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# Selected published abstracts of Baylor researchers

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## AMERICAN JOURNAL OF CARDIOLOGY

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### Effect on right ventricular volume of percutaneous Amplatzer closure of atrial septal defect in adults

Schussler JM, Anwar A, Phillips SD, Roberts BJ, Vallabhan RC, Grayburn PA

(*Am J Cardiol* 2005;95:993–995)

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In adult patients with atrial septal defects (ASDs), right ventricular (RV) cavity size may return to normal after operative closure. This study demonstrated improved RV volumes and right atrial areas in 20 adult patients after successful transcatheter closure of large ASDs. RV volumes decreased by 22%, 30%, and 41% at 1 day, 1 month, and 6 months, respectively, after the procedure. Right atrial areas decreased by 5%, 23%, and 26%, respectively, over the same time.

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## ANESTHESIOLOGY CLINICS OF NORTH AMERICA

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### Role of cyclooxygenase-2 inhibitors in postoperative pain management

Gajraj NM, Joshi GP

(*Anesthesiol Clin North America* 2005;23:49–72)

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Cyclooxygenase (COX)-2 inhibitors are as efficacious as nonselective nonsteroidal anti-inflammatory drugs for the treatment of postoperative pain but have the advantages of a better gastrointestinal side-effect profile as well as a lack of antiplatelet effects. There have been recent concerns regarding the cardiovascular side effects of COX-2 inhibitors. Nonetheless, they remain a valuable option for postoperative pain management. The pharmacology of these agents and available studies are reviewed.

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## ARCHIVES OF NEUROLOGY

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### Rabies encephalomyelitis: clinical, neuroradiological, and pathological findings in 4 transplant recipients

Burton EC, Burns DK, Opatowsky MJ, El-Feky WH, Fischbach B, Melton L, Sanchez E, Randall H, Watkins DL, Chang J, Klintmalm G

(*Arch Neurol* 2005;62:873–882)

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**Background:** Three patients received solid organ transplants from a common donor and were subsequently discharged from the hospital following an uneventful hospital course. Within 30 days, all 3 organ recipients returned to the hospital with varying symptoms that progressed to rapid neurological deterioration, coma, and death.

**Objective:** To describe the clinical, neuroradiological, and pathological findings of rabies virus infection in organ transplant recipients infected from a common donor.

**Design:** Case series involving a common donor and 3 organ recipients ascertained through review of clinical course and autopsy findings. A fourth case was determined by review of pending autopsy cases

in which death occurred within the same time interval. Portions of postmortem central nervous system and organ tissues were frozen and formalin-fixed. Fluids and tissues were also collected for cultures, serology, and molecular studies. Postmortem fluids and tissues and antemortem fluids and tissues from all 4 transplant recipients and serum and banked lymphocyte or spleen cells from the donors were sent to the Centers for Disease Control and Prevention for further evaluation.

**Setting:** Transplant unit of an urban teaching hospital.

**Results:** Antemortem cerebrospinal fluid analysis for 3 of the 4 recipients was consistent with a viral etiology. Neuroimaging and electroencephalogram studies were suggestive of an infectious encephalitis or a toxic encephalopathy. Initial laboratory testing did not demonstrate an infectious etiology. Postmortem histologic analysis, immunohistochemistry, electron microscopy, and direct fluorescence antibody testing revealed rabies virus infection. Serological testing done postmortem confirmed rabies virus infection in the common donor.

**Conclusions:** These cases demonstrate a risk for transmitting rabies virus infection through solid organ and tissue transplantation, and this diagnosis should be considered in any rapidly progressing neurological disease.

