ALIMENTARY PHARMACOLOGY AND THERAPEUTICS

Alpha fetoprotein, ultrasound, computerized tomography and magnetic resonance imaging for detection of hepatocellular carcinoma in patients with advanced cirrhosis

Snowberger N, Chinnakotla S, Lepe RM, Peattie J, Goldstein R, Klintmalm GB, Davis GL


Background: Serum alpha fetoprotein (AFP), ultrasound, computerized tomography scanning, and magnetic resonance imaging are commonly used to screen for hepatocellular carcinoma (HCC) in patients with cirrhosis.

Aim: To assess the accuracy of screening in advanced cirrhosis.

Methods: The study group consisted of 239 patients with proven HCC in the explanted liver at the time of liver transplant. AFP and imaging were done at referral and serially until transplant.

Results: Hepatocellular carcinoma was detected before liver transplant in 78% and discovered incidentally in 22%. The cause of cirrhosis was hepatitis C (HCV) (55%), hepatitis B (HBV) (17%), alcohol (9%), and other/unknown (19%). Although AFP was elevated 62%, the median level was 15 ng/mL. Only 26%, 15% and 13% were more than 100, 400 and 1000 ng/mL, respectively. By comparison, AFP was elevated in 20% without HCC, but exceeded 100 ng/mL in only 3%. The overall accuracy of AFP was poor regardless of the cutoff. Magnetic resonance imaging was more accurate than computerized tomography or ultrasound in detecting tumour, particularly when performed within 3 months of transplant.

Conclusions: Magnetic resonance imaging is most sensitive for imaging HCC and best reflects actual tumour size. AFP is insensitive and adds little to screening strategies, but has prognostic value when extremely elevated.

AMERICAN JOURNAL OF CARDIOLOGY

Valve structure and survival in quinquagenarians having aortic valve replacement for aortic stenosis (± aortic regurgitation) with versus without coronary artery bypass grafting at a single US medical center (1993 to 2005)

Roberts WC, Ko JM, Filardo G, Henry AC, Hebler RJ Jr, Cheung EH, Mattey GJ, Hamman BL


The purpose of this study was to determine the effect of simultaneous coronary artery bypass grafting (CABG) and the influence of valve structure on both early and late survival in quinquagenarians having aortic valve replacement (AVR) for aortic stenosis (AS) (with or without aortic regurgitation). We analyzed survival and valve structure in 120 quinquagenarians having AVR for AS from 1993 through 2005 at Baylor University Medical Center, including 44 (37%) with and 76 (63%) without simultaneous CABG. Of the 120 patients, 2 (2%) died within 30 days of operation and none from 31 to 60 days postoperatively. Fifteen other patients (13%) died from >60 days to up to 13 years postoperatively. The unadjusted survival analysis showed that late survival was significantly better in the unicuspid/bicuspid valve structure group than in the tricuspid valve structure group (log-rank test p = 0.001), but that it was not affected by gender (male vs female), preoperative severity of the AS (transvalvular peak pressure gradient >50 vs ≤50 mm Hg), or by performance of CABG. The aortic valve was congenitally unicuspid in 18 patients (15%), congenitally bicuspid in 84 (70%), and 3-cuspid in 18 (15%). In conclusion, aortic valve structure affected the unadjusted late survival in quinquagenarians undergoing AVR for AS, but concomitant CABG, gender, and transvalvular peak systolic gradient had no effect.

AMERICAN JOURNAL OF KIDNEY DISEASES

Bilateral infiltrating renal inflammatory pseudotumor responsive to corticosteroid therapy

Ma Y, Zieske AW, Fenves AZ


Inflammatory pseudotumor (IPT) is a quasi-neoplastic lesion that most commonly involves the lung, but has been shown to occur in nearly every tissue type. Renal involvement is very uncommon. We report the second case of IPT ever published presenting as bilateral infiltrating renal masses. Although most renal IPTs were treated with nephrectomy, our patient was managed successfully with conservative steroid treatment, thereby avoiding the alternative of dialysis or kidney transplantation.

