of either corticosteroids (Methylprednisolone 500 mg IV for 3 days or oral prednisone 2 mg/kg day with rapid taper over 3 weeks), OKT3 5 mg/day for 10 days or ATG 15 mg/kg/day for 10 days. All REJ episodes were routinely documented by biopsy. The majority of REJ were histologically characterized as mild-moderate. The study groups did not differ with respect to demographic and immunologic factors. Maintenance immunosuppression consisted predominantly of cyclosporine, prednisone ± azathioprine. The majority of patients (76%) received corticosteroids for treatment of their first REJ episode. There was a 68% reduction in the occurrence of recurrent REJ within the first year of transplant in patients receiving MMF. Only 14% of patients receiving MMF developed recurrent REJ compared to 44% of patients in the control group ($p<0.05$). Approximately 50% of patients developed MMF-associated adverse effects (leukopenia, GI toxicity). Only 52% of patients remained on MMF at 6 months. One-year graft survival was 86% in the MMF group and 89% in the control group ($p>0.05$). One-year patient survival was 93% and 100% respectively ($p>0.05$). In conclusion, the addition of MMF therapy to patients experiencing acute renal allograft may prevent recurrent rejection in patients at high-risk for allograft loss.

247. Pharmacokinetics and safety of two single doses of RAD001 in stable lung and heart/lung transplant recipients with and without cystic fibrosis. R.L. Doyle, M.D., M.I. Hertz, M.D., J.M. Dunitz, M.D., J.E. Loyd, M.D., A.A. Stecenko, M.D., *R.L. Wong, M.D.*, K. Chappell, Pharm.D., T. Brazelton, B.S., J.M. Kovarik, Ph.D., R.E. Morris, M.D.; Stanford University, Stanford, CA; University of Minnesota, Minneapolis, MN; Vanderbilt University, Nashville, TN; Novartis Pharmaceuticals, East Hanover, NJ; Novartis Pharma AG, Basel, Switzerland.

RAD001 (RAD) is a novel macrolide with potent immunosuppressive and antiproliferative activities that prevents obliterative airway disease in preclinical models. A randomized, double-blind, crossover study was conducted to assess the pharmacokinetics (PK) and safety of RAD in stable lung and heart/lung transplant recipients with and without cystic fibrosis (CF). Single doses of RAD at doses of 0.035 mg/kg (2.5 mg max) or 0.10 mg/kg (7.5 mg max) were co-administered with cyclosporine (CsA, Neoral®), steroids, and azathioprine on days 1 and 16. Vital signs, lab assessments and adverse events (AE) were measured during the study. RAD PK samples were taken on days 1-7 and 16-22. Steady-state CsA profiles were obtained at baseline and with each RAD dose.
RESULTS: Eight of 20 patients had CF (seven lung, one heart/lung) and 12 did not (nine lung, three heart/lung). PK: At both dose levels, CF patients had slightly lower dose-normalized C_{max} compared with non-CF patients ($p=0.03$). Overall exposure (AUC) did not differ between CF and non-CF patients with either the low dose (137 ± 72 vs 135 ± 34 ng•hour/ml/mg) or high dose (107 ± 50 vs 125 ± 41 ng•hour/ml/mg; $p=0.63$). C_{max}, C_{min} and AUC of CsA remained stable. CsA AUC values were 7019 ± 2393 (baseline), 7328 ± 2352 (low dose RAD), 7178 ± 2126 (high dose RAD) ng•hour/ml (p=NS). Safety: There were no deaths, adverse event dropouts, or significant differences in AEs among CF and non-CF patients. Headache (20%) was the most common AE along with edema (10%), tachycardia (15%), and hypertension (10%). One patient each reported leukopenia with granulocytopenia, and anemia. New or worsening lab values were reported by one CF patient for cholesterol and by five patients (one CF, four non-CF) for triglycerides.
CONCLUSIONS: Exposure to RAD was similar in CF and non-CF patients. Single-dose RAD did not affect the PK of CsA. Both RAD doses were safe and well tolerated by CF and non-CF patients. Ongoing studies are assessing the long-term safety of RAD in lung and heart/lung transplantation.

248. Lymphopenia as a marker of T-cell subset suppression induced by OKT3, ATGAM, azathioprine or mycophenolate treatment in lung transplant recipients. *Marcus Haug III, Pharm.D., M.S.*, Jodi Petrie, Pharm.D., Atul Mehta M.D., Omar Minai, M.D., Steve Gordon, M.D., Janet Maurer, M.D., Robert Schilz, D.O., Ph.D.; The Cleveland Clinic Foundation, Cleveland, OH.

INTRODUCTION: OKT3 or ATGAM treatment produces lymphopenia (< 500 cells/mL) and T-cell subset depletion. The purpose of this study was to: 1) determine lymphocyte number correlation with white blood count (WBC) and T-cell subset numbers CD_2, CD_3, CD_4 and CD_8 for patients that received OKT3, ATGAM, and azathioprine (AZA)/mycophenolate (MMF); and 2) determine if lymphopenia correlates with depletion of T-cell subsets for these medications.
METHODS: A retrospective review of 142 lung transplant recipients identified those with concurrent lymphocyte numbers and T-cell subset numbers measured while receiving OKT3, ATGAM, or AZA/MMF. Linear regression correlation of lymphocyte number versus WBC, and T-cell subsets during OKT3, ATGAM, or AZA /MMF treatment was performed.
RESULTS: Seven patients received OKT3, six patients received ATGAM and 16 patients receiving AZA/MMF were studied. AZA or MMF produced lymphopenia and T-cell subset depletion just as OKT3 or ATGAM. Lymphocyte number correlated significantly ($p<0.03$) with all T-cell subset numbers ($r=0.62$ to 0.92 or OKT3, $r=0.60$ to 0.64 for ATGAM, $r=0.76$ to 0.84 for AZA/MMF) but not with WBC ($r=0.27$, $p=0.101$).
CONCLUSIONS: Lymphocyte and T-cell subset numbers may be extremely suppressed by immunosuppressants such as AZA or MMF. There is no significant correlation of WBC with lymphocyte number and WBC cannot predict T-cell subset depletion. Lymphocyte number, rather than WBC, is a better measure of AZA or MMF toxicity in lung transplant patients. There is strong correlation of lymphocyte number with T-cell subset number during OKT3, ATGAM, AZA or MMF therapy.

249. Treatment of recurrent hepatitis C infection with ribavirin monotherapy after orthotopic liver transplant. *Gordon R. Ingle, Pharm.D.*, BCPS, Curtis D. Holt, Pharm.D., Leonard Goldstein, M.D., Gregg Kunder, R.N., Ronald W. Busuttil, M.D., Ph.D.; University of California; Los Angeles Medical Center, Los Angeles, CA.

PURPOSE: Due to extremely limited data, this study determined the effectiveness of ribavirin monotherapy for treatment of recurrent hepatitis C (HCV) post-orthotopic liver transplant (OLT).
METHODS: Twenty-three OLT patients experiencing recurrent HCV in 1999 documented by liver biopsy and quantitative HCV RNA were reviewed. Exclusion criteria included coinfection with another hepatotropic virus, hemoglobin < 9 g/dl, and decompensated liver disease. Oral ribavirin was started at 600-1000 mg/day and reduced to 400-600 mg/day for adverse effects (AEs). The primary end point was HCV-RNA clearance at 24 weeks. Secondary end points included ALT and total bilirubin (TB) normalization, incidence of acute rejection (AR), patient and graft survival, and AE profile.
RESULTS: Eighteen patients have completed 24 weeks of ribavirin. The mean age was 51 years and mean follow up was 258 days. Over 24 weeks, mean HCV RNA dropped from 33.22×10^6 to 10.88×10^6 copies/ml ($p=0.053$). Only four of 18 (22%) patients had HCV RNA clearance at 24 weeks and two had HCV RNA recur. Mean ALT and mean TB concentrations were significantly lower after 24 weeks. ALT declined from 242 to 109 U/L ($p=0.014$) and TB from 4.3 to 1.8 mg/dl ($p=0.012$). Fifteen of 18 (83%) patients experienced a biochemical response (normalization of ALT or TB). Two patients (8.7%) had ribavirin stopped due to AEs. No patient experienced AR. All patients are living with functioning grafts.
CONCLUSION: Ribavirin monotherapy is not effective for clearing HCV RNA from the blood; however, it does provide most patients with a biochemical response and is relatively well tolerated. Ribavirin monotherapy may improve time to allograft cirrhosis or re-transplantation, but long-term follow up is essential.

250. Efficacy and cost reduction with extended prophylactic acyclovir dosing interval. *Polly E. Kintzel, Pharm.D., BCPS, BCOP*, Jill Walsh, Pharm.D., Alan F. List, M.D.; Harper Hospital, Detroit, MI; Arizona Cancer Center, University of Arizona Health Sciences Center, Tucson, AZ.

PURPOSE: This report describes sustained efficacy and notable cost reduction following conversion of prophylactic intravenous (IV) acyclovir 250 mg/m^2 from every 8-hour (q8h) dosing to every 12-hour (q12h) dosing following autologous or allogeneic bone marrow transplantation (BMT).
METHODS: Based on a decision by the institutional BMT committee, the standard of prophylactic acyclovir 250 mg/m^2 IV q8h beginning day +1 after bone marrow transplantation until initiation of oral prophylactic acyclovir following hematologic recovery and resolution of mucositis, or requirement for antiviral treatment, was converted to the same dose and duration of acyclovir 250 mg/m^2 IV q12h. It was predetermined that the new dosing schedule would be reassessed for an incidence of ≥ 10% *Herpes simplex* virus (HSV) or ≥ 4% *Varicella zoster* virus (VZV). Prophylactic acyclovir doses administered to consecutive BMT patients were tallied retrospectively from pharmaceutical care records.
RESULTS: Efficacy and cost reduction were evaluated in 234 of 266 consecutive BMT patients 6, 18, and 30 months following implementation of the new regimen. Moderate to severe regimen-related mucositis was common and expected. A total of 6746 acyclovir doses were administered, and a total of 3746 acyclovir doses were avoided to achieve cost reduction of $149,840. The incidence of microbiologically documented and presumed HSV disease in patients receiving prophylactic IV acyclovir q12h were 1.3% and 2%, respectively. Documented or presumed VZV did not occur.
CONCLUSION: Conversion from q8h to q12h dosing of prophylactic acyclovir maintained effective HSV and VZV prophylaxis with notable cost reduction.

251. Influences on the interaction of fluconazole with calcineurin inhibitors. *A. Scott Mathis, Pharm.D.*, Teresa DiRenzo, Pharm.D., Gary Friedman, M.D., Bruce Kaplan, M.D., Robert Adamson, Pharm.D.; Rutgers University, New Brunswick, NJ; Saint Barnabas Medical Center, Livingston, NJ; University of Michigan, Ann Arbor, MI; Pfizer Pharmaceuticals, New York, NY.

PURPOSE: Our group has previously presented data demonstrating that the interaction of fluconazole with calcineurin inhibitors is not primarily

dependent on dose or route of fluconazole, contrary to previous belief. We present our analysis of the factors influencing the interaction of fluconazole with calcineurin inhibitors (CNI).
METHODS: Adult renal and simultaneous pancreas kidney transplant recipients receiving fluconazole for treatment or prophylaxis were included, if CNI trough blood levels during therapy and outpatient follow-up were available. CNI level per daily dose ratio (LDDR) was calculated (CNI trough/daily dose) to account for the influence of CNI dose on blood concentration. These were plotted against daily CNI dose ratio (dose/100 for cyclosporin, dose for tacrolimus) to determine individual metabolic pattern.
RESULTS: Nineteen patients (11 males) received 25 episodes of fluconazole. Two distinct metabolic patterns were noted, and this was not dependent on dose or route of fluconazole, age, or other drug interactions. Overall, five patients failed to exhibit an interaction, but one did have a significant interaction the first time fluconazole was introduced. When the 19 patients were evaluated with Fisher's exact test, female sex (p=0.018), and African American ethnicity predicted lack of interaction (p=0.024). When all 25 episodes were considered, African American ethnicity (p=0.022) and female sex (p=0.04) predicted lack of interaction.
CONCLUSIONS: Females and African Americans appear to have increased metabolic capacity. Drug interactions previously attributed to enzyme inhibitor dose and route may be affected by sex and ethnicity. Evidence indicates that intravenous P450 inhibitors may interact with both liver and intestinal P450, thus pharmacogenetic influences on P-glycoprotein and CYP3A function/expression, and possibly up-regulation after transplantation, may primarily influence these interactions.

252E. Pharmacokinetics and tolerability of RAD in pediatric renal transplant patients. *J. Mahan*, N. Webb, R. Vandamme-Lombaerts, J. Lemire, R. Ettenger, P. F. Hoyer, J. M. Kovarik, L. McMahon, S. Wehr, B. Boger for the RADB257 Study Group; Children's Hospital, Columbus, OH; Children's Hospital, Manchester, United Kingdom; University Hospital Gasthuisberg, Leuven, B; University of California, San Diego, CA; University of California, La Jolla, CA; University of California, Los Angeles, CA; Universitätsklinik Essen, Essen, D; Novartis Pharma AG, Basel, CH; Novartis Pharmaceuticals, East Hanover, NJ.

PURPOSE: To characterize the single-dose pharmacokinetics and acute tolerability of RAD, a novel macrolide with potent immunosuppressant and antiproliferative properties, in clinically stable pediatric kidney transplant recipients.
METHODS: Patients currently receiving a cyclosporine-based regimen were given a single dose of 1.2 mg/m^2 RAD as a fast-dispersible tablet formulation in water. Nine blood samples were collected over a 72-hour period. Whole blood concentrations of RAD and cyclosporine were determined simultaneously by LC/MS.
RESULTS: There were 11 patients (10 boys, 1 girl), age 7.7 ± 3.6 years (range: 3-14), weight 26 ± 14 kg (range: 16-56), body surface areas of 0.92 ± 0.32 m^2 (range: 0.67-1.61). The average RAD dose was 1.1 ± 0.4 mg (range: 0.8-1.9). RAD was rapidly absorbed with peak blood concentrations (C_{max}) reached by 1 hour (range: 1-2 hours). Clearance (CL/F) and distribution volume (Vc/F) increased with age, body surface area, and weight. Half-life ($t_{1/2}$) was not influenced by demographics.

	C_{max} (ng/ml)	AUC (ng•hour/ml)	CL/F (L/hour/m^2)	Vc/F (L/m^2)	$t_{1/2}$ (hour)
Mean ± SD	20 ± 5	229 ± 77	5.8 ± 1.9	37 ± 12	36 ± 14
Range	14 - 29	137 - 359	3.3 - 8.8	25 - 63	20 - 64

Compared with adults, apparent clearance in children was reduced which appeared to be due to a smaller apparent distribution volume rather than to differences in elimination half-lives. RAD was well tolerated. Three patients had adverse events; all were either mild or moderate in severity and fully reversible. There were no clinically relevant changes in vital signs or ECGs over the course of the study. The daily cyclosporine dose was 186 ± 97 mg or 7.6 ± 2.2 mg/kg. During RAD coadministration, C_{max} was 1439 ± 216 ng/ml and AUC was 5472 ± 1152 ng•hour/ml. Predose trough concentrations were 160 ± 48 ng/ml prior to RAD administration on day 1 and did not change over the 4-day period while RAD was detectable in blood: 165 ± 53 (day 2), 152 ± 51 (day 3), 154 ± 58 (day 4), p=0.66.
CONCLUSIONS: Single-dose RAD was well tolerated and had no discernible effect on cyclosporine pharmacokinetics. While the adult 12-hour dosing interval will likely be appropriate for pediatric patients, they will require a reduced dose based on body size compared with adults.
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253. Public survey of Asian attitudes on organ donation. *LanChi L. Bui, Pharm.D.*, Steve Takemoto, Ph.D., Sean Cao, M.D., Tu Le, M.D., David K. Imagawa, M.D., Ph.D.; UCI Medical Center, Irvine, CA; University of California, Los Angeles, CA.

PURPOSE: Ten people die every day while waiting for a transplant or a vital organ such as a kidney, heart, or liver. Asians have increased susceptibility to liver diseases, but their consent rate for organ donation is about one-third that of other ethnic groups. This study examines the result of a survey on Asian attitudes toward organ donation.
METHODS: A survey with 12 questions was distributed at two public events and the results of 198 responses are summarized here.
RESULTS: The majority of respondents felt Asians were more likely to suffer from illness that could be cured with a transplant, and that they would consider organ donation should a loved one die suddenly. Up to 20 percent had mistrust in the organ donation process; that a doctor may not try to save their lives after an accident, that rich and famous people are more likely to be transplanted, that organ donation is against their religious beliefs, or that organ transplantation is a risky experimental procedure. Older respondents were more likely to express mistrust than those who were younger.
CONCLUSION: The majority of Asians surveyed understood the major issues involving organ donation. Donor awareness education should be targeted to older individuals since they have greater mistrust of the process, and generally make the consent decision.

254E. Intramuscular hepatitis B immune globulin prophylaxis for recurrent hepatitis B in orthotopic liver transplant recipients. Steven D. Colquhoun M.D., Susan R. Post B.A., *Theodore M. Sievers, Pharm.D.*, Sergio Rojter, M.D., Federico Villamil, M.D., John M. Vierling, M.D.; Cedars-Sinai Medical Center, Los Angeles, CA.

PURPOSE: The efficacy of long-term intravenous (IV) hepatitis B immune globulin (HBIg) in the prevention of hepatitis B (HBV) recurrence after liver transplantation is well established. Our goal was to determine the safety and efficacy of the indefinite IM administration of HBIG in achieving protective anti-HBs titers.
METHODS: Twenty-six adult patients (23 male, 3 female, ages 35-63) with HBV cirrhosis underwent OLT between January 1994 and August 1998. The HBIg protocol included 10,000 IU IV in the anhepatic phase and daily for six days, followed by indefinite administration of 1,000 IU IM every 3-4 weeks. Protocol goals included a titer of ≥ 500 mIU/ml in the first month, and ≥ 100 mIU/ml thereafter.
RESULTS: Titers of > 500 mIU/ml were achieved in 85% of patients at 1 month post-op (range 135-6,466) while titers of ≥ 100 mIU/ml were maintained in 96% of patients at 3 months post-op (range 85-1600). Hepatitis B recurred in five patients. The anti-HBsAb titers prior to recurrence were therapeutic suggesting the emergence of HBs escape mutants. Overall survival in this group is 81% with a follow up of 90-1570 days. Three patients underwent re-OLT, but none due to recurrent HBV. There were no serious adverse events associated with IM injections.
CONCLUSIONS: IM administration of HBIg is well tolerated, achieves protective titers of anti-HBs and is as successful as prophylaxis utilizing ten-fold higher doses administered IV. Based on the average wholesale price of HBIg and typical IV dosing, long-term IM administration can account for significant annual cost savings.
Presented at the 25th Annual Meeting of the American Society of Transplant Surgeons, Chicago, IL, May 1999.