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## BONE MARROW TRANSPLANTATION

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### Modification of the Bu/Cy myeloablative regimen using daily parenteral busulfan: reduced toxicity without the need for pharmacokinetic monitoring

Mamlouk K, Saracino G, Berryman RB, Fay JW, Pineiro LA, Vance EA III, White M, Sandler I, Agura ED

(*Bone Marrow Transplant* 2005;35:747–754)

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Pharmacokinetic and clinical outcome measures among three groups of patients undergoing hematopoietic transplant were assessed: group A: parenteral busulfan (Bu) 3.2 mg/kg i.v. given qd, n = 20; group B: parenteral Bu 0.8 mg/kg i.v. given every 6 h, n = 11; group C: Bu 1 mg/kg p.o. given every 6 h, n = 25. All groups received Bu over 4 days followed by Cy 60 mg/kg i.v. qd over 2 days; followed by an infusion of allogeneic stem cells. Median Bu clearance was 3.21 mL/min/kg and median daily AUC was 4071  $\mu\text{mol}/\text{min}$  for the group A patients. The dosing formula for Bu i.v. qd was highly predictive of the AUC for patients whose mass  $\leq \text{IBW} + 20\%$ . For patients of greater mass, the dosing formula uniformly resulted in lower-than-predicted AUC. Neurologic toxicity, hepatic toxicity, hematologic engraftment, and relapse at 100 days were comparable across all three groups. Severe AGVHD was least among group A, followed by group B when compared with group C. Bu i.v. qd is a safe and effective regimen for allogeneic transplantation and is at least clinically equivalent to every 6 h dosing schemes using either oral or parenteral Bu.

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## CLINICAL LYMPHOMA

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### Immunoglobulin M myeloma: evaluation of molecular features and cytokine expression

Konduri K, Sahota SS, Babbage G, Tong AW, Kumar P, Newman JT, Stone MJ

(*Clin Lymphoma* 2005;5:285–289)

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Immunoglobulin (Ig) M myeloma is a distinct entity with features of multiple myeloma (MM) and Waldenström's macroglobulinemia (WM). The malignant cells in IgM myeloma have a distinctive chromosomal translocation that differentiates them from WM. These cells are postgerminal-center in origin with isotype-switch transcripts. They appear to be arrested at a point of maturation between that of WM and MM. Preliminary data indicate that a pattern of osteoclast-activating factor and osteoprotegerin expression similar to that observed in classic MM is present in IgM myeloma. Additional studies on patients with this rare tumor may provide further insight into the pathogenesis of bone disease in plasma cell dyscrasias.

### Autoantibody activity in Waldenström's macroglobulinemia

Stone MJ, Merlini G, Pascual V

(*Clin Lymphoma* 2005;5:225–229)

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Some monoclonal proteins from patients with Waldenström's macroglobulinemia (WM) or immunoglobulin (Ig) M monoclonal gammopathy of undetermined significance possess antigen-binding activity directed to autogenous or foreign antigens. These monoclonal IgM autoantibodies include cold agglutinins, mixed cryoglobulins, and antineural components. Because of the antigen-antibody interaction, patients with these autoimmune syndromes often present with hemolytic anemia, mixed cryoglobulinemia, or peripheral neuropathy, respectively, at an earlier stage than patients with typical WM who do not have evident antibody activity. The presence of monoclonal macroglobulin autoreactive antibodies thus influences clinical presentation and natural history. Monoclonal IgM antibodies display polyreactivity to antigens of microbial origin in addition to autogenous antigens and may arise through T-independent as well as T-dependent pathways. Waldenström proteins with antibody activity appear to provide a link between autoimmunity, infection, and lymphoproliferative disease. Study of the antigens reacting with monoclonal IgMs may provide further insight into the pathogenesis of WM.

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## CURRENT TREATMENT OPTIONS IN GASTROENTEROLOGY

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### Chronic diarrhea

Schiller LR

(*Curr Treat Options Gastroenterol* 2005;8:259–266)

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Chronic diarrhea can be due to any of several hundred conditions. When investigation fails to uncover a specific cause that can be treated successfully, nonspecific therapy is implemented. This includes dietary alterations if specific aggravating foods can be identified, enteral or parenteral nutrition if nutritional status is compromised, and use of oral rehydration solutions if diarrhea produces volume depletion. Strategic use of dietary fiber can improve stool consistency and can be of special value when fecal incontinence is present concurrently.