AMERICAN JOURNAL OF MEDICAL QUALITY

A hospital-randomized controlled trial of an educational quality improvement intervention in rural and small community hospitals in Texas following implementation of information technology


Rural and small community hospitals typically have few resources and little experience with quality improvement (QI) and, on average, demonstrate poorer quality of care than larger facilities. Formalized QI education shows promise in improving quality, but little is known about its effect in rural and small community hospitals. The authors describe a randomized controlled trial assigning 47 rural and small community Texas hospitals to such a program (n = 23) or to the control group (n = 24), following provision of a Web-based quality benchmarking and case review tool. Centers for Medicare and Medicaid Services Core Measures composite scores for congestive heart failure (CHF) and community-acquired pneumonia (CAP), using...
Texas Medical Foundation data collected via the QualityNet Exchange system, are compared for the groups, for 2 years postintervention. Given the estimated baseline rates for the CHF (68%) and CAP (66%) composites, the cohort enables the detection of 14% and 11% differences (alpha = .05; power = 0.8), respectively.

**AMERICAN JOURNAL OF PREVENTIVE MEDICINE**

**Improving delivery of clinical preventive services: a multi-year journey**

Ballard DJ, Nicewander DA, Qin H, Fullerton C, Winter FD Jr, Couch CE


**Background:** Adults in the United States typically do not receive all recommended clinical preventive services (CPS) for which they are eligible, missing opportunities for prevention and/or early detection. A multi-year quality improvement initiative targeting CPS delivery in a fee-for-service ambulatory care network is described.

**Methods:** Since 1999, HealthTexas Provider Network (HTPN) has implemented multiple initiatives to increase CPS delivery, including a flowsheet, a physician champion model, physician- and practice-level audit and feedback, and rapid-cycle quality improvement training.

**Results:** From 2000 to 2006, “recommended or done” CPS delivery increased from 68% to 92%, and “done” from 70% to 86% (2001 to 2006). “Perfect care” composite performance increased from 0.19 to 0.51 (2001 to 2006).

**Conclusions:** Long-term, multistrategy approaches can achieve substantial sustained improvement in CPS delivery throughout a large ambulatory care provider network.

**BREAST CANCER RESEARCH AND TREATMENT**

**A decade of letrozole: FACE**

O’Shaughnessy J


Third-generation nonsteroidal aromatase inhibitors (AIs), letrozole and anastrozole, are superior to tamoxifen as initial therapy for early breast cancer but have not been directly compared in a head-to-head adjuvant trial. Cumulative evidence suggests that AIs are not equivalent in terms of potency of estrogen suppression and that there may be differences in clinical efficacy. Thus, with no data from head-to-head comparisons of the AIs as adjuvant therapy yet available, the question of whether there are efficacy differences between the AIs remains. To help answer this question, the Femara versus Anastrozole Clinical Evaluation (FACE) is a phase IIIb open-label, randomized, multicenter trial designed to test whether letrozole or anastrozole has superior efficacy as adjuvant treatment of postmenopausal women with hormone receptor (HR) - and lymph node-positive breast cancer. Eligible patients (target accrual, N = 4,000) are randomized to receive either letrozole 2.5 mg or anastrozole 1 mg daily for up to 5 years. The primary objective is to compare disease-free survival at 5 years. Secondary end points include safety, overall survival, time to distant metastases, and time to contralateral breast cancer. The FACE trial will determine whether or not letrozole offers a greater clinical benefit to postmenopausal women with HR+ early breast cancer at increased risk of early recurrence compared with anastrozole.

**CANCER**

**Neoadjuvant therapy followed by prostatectomy for clinically localized prostate cancer**

Sonpavde G, Chi KN, Powles T, Sweeney CJ, Hahn N, Hutson TE, Galsky MD, Berry WR, Kadmon D


The results of this assessment of the literature indicated that neoadjuvant therapy followed by prostatectomy may improve long-term outcomes for patients with high-risk localized disease. In addition, this approach provides a paradigm for evaluating the activity and mechanism of action of new agents as correlative studies are facilitated by the availability of tumor tissue before and after therapy. The authors determined that a multidisciplinary approach involving oncologists, urologists, and pathologists is critical to the success of this model. Recent and ongoing studies of neoadjuvant therapy followed by prostatectomy were reviewed.

**CARDIOLOGY**

**Clinical and morphologic features of the congenitally unicuspid acommissural stenotic and regurgitant aortic valve**

Roberts WC, Ko JM


Five adults, aged 30–75 years, are described with stenotic and regurgitant unicuspid acommissural aortic valves. Because none of these patients had clinical, echocardiographic or hemodynamic evidence of mitral valve disease, a case is made that these valves were congenitally malformed and not the result of an acquired condition.

**CURRENT OPINION IN ANAESTHESIOLOGY**

**The new generation of graduating anesthesia residents: what is the impact on a major tertiary referral private practice medical center?**

Ramsay M


**Purpose of review:** The new graduate entering the private practice arena faces many challenges. Expectations regarding both the professional environment and personal lifestyle have changed from previous generations, and these are reviewed and discussed. The challenges for both professional and personal development and the responsibilities of the new graduate to continue to learn and stay on top of the specialty are enormous.