255. Pharmaceutical care services reduce adverse drug reactions in renal transplant patients. *Marie A. Chisholm, Pharm.D.*, Leslie J. Vollenweider, Pharm.D., Laura L. Mulloy, D.O., Muralidharan Jagadeesan, M.D., Bradley C. Martin, Ph.D., Joseph T. DiPiro, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: To determine the influence of pharmaceutical care services on the occurrence of adverse drug reactions (ADRs) in renal transplant patients. This interim data analysis is part of a larger, prospective study to assess the impact of pharmaceutical care on health outcomes.
METHODS: Renal transplant patients at the Medical College of Georgia Renal Transplant Clinic were prospectively randomized into an intervention group or a control group. Patients in the intervention group received monthly pharmaceutical care services which included ongoing medication reviews, with emphasis on preventing or resolving medication-related problems and providing pharmacotherapy recommendations. Patients in the control group had no clinical pharmacist interaction. The occurrence of an ADR, defined as any noxious, unintended, and undesired effect of a drug which occurs at doses used in humans for prophylaxis, diagnosis, or therapy, was documented for all patients enrolled in the trial for at least 1 year as of June 1999. Mann Whitney U-Test was performed to detect differences in the number of ADRs experienced between patients in the intervention and control groups.
RESULTS: The groups were similar in sex, age, race, and kidney donor type. Patients in the intervention group (n=26) experienced fewer ADRs than patients in the control group (n=28), with a mean ADR of 1.04 ± 1.25 per patient per year compared to 1.96 ± 1.73 per patient per year, respectively ($p<0.05$).
CONCLUSION: Renal transplant clinic patients who received pharmaceutical care services experienced fewer adverse drug reactions than patients who did not receive pharmaceutical care services.

256. Gender-specific effect on pharmacokinetics of cyclosporine. *David I. Min, Pharm.D., M.S.*, Miyoung Lee, M.S.; University of Iowa, Iowa City, IA.

PURPOSE: To evaluate the gender-specific effect on intravenous and oral cyclosporine (CsA) pharmacokinetics (PK) in healthy subjects.

METHODS: As part of an on-going study, the PK data of CsA was analyzed to evaluate the gender effect on disposition of cyclosporine in healthy subjects. A total of 9 female (F) and 11 male (M) subjects completed both IV and oral CsA PK in the study. Each subject received oral dose of CsA (Neoral®, 5 mg/kg) and one intravenous dose of CsA (1.5 mg/kg) in a fasted condition, with each dose separated by at least a 1-week washout period. A total of 17 blood samples was collected for a 24-hour period, and whole blood concentrations of CsA were determined by HPLC method with UV detection.
RESULTS: The mean systemic clearance (Cls) and oral clearance (Cl/F) of CsA were significantly faster in F compared to M [for Cls, 283 ± 47 ml/minute/kg (F) vs 222 ± 32 ml/minute/kg (M), p=0.0028, and for Cl/F, 825 ± 279 ml/minute/kg (F) vs 627 ± 90 ml/minute/kg (M), p=0.0395]. The area under the curve (AUC) of IV CsA was smaller in F compared to M [5440 ± 1045 ng•hour/ml (F) vs 6813 ± 893 ng•hour/ml (M), p=0.005], but when the body weight was adjusted, the difference disappeared (p=0.7). All other pharmacokinetic parameters between F and M did not differ significantly.
CONCLUSION: This study shows that Cls and Cl/F of CsA in female subjects were significantly faster than those in male subjects, which is consistent with the results of other CYP3A substrates.

257. Effect of grapefruit juice on microemulsion cyclosporine in African-American subjects: does ethnic difference matter? *Miyoung Lee, M.S.*, David I. Min, Pharm.D., M.S., Yi-Min Ku, M.S., Pharm.D., Michael Flanigan, M.D.; University of Iowa, Iowa City, IA; University of Nebraska, NE.

PURPOSE: This study aims to determine the effect of grapefruit juice (GJ) on microemulsion cyclosporine (CsA) in 11 African-American (AA) subjects compared to 11 Caucasian subjects.
METHODS: Each subject received two oral doses of CsA-ME with water (W) or GJ. Each subject also received IV CsA on a separate occasion. Blood samples were collected for CsA assay during a 24-hour period, and were analyzed by a HPLC method.
RESULTS: Regardless of race, GJ significantly increased the peak concentration (C_{max}) and area under the time-curve (AUC) of CsA; however, the magnitude of GJ effects was different for AA subjects than for C subjects. GJ increased peak concentration of CsA by 39% in AA subjects (1220 ± 329 [W] vs 1691 ± 466 [GJ], p=0.0003), while the difference in C subjects was only 8% (2053 ± 349 [W] vs 2223 ± 427 ng/ml [GJ], p=0.06). GJ also increased AUC of CsA in AA subjects by 60% (5896 ± 1330 ng•hour/ml [W] vs 9431 ± 1869 ng•hour/ml, p<0.0001), while GJ increased that in C subjects by 44% (8772 ± 1669 ng•hour/ml [W] vs 12636 ± 3581 ng•hour/ml [GJ], p=0.0001). The absolute bioavailability of CsA was 21% lower in AA subjects compared to C subjects when it was given with water (33 ± 7% [AA] vs 39 ± 7% [C], p=0.048). These differences disappeared when it was given with GJ (53 ± 12 % [AA] vs 56 ± 14% [C], p=0.62), although the total amount of CsA absorbed as measured by AUC is still significantly lower in AA subjects compared to C subjects (9431 ± 1869 ng•hour/ml [AA] vs 12636 ± 3581 ng•hour/ml [C], p=0.016).
CONCLUSIONS: These findings suggest that concurrent administration of GJ increases the bioavailability of CsA in AA subjects in greater magnitude than in C subjects and that intestinal CYP3A and p-glycoprotein activity may be different between AA subjects and C subjects.

258. Efficacy of basiliximab versus muromonab CD3 (OKT3) and antithymocyte globulin induction therapy in preventing acute rejection in high-risk renal allograft recipients. *Nicole M. Sifontis, Pharm.D.*, Raymond Pollak, M.B., Luca Cicalese, M.D., Enrico Benedetti, M.D., Eva M. Vasquez, Pharm.D., FCCP; University of Illinois at Chicago, Chicago, IL.

PURPOSE: Limited data exist regarding the use of basiliximab induction therapy in high risk renal allograft recipients (HR-RAR), as many of these patients were largely excluded from phase III trials. The purpose of this study is to compare the efficacy of basiliximab versus conventional antilymphocyte induction therapy (CIT) in HR-RAR. We define HR-RAR as black patients, retransplants and patients with a PRA ≥ 30%.
METHODS: Twenty-six patients at our center have received induction therapy with basiliximab 20 mg on the day of transplant and on post-op day 4 from July 1, 1998, to November 30, 1999, and are included in this analysis. The control group consisted of 26 consecutive HR-RAR receiving CIT with OKT3 5 mg/day x 7 days, (n=18); or antithymocyte globulin (ATG) 15 mg/kg/day x 7 days, (n=8), from February 1, 1997, to June 30, 1998. Maintenance immunosuppression consisted predominantly of cyclosporine, prednisone and azathioprine. The primary outcome measures were the occurrence of acute rejection and graft and patient survival at 6 months post-transplant.
RESULTS: The two groups were comparable with respect to sex, age, race, HLA match, type of transplant (cadaveric vs living related), retransplants and PRA. There was a trend towards less rejection in the basiliximab group (27%) compared to patients receiving CIT (50%, p>0.05). Mean time to rejection was 35 ± 33 days in the basiliximab group and 35 ± 26 days in the CIT group, (p>0.05). Graft survival at 6 months was 85% vs 92%, (p>0.05) in patients receiving basiliximab vs CIT, respectively. Two patients in the basiliximab group lost their grafts due to non-immunologic causes (DVT and ruptured kidney). Patient survival at 6 months was 92% in the basiliximab group and 96% in the CIT group, (p>0.05).
CONCLUSION: Preliminary evidence suggests that induction therapy with basiliximab is as effective as CIT in preventing acute rejection episodes in HR-RAR.

259E. Peptic ulcer disease in liver transplant recipients is infrequently due to *Helicobacter pylori*. *Iman E. Bajjoka, Pharm.D., BCPS*, Kirenza Q. Francis, R.Ph., Viken Douzdjian, M.D., Marwan S. Abouljoud, M.D.; Henry Ford Hospital, Detroit, MI.

PURPOSE: To determine the prevalence of peptic ulcer disease (PUD) due to *Helicobacter pylori* (HP) infection in liver transplant recipients (LTR).
METHODS: All LTR transplanted at our hospital from 1992 to 1999 were evaluated. Only patients with PUD were included in this analysis.
RESULTS: One-hundred sixty-seven LTR were evaluated. Following the transplant, 62 (37%) presented with symptoms of PUD. Diagnosis was confirmed by upper gastrointestinal endoscopy (UGE). Thirty-five patients (56%) were male with average age of 53 years (range 31 to 69). Of the 62 patients, 20 (32%) had esophagitis with 15 were due to candidiasis, 1 due to herpes simplex virus, 1 due to cytomegalovirus (CMV) and 3 had esophagitis of unknown cause. Twenty-two (35%) patients had PUD with 18 (29%) occurrences of gastric ulcers and 7 (11%) occurrences of duodenal ulceration. Six patients (10%) demonstrated gastric erosions only while 25 (40%) demonstrated gastritis only. Tissue biopsy was done in 46 patients, and of those, 12 (19%) were positive for CMV disease. Only four patients (6%) were HP positive by histology using the Warthin-Starry silver stain and none of the patients were HP positive by the CLO test.
Sixteen patients (26%) were on daily aspirin (81-324 mg/day). Immunosuppression therapy was similar in patients with and without PUD. Nine patients with PUD received cyclosporine while 13 received tacrolimus. Eleven (50%) also received mycophenolate mofetil (MMF). Twenty-one patients with PUD were on steroids with an average dose of 11.5 mg/day, vs 31 patients without PUD with an average dose of 9.5 mg/day.
CONCLUSION: We conclude that HP is not a significant cause of PUD in LTR. This may be due to immunosuppressant agents such MMF. We propose that other cause of PUD might be significant in this population, such as the use of steroids.
Presented at the Annual Meeting of the American Society of Transplant Physicians, May 2000.

260. Factors influencing development of opportunistic infection after rabbit antithymocyte globulin. *A. Scott Mathis, Pharm.D.*, Gary Friedman, M.D., Teresa DiRenzo, Pharm.D., Victor Rossi, M.D., Shamkant Mulgaonkar, M.D.; Rutgers University, Saint Barnabas Medical Center, Livingston, NJ.

PURPOSE: Antilymphocyte preparations for treatment of acute cellular rejection (ACR) are associated with increased risk of infection. Rabbit antithymocyte globulin (RATG), was recently introduced in this country for the treatment of ACR (1.5 mg/kg IV QD x 7-14 days). We report our observations regarding the incidence of opportunistic infections (OI) and the factors influencing their occurrence in renal transplant recipients.
METHODS: Twenty consecutive adult renal allograft recipients receiving RATG for treatment of ACR were included. Patients were similar with regard to baseline characteristics, and thus were divided into two groups based of the development of an OI. Stepwise multiple regression evaluated bacterial infection, nadir absolute lymphocyte count (ALC), nadir absolute neutrophil count, nadir cluster designation (CD) markers, and days to CD marker nadirs. Number of doses and total dose were also analyzed.
RESULTS: Over 3.92 ± 1.7 months of follow up, 60% of patients developed an OI (10 cytomegalovirus [CMV], 2 aspergillus). Patients with aspergillus returned to dialysis, but ACR and/or CMV was successfully treated in all other patients. 91.6% of patients with OI received > 4 doses of RATG, compared with 50% without OI (p=0.109); however total dose per kg and dose per body mass index were similar (p=NS). Stepwise multiple regression identified lower nadir ALC as the most important predictor of OI (15.27 vs 55.86 cells/mm^3; p<0.001). Lower (1.56 vs 3.71 cells/mm^3; p=0.23) and delayed (5.33 vs 3.43 days; p=0.15) CD_3 count nadirs trended toward an increased risk of OI. No subsequent ACR episodes were noted during follow up.
CONCLUSIONS: ALC appears to be an important predictor of safety and efficacy of RATG. Minimizing RATG doses given may decrease OI risk, and this does not appear to compromise efficacy. RATG is effective for ACR, but further study is required to minimize infectious risk.

261E. Treatment of post-transplant osteoporosis in female patients with intranasal calcitonin. *Kathleen M. Tornatore, Pharm.D.*, Robert J. Fountaine, Pharm.D., Jennie Hom, M.D., Kristin A. Reed, R.N., Rocco C. Venuto, M.D.; University at Buffalo; Erie County Medical Center, Buffalo, NY.

PURPOSE: This pilot study evaluated the change in bone mineral density (BMD) and biochemical bone markers (BBM) in female renal transplant recipients (RTR) during intranasal calcitonin (NC) and calcium/vitamin D therapy.
METHODS: Twenty-one female RTR, 13 pre-menopausal (PRE) aged 31 to 50 and 8 post-menopausal (POST) aged 38 to 71, with stable renal function

(mean CrCL=48 ± 19 ml/minute) were evaluated at a mean time of 64 months post-transplant. During phase I, all patients had BMD at the lumbar spine and femoral neck assessed by dual-energy x-ray absorptiometry (DEXA) by the same technician. Diagnosis of BMD was consistent with criteria established by WHO. Serum BBM: osteocalcin (OST), bone specific alkaline phosphatase (BAP), and C-terminal propeptide of type I collagen (CTERM) with urinary BBM: pyridinoline (PYR), deoxypyridinoline (DPYR) were measured. All patients received 1500 mg calcium/ 600 IU vitamin D daily. Patients with abnormal BMD also received 200 IU/day of NC. During phase II (12 months later), a second DEXA with BBM was done.
RESULTS: The incidence of osteopenia/osteoporosis was 71% (6/13 PRE and 5/8 POST). During phase I, the BMD at the lumbar spine was 1.11 ± 0.13 g/cm^2 in PRE and 1.03 ± 0.18 g/cm^2 in POST. The BMD in the femoral neck was 0.86 ± 0.12 g/cm2 in PRE and 0.82 ± 0.12 g/cm^2 in POST. The mean OST was elevated in PRE (19.5 ± 9.1 ng/ml) and in POST (14.9 ± 9.1 ng/ml) with a significant inverse relationship with lumbar BMD (p=0.02). BAP was elevated in four PRE and four POST with a significant inverse relationship with lumbar (p=0.038) and femoral (p=0.019) BMD. Other BBM were within the normal range. During phase II, 15/21 patients completed a second DEXA scan with significant increase in BMD (p=0.045) at the lumbar site in combined patient groups. Six PRE and five POST had an increase in BMD at both sites (range: 1.3 to 11.3 %). These patients tolerated the NC with minor nasal congestion. During phase II, no significant change was noted in BBM except for CTERM, which as a significant independent factor affecting femoral BMD (p=0.025).
CONCLUSION: These results suggest that intranasal calcitonin coupled with calcium and vitamin D may provide a safe, efficacious therapeutic intervention for post-transplant osteoporosis.
Presented at the American Society of Transplantation, Chicago, IL, May 15, 2000.

262E. Verapamil inhibits or stimulates P-glycoprotein activity in human T-cells depending on the degree of constitutive P-glycoprotein activation. Vera S. Donnenberg, M.S., *Gilbert J. Burckart, Pharm.D.*, Adriana Zeevi, Ph.D., Bartley P. Griffith, M.D., Aldo Iacono, M.D., Albert D. Donnenberg, Ph.D.; University of Pittsburgh, Pittsburgh, PA.

PURPOSE: Verapamil (VERA) has been reported to be a competitive inhibitor of P-glycoprotein, but there are conflicting reports. The purpose of the study was to examine the differential effects of VERA in T-cells with low and with high constitutive P-glycoprotein activity.
METHODS: We measured P-glycoprotein activity in T-lymphocytes from patients (n=68) taking P-glycoprotein substrate drugs (cyclosporine [CsA], tacrolimus) and healthy control subjects (n=18), by uptake of the fluorescent substrate R123 in short-term culture (15 minutes). The cells were loaded with R123 in the presence or absence of P-glycoprotein inhibitors (VERA, CsA) for 15 minutes. The effect of the inhibitors was calculated as the difference in R123 fluorescence intensity between paired cultures with and without inhibitor.
RESULTS: Subjects could be classified on the basis of the R123 intensity into one of three groups: bright, intermediate, dim. VERA modulation was inversely correlated with R123 staining intensity (p<0.0005): 1) with VERA, dim cells loaded brightly, indicating a block in constitutive P-glycoprotein activity; 2) no change in R123 intensity was noted in subjects with intermediate loading; and 3) with R123 bright T-cells, VERA caused a decrease in R123 fluorescence (increase in P-glycoprotein activity). CsA uniformly loaded R123 in cells.
CONCLUSIONS: High P-glycoprotein activity (low R123 loading) was induced in patients' T-cells by in vivo exposure to P-glycoprotein substrate drugs. This activity was efficiently blocked by the addition of VERA. In contrast, T-cells from most healthy control subjects had little constitutive P-glycoprotein activity, and VERA enhanced exclusion of the dye R123 during loading. We postulate that in T-cells with low constitutive P-glycoprotein activity, VERA binding to the P-glycoprotein ON-site "primes" the pump by inducing ATPase activity.
Presented at the 29th Annual Meeting of the American College of Clinical Pharmacology, Chicago, IL, September 18, 2000.

263. Are clinicians doing enough to prevent and treat osteoporosis in transplant recipients? *Kristine S. Schonder, Pharm.D.*, Kevin J. Lynch, Pharm.D., BCPS; Stadtlander Operating Co., LLC, Pittsburgh, PA.

Osteoporosis occurs in 30-50% of transplant recipients and can cause bone fractures in up to one-third of recipients after 5-10 years. All of the immunosuppressants used to prevent organ rejection, particularly steroids, can cause bone loss or problems with bone formation, leading to osteoporosis. Many strategies have been employed to treat or minimize the risk of osteoporosis in transplant recipients. The literature reviews which strategies can potentially be used and center-specific regimens, but there is little information relating which preventative and treatment strategies are actually being used in practice.
METHODS: We analyzed a national database of almost 10,000 transplant recipients from various centers across the country. Patient profiles were examined for each patient to determine the most current snapshot of what medications patients were receiving. Patient demographics, including type of transplant, number of years post-transplant, age, sex and immunosuppressive regimen, were correlated with the osteoporosis strategies used.
RESULTS: Five hundred twenty-eight transplant recipients (5.3%) received an osteoporosis regimen at the time of the analysis. The majority of patients (61.7%) received a one-drug regimen; 30.9% received two drugs; 50.9% of patients received calcium; 47.7% received a vitamin D analogue; and 26.7% received a bisphosphonate. Of the recipients receiving an osteoporosis strategy, 87.3% received corticosteroids, primarily prednisone at an average dose of 10 mg/day. 13.8% of patients were less than 1 year post-transplant. The majority of patients (48.9%) were 1-5 years post-transplant.
CONCLUSION: Given the significant risk of developing osteoporosis after transplantation, therapeutic modalities to prevent and treat osteoporosis may be underutilized in transplant recipients.

264E. Efficacy of interleukin-2 receptor antibodies in lung transplantation. *Mary S. Hayney, Pharm.D., BCPS*, Richard D. Cornwell, M.D., Keith C. Meyer, M.D., Katherine J. Marty, Pharm.D., Deborah L. Welter, R.N., Emily C. Golz, R.N., Glen E. Leverson, Ph.D., Robert B. Love, M.D.; University of Wisconsin, Madison, WI.