Medications of value include opiate antidiarrheal drugs, clonidine, octreotide, and bile acid-binding agents. Less potent opiates such as loperamide and diphenoxylate should be tried first, with more potent agents such as codeine, opium, and morphine used in refractory cases. Clonidine has both proabsorptive and motility effects that facilitate its antidiarrheal effect, but its antihypertensive action limits its utility. Octreotide is of great value in treating diarrhea due to endocrine tumors and dumping syndrome; its efficacy in other conditions or in nonspecific diarrhea is less well established. Bile acid binders such as cholestyramine or colestipol have several specific uses but have limited utility in nonspecific chronic diarrhea.

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## EXPERT OPINION ON BIOLOGICAL THERAPY

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### Efalizumab: continuous therapy for chronic psoriasis

Cather JC, Menter A

(*Expert Opin Biol Ther* 2005;5:393–403.)

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Efalizumab is a humanised monoclonal antibody targeting the CD11a subunit of lymphocyte function-associated antigen-1, specifically developed for psoriasis. Indicated for patients with moderate-to-severe plaque psoriasis, efalizumab is FDA-approved in the US for patients aged  $\geq 18$ , as well as being approved in several other European countries. Clinical studies have proven the efficacy of efalizumab for a majority of patients, improving quality of life with continuous maintenance therapy by means of weekly subcutaneous self-injections. Controlled trials have demonstrated the safety and tolerability of efalizumab. Clinical trials have established that approximately 30% of patients can achieve a PASI-75 response within 12 weeks of initiating treatment, with further clinical benefit noted with continued therapy up to 24 and even 36 months of therapy. Efalizumab may thus potentially offer patients a safe option for long-term safe control in managing their disease.

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## JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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### Echocardiographic predictors of morbidity and mortality in patients with advanced heart failure: the Beta-blocker Evaluation of Survival Trial (BEST)

Grayburn PA, Appleton CP, DeMaria AN, Greenberg B, Lowes B, Oh J, Plehn JF, Rahko P, St John Sutton M, Eichhorn EJ; BEST Trial Echocardiographic Substudy Investigators

(*J Am Coll Cardiol* 2005;45:1064–1071)

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**Objectives:** The aim of this study was to determine echocardiographic predictors of outcome in patients with advanced heart failure (HF) due to severe left ventricular (LV) systolic dysfunction in the Beta-blocker Evaluation of Survival Trial (BEST).

**Background:** Previous studies indicate that echocardiographic measurements of LV size and function, mitral deceleration time, and mitral regurgitation (MR) predict adverse outcomes in HF. However, complete quantitative echocardiograms evaluating all of these parameters have not been reported in a prospective randomized clinical trial in the era of modern HF therapy.

**Methods:** Complete echocardiograms were performed in 336 patients at 26 sites and analyzed by a core laboratory. A Cox proportional-hazards regression model was used to determine which echocardiographic variables predicted the primary end point of death or the

secondary end point of death, HF hospitalization, or transplant. Significant variables were then entered into a multivariable model adjusted for clinical and demographic covariates.

**Results:** On multivariable analysis adjusted for clinical covariates, only LV end-diastolic volume index predicted death (events = 75), with a cut point of 120 mL/m<sup>2</sup>. Three echocardiographic variables predicted the combined end point of death (events = 75), HF hospitalization (events = 97), and transplant (events = 9): LV end-diastolic volume index, mitral deceleration time, and the vena contracta width of MR. Optimal cut points for these variables were 120 mL/m<sup>2</sup>, 150 ms, and 0.4 cm, respectively.

**Conclusions:** Echocardiographic predictors of outcome in advanced HF include LV end-diastolic volume index, mitral deceleration time, and vena contracta width. These variables indicate that LV remodeling, increased LV stiffness, and MR are independent predictors of outcome in patients with advanced HF.

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## JOURNAL OF CLINICAL ANESTHESIA

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### Continuous transesophageal echo-Doppler assessment of hemodynamic function during laparoscopic cholecystectomy

Joshi GP, Tillmann Hein HA, Mascarenhas WL, Ramsay MAE, Bayer O, Klotz P

(*J Clin Anesth* 2005;17:117–121)

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**Study objective:** The objective of this study was to examine the utility of the transesophageal echo-Doppler device in evaluating hemodynamic changes during laparoscopic cholecystectomy.