**Recent findings:** The best graduates add to the reputation and performance of a department. Marginal graduates have a much tougher experience; their career in a tertiary care, level 1 trauma center environment is unlikely to be sustainable. The motivation and expectations of the new graduates, as they relate to lifestyle, schedules, and reimbursement,
have changed. The expectations of the practice, the institution, the payers, and the public also have changed and are increasingly focused on performance, efficiency, and safety.

**Summary:** Anesthesiology continues to attract some of our best physicians, and this is vital for the survival of anesthesiology as a medical specialty. The new generation challenges us to make the necessary changes in practice pattern and lifestyle to sustain this goal. The new generation is also challenged by an environment of performance-based expectations.

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**CURRENT OPINION IN IMMUNOLOGY**

Microarray-based identification of novel biomarkers in IL-1-mediated diseases

Allantaz F, Chaussabel D, Banchereau J, Pascual V


Interleukin 1b (IL-1b) is emerging as mediator of a wide range of human diseases. Availability of IL-1 blockers that result in clinical benefits to patients with these diseases is creating a demand for biomarkers to diagnose as well as to predict and follow responses to therapy. Blood gene expression profiling can be used to identify such biomarkers. This review will summarize recent studies in the field and will discuss some of the challenges raised by the use of this technology in biomarker discovery.

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**EXPERT REVIEW OF ANTICANCER THERAPY**

Current optimal chemotherapy for advanced urothelial cancer

Sonpavde G, Galsky MD, Hutson TE


Conventional frontline cisplatin-based combination chemotherapy with gemcitabine and cisplatin, or traditional or dose-dense methotrexate, vinblastine, doxorubicin and cisplatin, yields high response rates but few durable remissions for advanced urothelial cancer. Salvage therapy is generally disappointing with few responses. A significant proportion of patients exhibit renal dysfunction, entailing carboplatin-based regimens that appear inferior to cisplatin-based regimens, which warrants a special focus in this population. The profusion of novel biologic agents offers the promise of improved outcomes. A multidisciplinary approach is necessary to make therapeutic advances.

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**GASTROENTEROLOGY**

Epiogenetic and genetic alterations in Netrin-1 receptors *UNC5C* and *DCC* in human colon cancer

Shin SK, Nagasaka T, Jung BH, Matsubara N, Kim WH, Carethers JM, Boland CR, Goel A


**Background and aims:** *DCC* and *UNC5C*, Netrin-1 dependence receptors, perform an important role in intestinal epithelial biology. Both receptors frequently are down-regulated in colorectal cancer (CRC). Although CRCs frequently lose *DCC* owing to deletions at 18q, the mechanism for the *UNC5C* loss is poorly understood. We hypothesized that *UNC5C* is silenced epigenetically in CRC, and that there are interactions between losses of *UNC5C* and *DCC* in colorectal tumorigenesis.

**Methods:** Gene expression and epigenetic analysis of *UNC5C* was examined in 8 CRC cell lines, 147 sporadic CRCs with corresponding normal mucosa, and 52 adenomatous polyps (APs). Allelic imbalances at *DCC* were determined in CRCs. The molecular analyses were compared with genetic and clinicopathologic features.

**Results:** All CRC cell lines showed *UNC5C* methylation and an associated loss of gene expression. Treatment with 5-Aza-2’-deoxycytidine resulted in restoration of gene transcription. *UNC5C* methylation was significantly higher in CRCs (76.2%) and APs (63.5%) than in corresponding normal mucosa (6%; *P* < .0001). Allelic imbalance at *DCC* was observed in 61% of CRCs. Overall, 89.3% of CRCs had alterations of one of the dependence receptors. *UNC5C* methylation occurred predominantly in the earlier lesions (APs and early CRCs), whereas *DCC* losses were more often in advanced CRCs.

**Conclusions:** The majority of CRCs harbor defects in Netrin-1 receptors, emphasizing the importance of this growth regulatory pathway in cancer. Furthermore, the timing of the molecular alterations in the Netrin-1 receptors is not random because *UNC5C* inactivation occurs early, whereas *DCC* losses occur in later stages of multistep colorectal carcinogenesis.

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**GASTROINTESTINAL ENDOSCOPY**

Double-balloon ERCP in patients who have undergone Roux-en-Y surgery: a case series

Emmett DS, Mallat DB


**Background:** ERCP is technically challenging in patients who have had a long-limb Roux-en-Y surgical procedure. The recent introduction of the double-balloon endoscope permits the examination of a much longer segment of the small bowel compared with a standard endoscope and may be used to perform ERCP in these patients.