PURPOSE: To determine if IL-2 receptor antibodies (IL2RAb) (daclizumab or basiliximab) as part of an induction regimen aid in improving survival and maintaining lung function in patients undergoing primary lung transplantation.
METHODS: We compared patients who received IL2RAb as part of their immunosuppression induction regimen (n=20) to those who did not (n=80). All patients received cyclosporine (CSA)-based or tacrolimus (FK506)-based three drug immunosuppression regimens. Graft survival time and FEV_1 as percent predicted after stratifying for single (SLT) and bilateral lung transplants (BLT) at 3, 6, and 12 months were compared using the log rank test and Wilcoxon rank sum test respectively. We also compared time to first CMV infection post-transplant using the log rank test.
RESULTS: FEV_1 at 3 months was higher for patients who received IL2RAb than those who did not (BLT 83% vs 69%; p=0.038; SLT 67% vs 52%; p=0.029). The fact that these differences did not hold up at 6 and 12 months was possibly due to the limited numbers of patients receiving IL2RAb with follow-up data. There was a statistically significant difference in time to CMV infection between the groups (p=0.015). At 1 year post-transplant, 61% who did not received IL2RAb and 32% of those who did receive IL2RAb remained free of CMV infection. These comparisons held up after considering recipient pre-transplant CMV status and donor serostatus.
CONCLUSION: IL2RAb improve graft function when included in the induction regimen for primary lung transplant. The more intensive immunosuppression regimen likely results in higher rates of CMV infection.
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265E. Th2 response follows immunization with inactivated hepatitis A vaccine. *Mary S. Hayney, Pharm.D., BCPS*, Jessica. M. Buck, Daniel Muller, M.D., Ph.D.; University of Wisconsin, Madison, WI.

PURPOSE: Passive and active immunization are effective in the prevention of hepatitis A infection though both produce very low levels of circulating antibody compared to natural infection. Because hepatitis A vaccine is highly immunogenic, characterization of the T helper cell immune response to this antigen would be useful in the evaluation of other novel antigens. We hypothesized that a Th2-type response would be elicited by hepatitis A vaccination.
METHODS: Thirteen individuals were immunized with a dose of hepatitis A vaccine. Blood was drawn to measure cytokine production in peripheral blood mononuclear cell (PBMC) culture prior to and 28 days following immunization. PBMC were cultured with no antigen, hepatitis A vaccine 0.1 unit/L, or PHA 2.5 µg/ml. PBMC cultures were maintained for 48 hours. Cytokine production was measured in cell culture supernatant using ELISA (OptEIA, Pharmingen). Changes in interferon-gamma (IFNγ) and interleukin-10 (IL-10) production over control were compared using paired t-tests.
RESULTS: PBMC stimulated with hepatitis A vaccine in culture produced significantly more IL-10 over control after vaccination than before ($\bar{x}$ -16 pg/ml [SD 78] vs $\bar{x}$ 305 pg/ml [SD 292]; p=0.005). No difference in IFNγ production was detected ($\bar{x}$ -15 pg/ml [SD 49] vs $\bar{x}$ –86 pg/ml [SD 254] p=0.33).
CONCLUSION: Vigorous IL-10 production by PBMC obtained from vaccinated individuals indicates that a Th2 response is important in the immune response to hepatitis A vaccination. Protection conferred by immunization may be largely due to the induction of antibodies. Supported by ACCP Research Institute, Merck, Inc., and NIH MO1 RR03186.
Presented at the 3rd Annual Conference on Vaccine Research, Washington, D.C., April 1, 2000.

Women's Health

266E. The relationship between the menstrual cycle and the occurrence of

acute coronary events in women. *Julie Méthot, M.S.,* Peter Bogaty, M.D., Paul Poirier, M.D., Marie Arsenault, M.D., Sylvie Pilote, M.S., Sylvain Plante, M.D., Bettina A. Hamelin, Pharm.D.; Quebec Heart Institute, Laval University, Ste-Foy, PQ, Canada.

BACKGROUND: The hormone/cardiovascular hypothesis stipulates that high levels of circulating estrogens are cardioprotective. Cardiovascular disease risk increases when hormone levels decrease after menopause. It has been shown that acute administration of 17β-estradiol prolonged time to ST segment depression during exercise treadmill testing.
PURPOSE: We hypothesized that acute fluctuations of 17β-estradiol during the menstrual cycle would modulate the risk of coronary events such that women would suffer acute coronary events preferentially during the early follicular phase of ovarian cycle (during and immediately after menses).
METHODS: We have already studied prospectively 28 premenopausal Caucasian women admitted with myocardial infarction (MI) or unstable angina (UA) with ECG changes. All women answered a detailed questionnaire assessing disease, medication history, symptoms, hormonal status and risk factor profiles.
RESULTS: Age at the time of the event was 41 ± 6 years (mean ± SD). Risk factors were hypercholesterolemia (43%), high blood pressure (42%), current (36%) and past (24%) smoking and diabetes (7%). Significantly more women had their acute coronary event within 5 days after onset of menstruation ($p<0.02$).

Interval Between Menses and MI/UA	n	
≤ 5 days	20	p=0.012
> 7 days	8	

CONCLUSION: This finding suggests that there is increased vulnerability to acute coronary events in women during and immediately after menses. In the presence of risk factors, the acute decrease in 17β-estradiol in the menstrual cycle may trigger acute coronary events.
Presented at the 73rd Scientific Sessions of the American Heart Association, New Orleans, LA, November 12-15, 2000.

267E. Association of polymorphisms in the renin-angiotensin system with acute coronary events in women. *Julie Méthot, M.S.,* Peter Bogaty, M.D., Paul Poirier, M.D., Marie Arsenault, M.D., Jocelyne Simard, Sylvain Plante, M.D., N. Michelle Robitaille, M.D., Bettina A. Hamelin, Pharm.D.; Quebec Heart Institute, Ste-Foy, PQ, Canada.

BACKGROUND: The insertion/deletion (I/D) polymorphism of angiotensin converting enzyme (ACE), the A1166C polymorphism in the angiotensin type 1 receptor (AT1R), and the M235T polymorphism in the angiotensinogen gene (AGT) have been shown to be associated with cardiovascular disease, in particular in young men. However, few data are available on genetic disease risk in relationship to hormonal status in women.
PURPOSE: In the present investigation, the prevalence of mutant alleles in the ACE, AGT and AT1R genes in premenopausal (PREMW) and postmenopausal (POSTMW) Caucasian women with and without a history of at least one acute coronary event (myocardial infarction [MI] or unstable angina UA]) was investigated.
METHODS: DNA was isolated from leukocytes and genotypes determined by polymerase chain reaction.
RESULTS: We have already recruited 60 PREMW and 169 POSTMW with disease and 330 control PREMW.

	ACE-DD	AT1R-CC	AGT-CC
POSTMW with MI/UA (n=169)	27.2%	9.0%	21.11%
With HRT (n=47)	22.5%	10.2%	22.5%
Without HRT (n=122)	27.9%	8.6%	20.6%
PREMW WITH MI/UA all (n=60)	35.7%	11.9%	11.9%
≤ 40 years (n=25)	47.8%*	20.0%#	8.7%
> 40 years (n=35)	27.3%*	5.9%#	14.7%
Control PREMW (n=330)	34.7%	8.9%	11.7%

HRT = hormone replacement therapy; *p=0.26; #p=0.14

CONCLUSION: Similar prevalence of mutant genotypes (ACE-DD, AT1R-CC, AGT-CC) was found in women with and without MI/UA, independent of endogenous or exogenous hormonal status (p=NS). Future research is needed to determine if the greater prevalence of ACE-DD and AT1R-CC genotypes in women ≤ 40 years old is clinically relevant.
Presented at the 73rd Scientific Sessions of the American Heart Association, New Orleans, LA, November 12-15, 2000.

268E. Transdermal testosterone replacement for young women with spontaneous premature ovarian failure: a pilot study. Sophia N. Kalantaridou, M.D., Ph.D., *Karim A. Calis, Pharm.D., MPH, FASHP,* Heidi Godoy, Norman A. Mazer, M.D., Ph.D., Carolyn A. Bondy, M.D., Lawrence M. Nelson, M.D., MBA; NICHD, WGMCC, National Institutes of Health, Bethesda, MD; Watson Laboratories, Inc., Salt Lake City, UT.

PURPOSE: Young women with premature ovarian failure (POF) have significantly lower serum androgen levels than regularly menstruating women. This may in part explain why two-thirds of these women have significantly reduced bone mineral density despite prior estrogen/progestin replacement. This pilot study evaluated a testosterone transdermal delivery system to determine 1) if women with POF demonstrate scheduled bleeding with the addition of testosterone; and 2) if the system is well tolerated and achieves free serum testosterone concentrations within or near the normal reference range (1.3 to 6.8 pg/ml) in women on cyclic estrogen/progestin treatment.
METHODS: We treated nine women with POF (mean age of 34 years; mean body mass index of 24.7) using a twice-weekly testosterone patch (TMTDS, Watson Laboratories, Inc.) specifically designed for women. For 2 months, the women received 0.1 mg per day of transdermal estradiol continuously and 10 mg of oral medroxyprogesterone acetate during the last 12 days of each 28-day cycle. For the subsequent 2 months, the testosterone patch (providing the equivalent of the normal daily ovarian testosterone production of 150 µg per day) was added to the estrogen/progestin regimen. Testosterone serum concentrations were measured by a central laboratory using a validated RIA method. One woman with abnormally low serum sex hormone binding-globulin was excluded from the analysis.
RESULTS: The mean ± SEM time-averaged free testosterone concentration in the eight women was 2.4 ± 0.4 pg/ml during the estrogen-only phase and 7.2 ± 1.06 pg/ml during the estrogen/testosterone phase (p=0.0005). Testosterone levels were similar during the progestin phase. While on transdermal testosterone, the women continued to have scheduled bleeding patterns with no significant changes in onset or duration of menstruation. None of the patients experienced hirsutism or acne, and no significant changes were observed in liver function, lipid profile, or fasting serum insulin concentrations.
CONCLUSION: We found that addition of the TMTDS to the usual estrogen/progestin replacement achieved acceptable free serum testosterone concentrations and was well tolerated in women with POF. We plan to employ this transdermal testosterone system in a long-term hormone replacement study to evaluate its effectiveness in protecting women with POF from bone loss.
Presented at the 82nd Annual Meeting of the Endocrine Society, Toronto, Canada, June 22, 2000.

269. Characterizing menstrual cycle-related urinary leukotriene E_4 variability in asthmatic and non-asthmatic females. *Mary H.H. Ensom, Pharm.D., FASHP, FCCP,* Gina Chong, B.S., Jenny W.L. Chou, B.S., Diane Decarie, B.S.; University of British Columbia; Children's and Women's Health Centre of British Columbia, Vancouver, BC.

PURPOSE: To characterize intra-subject variability in urinary leukotriene E_4 (LTE_4) excretion in asthmatic and non-asthmatic females at three different times of the menstrual cycle.
METHODS: Following informed consent, four asthmatic females and four healthy, non-asthmatic females collected 24-hour urine samples on days 8 (follicular), 22 (luteal), and 28 (premenstrual) of one complete cycle. All subjects had normal menstrual cycles and none smoked or used hormonal contraceptives. Urine LTE_4 and creatinine concentrations were analyzed via enzyme immunoassay and creatinine amidohydrolase reaction, respectively. Menstrual cycle-related intra-subject variability was expressed as coefficient of variation (CV), calculated as standard deviation/mean x 100%.
RESULTS: Subjects' mean (± SD) ages were 33.8 ± 5.2 years (asthmatics) and 28.8 ± 10.1 years (non-asthmatics) and weights were 72.6 ± 1.9 kg (asthmatics) and 57.5 ± 3.8 kg (non-asthmatics). Urinary LTE_4 excretion, expressed as pg LTE_4/mg creatinine, for each subject is as follows:

	Asthmatics					Non-Asthmatics				
Subject #	1	2	3	4	Mean ± SD	5	6	7	8	Mean ± SD
Day 8	387.9	597.7	603.8	122.2	427.9 ± 227.2	509.4	117.9	232.5	579.2	359.8 ± 220.0
Day 22	400.5	302.7	423.1	257.2	345.9 ± 78.9	343.4	156.4	330.1	744.5	393.6 ± 249.0
Day 28	324.8	279.1	373.6	311.3	322.2 ± 39.3	335.1	160.4	167	598.6	315.3 ± 205.5
CV (%)	10.9	45.2	26.0	42.3		24.8	16.2	33.7	14.1	

We found mean urinary LTE_4 excretion to be similar between asthmatics and non-asthmatics, with no consistent menstrual-cycle trends observed.
CONCLUSIONS: Despite the frequent use of urinary LTE_4 as a biomarker of airway inflammation in the scientific literature, this is the first study, to our knowledge, that characterizes the effect of the menstrual cycle on urinary LTE_4 excretion. For future studies seeking to evaluate the effect of drugs (e.g., leukotriene modifiers, estrogen, etc.) on urinary LTE_4 excretion, the magnitude of effect for the drug must be greater than the baseline variability we observed.

270. Pharmacokinetics of low molecular weight heparin and unfractionated heparin in females with antiphospholipid antibody syndrome. *Mary H.H. Ensom, Pharm.D., FASHP, FCCP,* Penny J. Ballem, M.S., M.D. FRCP(C), Gina Chong, B.S., Mary D. Stephenson, M.D., FRCSC, M.S.; University of British Columbia; Children's and Women's Health Centre of British Columbia, Vancouver, BC.

PURPOSE: To characterize low molecular weight heparin (LMWH) and unfractionated heparin (UFH) pharmacokinetics in females with antiphospholipid antibody syndrome (APS) who are contemplating pregnancy. To date, no pharmacokinetic data for LMWH and UFH exist for this patient population.

METHODS: Following informed consent, 18 non-pregnant females with APS were randomized to one of two treatment groups: LMWH (dalteparin) 2500 U SC q24h (n=9) or UFH 5,000 U SC q12h (n=9). All patients received aspirin 81 mg per day concurrently. After at least 1 week of heparin therapy, blood samples were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours following a dose of LMWH and at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 8, and 12 hours following a morning dose of UFH. Plasma concentrations of heparin were measured by determining anti-factor Xa activity using an aminolytic method with chromogenic substrate. Pharmacokinetic parameters were calculated by non-compartmental methods.
RESULTS: Mean (± SD) age was 33 ± 4 years and weight was 69.7 ± 11.3 kg. Patients had a history of 3.8 ± 1.6 spontaneous abortions. Pharmacokinetic parameters (mean ± SD) were as follows:

Type of Heparin	C_{max} (U/ml)	C_{min} (U/ml)	t_{max}	$t_{1/2}$	$AUC_{0\text{-}TAU}$	$Cl_{apparent}$/kg
(hour)	(hour)	(U•hour/ml)	(ml/hour/kg)			
LMWH (n=9)	0.29 ± 0.10	0.03 ± 0.02	3.0 ± 1.5	9.0 ± 7.5	2.44 ± 0.82	16.16 ± 3.72
UFH (n=7)[a]	0.04 ± 0.03	0.01 ± 0.02	2.2 ± 0.8	- [b]	0.17 ± 0.15	3620 ± 8272

[a] Parameters could not be calculated for two patients who had virtually undetectable serial concentrations; [b] the $t_{1/2}$ of UFH was not calculated, due to UFH's nonlinear pharmacokinetic properties

CONCLUSIONS: In females with APS, our pre-pregnancy dosing regimen of LMWH appears to achieve target anti-factor Xa activity, whereas the UFH regimen does not. These pre-pregnancy data will be useful as baseline values to track pharmacokinetic changes that may occur with LMWH and UFH throughout pregnancy.

271. Asian college students' awareness of osteoporosis. *Diem N. Nguyen, Pharm.D.*, Mary Beth O'Connell, Pharm.D., BCPS, FCCP, FSHP. Walgreens, Oakdale, MN; University of Minnesota, Minneapolis, MN.

PURPOSE: To quantify osteoporosis awareness, knowledge and preventive health behaviors in Asian college students, a high-risk group for osteoporosis.
METHODS: A 64-question survey about demographics and lifestyle practices (n=25), osteoporosis facts (n=30) and personal/cultural opinions of osteoporosis (n=9) was mailed or distributed on campus to Asian students. Descriptive and Pearson chi-square statistics ($p \leq 0.05$) were conducted with SPSS version 6.0.
RESULTS: The 168 participants were 21 ± 3.4 years old, 77% female and 64% Asian born. Predominant backgrounds were 39% Vietnamese, 20% Hmong, and 7% Chinese. Half consumed less than one calcium serving/day. The majority exercised less than 2.5 hours/week. Eighty percent consumed at least one phytoestrogen serving/day. Most participants (90%) had never discussed osteoporosis with a health care provider, and 52% had not read anything. Only 9% answered 75% of the osteoporosis fact questions correctly. Questions with < 30% correct responses (true/false) were Asian heritage, number of children, vitamin C deficiency and diabetes as risk factors, estrogen effects on heart and breast cancer, menopause treatment, and continuous bone loss. Women were more concerned about developing osteoporosis ($p=0.026$) and more apt to change their health behaviors ($p=0.011$) than men. More U.S.-born Asians thought osteoporosis should be a major public concern ($p<0.001$) and would change health behaviors ($p=0.006$) than Asian-born participants. Hmong participants were more likely to attribute osteoporosis to fate and luck while the Vietnamese participants related it more to diet. Most participants (63%) did not know if their culture allowed ERT and 42% said menopause was natural for which treatment should not be used.
CONCLUSIONS: Asian college students lacked knowledge about osteoporosis and minimally practiced health behaviors for osteoporosis prevention.

Clinical Pharmacy Forum

These abstracts describe the delivery, development, justification, or documentation of innovative clinical pharmacy services; they may be descriptive only and need not contain an evaluative component.

272. Impact of a pharmacy consultation service provided in a surgical pre-admission clinic on pre- and post-operative medication errors. *André J. Bonnici, M.S.*, Valérie Bouchard, M.S., Gilliane Beaudet, M.S.; The Montreal General Hospital, Montréal, PQ, Canada; Cité de la Santé de Laval, Laval, PQ, Canada.

PURPOSE: In June 1997, a surgical pre-admission clinic (SPAC) including an innovative pharmacy consultation service was implemented at the Montreal General Hospital (MGH). The pharmacist systematically meets all patients taking medications pre-operatively and documents in the chart: the medication history, recommendations concerning peri-operative drug management and instructions given to patients on which medications to stop or continue pre-operatively. This study was designed to compare 1) the frequency of pre-operative medication errors; and 2) the frequency of post-operative prescribing errors in patients seen at comparable SPACs of two academic institutions: The MGH, which includes a pharmacy consultation service and the Cité de la Santé de Laval (CSL), Laval, PQ, Canada, which does not.
METHODS: From February to April 1999, same day surgery patients admitted at both institutions were interviewed at least 1 day after surgery to determine conformity of pre-operative medication intake according to 17 pre-determined criteria. Post-operative prescriptions were screened for discrepancies with the medication history.
RESULTS: Interviews were conducted with 25 and 41 patients at the MGH and the CSL, respectively. A significantly greater proportion of pre-operative medications were taken according to criteria in the MGH group compared to the CSL group (90.4% versus 64.1%, respectively, $p=0.003$). A significantly lesser proportion of patients had one or more errors in their post-operative prescription in the MGH group compared to the CSL group (12% versus 55%, respectively, $p=0.0017$).
CONCLUSION: This study suggests that a pharmacy consultation service provided in a surgical pre-admission clinic is associated with a lower proportion of pre-operative medication errors and post-operative prescribing errors.

273. Investigating adverse drug events further in a community hospital setting. Grant Lum, Pharm.D., *Michele Fujioka, Pharm.D.*, Stuart Laiken, M.D., Elaine Levy, R.Ph., Albert Rizos, Pharm.D., Miles Hildebrand, Pharm.D.; Sharp Healthcare, San Diego, CA.