**Design:** This was a prospective, controlled, observational open study.

**Setting:** The study took place in a university hospital.

**Patients:** Twenty patients with ASA physical statuses II and III undergoing laparoscopic cholecystectomy were enrolled into the study.

**Interventions and measurements:** A standardized general anesthetic and surgical technique was used for all patients. Similar depth of hypnosis (using bispectral index monitoring) was maintained in all patients. Hemodynamic parameters including mean arterial pressure (MAP), cardiac index (CI), left ventricular (LV) ejection time interval indexed to the heart rate, maximum acceleration, peak velocity, and systemic vascular resistance (SVR) were recorded at predetermined intervals: before incision, after peritoneal CO<sub>2</sub> insufflation and head-up tilt, every 10 minutes thereafter, and after deflation of the abdomen and return to supine position.

**Main results:** The transesophageal echo-Doppler probe placement was achieved in 3 to 5 minutes in all patients, and the probe position was maintained after creation of pneumoperitoneum and change in positioning. Induction of pneumoperitoneum and head-up tilt resulted in a significant increase in MAP and SVR ( $P < .05$ ) that remained higher until deflation. The CI, LV ejection time interval indexed to the heart rate (a measure of LV filling), and maximum acceleration (a measure of contractility and global ventricular function) remained stable.

**Conclusions:** The transesophageal echo-Doppler device can be used during laparoscopic cholecystectomy. The LV function, as determined by measurement of CI and maximum acceleration, was preserved during laparoscopic cholecystectomy despite significant increases in afterload (i.e., MAP and SVR).

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## JOURNAL OF EXPERIMENTAL MEDICINE

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### Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade

Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J

(*J Exp Med* 2005;201:1479–1486)

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Systemic onset juvenile idiopathic arthritis (SoJIA) encompasses approximately 10% of cases of arthritis that begin in childhood. The disease is unique in terms of clinical manifestations, severity of joint involvement, and lack of response to tumor necrosis factor blockade. Here, we show that serum from SoJIA patients induces the transcription of innate immunity genes, including interleukin (IL)-1 in healthy peripheral blood mononuclear cells (PBMCs). Upon activation, SoJIA PBMCs release large amounts of IL-1 $\beta$ . We administered recombinant IL-1 receptor antagonist to nine SoJIA patients who were refractory to other therapies. Complete remission was obtained in seven out of nine patients and a partial response was obtained in the other two patients. We conclude that IL-1 is a major mediator of the inflammatory cascade that underlies SoJIA and that this cytokine represents a target for therapy in this disease.

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## JOURNAL OF IMMUNOTHERAPY

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### Measuring melanoma-specific cytotoxic T lymphocytes elicited by dendritic cell vaccines with a tumor inhibition assay in vitro

Paczesny S, Shi H, Saito H, Mannoni P, Fay J, Banchereau J, Palucka AK

(*J Immunother* 2005;28:148–157)

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Improving cancer vaccines depends on assays measuring elicited tumor-specific T-cell immunity. Cytotoxic effector cells are essential for tumor clearance and are commonly evaluated using <sup>51</sup>Cr release from labeled target cells after a short (4 hours) incubation with T cells. The authors used a tumor inhibition assay (TIA) that assesses the capacity of cytotoxic T lymphocytes (CTLs) to control the survival/growth of EGFP-labeled tumor cell lines. TIA was validated using CD8<sup>+</sup> T cells primed in vitro against melanoma and breast cancer cells. TIA was then used to assess the CTL function of cultured CD8<sup>+</sup> T cells isolated from patients with metastatic melanoma who underwent vaccination with peptide-pulsed CD34<sup>+</sup> HPCs-derived DCs. After the DC vaccination, T cells from six of eight patients yielded CTLs that could inhibit the survival/growth of melanoma cells. The results of TIA correlated with killing of tumor cells in a standard 4-hour <sup>51</sup>Cr release assay, yet TIA allowed detection of CTL activities that appeared marginal in the <sup>51</sup>Cr release assay. Thus, TIA might prove valuable for measuring spontaneous and induced antigen-specific cytotoxic T cells.