**Objective:** To report successful use of double-balloon ERCP in patients who have had a Roux-en-Y surgical procedure.

**Patients:** Fourteen patients with a history of either Roux-en-Y gastric bypass weight-reduction surgery or Roux-en-Y pancreaticobiliary surgery required diagnostic and/or therapeutic pancreaticobiliary intervention.

**Design:** Case report.

**Intervention:** Double-balloon ERCP.

**Results:** Fourteen patients underwent a total of 20 ERCPs with the double-balloon endoscopy system. The ampulla was successfully reached in 85% of total cases (100% of patients who have had Roux-en-Y weight reductive surgery), with adequate cannulation of either the biliary or pancreatic duct in 80% (88% of patients for weight reduction). Therapeutic intervention, including stone removal, pancreaticobiliary-duct dilation, sphincterotomy, stent placement, and removal of previously placed stents, was performed successfully in 6 cases. The mean age was 47 years old. The mean (± standard deviation) total duration
of the procedure was 99 ± 48 minutes. There were no immediate or short-term complications.

Conclusions: The double-balloon endoscopy system permits diagnostic and therapeutic ERCP in patients who have had long-limb surgical procedures. Our experience demonstrated that this procedure is well tolerated, safe, and has a high success rate.

JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY

Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial

Background: Adalimumab is a fully human monoclonal antibody that binds tumor necrosis factor, a key proinflammatory cytokine involved in the pathogenesis of psoriasis.

Objective: We sought to evaluate clinical efficacy and safety of adalimumab for moderate to severe psoriasis and investigate continuous versus interrupted therapy.

Methods: We conducted a 52-week, multicenter study of 1212 patients randomized to receive adalimumab (40 mg) or placebo every other week for the first 15 weeks. At least 75% improvement in the Psoriasis Area and Severity Index (PASI) score was the criterion for advancement through this multiphase study.

Results: At week 16, 71% (578 of 814) of adalimumab- and 7% (26 of 398) of placebo-treated patients achieved greater than or equal to 75% improvement in the PASI score. During weeks 33 to 52, the percentage of patients rerandomized to placebo who lost adequate response (defined as <50% improvement in the PASI response relative to baseline and at least a 6-point increase in PASI score from week 33) was 28% compared with 5% of patients treated continuously with adalimumab.

Limitations: Lack of an active comparator and evaluation of maintenance of response beyond week 52 are limitations.

Conclusion: Adalimumab is efficacious and well tolerated in the treatment of chronic plaque psoriasis.

Alefacept revisited: our 3-year clinical experience in 200 patients with chronic plaque psoriasis
Perlmutter A, Cather J, Franks B, Jaracz E, Menter A

Background: Alefacept was the first biologic agent approved in the United States for the treatment of moderate to severe chronic plaque psoriasis (January 2003). Standard prescription is 12 weekly intramuscular doses. The mechanism of action involves the inhibition of T-cell activation and the selective induction of apoptosis of memory T cells. A proportion of patients responding to therapy have been reported to experience remissions of approximately 7 to 8 months, characterized by disease-free and treatment-free intervals.

Objective: We sought to evaluate the efficacy and safety of alefacept treatment in patients with psoriasis during routine clinical practice.

Methods: We conducted a retrospective chart analysis of data involving 201 patients and 296 courses of alefacept from February 2003 to January 2006. Standard informed consent was obtained.

Results: Of the 62 patients (32.6%) who achieved an excellent response, 45% received dosage regimens defined as alternative and 73% had concomitant therapy in at least one of the treatment courses that they received. The average remission time of these patients who achieved an excellent response was approximately 7 months, with a maximum of up to 25 months. Adverse events were generally manageable and rarely led to treatment discontinuation.

Limitations: Study data rely on retrospective analysis of chart-documented clinical examination findings, and patient compliance with visit schedules.

Conclusion: Alefacept is a long-term treatment option for psoriasis with long-term remissions noted in a proportion of patients.

KIDNEY INTERNATIONAL

What does serum fibroblast growth factor 23 do in hemodialysis patients?
Emmett M

Fibroblast growth factor 23 (FGF-23) is a phosphate-regulating substance largely produced by osteocytes. Its major action, in normal subjects, is the inhibition of Na-coupled reabsorption of inorganic phosphate in the renal proximal tubule. FGF-23 levels increase markedly in dialysis patients. Why do the FGF-23 levels increase in these patients, and do they have any physiologic or pathophysiologic effects?