PURPOSE: A typical community hospital identified that the their current adverse drug reaction (ADR) rate was very low (1.6% of total admissions), probably due to underreporting. The current system relied primarily on retrospective chart review, and many of the events captured did not occur within the hospital but were events leading up to a medication related admission. This study was conducted to 1) determine the true adverse drug event (ADE) rate for this community hospital; and 2) determine where key problem areas exist within the medication process.
METHODS: A four-week study was conducted at Sharp Chula Vista Medical Center, a 200-bed hospital that averages approximately 10,000 admissions per year. A clinical pharmacist gathered data approximately 10 hours per week by soliciting reports from staff nurses, collecting alerting orders from the pharmacy department, completing chart reviews up on the floors, and conducting admission patient interviews to retrieve more accurate medication histories. All events were reported concurrently and were categorized by preventability, severity, and stage in which they occurred within the medication process.
RESULTS: The study revealed the true adverse event rate for the hospital to be 6.8% of total admissions (3.8% of these were actual preventable adverse events). The potential ADE rate (those errors that had the potential for harm but were intercepted or did not cause injury to the patient) was 23%. Of the both actual preventable events and potential events, ordering errors accounted for 68% of the total errors, whereas processing and delivery (delivery is defined as the delivery of the medication from the pharmacy to the patient care area) accounted for 28% and 4.8% of all errors, respectively. It is important to note that the administration of the medication to the patient was not evaluated in this study. In addition, the most common medications causing ADEs were warfarin, pain medications, insulin, and digoxin.
CONCLUSION: By instituting a concurrent reporting system for adverse drug events, the number of reported events increased dramatically. As a result, a more in depth analysis can be completed and used to point out key areas where performance improvement efforts can be directed. This study must be followed by in depth performance improvement efforts and remeasurement on a consistent basis.

274. Development of a network-based database program to enhance adverse drug reaction reporting and analysis. Darrin S. Richman, R.Ph., *Dwight D. Kloth, Pharm.D.*; Fox Chase Cancer Center, Philadelphia, PA.

PURPOSE: To create a paperless mechanism for enhancing pharmacist's reporting of suspected adverse drug reactions (ADRs) to a master database overseen by the P&T Committee.
METHODS: Using Borland Delphi 3, on PCs running the Windows NT 4.0 OS, a relational database program was developed to enable any pharmacist, from a remote PC, the ability to input an ADR report. Previously, all reports were submitted on paper forms, for transcription into the database by the clinical coordinator of pharmacy, in preparation for monthly review and analysis by the P&T Committee and M&M Conference. The ADR reporting program automatically extracts preexisting data (e.g., patient height, weight, medical record number, treatment location) from information previously entered for clinical drug monitoring. The program allows reporter assessment of outcome severity (using FDA MedWatch criteria), and automatically calculates estimated causality scores based on a method modified from Naranjo, et al. CP&T 1981. The program requires the clinical coordinator's final verification of a suspected reaction before reporting these data to the master database for review by the P&T Committee and Morbidity and Mortality Conference, assuring quality control and inclusion of essential data elements.
RESULTS: From August of 1998 to June 2000, 208 of 278 total ADRs (74.8%) have been reported using this method. Substantial added efficiencies have been achieved as well as added pharmacist intellectual involvement and interest in ADR reporting. This system also allows pharmacists to review

(read only format) any ADR previously input into the system, further enabling efficient access to previous ADR data on their patients.
CONCLUSIONS: This program has been very well received by staff pharmacists and enhanced the accuracy and efficiency of ADR reporting. We are currently considering future modifications to allow data input by our professional colleagues in nursing and medicine.

275. Use of preventable adverse drug reaction data to target additional clinical pharmacy services in a community teaching hospital. *Ann E. Wehmeyer, Pharm.D.*, Todd P. Semla, M.S., Pharm.D., FCCP; Evanston Northwestern Healthcare, Evanston, IL.

PURPOSE: The focus of an adverse drug reaction (ADR) reporting program is to prevent or to reduce the incidence of ADRs and to improve clinical outcomes. This presentation demonstrates how the evaluation of preventable ADRs can lead to multidisciplinary and pharmacy-based strategies to prevent ADRs.
METHODS: Adverse drug reactions were identified through spontaneous reporting and medical records codes. All ADRs for 1998-1999 were reviewed by pharmacists and classified as preventable or nonpreventable according to Schumock criteria. A multidisciplinary review of ADR data identified trends and prioritized strategies for prevention.
RESULTS: Of the 1068 reported inpatient ADRs, 232 (22 %) were preventable. Of the 232 reactions, 20 (9%) required intervention to prevent permanent harm, 16 (7%) resulted in admission to an ICU, and 14 (6%) resulted in prolonged hospitalization. The most common medications involved were warfarin (25%), antibiotics (13%), digoxin (10%), and opioid analgesics (9%). The most common types of reactions include drug or electrolyte levels outside of the normal range (41%), allergic reactions with a history of previous reaction (13%), oversedation (10%), and bleeding episodes (5%). As a result of these findings, adult bowel preparation and IV phenytoin administration guidelines were implemented. Sedation guidelines including monitoring of propofol and IV medication administration guidelines were revised. An inpatient anticoagulation monitoring service, digoxin guidelines, and improvements in allergy documentation have been initiated.
CONCLUSIONS: Identification of preventable ADRs allows for development of clinical programs targeted to reduce the ADR frequency. Preventable ADR data can be utilized for justification of new services.

276. Implementation of a pharmacist-managed dyslipidemia service within a U.S. Air Force medical group. *Robin R. Feuge, Pharm.D., BCPS*, Mary Ann Halloran, Pharm.D., BCPS; University of Oklahoma Health Sciences Center, Oklahoma City, OK; 72nd Medical Group, Tinker Air Force Base, OK.

PURPOSE: To describe the development of a pharmacist-managed dyslipidemia clinic for patients served by the family medicine and internal medicine clinics within a U.S. Air Force medical group.
METHODS: Medical, pharmacy, and laboratory records were reviewed for 100 diabetic and 100 non-diabetic patients in an Air Force medical group. Baseline data were collected to establish current levels of cholesterol control and patterns of dyslipidemia management. Results were presented to the medical staff for review. A dyslipidemia service was established under an approved protocol, enabling management of dyslipidemic patients by clinical pharmacists. Patients with coronary artery disease or diabetes mellitus have been identified for targeted intervention, with referrals initiated on a consult basis. Services provided include patient education, drug therapy management, and laboratory monitoring as appropriate.
RESULTS: Baseline data indicated that the LDL goal per established guidelines had been met in 31.8% of all charts reviewed and in 22.7% of patients with CAD, 29.0% of diabetics and 22.8% of patients without CAD and ≥ 2 risk factors. Sixty-two percent of patients had received dietary counseling. Thirty-seven percent of patients were receiving pharmacologic therapy for dyslipidemia, with 40.5% achieving their LDL goal. Patients are currently being enrolled in the clinic. Outcome data will be collected to determine the impact of the service on lipid management.
CONCLUSIONS: Baseline results are consistent with published data indicating a low percent of patients attaining established LDL goals. Institution of a pharmacist-managed dyslipidemia service is expected to optimize management of patients at high risk for cardiovascular events.

277. Effect of random therapeutic interchange of antihypertensive agents on blood pressure control. *Julie A. Hixson-Wallace, Pharm.D., BCPS*, Donna Josiah, Sybelle A. Blakey, Pharm.D., BCPS; Mercer University, Atlanta, GA.

PURPOSE: Limited financial resources lead to frequent interchange among antihypertensive agents in our indigent primary care clinic. We sought to determine whether this frequent interchange resulted in blood pressure control comparable to either consistent antihypertensive monotherapy and/or that reported in NHANES-III.
METHODS: Medical records of patients receiving antihypertensive therapy from December 1992 to April 1998 were reviewed for blood pressure measurements. A minimum of 6 months of hypertension treatment and compliance with therapy were required for inclusion. Classification of blood pressure control was based on JNC-VI guidelines. Patients were classified into three groups, (monotherapy, multiple therapy, or combination-multiple therapy), and blood pressure control within each group was analyzed and compared.
RESULTS: One hundred five patients were included. Analysis of the three groups revealed that 80% of patients were receiving multiple agents from different therapeutic classes. Six percent received multiple agents from the same therapeutic class, and 14% consistently received the same agent. Hypertension was controlled in 40% of monotherapy patients, 33% of multiple therapy patients, and 26% of combination-multiple therapy patients. The overall hypertension control rate for all patients was 29%. These results match the expected control rate in the general population as reported in NHANES-III. The comparison between groups for hypertension control showed no difference based on agents used, (p=0.53).
CONCLUSION: Comparable hypertension management can be provided with limited financial resources and alternating medication regimens.

278. The use of pharmacy-led clinical audit to improve the quality of statin prescribing post-myocardial infarction. *Duncan McRobbie, M.S., M.R.Pharms.*, Michelle Hughes, B.Pharm., M.R.Pharms., Andrew Bishop, M.D., MRCP; Guy's and St. Thomas' Hospital, London, United Kingdom.

INTRODUCTION: Lowering serum cholesterol levels with HMG CoA reductase inhibitors (statins) in patients who have suffered a myocardial infarction (MI) even at serum cholesterol levels previously considered to carry low risk, is associated with a decrease in re-infarction and morbidity. This work was undertaken to evaluate the prescribing of statins for MI prior to admission, at discharge and after 6 months.
METHODS: Six-month data of patients suffering myocardial infarction were identified from the coronary care record. A data collection form was designed and piloted. Case notes were reviewed. Cholesterol levels and prescribed statin medication were recorded. The follow up was via letter, fax or telephone call to the GP, 6 months after discharge from hospital.
RESULTS: Data were available for 32 patients (22 male/10 female). Five out of 32 (16%) of patients were taking a statin on admission, and 26/32 (81%) on discharge. Twenty-seven patients were available at the 6-month follow-up. Twenty-three out of 27 (85%) of these were prescribed a statin. GP's occasionally switched to a cheaper brand. Cholesterol levels remained unknown for three-fourths of patients on discharge and at follow up. Following this audit, a policy of prescribing high-dose statins (equivalent to 40 mg of pravastatin) was introduced and the GP's were encouraged to adjust the dose according to cholesterol level.
CONCLUSION: Pharmacy-led audit improved the prescribing of statins in hospital.

279. Outcomes of a pharmacist-directed lipid management clinic: collaborative efforts of pharmacists, pharmacy students, and physicians. *Melissa A. Somma, Pharm.D.*, Michael J. Fox, M.D., Jacquelyn M. Evans-Shields, Pharm.D., Richard W. Seipp; Wilkes University, Wilkes-Barre, PA; Geisinger Health Group, Lake Scranton, PA.

PURPOSE: The objective of this report is to describe preliminary outcomes of a lipid management clinic which is staffed by pharmacists and pharmacy students on their ambulatory care clerkships. The clinic is established under a collaborative agreement within a physicians' group practice model. The goal of the clinic is to provide patients intensive cholesterol management by a pharmacist with regard to diet, exercise and medication. Additionally, the clinic serves as a training site for doctor of pharmacy students.
METHODS: Patients are identified through physician referral or prospective chart review and contacted by a pharmacist or student to schedule an individualized patient counseling appointment. Patient-specific risk factors and cholesterol goals are identified during the initial workup as defined by the Second National Cholesterol Education Program (NCEP) Guidelines. In addition to the lifestyle modification discussion, a medication regimen review occurs during all visits. After each visit, patients receive a satisfaction survey regarding their perception of the clinic and clinical pharmacy services. Patients are evaluated every 3 months for appropriateness of lipid lowering medication.
RESULTS: Results reported include the initial 56 patients enrolled in the clinic for a minimum of 3 months. At the time of analysis, follow-up data were available on 40 patients; 50% have reached their NCEP goal, while an additional 25% have decreased their low-density lipoprotein (LDL) from baseline.
CONCLUSION: We intend to demonstrate how the collaborative efforts of pharmacists, pharmacy students, and physicians can lead to improved patient lipid management outcomes.

280. Effectiveness of a pharmacist-run lipid consult service in diabetic and non-diabetic patients. *Chris M. Terpening, Ph.D., Pharm.D.*, John G. Gums, Pharm.D.; University of Florida, Gainesville, FL.

PURPOSE: Diabetic patients frequently have atypical lipid profiles. This study compares the effectiveness of pharmacist interventions on lipid profiles of diabetic and non-diabetic patients.
METHODS: Patients were seen in a pharmacist-run lipid consult service located within a family practice clinic. All patients receiving two or more

consults between 12/95 and 4/00 were evaluated, comparing values from their first and last consults. Patients were categorized as diabetic or non-diabetic based on diagnosis at the time of their enrollment in the consult service.
RESULTS: Of 90 patients meeting inclusion criteria, 28 were diabetic (median duration of therapy – 6 months) and 62 were non-diabetic (median duration – 9 months). At enrollment, the diabetic patients had significantly higher total cholesterol and triglyceride levels, as well as lower high density lipoprotein (HDL) levels, than non-diabetic patients. After receiving consultation, the relative lipid values were unchanged. However, both groups had significantly improved low density lipoprotein (LDL) levels. These improvements translated into marked increases in the percentage of patients achieving their LDL cholesterol goals. The non-diabetic group also had significantly improved HDL levels and a trend toward improved triglyceride levels. The diabetic group had only a non-significant improvement in HDL levels and slightly worsened triglyceride levels. These occurred in spite of significantly improved glucose control.
CONCLUSION: It is possible to achieve clinically important improvements in LDL levels, in both diabetic and non-diabetic patients, within a relatively small number of consultations. However, clinically significant improvements in HDL and triglyceride levels are more difficult to obtain, especially in diabetic patients.

281. Cost-benefit analysis of a pharmacist-conducted warfarin patient education program in Taiwan. *Hsiang-Yin Chen, M.S.*, Pharm.D., Yang Chang. M.S., Jia-You Fang, Ph.D., Shing-Mei Hsu-Lee, B.S., Kuang-Yang Hsu, Ph.D.; Taipei Medical College; Taipei Municipal Wang Fang Hospital, Taipei, Taiwan.

PURPOSE: A cost-benefit analysis of a pharmacist-conducted warfarin patient education was performed to evaluate the economic impacts and practicability of the preliminary model of anticoagulation therapy in Taiwan.
METHOD: Patients who filled prescriptions with warfarin from the outpatient pharmacy at the Taipei Municipal Wang-Fang Hospital (TMWFH) were enrolled with written inform consent. Two sections of oral anticoagulation education programs were completed individually. Patients were followed-up for additional 5 months after completing the education. Number of hemorrhage, thromboembolic events and emergency or hospital admissions related to these events were calculated for 5 months before and after the education. The medical expenditures related to warfarin use were compared for the two periods of time to calculate the benefit-cost ratio of program.
RESULTS: Sixty patients consented into the warfarin patient education program from July 1999 to October 1999, in TMWFH. The number of warfarin-related hospital admissions was decreased from 31 to 6 times ($p<0.001$), and that of emergency admissions was reduced from 21 to 6 ($p=0.006$). The number of thromboembolic events was decreased significantly after education (52 vs 12, $p<0.001$). The benefit-cost ratio was 3.16, suggesting that the education program was economically valuable.
CONCLUSION: Current study demonstrated that this warfarin patient education program was clinically practical with respect to clinical and economic outcomes in Taiwan. A better effectiveness could be achieved by extending the range of service to anticoagulation clinic.

282. Pharmacist-initiated diabetic patient education on the impact of hospitalization and quality of life parameters. *Charles Ruchalski, Pharm.D.*, Kristen Schwetschenau, Pharm.D., Angela Nace, Pharm.D.; Temple University, Philadelphia, PA.

PURPOSE: To prove that pharmacist-initiated diabetic patient education could improve the quality of life of patients with diabetes and decrease diabetes-related hospital admissions.
METHODS: Patients were identified through a prospective pharmacy profile review that were admitted to Temple University Hospital with a primary diagnosis of diabetic ketoacidosis or significant hypoglycemic episodes during the months of November 1998, to May 2000. Baseline quality of life was obtained using a validated diabetes quality-of-life survey. A chart review and patient interview identified the number of hospitalizations related to diabetes complications in the previous 6 months. Each patient was intensely educated regarding diabetes, diabetic medications and lifestyle issues. Patients were followed up 4 weeks after discharge and the quality of life survey was repeated. To assess the number of diabetes-related hospitalizations during the post-education period, a second chart review was performed. Pre-education results were compared to post-education results in order to assess the impact of pharmacist-initiated diabetic patient education.
RESULTS: Twelve patients completed the pre and post-education portions of the trial. Four out of 12 quality of life parameters demonstrated statistical significance ($p<0.05$). There was also a decrease in the number of diabetes-related hospitalizations following the education period.
CONCLUSIONS: The results of this trial show that pharmacist-initiated diabetic patient education helps to improve the quality of life of patients with diabetes. Moreover, pharmacist education to diabetic patients also reduced the number of hospitalizations-related to diabetes.

283E. Prescription for change: pharmacist-assisted tobacco cessation© — implementing a tobacco cessation curriculum in California pharmacy schools. *Robin L. Corelli, Pharm.D.*, Karen S. Hudmon, Dr.P.H., R.Ph., Lisa A. Kroon, Pharm.D., Leanne M. Sakamoto, Pharm.D., Eunice Chung, Pharm.D., Marian Paynter, Pharm.D., Berit Gundersen, Pharm.D.; University of California-San Francisco; San Francisco, CA; University of Southern California, Los Angeles, CA; Western University of Health Sciences, Pomona, CA; University of the Pacific, Stockton, CA.

PURPOSE: Research shows that fewer than 10% of practicing pharmacists have received formal training for tobacco cessation counseling. In response to this educational need, faculty from the four California pharmacy schools has developed a comprehensive tobacco cessation curriculum for pharmacy students.
METHODS: A 6- to 8-hour curriculum was developed and incorporated into the required 1st- or 2nd-year coursework at each California pharmacy school. The lecture component covers topics such as the epidemiology of tobacco-related disease, pharmacology of nicotine and nicotine addiction, aids for cessation, and a theory-based approach to helping patients quit. The workshop component includes hands-on experience with pharmaceutical aids cessation and role-playing. Evaluation forms assess the program's impact on student learning and confidence in treating patients for tobacco dependence.
RESULTS: The program has been implemented in three schools (n=376 students). Students estimated that 66% of the material was new, 25% had been taught to them before but was a necessary review, and 9% was an unnecessary review. Participants estimated that 74% of the material will be used when assisting patients. Students rated their pre- and post-training ability to counsel for tobacco cessation (1=poor, 2=fair, 3=good, 4=very good, 5=excellent). Results indicated a significant increase, from 1.78 to 3.54 ($p<0.0001$). Eighty-six percent believed the training will increase the number of patients they counsel for cessation; 92% believed it will improve the quality of counseling they provide.
CONCLUSION: By equipping pharmacy students with specialized training for comprehensive tobacco cessation counseling, the profession of pharmacy could become a cornerstone for anti-tobacco efforts.
Presented at the Annual Meeting of the American Association of Colleges of Pharmacy, San Diego, CA, July 7-12, 2000.

284E. Use of Web technology and active learning strategies in a quality assessment methods course. Therese I. Poirier, Pharm.D., *Christine K. O'Neil, Pharm.D.*; Duquesne University, Pittsburgh, PA.