**Mobilization of plasmacytoid and myeloid dendritic cells to mucosal sites in children with respiratory syncytial virus and other viral respiratory infections**

Gill MA, Palucka AK, Barton T, Ghaffar F, Jafri H, Banchereau J, Ramilo O (*J Infect Dis* 2005;191:1105–1115)

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**Background:** Respiratory syncytial virus (RSV) is the principal etiologic agent of bronchiolitis and viral pneumonia in infants and young children. Yet, many aspects of its immunopathogenesis are not well understood.

**Methods:** We analyzed the immune cells that are mobilized by RSV and other respiratory viruses, by studying nasal wash samples from children hospitalized with acute viral respiratory infections.

**Results:** RSV mobilizes virtually all blood immune cells, including myeloid dendritic cells (DCs) and plasmacytoid DCs (pDCs), to the nasal mucosa. DCs were also mobilized to the nasal mucosa of children with other viral respiratory infections. The increased number of pDCs in the nasal compartment significantly correlates with RSV load ( $P = .022$ ), and it is associated with a significant decrease in the number of pDCs in the blood ( $P = .007$ ). The influx of DCs in the nasal mucosa is not transient, as even higher numbers of both DC subsets were found in respiratory secretions weeks after the acute symptoms of RSV infection had resolved. Immunochemistry analysis of respiratory samples has demonstrated the presence of the RSV fusion protein within HLA-DR-positive cells.

**Conclusion:** Infection with RSV and other respiratory viruses mobilizes DCs to the site of viral entry.

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**JOURNAL OF PAIN**

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**Botulinum toxin A injection of the obturator internus muscle for chronic perineal pain**

Gajraj NM

(*J Pain* 2005;6:333–337)

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Chronic perineal pain is often a difficult condition to manage. Current treatments include pudendal nerve injections and pudendal nerve release surgery. The obturator internus muscle has a close relationship to the pudendal nerve and might be a potential target for therapeutic intervention.

**Perspective:** A case is presented of refractory perineal pain that was successfully treated by injecting the obturator internus muscle with botulinum toxin A.

**Combining traditional agents and biologics for the treatment of psoriasis**

Cather JC, Menter A

(*Semin Cutan Med Surg* 2005;24:37–45)

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Psoriasis patients deserve long-term control of their disease with optimal safety. Traditional agents (methotrexate, cyclosporine, retinoids, and photochemotherapy [PUVS]), although providing excellent short-term control, may produce acute or chronic toxicities, thus limiting their usage. Dermatologists are well versed in combination and rotational therapies for psoriasis, using these and other agents. With the advent of biologic therapies (three currently approved, and others pending), the potential for safer long-term psoriasis control is being realized. A review of the literature, plus our personal experience in using combinations of traditional agents and biologics, is presented.

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**TISSUE ANTIGENS**

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**HLA class I null alleles and new alleles affect unrelated bone marrow donor searches**

Smith DM, Baker JE, Gardner WB, Martens GW, Agura ED

(*Tissue Antigens* 2005;66:93–98)

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Unrecognized HLA null alleles or new alleles may affect the outcome of bone marrow transplants using unrelated donors. Some reports suggest that null alleles occur in the range of 0.003–0.07% (1, 2), which has led some transplant programs to stop performing serologic typing. We describe nine cases involving expression variants or new alleles. Three cases involved expression variants, including two null alleles and A\*24020102L. One of the null alleles was a new variant of A\*02. Seven cases involved new alleles. In five cases, there were discrepancies between HLA typing by serology and PCR-SSP. These included the three expression variants, one new B40 allele that typed serologically as B41 and one new B\*07 allele that typed serologically as B42. Eight of these cases were found in the course of typing bone marrow transplant patients or potential unrelated donors since May of 2001 (total tested, 710 patients, 1914 donors). Thus, the incidence of null alleles was two in 2,624 (0.08%). Sequence-based typing (SBT) was performed on 676 of these samples. The decision to perform SBT was influenced by finding a serologic typing discrepancy in two cases. In one of those cases, SBT would probably have been performed at a later time, prior to final selection of a donor. Thus, the incidence of new alleles was between 4 and 6 of 676 (0.59–0.89%). We conclude that new HLA alleles and null alleles are uncommon but not extremely rare, and they continue to affect a significant number of unrelated donor searches.