LIVER TRANSPLANTATION

Corticosteroid-free immunosuppression with daclizumab in HCV+ liver transplant recipients: 1-year interim results of the HCV-3 study

This work is a 1-yr interim analysis of a prospective, randomized, multicenter trial evaluating the effect of corticosteroid-free immunosuppression on hepatitis C virus-positive (HCV+) liver transplant recipients following liver transplantation (LT). Patients received tacrolimus and corticosteroids (Arm 1; n = 80); tacrolimus, corticosteroids, and mycophenolate mofetil (MMF) (Arm 2; n = 79); or daclizumab induction, tacrolimus, and MMF (Arm 3; n = 153). At 1 yr, 64.1%, 63.4%, and 69.4% of patients achieved the composite primary endpoint of freedom from rejection, freedom from HCV recurrence, and freedom from treatment failure, respectively. Excellent patient and graft survival did not differ significantly among treatment arms. Freedom from HCV recurrence at 1 yr was 61.8 ± 6.2%, 60.1 ± 6.1%, and 67.0 ± 4.3% in Arms 1, 2, and 3, respectively (P = not significant).
Freedom from rejection was significantly higher in Arm 3 compared to Arm 1 (93.0 ± 2.2% vs 81.9 ± 4.4%; \( P = 0.011 \)). Multivariate analysis identified acute rejection (hazard ratio = 2.692; \( P = 0.001 \)) and donor age (hazard ratio = 1.015; \( P = 0.001 \)) as significant risk factors for HCV recurrence. HCV recurrence was not influenced by recipient demographics, HCV genotype, or immunosuppression. In conclusion, these results suggest that a corticosteroid-free regimen of tacrolimus and MMF following daclizumab induction is safe and effective in HCV+ liver transplant recipients.

**PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA**

**Circulating tumor antigen-specific regulatory T cells in patients with metastatic melanoma**


Although it is accepted that regulatory T cells (T regs) contribute to cancer progression, most studies in the field consider nonantigen-specific suppression. Here, we show the presence of tumor antigen-specific CD4+ T regs in the blood of patients with metastatic melanoma. These CD4+ T regs recognize a broad range of tumor antigens, including gp100 and TRP1 (melanoma tissue differentiation antigens), NY-ESO-1 (cancer/testis antigen) and survivin (inhibitor of apoptosis protein (IAP) family antigen). These tumor antigen-specific T regs proliferate in peripheral blood mononuclear cells (PBMC) cultures in response to specific 15-mer peptides, produce preferentially IL-10 and express high levels of FoxP3. They suppress autologous CD4+CD25+ T cell responses in a cell contact-dependent manner and thus share properties of both naturally occurring regulatory T cells and type 1 regulatory T cells. Such tumor antigen-specific T regs were not detected in healthy individuals. These tumor antigen-specific T regs might thus represent another target for immunotherapy of metastatic melanoma.

**Surgery Today**

**Liver transplantation for cystic fibrosis in adults**

Ikegami T, Sanchez EQ, Uemura T, Narasimhan G, Masannat O, Chinnakotta S, McKenna GJ, Randall HB, Levy MF, Goldstein RM, Klintmalm GB


**Purpose:** To expand our knowledge on liver transplantation for cirrhosis associated with cystic fibrosis in adults.

**Methods:** Five patients who underwent a liver transplantation due to cystic fibrosis were reviewed. The outcome of the patients in terms of age, immunosuppression regimen, patient and graft survival, and pre- and post-transplant complications were investigated.

**Results:** Five adult liver transplant patients had cystic fibrosis (0.2%). These included 4 men and 1 woman with a mean age of 31 ± 10, ranging from 22 to 52 years old at the time of transplantation. All patients had lung problems. Four patients had exocrine and two had endocrine pancreatic insufficiency. Two are currently alive with a follow-up of 5.8 years and 4 months after transplantation, respectively. There were three deaths from pulmonary embolism at 4.5 years, myocardial infarction with cyclosporine nephrotoxicity at 10.7 years, and lymphoproliferative disorder at 5 months after transplantation. No deaths occurred from lung infection. Only one patient had postoperative pulmonary infectious complications, which were successfully treated with antibiotics and did not result in mortality.

**Conclusion:** Adult liver transplantation for end-stage liver disease associated with cystic fibrosis offers encouraging results with a rapid general improvement after surgery and it is now considered to be a safe and acceptable treatment for this disease population.

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