PURPOSE: The goals were to design this course to adhere to principles of good practice in education. The use of Web technology to enhance active student learning in a required Pharm.D. course, Quality Assessment Methods in Health Care is described and evaluated. The course is designed to meet new competencies for pharmacy practice.
METHODS: The one-credit course was designed for seven, 2-hour class sessions. Each section was comprised of 30-33 students. WebCT®, a course management software, was used to post course syllabus, lecture slides, course calendar, readings, and assignments. WebCT® also allowed for students' e-mail, use of bulletin board for posting questions for class discussion, and three online quizzes. Active learning strategies included bulletin board and classroom discussions; innovative written assignments; and participation in a game called "risk-sharing". In this knowledge game, student teams were required to answer Jeopardy!®-like questions.
RESULTS: Student learning was assessed using graded and non-graded components. Baseline and post course knowledge were assessed. Pre- and post-course surveys examining perceptions of competencies and instructional methods were conducted. Comments from student evaluations are also provided.
CONCLUSION: Instructional strategies including Web-based technology and various active learning strategies can be used to address quality assessment competencies. This should foster enhanced learning of these difficult concepts.
Presented at the American Association of Colleges of Pharmacy Meeting, San Diego, CA, July 2000.

285. Improving diabetes management: a collaborative approach. *Kenneth R. Eugenio, Pharm.D.*, Robert G. Henault, R.Ph., CDE, George Alexis, M.S., R.Ph., Andrew F. Kelliher, M.S., R.Ph., MBA, Paul R. Conlin, M.D.; VA Boston Healthcare System, Boston, MA; Massachusetts College of Pharmacy and Health Sciences, Lakeville, MA; Harvard Medical School, Boston, MA.

PURPOSE: This project identified patients with poorly controlled type 2 diabetes mellitus receiving care within the VA Boston Healthcare System in order to 1) determine potential areas of therapeutic improvement; 2) electronically recommend interventions to primary care providers; and 3) evaluate responses to the interventions.
METHODS: Laboratory data were obtained and screened monthly between January 1, and March 31, 2000. Inclusion criteria included a HbA_{1c} level ≥ 9% and no change in diabetes therapy within the past 60 days. Those patient records were then reviewed for past medical history, pertinent laboratory data, and current diabetes management. A recommendation was then sent via e-mail to the primary care provider.

RESULTS: Forty-six patients (45 men, 1 woman) met the inclusion criteria. The average age was 67.2 years (range 41–87) and the mean HbA_{1c} was 10.3% (9.1–13.2%). Twenty-nine patients were receiving monotherapy, 16 were on combination therapy, and one patient was receiving no pharmacologic therapy. Sixteen patients were then excluded from the study due to repeat non-adherence with clinic appointments. Thirty recommendations were sent via e-mail, 24 were accepted, 1 was declined, and 5 received no response. Recommendations included 1) adding glyburide (4.2%), metformin (25%), rosiglitazone (8.3%), bedtime NPH insulin (12.5%); 2) insulin dosage adjustment (41.7%); or 3) formal diabetes education (8.3%).
CONCLUSION: Interventions sent via e-mail were well accepted and proved to be an effective method of improving diabetes management. Further investigation is needed to assess the impact of these recommendations on glycemic control.

286. Impact of clinical pharmacy services in patients with type 2 diabetes. *Joan Jovero McNicholl, Pharm.D.*, Melvin J. Butler, M.D., Johnetta Craig, M.D.; Saint Louis College of Pharmacy; Lindell Health Center, Saint Louis, MO.

PURPOSE: Assess the effect of a clinical pharmacist as a direct patient care provider in managing diabetic patients
METHODS: From April 1, 1999 to June 12, 2000, data was prospectively collected on all diabetic patients referred to clinical pharmacy services. Data collected included demographics, medical history, pertinent laboratory tests, past/ current medications, diet, exercise, medication, and clinic/laboratory appointment adherence. Hemoglobin A_{1c} ($HgbA_{1c}$) was chosen as an objective marker to assess glycemic control. Clinic physician and pharmacist solely managed patients' diabetes. Follow up was scheduled for every 6-12 weeks.
RESULTS: One hundred fifty-seven patients were assessed with 43 patients lost to follow up and 36 patients excluded until second visit data can be collected. For the remaining 78 patients, mean age was 62 ± 11 years and 97% were African-American. Baseline $HgbA_{1c}$ was 9.4 ± 1.9% and at follow-up #1 $HgbA_{1c}$ was 8.0 ± 1.5% (n=78), $p<0.0001$. Mean change in $HgbA_{1c}$ was -1.3 ± 1.8%. $HgbA_{1c}$ was typically checked between 3-6 months. At baseline, 28.2% of patients had $HgbA_{1c} < 8.0\%$ compared to 66.2% at follow up #1($p<0.0001$). Only 8% had $HgbA_{1c} < 7.0\%$ (goal) at baseline compared to 32% of patients at follow up #1($p<0.0005$). Follow-up data continues to be collected.
CONCLUSION: Clinical pharmacy service has a positive impact on the likelihood of diabetic patients achieving glycemic control. The outcomes of this study strongly supports the utilization of clinical pharmacists to provide direct patient care, complementing the services physicians provide.

287. Development and implementation of a clinical pharmacist-based diabetes care program for an indigent Puerto Rican population. *Pat S. Rafferty, Pharm.D.*; University of Connecticut, Storrs, CT; Saint Francis Medical Center, Hartford, CT.

PURPOSE: Develop a clinical pharmacy service for indigent Puerto Rican patients with type II diabetes, and assess the impact of pharmaceutical care on clinical outcomes in a setting with no previous exposure to clinical pharmacy.
METHODS: A baseline evaluation of 100 Puerto Rican diabetic patients in an adult medicine clinic in a teaching hospital was performed to assess care and serve as a historical control. Care provided by physicians was evaluated according to American Diabetes Association guidelines. Barriers to effective care were identified.
RESULTS: Sixty-seven female and 33 male patients were identified (57 ± 11 years). Adherence to care guidelines was: 53% met LDL goal < 100, 17% had $HbA_{1c} < 7\%$, 56% at BP < 130/85, 58% evaluated for microalbuminuria, 76% annual dilated eye exam, and 43% of patients eligible for aspirin therapy were receiving it. Barriers to care include language, finances, education level, lack of educational and monitoring tools, and inconsistent follow up. Any patient with $HbA_{1c} > 8\%$ will be scheduled to see the clinical pharmacist; however, all diabetic patients will have access to pharmacy clinic. Educational materials will be available in English and Spanish, with medically trained translators, and free glucose meters. Patients will be enrolled in indigent medication programs when necessary, and will be given a diabetes-specific treatment satisfaction questionnaire.
CONCLUSIONS: The level of care for diabetics in this setting can be greatly improved, and substantial barriers to care exist. Specific educational initiatives will be presented with outcomes data for patients followed by the clinical pharmacist.

288. Development, implementation and evaluation of a process to manage patients receiving cisapride therapy. *Christine L. Papoushek, Pharm.D.*; Toronto Western Hospital, Toronto, Ontario, Canada.

PURPOSE: In an effort to minimize risk associated with cisapride and optimize management of gastrointestinal disorders in our ambulatory, family practice population, a pharmacist-facilitated process was developed and implemented. This process included the identification of patients receiving cisapride therapy from a computerized database, dissemination of prescribing information on recommended alternatives and implementation of a quality assurance program to ensure appropriate patient assessment and follow up on the management of specific gastrointestinal (GI) disorders.
METHODS: A list of all patients prescribed cisapride by our family physicians was generated and disseminated with an educational memo describing the adverse reactions and risks associated with cisapride. In addition, a table of recommended alternatives was provided. A chart review will be conducted to document the actions of each physician in response to this notification. Patients requiring modification to cisapride therapy will be scheduled for an appointment with the clinic pharmacist to assess the appropriateness of therapy for specific GI disorder and response and tolerability to current management.
RESULTS: The initial physician response rate (%) to the notification will be reported and a descriptive evaluation on patient-specific assessments will be analyzed.
CONCLUSIONS: Utilizing a computerized database has assisted with the implementation of this pharmacist-facilitated process in ensuring appropriate pharmacotherapeutic outcomes in the management of GI disorders in patients receiving cisapride therapy.

289. Implementation and evaluation of guidelines for lansoprazole use in the maintenance therapy of gastroesophageal reflux disease. *Cynthia N. Spann, Pharm.D.*, Susan Lee, Pharm.D., Gregory H. Ono, Pharm.D.; Northern California Health Care System, Sacramento, Sacramento, CA; Mather Outpatient Clinics, Mather, CA.

PURPOSE: This study evaluates the impact of a two-part program addressing proton pump inhibitor (PPI) use in the maintenance therapy of gastroesophageal reflux disease (GERD). It investigates efficacy of alternative regimens and patient tolerance to therapeutic changes. It also analyzes provider prescribing habits prior to and after initiation of the program.
METHODS: The first part of guideline implementation emphasized an education and step-down therapeutic conversion for patients on long-term lansoprazole. Medical records were reviewed for all patients who had an active lansoprazole prescription. Patients were excluded from possible step-down therapy if they had an indication for long-term PPI therapy or history of failure of high-dose histamine-2 blocker therapy. Baseline questionnaires quantifying GERD symptoms and GERD-related lifestyle factors, including caffeine consumption, smoking and antacid use. Eligible patients were changed to one of three regimens, ranitidine 150 mg or 300 mg twice daily or lansoprazole 30 mg alternating with high dose ranitidine. Repeat questionnaires were administered 2-3 months after step-down therapy. The second part of the program required an evaluation form completed by all providers prescribing PPIs. The form clarified the reason for the PPI prescription and differentiated between acute and chronic therapy. Forms were reviewed for indication and prescriber and computer records were evaluated for clinic lansoprazole use before and after implementation of the form.
RESULTS: Outcomes of therapeutic conversion from lansoprazole to alternative maintenance regimens will be presented. Further, comparison of PPI use prior to and after program implementation will be examined.

290. Impact of a pharmacy resident-managed anticoagulation service in a Veterans Affairs medical center setting. *Rita E. Lakamp, Pharm.D.*, Roberta M. Farrah, Pharm.D., Carole L. Bradley, Pharm.D., BCPS, Tanya M. Konn, Pharm.D., Monica A. Dunnam, Pharm.D; St. Louis College of Pharmacy; St. Louis VA Medical Center – John Cochran, St.Louis, MO.

PURPOSE: Clinical pharmacist-managed anticoagulation services have been shown to improve patient outcomes. Few data are available regarding outcomes of pharmacy resident-managed anticoagulation services.
METHODS: A pharmacy resident anticoagulation monitoring service (AMS) operates in a Veterans Affairs (VA) medical center PRIME clinic. Medical residents serving as primary care providers refer patients to the AMS. Primary care pharmacy residents are responsible for day-to-day operations with supervision from clinical pharmacy preceptors. Therapeutic international normalized ratios (INRs), major and minor hemorrhagic events, and patient demographics were recorded. Major hemorrhagic events required hospitalization or blood transfusion or caused death. Minor hemorrhagic events include epistaxis, abnormal bruising, bleeding gums, or hemorrhoid bleeding. These data were compared (χ^2) to results of published reports of pharmacist-managed AMS to determine if pharmacy resident AMS differed.
RESULTS: One hundred twenty-five patients with 98 patient years representing 817 patient visits were monitored. Sixty-seven percent of INRs at scheduled visits were within goal (± 0.2). Major hemorrhage occurred in 5.6% of patients. Minor hemorrhage occurred in 24% of patients. Major hemorrhage in resident AMS was comparable to published reports (n=2, resident better; n=1, literature better; n=7, no difference). Minor hemorrhage in resident AMS was also comparable (n=5, resident better; n=3, literature better; n=2, no difference). Therapeutic INRs were comparable (n=1, resident better; n=1, literature better).
CONCLUSIONS: Pharmacy resident-managed AMS can produce patient outcomes similar to services provided by clinical pharmacists. Delegation of clinic operation in hopes of promoting resident independence is not detrimental to patient care.

291. Intervention efforts of a multidisciplinary inpatient anticoagulation service in renal failure patients on low molecular weight heparins. *Lisa M*

Tong, Pharm.D., Steven R. Kayser, Pharm.D., Julie Hambleton, M.D.; University of California San Francisco Medical Center, San Francisco, CA.

The Comprehensive Hemostasis and Antithrombotic Service (CHAS) is a collaborative, multidisciplinary service, established in August 1999, that monitors adult hospitalized patients on antithrombotic therapy. In the past 10 months, 10.5% of the interventions made by CHAS were in renal failure patients (creatinine clearance < 30 ml/minute) receiving a low molecular weight heparin (LMWH). Low molecular weight heparins are metabolized renally, and to date, there is no large safety and efficacy study using LMWHs in these patients. Limited data have demonstrated that the drug's half-life is prolonged in these patients, increasing the risk for bleeding. The providers of CHAS have been working collaboratively with physicians at the University of California San Francisco Medical Center to discourage the use of LMWHs in these patients. In a 10-month period, there were 59 interventions. Of these interventions, 71% of patients were on full doses of enoxaparin (1 mg/kg twice daily) and 29% on prophylactic doses (30 mg twice daily or 40 mg once daily). Seventy-five percent of the recommendations to discontinue, switch to unfractionated heparin, decrease the dose, or order antiXa levels were accepted. The major reasons for the rejected recommendations include: improving renal function, short-term use (1 to 2 days), and physicians' discretion. The CHAS believes that with further larger studies using LMWH in patients with poor renal function, dosing guidelines may be established. However, to prevent potential fatal complications with LMWH and without further studies or clinical experience, CHAS will continue to provide surveillance and to advocate prescribing unfractionated heparin to patients with poor renal function.

292. Development and provision of clinical pharmacy services into community-based outreach clinics for patients with HIV infection. *R.O. Smith, Pharm.D.*, P.E. Kokoski, Pharm.D., A. Wendrow, B.S. Pharm, M. Diaz-Linares, Pharm.D., L. H. Danziger, Pharm.D.; University of Illinois at Chicago, Chicago, IL.

PURPOSE: To describe the services developed and provided by clinical pharmacists to patients in four community-based HIV outreach clinics.
METHODS: The HIV outreach clinics were established in 1992 utilizing a community-based model. These clinics provide health care services to undeserved areas of Chicago. The clinics' populations includes intravenous drug users, indigent patients and minority homosexual and transgender men. The clinic staff may include any combination of the following: AIDS-certified nurses or physicians, outreach workers, case managers, and nutritionists. As the complexity of HIV therapy increased funding was pursued and approved for clinical pharmacist services (CPSs). These services were established in 1998. The services include medication histories, counseling prior and post initiation of new therapy, evaluation of adherence, developing tools to increase it, monitoring drug therapy for adverse events, drug-drug interactions and treatment outcomes, interpretation/treatment recommendations based on resistance testing, coordinating medication refills and deliveries, and maintaining updated patient profiles. Due to the large number of indigent patients the pharmacists facilitate patient enrollment in prescription assistance programs and solicit drug samples for other co-morbid diseases. Pharmacists are an active component of the weekly multidisciplinary conference where patients' records are reviewed and therapeutic recommendations are made. In addition, to patient services the outreach pharmacists provide academic teaching to entry level Pharm.D. students and pharmacy practice residents.
CONCLUSION: Clinical pharmacist services have been met with a high level of acceptance by the health care providers and patients. The CPSs have been and continue to be supported by external funding from various sources.

293. Decrease in vancomycin-resistant enterococcus resulting from the implementation of a pharmacist-managed program to improve appropriate vancomycin utilization. *Pamela S. Bozek, Pharm.D.*, Chris W. Manthey, Pharm.D., Micheal Otto, M.D.; St. Joseph Mercy Hospital, Ann Arbor, MI.

PURPOSE: Significant increases in VRE rates and inappropriate vancomycin prescribing prompted hospital-wide system changes and a concurrent vancomycin use evaluation. Program goals were to 1) prevent increasing bacterial resistance to vancomycin; 2) assure proper prescribing of vancomycin; 3) monitor overall vancomycin use.
METHODS: Beginning March 1999, revisions to computerized physician order entry screens mandated the selection of an approved vancomycin indication before order processing continued. Seventy-two-hour automatic stops for empiric orders and 24-hour surgical prophylaxis limitations (in penicillin-allergic patients) were implemented. Justification for changes and education regarding penicillin cross-resistance was communicated (written and verbal) to physicians, nurses, and pharmacists. Pharmacists concurrently evaluated and verified vancomycin appropriateness and physicians notified for inappropriate indications or duration. Quarterly feedback was provided to physicians and pharmacists.
RESULTS: Four hundred thirteen vancomycin cases were evaluated from March 1999 to March 2000. Patients with Gram+ resistant organisms and severe penicillin allergy accounted for 42% and 38% of vancomycin indications, respectively. Twenty-four percent of these penicillin allergies were determined non-severe. Orders for appropriate indications increased from 62% to 89%. Overall, orders for prophylaxis decreased from 37% to 20% and appropriate duration increased from 54% to 89%. Pharmacists contacted physicians for 80% of inappropriate orders (50%-60% of recommendations were accepted, and an additional 20% prompted ID consultation). Use in patients with non-severe penicillin allergies decreased by 10%. Comparing pre- and post-intervention VRE rates, there was a statistically significant decrease from 15.3% to 9.3% at 6 months and 12% to 6.2% at 1 year ($p<0.01$). Average monthly vancomycin drug costs decreased from $3018 to $1250.
CONCLUSIONS: Physician order entry restrictions on vancomycin and pharmacist monitoring proved successful in achieving program goals. VRE rates were significantly reduced. Appropriate vancomycin prescribing improved as a result of increased physician awareness and feedback, allergy education, and diligent pharmacist follow up. Decreased costs reflected more appropriate vancomycin use.

294. Clinical evaluation, epidemiology and patient outcome assessment of quinupristin/dalfopristin (Synercid®) use in a large teaching hospital. *Debra A. Goff, Pharm.D.*, Sondra J. Sierawski, R.Ph.; Ohio State University Medical Center, Columbus, OH.

Quinupristin/dalfopristin (Q/D) was added to formulary November 1999 for vancomycin-resistant enterococcal (VRE) bacteremia or VRE non-bacteremia with clinical signs and symptoms of infection.
PURPOSE: Evaluate use of Q/D, frequency of VRE infections, and patient outcome.
METHODS: Patients who received Q/D from November 1999 to April 2000, were evaluated. Microbiology identified all patients with VRE bacteremia. Epidemiology data included room location at time of VRE culture and length of stay (LOS) from admission to positive culture. Outcome data included treatment, length of stay, and mortality.
RESULTS: Forty-one patients received Q/D or had VRE bacteremia.

16 VRE Bacteremic		25 VRE Non-Bacteremic or MRSA/MRSE*			
10 no Q/D	6 received Q/D	25 received Q/D			
5 died	2 died	17	3*	3*	2
		failed other antibiotics	failed other vanco	allergy to vanco	other
		8 died	0 died	0 died	0 died

LOS = 29.5 days; n=31 who received Q/D; LOS = 28.7 days

The patients' location when culture positive was: MICU (49%), oncology unit (22%), solid organ transplant unit (22%), SICU (5%) and other (2%). The LOS in days from admission to positive culture was 16.3 respiratory (BAL or sputum), 13.5 blood, 8.6 wound, and 4.8 urine. VRE infected patients had a 43% (15/35) mortality rate. Several VRE bacteremics did not receive Q/D after families chose to withhold treatment in terminally ill patients.
CONCLUSION: Q/D was used appropriately for VRE infection. Nineteen percent (6/31) of Q/D use was for staphylococcal infections. The patients acquired VRE most frequently while in the MICU. Vancomycin resistant enterococcal infected patients had a high mortality rate, a LOS of 2 weeks until bacteremic and long hospital LOS.

295. A pharmacist-managed influenza immunization campaign for a high-risk rural population. *Jenny A. Van Amburgh, Pharm.D.*, Nancy M. Waite, Pharm.D., Eric H. Hobson, Ph.D., Hedy Migden, M.D.; Northeastern University, Boston, MA; Albany College of Pharmacy, Albany, NY; Altamont Internal Medicine and Pediatrics, Altamont, NY.

PURPOSE: The immunization campaign implemented in a rural primary care clinic was designed to 1) identify patients at high risk for influenza complications; 2) implement a pharmacist-managed, education-based immunization program; and 3) assess the program's effectiveness in improving influenza immunization rates.
METHODS: A patient chart review was conducted to identify patients at high risk for influenza complications. An educational packet was sent to all identified patients and advertisements were placed in the clinic. Vaccines were administered during a designated flu clinic or during regular clinic appointments. Follow-up surveys collected information on the success of the campaign and reasons why patients remained unvaccinated.
RESULTS: The review of 2271 patient charts identified 657 patients with indications. Influenza immunizations significantly increased from 128 patients (27%) in 1998 to 354 patients (54%) in 1999. Vaccinated patients were significantly older, had cardiovascular disease or diabetes and lived in rural communities. One hundred ninety-nine vaccinated patients had both completed the survey and received the mailing (56.4% response rate). Patients consistently identified the mailing and their health care providers as the primary reasons why they were vaccinated. Over one-half (51.5%) of the unvaccinated patients completed the other survey. Of these patients, 78% remember receiving the mailing from the clinic. Fifty-seven patients (36.5%) reported that they had received the vaccine elsewhere. Nearly two-thirds (63.5%) remained unvaccinated because they believed the influenza vaccine

was not necessary or clinic times were inconvenient.
CONCLUSIONS: The pharmacist-managed vaccine program successfully increased the number of patients vaccinated during the 1999–2000 influenza season. Future programs need to further address education and convenience.

296. A pneumococcal vaccine intervention in a high-risk rural population. *Courtney H. Izzo, Pharm.D.*, Jenny A. Van Amburgh, Pharm.D., Nancy M. Waite, Pharm.D., Eric H. Hobson, Ph.D., Hedy Migden, M.D.; Albany College of Pharmacy, Albany, NY; Northeastern University, Boston, MA; Altamont Internal Medicine and Pediatrics, Altamont, NY.

PURPOSE: This study was conducted in a rural primary care clinic and was designed to 1) determine the vaccination status of patients who were at high risk of developing pneumococcal complications; 2) implement a pharmacist-managed educational program; and 3) assess the program's effect on pneumococcal vaccination rates.
METHODS: Patients were identified via a database as being at high risk for pneumococcal disease, using Center for Disease Control guidelines. A low-literacy educational packet was sent to the identified patients to inform them of where, when and why they needed to be vaccinated. The educational packet was supplemented with advertisement; providing the same information placed in the clinic's patient waiting area. Pneumococcal vaccines were given during clinic appointments or in conjunction with the influenza vaccine at the designated influenza clinic, which was offered in early November 1999.
RESULTS: Five hundred fifty-nine patients were identified as high risk for pneumococcal complications. Of the patients, 104 (18.6%) had received their vaccination prior to the pharmacist intervention. From September 1999 to December 1999, an additional 132 patients were successfully vaccinated against pneumococcal disease, resulting in a total of 236 (42.2%) vaccinated patients ($p<0.05$). Almost two-thirds (64.4%) of the patients received their pneumococcal vaccines during the designated influenza clinic, 25.8% received the pneumococcal vaccine during clinic appointment, and 9.8% patients reported they had received their pneumococcal vaccine at another location.
CONCLUSIONS: The pharmacist-managed educational program successfully increased the number of patients vaccinated in a 3-month period. Further analysis of program outcomes for months 5-12 will allow for future refinement.

297. Impact of a clinical pharmacist as a team member in heart failure management in health maintenance organization patients. *Carrie L. Johnson, Pharm.D.*; University of Cincinnati; Group Health Associates, Cincinnati, OH.

PURPOSE: To evaluate the clinical outcomes in heart failure patients cared for by a recently implemented multidisciplinary management team (OFB) including a clinical pharmacist compared to usual care (UC) in a health maintenance organization setting.
METHODS: Hospitalization claims data from 1999 and chart reviews for these patients with CHF admissions were performed to obtain patients in the UC group. Patients eligible for the OFB program either had a recent CHF hospitalization or based upon random chart reviews from outpatient claims data they were deemed appropriate candidates by their physician. In a historical design, patients' outcomes for 5 months prior were compared to those 5 months after. Sixteen patients were in the UC group and 13 patients were in the OFB group.
RESULTS: CHF admissions decreased from 89% (16/18) prior to 54% (7/13) in the 5 months post event in the UC group. However, CHF admissions decreased from 83% (10/12) to 20% (2/10) post enrollment/event in the OFB group. A 25% increase was seen in optimization of angiotensin-converting enzyme inhibitors and β-blockers to maximum tolerated and/or target doses in the OFB group over UC. A 26% improvement in vaccinations also occurred. 75% (36/48) of the pharmacist recommendations were accepted in this 5-month period.
CONCLUSION: Overall, a 28% decrease in CHF readmissions was seen with the OFB group over UC and adherence to national recognized heart failure treatment guidelines improved with a clinical pharmacist's care.

298. Establishing a policy to improve the utility of drug information provided by pharmaceutical industry representatives. *Stacey L. Abby, Pharm.D.*, Megan N. Lavin, Pharm.D., Richard O. Schamp, M.D.; Family Medicine of St. Louis; St. Louis College of Pharmacy; St. Louis, MO

PURPOSE: A family medicine residency program developed an industry representative policy to standardize services provided by the pharmaceutical industry and educate family medicine residents on how to evaluate information provided by representatives using an evaluation form with assigned usefulness scores. Feedback is given to representatives to improve the usefulness of information provided.
METHODS: The industry review committee reviewed published literature on the impact of pharmaceutical representatives on physicians and then implemented and a policy and residents were educated on the policy and trained to evaluate information provided by pharmaceutical representatives, who were assessed on the type of information presented, techniques of promotion used, appeals, and overall impression. The pharmaceutical representatives schedule an appointment with the clinical pharmacist to receive feedback on their performance.
RESULTS: We are evaluating if this experience is of educational value to the medical residents and if it has improved the amount of useful information provided by pharmaceutical representatives. Preliminary survey results show improved resident understanding of the types of information and promotional techniques used by representatives. Preliminary data show more useful information provided to medical residents by the pharmaceutical representatives following initial feedback.
IMPLICATIONS: The implementation of a pharmaceutical industry policy has standardized the services provided by representatives within a family medicine residency training program. The policy also serves as a method for teaching residents how to evaluate information provided by representatives. Evaluation and feedback to representatives may improve the usefulness of information provided to physician residents.

299E. Community pharmacists: an under-utilized health care resource in the United Kingdom? *Ruth Bednall, M.S., M.R.PharmS.*, Duncan McRobbie, M.S., M.R.PharmS. David Williams, FRCP, FRCS, FFAEM; St. Thomas' Hospital, London, United Kingdom.

PURPOSE: Community pharmacists in the United Kingdom (UK) have been identified as an accessible and under utilized group of health care professionals. Areas where they have specific expertise include management of minor illness and management and prevention of drug-related problems. Research has identified increasing use of emergency medical services for the management of primary health care problems. No published data identified the proportion of primary care patients who were suitable for management by community pharmacists. This study sought to establish the proportion of adult patients that attended the A&E department of a central London hospital with problems that could be managed by a community pharmacist.
METHODS: A cross-sectional, retrospective review of A&E records for adult patients (> 16 years) was conducted during the first 2 weeks of March 1999. Using recognized criteria (the RPSGB-recommended questioning technique and Symptoms in the Pharmacy) patients suitable for community pharmacist management were identified.
RESULTS: The notes of 1930 adult patients were reviewed. Two hundred eight (10.7%) of these were considered suitable for management by a community pharmacist. This equates to 11,000 patients each year. The majority (192) presented with minor illness that could have been managed by medicines available over-the-counter in a community pharmacy. Demographic detail revealed that this population was predominantly young, not resident in the hospital's catchment area and attended during working hours (8 a.m.-8 p.m.). The remaining 16 patients had medication-related problems that were considered suitable for community pharmacist management.
CONCLUSIONS: Community pharmacists could increase their contribution to patient care and relieve the burden of already stretched emergency services, if their skills were appropriately utilized by patients. Further work is needed to establish why patients chose to attend A&E rather than their community pharmacy.
Presented at the Health Services Research and Pharmacy Practice Conference, Aberdeen, United Kingdom, April 12-13, 2000.

300. Health care professional attitudes concerning a pharmacist-administered immunization program. *Melissa M. Blair, Pharm.D., BCPS*, Rachel L. Couchenour, Pharm.D., BCPS; Medical University of South Carolina, Charleston, SC.

PURPOSE: To assess health care providers' comfort levels and satisfaction with a pharmacist-administered adult immunization program in a family medicine clinic.
METHODS: Distributed an anonymous seven-item survey to 28 health care providers in a family medicine clinic after clinical pharmacists provided over 400 adult immunizations.
RESULTS: Response rate was 71% (20/28). Respondents included nine physicians (MD; 45%), five licensed practical nurses (LPN; 25%), four registered nurses (RN; 20%), one mid-level provider (MLP; 5%), and one patient care assistant (PCA; 5%). Ninety percent of the respondents felt comfortable with the clinical pharmacists providing adult immunizations in the clinic and 80% felt it was appropriate for clinical pharmacists to perform this task. The majority of respondents felt the documentation of services was appropriate and the immunization service gave them more time to spend in other areas of their practice. Seventy-five percent of the respondents felt adult immunizations were a good service for all pharmacists to provide; however, 35% were either undecided or did not feel that trained pharmacists should be providing adult immunizations in local pharmacies (2 LPNs, 3 MDs, 1 MLP, and 1 RN).
CONCLUSIONS: Adult immunizations are regarded as a valuable service to provide in a clinic setting when given by clinical pharmacists who have an established relationship with other health care practitioners. Comfort level was decreased when clinic health care providers were queried about trained pharmacists providing adult immunizations in local pharmacies.

301. Clinical and economic impact of a pharmacy practice resident: a cost-benefit analysis. *Margarita V. Desyatnik, Pharm.D.*, Toby Trujillo, Pharm.D., BCPS; Beth Israel Deaconess Medical Center; Massachusetts College of Pharmacy and Health Sciences, Boston, MA.

In an era of limited health care resources pharmacists often must justify the value they add to patient care.
OBJECTIVE: We aimed to quantify the clinical and economic impact of a pharmacy practice resident during rotation on a general medical service.
METHODS: A database (Microsoft Access 97) was developed to track daily activities and clinical interventions. Interventions were classified by type, their acceptance by physicians, and by clinical and economic outcomes. Components of cost savings were drug acquisition and lab-monitoring costs (available from the hospital), as well as cost savings associated with prevention of potential adverse drug reactions (ADRs) and medical errors (MEs); (published average costs were utilized). A pharmacy research committee reviewed and verified all interventions that resulted in ADR/ME prevention. Costs avoided due to ADR/ME prevention were estimated by multiplying the cost of an ADR by the probability of the event occurring.
RESULTS: Over a 6-week period, data on 108 interventions were collected. Acceptance rate was 92%. The most common intervention categories were dosage adjustment (23%), IV to PO conversion (11%), untreated indication (10%) and drug information/education (10%). Interventions were classified as clinically significant in 76% of cases. Estimated savings from the 6-week period included $1551 in drug costs, $2843 in lab costs, and $28,904-50,757 in potential ADRs/MEs avoided. These savings projected to $288-478K per year. The calculated return on investment was 10-17 to 1.
CONCLUSION: We concluded that residents' participation on a medical team was accepted by physicians and resulted in significant cost-benefit to the hospital.

302. Clinical activities of pharmacists in family practice residency programs. *Anne M. Denham, Pharm.D.*, Lori Dickerson, Pharm.D., BCPS, Tom Lynch, R.Ph., BCPS; Medical University of South Carolina, Charleston, SC; Lehigh Valley Hospital, Allentown, PA.

PURPOSE: This survey was designed to identify clinical pharmacists in family medicine residency programs (FMRP) and to document the clinical activities of these pharmacists.
METHODS: All residency program directors were contacted to identify clinical pharmacists working with the FMRP. A thirty-item survey was created and pilot tested, and the completed survey was posted at rxsurvey.musc.edu. Each clinical pharmacist was e-mailed an individual password and explanation of the survey, and asked to submit responses via the Web site.
RESULTS: From a total of 579 FMRP, 155 (27%) residency programs stated they worked with clinical pharmacists. Specifically, there were 176 clinical pharmacists identified within the 155 residency programs. After initial and follow-up e-mails to pharmacists, the survey response rate was 75%. Clinical pharmacists were a mean age of 36.5 years, and 46% were male. Sixty-eight percent had completed a pharmacy residency program, and 44% were certified by the Board of Pharmaceutical Specialties. Most pharmacists had been practicing in family medicine for less than 10 years. On average, the pharmacists spent 40% of time in clinical practice, 40% of time in educational activities, 10% of time in research activities, and 10% of time on administrative functions. Fifty percent of activities involved direct patient care, through formal consultations and specialty clinic services. Clinical activities were provided primarily in the outpatient setting (60%), although services were also provided in the inpatient and nursing home settings.
CONCLUSIONS: Pharmacists are actively involved in providing clinical services in some FMRP. Further descriptions of activities will be presented.

303. Clinical privileging for pharmacists in the U.S. Air Force. *Mary Ann Halloran, Pharm.D., BCPS*, Mark L. Britton, Pharm.D., CDE, Robert C. Buswell, R.Ph., MBA, Robin R. Feuge, Pharm.D., BCPS, Shirley R. Lockie, M.D.; University of Oklahoma Health Sciences Center, Oklahoma City, OK; 72nd Medical Group, Tinker Air Force Base, OK; Samaritan Health Services, Albany, OR.

PURPOSE: To describe the process for obtaining privileged provider status through the U.S. Air Force Major Command. While clinical pharmacists have provided patient care in certain military health care facilities, existing Air Force regulations did not recognize pharmacists as privileged providers. Obtaining provider status would allow facility reimbursement for direct patient care by pharmacists and would support further service development.
METHODS: Current practice guidelines were outlined through review of Air Force regulations. A scope of practice document was developed to define clinical practice levels based on professional degree, level of experience and specific performance criteria. A privilege list was developed and approved to clearly define the specific privileges each provider would be granted. Professional status and licensing history were verified through appropriate government agencies. Reference letters supporting applicant competence were completed. A pharmacist privileging application was approved by Air Force Major Command. Required documentation was submitted to the facility credentialing officer for verification and approval.
RESULTS: Clinical privileging has enhanced recognition of clinical pharmacy services by medical providers within the facility. Two civilian clinical pharmacists have been privileged as health care providers with four additional pharmacists awaiting final approval. Processes for facility reimbursement for these services are currently under development.
CONCLUSION: Coordination of the credentialing process through Air Force Major Command established an official regulation with world wide Air Force applicability. This accomplishment should facilitate the attainment of provider status by clinical pharmacists in other Air Force facilities.

304. The value of institution-specific data in justifying a therapeutic drug monitoring clinic in an internal medicine outpatient clinic. *Patricia A. Rozek, Pharm.D.*, Bruce R. Canaday, Pharm.D., Kimberly A. Thrasher, Pharm.D.; New Hanover Regional Medical Center; Coastal AHEC, Wilmington, NC.

PURPOSE: To establish a pharmacist-managed therapeutic drug monitoring (TDM) clinic in an internal medicine outpatient clinic using a medication use evaluation (MUE) and published data to justify patient need.
METHODS: A literature review was performed to analyze similar programs which had implemented TDM clinics. A retrospective MUE was conducted of 40 randomly selected outpatients who had requested refill authorization within the past week. Data collection was based on Hepler-Strand criteria.
RESULTS: This evaluation identified several patient populations who would benefit from a TDM clinic.
One group consisted of 10 patients (25%) who had a blood pressure > 150/90, which was not addressed by their primary care provider during the last clinic visit. A second group consisted of five patients (13%) who had not been seen in > 1 year; three of whom (60%) received refills on requested items. Attending physicians and residents were in-serviced on the MUE results and published TDM data. While the five attending physicians recognized the importance of the published data, they each stated the MUE data was instrumental in obtaining their support of a TDM clinic at this institution. The pilot was initiated in February 2000. Fourteen patients have been evaluated. Ninety-six percent (26/27) of the interventions have been accepted. Follow-up appointments have been scheduled for all 14 patients (100%).
CONCLUSIONS: The development of this successful clinic at this institution was dependent upon the
MUE data. The limited data required to influence physician support are noteworthy. Other institutions may benefit from a similar process.

305. Knowledge of hospital acquisition costs of antibiotics among physicians in a community hospital. *Sara L. Schroeder, Pharm.D., BCPS*, Joy R. Abu-Shanab, Pharm.D., BCPS, Paul P. Dobesh, Pharm.D., BCPS, Jonathan E. Lakamp, Pharm.D., BCPS; Saint Louis College of Pharmacy; St. Luke's Hospital, Saint Louis, MO.

PURPOSE: Antibiotics are one of the leading drug class costs in hospitals. Cost conscious prescribing can not take place without physician knowledge of antibiotic costs. A method of educating physicians on cost in our facility is through the distribution of a cost card. This survey was conducted to determine physician knowledge of hospital acquisition antibiotic costs in a community setting.
METHODS: Surveys were sent to 433 physicians in the departments of medicine and surgery with admitting privileges at our facility. From a series of fixed cost intervals, physicians were asked to designate a hospital cost for 25 antibiotics currently on formulary. Percentages of correct responses were determined for all antibiotics. Physicians were also asked a series of questions regarding their source of drug cost information and if it was sufficient.
RESULTS: Of the 54 respondents, the average percent correct was 26.7%. Of those surveyed, 69.4% felt they did not receive enough information regarding cost and 71.1% felt it would be helpful to have regular updates on drug costs. Only 29.7% indicated that they received information from the pharmacy regarding cost of antibiotics.
CONCLUSIONS: Despite efforts to provide antibiotic cost information via a cost card to admitting physicians, for the most part they are not cognizant of antibiotic cost. Physicians recognize a lack of knowledge of antibiotic cost and desire further information and education. Educational initiatives will be implemented to enhance knowledge of cost and facilitate cost conscious prescribing.

306. Reimbursement and cost justification for clinical services in an outpatient community mental health center. *Michelle A. Gravlin, Pharm.D., BCPP*, Tim Swinfard, M.S., LPC; Todd D. Schaible, Ph.D.; Burrell Behavioral Health, Springfield, MO.

PURPOSE: Traditionally, clinical psychiatric pharmacist salaries have been supported through academic and/or hospital-based positions. In Missouri, no full-time, outpatient, clinical psychiatric pharmacist positions existed prior to 1999. A behavioral health care system justified a clinical psychiatric pharmacist position by obtaining billing authorization. The behavioral health system does not own or operate any dispensing pharmacies.
METHODS: In May 1999, psychiatric pharmacists at Missouri Department of

Mental Health outpatient administrative agencies became authorized to bill purchase of service (POS) funds for clinical services. Pharmacist and nurse practitioner billing rates are identical. In September 1999, psychiatric pharmacists were authorized to bill Medicaid for selected services through the behavioral health carve-out. Only BPS Board Certified Psychiatric Pharmacists may bill and are designated as qualified mental health professionals.
RESULTS: Between September 1, 1999 and April 30, 2000, 228 clients were served and $17,354.93 was billed. Billable services for Medicaid include professional consultation, medication administration, brief evaluation, and medication services. POS billable services include case management, treatment planning, group psychotherapy, psychiatric evaluation and Medicaid billable services. Billing time was 151.75 hours or 62.3 minutes per working day during this time period. Gross income received generates approximately 50% of the pharmacist's salary, while equaling 13% of time. Pharmacist-initiated medication purchasing recommendations generated cost savings equivalent to approximately 30% of the pharmacist's salary. Twelve-month data, limitations, other revenue sources and available outcomes will be presented.
CONCLUSIONS: Clinical pharmacy services in Missouri community mental health centers can be financially viable. Future assessments measuring effects on patient satisfaction and quality and cost of care are suggested.

307. The benefit of different asthma patient education in a medical center in Taiwan. *Hsiang-Wen Lin, M.S.*, Sow-Hsong Kuo, M.D.; National Taiwan University, Taiwan.

PURPOSE: This study evaluated post-program asthma related benefits of two asthma patient education programs and compared with non-receiving any asthma-related consultation group for 1 year in a medical center in Taiwan.
METHODS: There were two kinds of asthma patient education programs in this medical center in Taiwan since November 1997 to January 1998. One of the asthma patient education programs was pharmacist-directed (PE group). Each patient received at least three times of pharmacist's intervention during two months, including the instruction on techniques of inhaling medications; concepts of self-management and so on. Due to strict inclusion criteria, this group was under small population. The other program was physician-directed (AHC group). Each patient received physician's consultation included self-management depending on asthma health card and so on. We reviewed hospital utilization information of asthma patients who visited hospital because of asthma problems since November 1997 to January 1998. Then to take at random from the two groups, one was AHC group; the other was non-receiving any asthma related consultation group (non-consultation group) paired to age and sex depending on PE group. Finally, we retrospect the two kinds of asthma patient education programs and compared the post-program asthma related hospital resource charge with non-receiving any asthma related consultation patient since January 1998 to December 1998.
RESULTS: Initial we had 15 patients in every group. Eight patients in PE group were excluded due to shifting to visit other hospitals or other reasons and the remaining seven patients in PE group including a patient who extraordinarily frequently visited hospital due to secondary infections. So finally we have three groups, including AHC group, non-consultation group, PE group excluded the frequent secondary infection patient. The total outpatient clinic visits number in every group was 1,492,139. The average total visit ambulatory medication charge per visiting was $113, $1317, $1184; the average total hospital utilization charge per visit was $4514.80, $50,094, $4080 NT.
CONCLUSION: By comparing these hospital utilization, the pharmacist-directed asthma patient education program and physician-directed program showed benefit more than non-receiving consultation group. Reinforce appropriate asthma patient education could improve patients' outcomes and have benefit to health care systems in the further in Taiwan.

308. Establishment of a pharmacist-managed asthma education program in an outpatient clinic. *Janet L. Ritter, Pharm.D.*, Annie C. Mathew, Pharm.D.; Midwestern University, Chicago, IL.

PURPOSE: To establish a pharmacist-managed asthma education program (AEP) at Suburban Heights Medical Center (SHMC), a multispecialty practice in Chicago Heights, IL. The AEP serves as the foundation for the implementation of an asthma disease management program.
METHODS: Suburban Heights Medical Center has over 200,000 annual asthma visits. Most primary physicians refer patients to one allergy specialist for management. There is a lack of available resources and personnel to appropriately perform asthma education. A large marketing campaign is planned, including an AEP brochure which details the referral process and patient visits. Asthmatics are identified by ICD-9 codes and a mass mailing will be completed. After referral to AEP, three visits are scheduled with the clinical pharmacist to: perform asthma education and medication reviews; provide assessment on inhaler/peak flow meter technique; establish an asthma action plan; and make adjustments to drug therapy as warranted. Communication with the referring physician is by a standardized medical chart notation. Patients or caregivers complete an asthma survey, questionnaire, and program evaluation.
RESULTS: To date, eight patients are enrolled in AEP. Multiple therapeutic interventions have been implemented: dose adjustment of inhaled corticosteroids, bronchodilators, and leukotriene antagonists; and instituting β_2-agonist therapy prior to exercise. Asthma knowledge has improved significantly and patient satisfaction with the program is exceptional. Ongoing analysis will be performed and preliminary results presented.
CONCLUSION: The AEP is expected to make a large impact as the foundation for the multidisciplinary asthma disease management program.

309. Outcomes from a pharmacist-managed smoking cessation clinic in an outpatient setting. *Miranda R. Andrus, Pharm.D.*, Mary T. Roth, Pharm.D., Eric C. Westman, M.D., M.H.S.; Ambulatory Care Clinics and the Smoking Research Laboratory; Durham Veterans Affairs Medical Center; Duke University Medical Center; University of North Carolina, Durham, NC.

PURPOSE: To report outcomes of a pharmacist-managed smoking cessation clinic in an outpatient setting.
METHODS: Patients were referred by primary care providers to a pharmacist-managed smoking cessation clinic. Baseline questionnaires were completed, including the Fagerstrom Test for Nicotine Dependence. At each visit, patients received tailored behavioral counseling, educational materials, and pharmacologic therapy. Drug therapy included bupropion SR; nicotine patch, inhaler or nasal spray; or combination therapy, and was selected based on patient preference, smoking history, and adverse effect profile.
RESULTS: Over a 2-year period, 200 patients were enrolled: 97.5% were male, 62.5% were Caucasian, 35.5% were African American, mean age was 52.0 years (SD = 11.3), mean cigarettes smoked per day was 24.9 (SD = 13.8), and mean Fagerstrom score was 5.5 (SD = 2.5). At the initial visit, 35% received the patch, 33% bupropion SR, 18% combination patch plus inhaler, 9.5% inhaler alone, and fewer than 5% received other therapies. Point prevalence abstinence rates 8 weeks after the initial visit were 15.7%, 19.7%, 22.2% and 21.1%, respectively, for the patch, bupropion SR, patch plus inhaler, and inhaler alone. The corresponding abstinence rates at 12 weeks were 15.7%, 16.7%, 10.5%, and 16.7%. There was no statistical difference in abstinence rates between the products at 8 ($p=0.85$) or 12 weeks ($p=0.93$).
CONCLUSION: A tailored approach to smoking cessation pharmacotherapy in a pharmacist-managed program demonstrated improvements in abstinence rates; however, no substantial differences were noted among the treatment options.

310. Attitudes and knowledge base of community pharmacists pertaining to bio-terrorism emergency response. *Emily Ann Baker, Pharm.D.*, Michael G. Kendrach, Pharm.D.; Samford University Global Drug Information Service, Birmingham, AL.

PURPOSE: This study, conducted as part of a federally mandated disaster preparedness program for the city of Birmingham, AL, surveyed pharmacists to determine areas of educational need regarding bio-terrorism and the feasibility of implementing a pharmacist-manned disaster response team.
METHODS: Licensed pharmacists, regardless of practice site, living in Birmingham were surveyed regarding bio-terrorism emergency response. Pharmacists were eligible for study inclusion if they practiced community pharmacy (or in a dispensing setting) for ≥ 1 day per month.
RESULTS: A total of 809 surveys were mailed; 174 (22%) were returned. Survey recipients were allowed to exclude themselves from the study; thus, the number of eligible pharmacists was unable to be determined. Of the eligible returned surveys (n=140), one-third of respondents believed an attack on Birmingham was probable (second-highest ranking based upon a five point scale). Approximately 75% of pharmacists were willing to assist on a response team. Although 52% of pharmacists considered themselves not at all knowledgeable regarding bio-terrorism, 59% were able to identify the most likely pathogens anticipated in an attack. However, only 14% of pharmacists identified the correct antibiotics for prophylaxis of an attack. Although the majority of the respondents (74%) were untrained in vaccine administration, 65% were willing to learn.
CONCLUSION: Pharmacists potentially can contribute as members of biological warfare catastrophe response teams. The majority of pharmacists are willing to respond to a bio-terrorist attack and are somewhat knowledgeable regarding bio-terrorism. Areas of need identified include education regarding appropriate therapies and vaccine administration techniques.

311. Development and implementation of an alcohol withdrawal protocol at two community hospitals. *Patrick K.H. Leung, Pharm.D., BCPS*; Washington State University, Spokane, WA; Providence Yakima Medical Center, Yakima, WA.

PURPOSE: To develop and implement an alcohol withdrawal protocol (AWP) at two community hospitals. The effectiveness of the joint program in preventing severe withdrawal symptoms was evaluated.
METHODS: A multi-disciplinary team met and designed the joint AWP using literature resources and expert opinion. An assessment scale was developed for nurses to recognize and monitor alcohol withdrawal symptoms. Inservices were provided to nursing and medical staffs before the protocol was implemented. Effectiveness and safety of the protocol were monitored during the implementation phase by chart reviews and personal communications.

Data were collected for 32 protocol patients, and 13 historical control patients. Protocol patients received lorazepam based on assessment scale scores, while the control group received lorazepam and other benzodiazepines on schedule and/or an as-needed basis.
RESULTS: Protocol patients received an average lorazepam dose of 10.9 mg ± 17.5 mg compared to 27 mg ± 22.8 mg for control group (p=0.01). More patients in control group were oversedated (30.8% versus 6.3%, chi-squared=0.04). Physical restraint use was not significantly different between protocol patients and controls (28% versus 30.8%, chi-squared=0.88). A trend existed for a greater frequency of severe agitation/delirium tremens in control group (38.5% versus 25%, chi-squared=0.45). There was also a trend that the average length of hospitalization was shorter in protocol group (4.7 days ± 2.6 days versus 5.5 days ± 4.1 days, p=0.45). Nursing and medical staffs were satisfied with the protocol.
CONCLUSIONS: A multi-disciplinary team successfully developed and implemented a joint AWP at two community hospitals. Protocol patients required significantly less pharmacologic sedation and were significantly less oversedated compared to historical controls.

312. Development of a statewide program to increase medication access for indigent solid-organ transplant patients. *Marie A. Chisholm, Pharm.D.*, Bridgett D. Kendrick, C.Ph.T., Leslie J. Vollenweider, Pharm.D., Joseph T. DiPiro, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: Many solid-organ transplant patients (SOT) have inadequate prescription insurance coverage and do not have the financial resources to pay for all of their medication needs. In recognition of this, many pharmaceutical manufacturers make medications available free or at reduced costs to eligible patients who do not have access to essential medications by any other means. To educate health care professionals and to assist patients enroll in medication assistance programs, the Medication Access Program (MAP) was developed.
METHODS: The MAP office was created with two full-time employees (one pharmacist). Georgia's SOT patients in need of medication assistance or their health care professionals contact MAP concerning the availability of assistance programs. MAP instructed patients and health care personnel on the application process required by the pharmaceutical companies and served as a liaison between the patient, physician, and the pharmaceutical companies. Program personnel recorded the number of patients served and the average wholesale price (AWP) of medications supplied through the program. Patients who used MAP's services as of January 1999 were asked to complete a patient satisfaction survey.
RESULTS: From October 1999 to June 2000, MAP has assisted over 120 SOT patients enroll in medication assistance programs, accounting for approximately $340,000 (AWP cost) of medications. Approximately 58% of the $340,000 represents immunosuppressant medications, the other 42% mostly represents that of cardiovascular, antimicrobial, and gastrointestinal medications. Patients (n=44) had a mean score of 91.4 ± 9.6 (highest achievable survey score is 100) on the satisfaction survey indicating that MAP provided a valuable service to them.
CONCLUSION: The MAP was successful in helping needy SOT patients obtain medications and patients are pleased with the services provided.

313. Pharmaceutical care provided by a clinical pharmacist in a renal transplant clinic: a 2-year analysis. *Leslie Vollenweider, Pharm.D.*, Joseph T. DiPiro, Pharm.D., Marie A. Chisholm, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: This is a prospective trial to determine the influence of clinical pharmacist involvement on outcomes in renal transplant patients. Objectives included: 1) identifying, documenting, preventing, and solving medication-related problems; 2) documenting the number and types of recommendations made by the clinical pharmacist to the clinic's physicians; 3) determining the physician acceptance rate of these suggestions; and 4) determining the potential impact of the clinical pharmacist's recommendations on patient outcomes.
METHODS: The renal transplant pharmacist performed medication reviews and was responsible for preventing or resolving patients' medication-related problems and providing appropriate pharmacotherapy recommendations for renal transplant patients seen in the Medical College of Georgia Renal Transplant Clinic. All recommendations that were made by the renal transplant clinical pharmacist from November 1997 to November 1999, were classified according to medication-related problem and class of medication. Two pharmacists (other than the Renal Transplant Pharmacist) independently evaluated each accepted recommendation by using Hatoum's criteria for assessing potential impact on patient care.
RESULTS: Nine hundred twenty-eight recommendations were made during the 2 year study period, and approximately 96% (n=927) of the recommendations were accepted by the clinic's physicians. Untreated indication (25%), overdosage (24%), and subtherapeutic dosage (17%) accounted for greater than 65% of the medication-related problems. The most commonly accepted recommendations involved cardiovascular (32%) and immunosuppressant (30%) medications. Approximately 98% of the recommendations was judged to have a significant (79%) or a very significant (19%) potential impact on patient outcomes.
CONCLUSION: During the first 2 years of renal transplant clinical pharmacy services, the pharmacist performed pharmaceutical care activities that were well accepted by the clinic's physicians and potentially had a positive impact on patient outcomes.

314. Renal transplant clinic patients' satisfaction with health care quality at 1 and 2 years post-implementation of pharmaceutical care services. *Leslie J. Vollenweider, Pharm.D.,* Joseph T. DiPiro, Pharm.D., Laura L. Mulloy, D.O., Muralidharan Jagadeesan, M.D., Marie A. Chisholm, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: This is a prospective trial to determine the influence of pharmaceutical care services on renal transplant patients' satisfaction with the quality of health care received from a renal transplant clinic.
METHODS: Patients at the Medical College of Georgia Renal Transplant Clinic were randomized into an intervention group and a control group. The intervention group received pharmaceutical care services which included ongoing medication reviews for each patient, with emphasis on preventing or resolving medication-related problems and providing pharmacotherapy recommendations. The control group received no pharmacist intervention in addition to the routine services received by all patients in the clinic. At the end of 1 year and 2 years post-study enrollment, patients were given the Health Care Attitude Questionnaire (HCAQ) to measure satisfaction with health care quality based on whether or not they received pharmaceutical care services. Differences in HCAQ scale scores for "overall quality of health care provided by the clinic" and "pharmacy-related" were tested.
RESULTS: Seventy-four patients (71.2% response rate) completed the HCAQ at 1 year post-study enrollment and 24 patients (58.5% response rate) at 2 years post-study enrollment. At 1 year post-study enrollment, patients who received pharmaceutical care services (n=35) had mean HCAQ scores of 91 and 88 (highest achievable satisfaction score on each scale is 100) on the "overall quality of health care provided by the clinic" and "pharmacy-related" scales, respectively. Patients who did not receive pharmaceutical care services (n=39) had significantly lower mean HCAQ scores of 83 and 78, for the same measures, respectively ($p<0.01$). At two years post-enrollment, there was no difference in scores between the intervention and control groups for the "overall health care provided by the clinic" scale (91 for the intervention group vs 83 for the control group); however, patients in the intervention group (n=24) had higher scores than the control group on the "pharmacy-related" scale (97 vs 84; $p<0.01$).
CONCLUSION: Patients who received pharmaceutical care services from the renal transplant pharmacist were more satisfied with the quality of health care than patients who did not receive pharmaceutical care services in the clinic.

315. Pharmaceutical care services reduce the cost of medications prescribed in renal transplant clinic patients. *Marie A. Chisholm, Pharm.D.*; Leslie J. Vollenweider, Pharm.D.; Laura L. Mulloy, D.O.; Muralidharan Jagadeesan, M.D.; Bradley C. Martin, Ph.D; Joseph T. DiPiro, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: To determine the influence of pharmaceutical care services on the cost of medications prescribed in renal transplant clinic patients.
METHODS: Renal transplant patients at the Medical College of Georgia (MCG) Renal Transplant Clinic were prospectively randomized into an intervention group or a control group. In addition to routine clinic services, patients in the intervention group received monthly pharmaceutical care services which included ongoing medication reviews, with emphasis on preventing or resolving medication-related problems and providing pharmacotherapy recommendations. Patients in the control group received the same routine clinic services as the intervention group except they did not have any clinical pharmacist interaction. By using patient medical charts, the total average wholesale price (AWP) for all medications prescribed for each patient during the first year post-transplant was calculated. Each patient's MCG hospitalization charges, clinic charges, and emergency department charges during the first year post-transplant were also collected. Descriptive statistics and analysis to detect differences in cost of medications for the study period between patients in the intervention and control groups were performed. Descriptive statistics and analyses to detect differences in hospitalization, clinic, and emergency department charges for the study period between the intervention and control groups were also performed.
RESULTS: Fifty-four patients were included in the analysis, 26 in the intervention group and 28 in the control group. The groups were similar in gender, age, race, and kidney donor type. Medication cost for patients in the intervention group was significantly lower than patients in the control group ($13,033 ± 4311 vs $15,726 ± 5454; $p<0.05$). There were no significant differences in hospitalization, clinic visit, and emergency department visit charges between the intervention and control groups.
CONCLUSION: The medication cost for renal transplant clinic patients who received pharmaceutical care services in addition to routine clinic services was significantly lower than patients who did not receive these services.

315A. Implementation of a pain management strategy identifying pain as

the fifth vital sign. *Hildegarde J. Berdine, Pharm.D.*, Barbara A. Kirsch, CRNP, Gloria R.Wenzel, BSN, Christine A. Meyer, BSN, Doreen A. Zablostsky, BSPA, Timothy P. McNulty, M.D.; Veteran's Administration Medical Center, Butler, PA; Duquesne University, Pittsburgh, PA.

PURPOSE: A strategy is described to identify, assess, document, treat, and follow up the patient who has pain, in response to the Veteran's Health Administration national pain management initiative mandated in 1998. This is accomplished through education to improve patient care by preventing the suffering from pain, recognizing and documenting pain as the fifth vital sign, and implementing effective pain management.
METHODS: An interdisciplinary team used a familiar method in the veteran's system for problem solving , the U AND I approach or Understand, Analyze, and Improve. The team used this approach to develop and implement the strategy for pain management in our institution.
RESULTS: The interdisciplinary team developed the methods for recognizing pain as the fifth vital sign, documenting assessments, and implementing pain management. These methods are incorporated into medical center documents, the vital signs package, and the electronic ID-pain assessment templates. The team also developed and launched the educational package for the hospital staff emphasizing awareness of clinician attitudes while recognizing the barriers to effective pain management.
CONCLUSIONS: A strategy is in place at this institution to recognize and document pain as the fifth vital sign along with a method to manage and follow up the patient with pain. Education was completed to heighten the awareness of clinicians mandated by this initiative. The next step will be to collect data as to the frequency of use of the documentation tools, survey clinician attitudes, and survey patient satisfaction and health outcomes.

Research Institute

The following papers, based on Fellowships and Research Awards provided by the ACCP Research Institute, will be presented. Full titles and authors are listed, although a complete abstract may not be available for all papers at the time of this printing.

316. Aventis Oncology Fellowship: Effect of mercaptopurine on recombinant thiopurine methyltransferase cell lines. *Thierry Dervieux, Pharm.D.*, Elio Vanin, Ph.D., Martine Roussel, Ph.D., Eugene Krynetski, Ph.D., Patrick Kelly, Ph.D., Mary V. Relling, Pharm.D.; St. Jude Children's Research Hospital, Memphis, TN.

317. Bayer Pharmaceutical Critical Care Fellowship: Aerosolized ceftazidime for the prevention of ventilator-associated pneumonia and its effects on pulmonary IL-6 in critically ill trauma patients. *G. Christopher Wood, Pharm.D.*, Bradley A. Boucher, Pharm.D., FCCP, Martin A. Croce, M.D, Scott D. Hanes, Pharm.D., Vanessa L. Herring, B.S., Timothy C. Fabian, M.D.; University of Tennessee, Memphis, TN.

PURPOSE: No widely accepted antibiotic regimen currently exists for preventing ventilator-associated pneumonia (VAP). In addition, antibiotics may have beneficial effects in attenuating release of proinflammatory mediators in the lung. This study describes the use of aerosolized ceftazidime (CTZ) for VAP prevention and its effects on bronchoalveolar IL-6 concentrations.
METHODS: Trauma patients at high risk for VAP (e.g., severe closed head injury, ISS > 25, pulmonary contusions, rib fractures) and expected to require 7 days of mechanical ventilation (MV) were randomized in this double-blinded study to receive aerosolized CTZ 250 mg or placebo q12 hours for 7 days via jet nebulization. Bronchoalveolar lavage (BAL) samples were collected for IL-6 analysis on day 1 and between days 4 and 7 of study treatment. The primary outcome variable was the development of VAP (quantitative BAL culture > 10^5 CFU/ml). IL-6 was analyzed using ELISA. Data were analyzed using the Mann-Whitney Rank Sum test and chi-square statistic. Continuous data are reported as medians.
RESULTS: Forty patients completed the study (20 CTZ, 20 placebo). Age and APACHE II scores were similar between groups ($p>0.05$). Development of VAP by day 14 and during the ICU stay was significantly lower in the CTZ group vs placebo (15% vs 55%, $p=0.021$; 30% vs 65%, $p=0.022$). Duration of MV (11.5 vs 13.0 days), ICU days (13.5 vs 17.0), and mortality (15% vs 30%) were all similar ($p>0.05$). BAL IL-6 decreased over time in the CTZ group (n=16) but increased in the placebo group (n=17) (-954 vs 4832 pg/ml, $p=0.05$).
CONCLUSIONS: Aerosolized CTZ decreased the incidence of VAP and reversed the rise in pulmonary IL-6 concentrations in critically ill trauma patients.

318. Merck & Co. Cardiovascular Fellowship: Effects of inhaled salmeterol in heart failure. *Tien M.H. Ng, Pharm.D.*, Mark A. Munger, Pharm.D., E. Michael Gilbert, M.D., William Lombardi, M.D.; University of Utah, Salt Lake City, UT.

319. Merck & Co. Pharmacoeconomics Fellowship: Clinical and economic impact of ambulatory care clinical pharmacists in management of dyslipidemia in older adults: the IMPROVE study. *Samuel L. Ellis, Pharm.D.*, Barry L. Carter, Pharm.D., FCCP, Daniel C. Malone, Ph.D.; University of Colorado Health Sciences Center, Denver, CO; University of Arizona, Tucson, AZ.

PURPOSE: This analysis evaluated the impact of ambulatory care clinical pharmacists on the clinical and economic outcomes of managing patients with dyslipidemia during the IMPROVE (Impact of Managed Pharmaceutical care on Resource utilization and Outcomes in Veterans affairs medical centers) study.
METHODS: The IMPROVE study was a randomized, prospective, multi-centered study. Patients were selected for this study if they were considered to be a high risk for medication-related problems. Ambulatory care clinical pharmacists were responsible for providing pharmaceutical care in addition to usual medical care for patients in the intervention group, while the control group remained pharmacist naïve.
RESULTS: A total of 208 and 229 patients with a diagnosis of dyslipidemia were randomized to intervention and control groups, respectively. Seventy-two percent (n=150) of the intervention group and 70% (n=161) of the control group were considered in need of secondary prevention. Ambulatory care clinical pharmacists significantly increased the number patients receiving a fasting lipid profile compared to the control group ($p=0.021$). Reduction in total cholesterol (17.7 mg/dl vs 7.4 mg/dl, $p=0.028$) and low density lipoprotein cholesterol (23.4 mg/dl vs 12.8 mg/dl, $p=0.042$) in the intervention group was significant compared to the control group. There was no significant difference in the mean increase of costs for hospitalizations, clinic visits, laboratory costs, medication costs and cost of lipid therapy between control and intervention groups.
CONCLUSION: This study demonstrates that ambulatory care clinical pharmacists can significantly lower cholesterol levels in dyslipidemic patients who are at high risk for drug-related problems while not increasing health care expenditures.

320. Merck & Co. Pharmacoeconomics Fellowship: Clinical and economic impact of ambulatory care clinical pharmacists in management of type 2 diabetes: the IMPROVE study. *Samuel L. Ellis, Pharm.D.*, Barry L. Carter, Pharm.D., FCCP, Daniel C. Malone, Ph.D.; University of Colorado Health Sciences Center, Denver, CO; University of Arizona, Tucson, AZ.

PURPOSE: To determine the impact of ambulatory care clinical pharmacists on the clinical and economic outcomes of managing patients with type 2 diabetes during the IMPROVE (Impact of Managed Pharmaceutical care on Resource utilization and Outcomes in Veterans affairs medical centers) study.
METHODS: This analysis evaluates diabetic patients enrolled in the IMPROVE study. This study was a randomized, controlled, multi-site trial involving patients at high risk of drug-related problems. Ambulatory care clinical pharmacists were responsible for providing pharmaceutical care services in addition to usual medical care for patients in the intervention group.
RESULTS: A total of 177 and 158 patients with a diagnosis of type 2 diabetes were randomized into the intervention and control groups, respectively. Baseline hemoglobin A_{1C}s were 8.13 ± 1.66% and 8.14 ± 1.60% in the intervention and control groups, respectively. Ambulatory care clinical pharmacists significantly increased the number of patients receiving a hemoglobin A_{1C} compared to the control group ($p=0.035$). There was no difference in the mean reduction in hemoglobin A_{1C} (0.14% and 0.36% in the intervention and control groups, $p=0.27$). A hemoglobin A_{1C} of < 8% was achieved in 55.2% and 56.7% of subjects in the intervention and control groups. There was no significant difference in the mean increase of costs for hospitalizations, clinic visits, laboratory costs and medication costs between control and intervention groups.
CONCLUSION: Ambulatory care clinical pharmacists significantly improved the monitoring of type 2 diabetes. However, this did not result in significant reductions in hemoglobin A_{1C}s.

321. Wyeth-Ayerst Laboratories Psychopharmacy Fellowship: Discharge and readmission rates with atypical antipsychotic use. *Jessica L. Goren, Pharm.D., BCPP*, Gary M. Levin, Pharm.D., BCPP, FCCP; Northeastern University, Boston, MA; University of Florida, Gainesville, FL.

PURPOSE: Newer atypical antipsychotic agents offer many advantages over conventional antipsychotic agents. They may offer a decreased side effect burden, improved compliance, and superior efficacy. However, the atypical antipsychotic agents are much more expensive than conventional agents. We conducted a retrospective review to determine if one atypical anti-psychotic agent conferred a significant advantage with regard to discharge or readmission rates in the inpatient population of a state psychiatric facility.
METHODS: All records for patients started on clozapine, risperidone or olanzapine at any time in 1997 were reviewed. Each inpatient started on a study medication had their records' reviewed for one full year following the medication start date. Each record was assessed for discharge status and concomitant psychotropic medication use. For those patients discharged, their readmission status was followed.

RESULTS:

Drug	n	Discharge	Readmission	Other Psychotropics
Clozapine	22	12 (54%)	2 (16%)	11 (50%)
Olanzapine	31	13 (42%)	3 (23%)	10 (32%)
Risperidone	49	19 (39%)	5 (26%)	30 (61%)
p value		0.75	0.88	0.33

CONCLUSION: The highest discharge rate was seen in-patients receiving clozapine. Treatment with risperidone was associated with the highest readmission rate and concomitant psychotropic use. While these results are not statistically significant our sample size was small. Larger studies are necessary to draw definitive conclusions.

322. Amgen Biotechnology Research Award: Effects of adjunctive treatment with combined cytokines in a neutropenic mouse model of multidrug-resistant *Enterococcus faecalis* septicemia. *David P. Nicolau, Pharm.D.*, Cyprian O. Onyeji, Ph.D., Mary Anne Banevicius, B.S., Jing Li, M.S., Charles H. Nightingale, Ph.D.; Hartford Hospital, Hartford, CT; Obafemi Awolowo University, Ile-Ife, Nigeria.

PURPOSE: Our previous report suggests that granulocyte colony-stimulating factor (G-CSF) may be a useful adjunct to gentamicin and vancomycin for the treatment of multidrug-resistant enterococci (MDRE) infection in the neutropenic host. In furtherance of this finding, the present study examined whether the antienterococcal efficacy of the antibiotic-GCSF regimen could be enhanced by concurrent therapy with interferon-γ.
METHODS: Mice rendered neutropenic by cyclophosphamide were intraperitoneally inoculated with a gentamicin- and vancomycin-resistant *Enterococcus faecalis* isolate. The infected animals were randomized into treatment groups that received determined dosing regimens of vancomycin, G-CSF, or a combination of either or both agents with interferon-γ.
RESULTS: Addition of varying doses of interferon-γ to G-CSF regimen resulted in no significant change ($p>0.05$) in survival of infected animals, compared to treatment with G-CSF alone. Also, the antienterococcal efficacy of antibiotic plus G-CSF therapy was not modified by co-administration of interferon-γ.
CONCLUSION: This study suggests that adjunctive application of combined cytokines (G-CSF and interferon-γ) may not be more beneficial than the use of only G-CSF in combination with antibiotic in the therapy of MDRE infections in neutropenic patients.

323. Amgen Biotechnology Research Award: Preliminary results: High-dose hepatitis B vaccine series in lung transplant patients. *Mary S Hayney, Pharm.D.*, Deborah L. Welter, R.N., Ann Marie Hoffman, R.N., Robert B. Love, M.D.; University of Wisconsin, Madison, WI.

BACKGROUND: Patients with endstage lung disease waiting for transplant are candidates for hepatitis B vaccination. The antibody response rate to the conventional hepatitis B vaccine series is poor. We hypothesize that a higher dose of the hepatitis B vaccine (40 µg/dose) will induce protective levels (> 10 mIU/ml) of antibodies to the hepatitis B virus in more patients than does the routine dose of 10-20 µg/dose.
METHODS: Each subject received the high dose hepatitis B vaccine of 40 µg by intramuscular injection on a 0, 1, and 6 month schedule. Anti-HBs levels were measured after completion of the high dose series via blood draw 1-2 months following completion of the series. The response rate to the high dose series was compared to the response rate in a historical group of transplant patients who received the conventional dose.
RESULTS: The historical control group had a seroconversion rate of 13.3%. We have enrolled 18 patients waiting for lung transplant and have post-vaccination serology on six subjects. Three of four subjects who completed the series before transplant have responded to the vaccine series. Two completed the series after receiving their lung transplants and do not have protective antibody levels.
CONCLUSIONS: We are cautiously optimistic that the high dose hepatitis B vaccine series used in our study produces a protective immune response in lung transplant patients.
Supported by ACCP Amgen Biotechnology Research Award.

324. AstraZeneca Pharmaceuticals Psychiatry Research Award: Comparison of atypical antipsychotics in elderly patients with dementia and psychosis. *Vicki L. Ellingrod, Pharm.D., BCPP*, Susan K. Schultz, M.D., Karen Esktam-Smith, BSN, Stephen Amat, Ph.D.; University of Iowa, Iowa City, IA.

325. Aventis Oncology Research Award: Inter- and intratumoral disposition of platinum in B16 murine melanoma tumors after administration of cisplatin. *William C. Zamboni, Pharm.D.*, A.C. Gervais, M.J. Egorin, M.D., J.H.M. Schellens, M.D., Ph.D., B.J. Delauter, E.G. Zuhowski, B.S., D. Pluim, B.S., D.R. Hamburger, B.S., J.L. Eiseman, Ph.D.; University of Pittsburgh Cancer Institute, Pittsburgh, PA; The Netherlands Cancer Institute, Amsterdam, The Netherlands.

PURPOSE: It is currently unclear why within in a single patient with multiple solid tumors, such as melanoma, there is a reduction in the size of some tumors, while others progress. One possible explanation may be related to the delivery of chemotherapeutic agents to the specific tumor sites. Thus, we used microdialysis to evaluate the inter- and intra-tumor disposition of cisplatin in mice bearing B16 murine melanoma tumors.
METHODS: Cisplatin (3 and 10 mg/kg) was administered IV. Tumor extracellular fluid (ECF) samples were collected via microdialysis (MD) every 12 minutes for 2 hours from probes placed in the right and left sides of the tumor. After MD, tumor samples were obtained at each probe site. Unbound-platinum (Pt) in tumor ECF and total-Pt in tumor extracts were measured by atomic absorption spectrophotometry. Area under the tumor ECF (AUCECF) concentration-time curve of unbound-Pt from zero to infinity were calculated.
RESULTS: After cisplatin at 3 and 10 mg/kg, median (range, CV%) AUCECF and total-Pt were 0.4 (0.2 to 0.8, 29.5%) µg/ml•hour and 0.6 (0.05 to 1.6, 78.2%) µg/ml•hour, respectively, and 0.8 (0.3 to 1.2, 36.7%) µg/g and 1.6 (0.2 to 2.5, 53.2%) µg/g, respectively. After 3 and 10 mg/kg, median (range, CV%) ratio AUCECF within a tumor were 1.3 (1.1 to 1.5, 15.0%) and 1.8 (1.3 to 5.5, 54.7%).
CONCLUSIONS: There is a relatively high (30-fold) inter- and low (2-fold) intra-tumoral variability in platinum exposure in B16 tumors after administration of cisplatin.

326. Bristol-Myers Squibb Central Nervous System Research Award: Drug-cytokine interaction: IL-6 impact on blood-brain barrier transport. *Mark S. Luer, Pharm.D.*, Maggie W. Miller, Pharm.D. candidate, Nathan M. Petty, B.S., Melissa Lamb Shannon, B.S., Kathryn K. Neill, Pharm.D., Russell B. Melchert, Ph.D.; University of Arkansas, Little Rock, AR.

327. Pharmacia Corporation Applied Health Outcomes Research Award: Pharmaceutical care services impact on health care cost of renal transplant clinic patients. *Marie A. Chisholm, Pharm.D.*, Leslie J. Vollenweider, Pharm.D., Laura L. Mulloy, D.O., Bradley C. Martin, Ph.D., Kalen Beauchamp, Pharm.D. candidate, Joseph T. DiPiro, Pharm.D.; University of Georgia, Athens, GA; Medical College of Georgia, Augusta, GA.

PURPOSE: To determine the influence of pharmaceutical care services on renal transplant patients' hospitalizations charges, emergency room visit charges, clinic visit charges, and outpatient medication cost.
METHODS: Renal transplant patients at the Medical College of Georgia Renal Transplant Clinic were prospectively randomized into an intervention group or a control group. Patients in the intervention group received monthly pharmaceutical care services which included ongoing medication reviews, with emphasis on preventing or resolving medication-related problems and providing pharmacotherapy recommendations. Patients in the control group had no clinical pharmacist interaction. The average whole prices (AWP) of all medications that each patient were prescribed during the 1-year post transplant period were collected and used in the analysis. Each patient's hospitalization charges, clinic charges, and emergency room charges during the 1-year post transplant period were also collected and used in the analysis. Descriptive statistics and t-tests were used to detect differences in cost of medications, clinic visit charges, emergency room visit charges, hospitalization charges, and the total of these cost/charges between patients in the intervention and control groups.
RESULTS: The groups were similar in gender, age, race, and kidney donor type. Patients in the intervention group (n=26) had a mean cost of $13,033 ± 4311, $14,569 ± 27,806, 4712 ± 1625, $72 ± 281, and 32,386 ± 28,536 for medications, hospitalizations, clinic visits, emergency room visits, and total cost/charges, respectively. Patients in the control group (n=28) had a mean cost of $15,726 ± 5454, $14,871 ± 32,282, $4296 ± 2159, $107 ± 295, and $35,000 ± $32,822 for medications, hospitalizations, clinic visits, emergency room visits, and total cost, respectively. Medication cost for patients in the intervention group were significantly lower than patients in the control group ($p<0.05$). Although hospitalizations, clinic visits, emergency room visits, and total charges were not statistically different between the groups, patients in the intervention group had mean total cost/charge of $2614 less per patient than patients in the control group.
CONCLUSION: Renal transplant clinic patients who received pharmaceutical care services in addition to routine clinic services had significantly lower medication cost. Patients in the intervention group had a mean lower total cost/charge of care of $2614 per patient compared to patients who did not receive these services.

328E. Wyeth-Ayerst Women's Health Care Research Award: Presence of significant interaction between CYP2D6 substrate metoprolol and nonprescription antihistamine diphenhydramine in healthy, young women. *Ashish Sharma, M.S., DPMP, Sylvie* Pilote M.S., Philippe Pibarot, Ph.D., DMV, FACC, Jean Jobin, Ph.D., FACSM, Jean G Dumesnil, M.D., FACC, Marie Arsenault, M.D., FRCPC, Bettina A Hamelin, Pharm.D.; University Laval; Quebec Heart and Lung Institute, Hospital Laval, Ste-Foy, PQ, Canada.

PURPOSE: Investigation of any potential interaction between the CYP2D6 substrate metoprolol (met) and the classic nonprescription antihistamine diphenhydramine (dp) in young, healthy women with high (extensive metabolizers or EMs) or low (poor metabolizers or PMs) levels of CYP2D6.

METHODS: This was a randomized, double-blind, cross over placebo controlled study of 16 EM and 4 PM women. The volunteers received, after menstruation and before ovulation, a single oral dose of 100 mg met in the morning at steady state concentrations of either dp or placebo. Plasma and urine samples were collected for 48 hours and analyzed for met and OH-metoprolol (OH-met) using HPLC. Resting and exercising heart rate (HR), blood pressure (BP), and doppler derived hemodynamic parameters were examined immediately before and during 12 hours following met.

RESULTS: Met produced a significant reduction of the exercising HR, rate pressure parameter, and cardiac index (all $p<0.05$) and augmentation of the exercising stroke volume index ($p<0.05$). The hemodynamic profile of the subjects tended to return to the baseline levels over time however the recovery was incomplete in PMs and EMs administered dp. At the time of the peak effect, met produced a more severe hemodynamic response in PMs regardless of the treatment. Preliminary data (four EMs and four PMs) suggests that the pharmacokinetic profile of met is significantly different ($p<0.05$) in EMs compared to PMs. dp coadministration significantly reduced ($p<0.05$) the oral, non-renal and partial metabolic clearances of met to α-OH met in EMs but not in PMs, suggesting a significant in vivo inhibition of the alpha hydroxylation of met amongst EMs.

CONCLUSIONS: Our data suggests that dp inhibits the CYP2D6 mediated met metabolism in EMs, thereby prolonging the negative chronotropic effects of the drug. In clinical practice, PMs or EMs treated with CYP2D6 substrates such as met, when coadministered with a drug that inhibits CYP2D6 may exhibit an exaggerated response to the former (for instance bradycardia in response to met).

Presented at the Canadian Society of Pharmaceutical Sciences annual Conference in Vancouver, BC, Canada, June 9, 2000.

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