ENTREZ PUBMED LITERATURE REVIEW (26 NEW ARTICLE(S))


**Desferrioxamine treatment of aceruloplasminemia: Long-term follow-up.**

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PMID: 21594898 [PubMed - as supplied by publisher]


**Myelodysplastic syndromes: 2011 update on diagnosis, risk-stratification, and management.**

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DISEASE OVERVIEW: The myelodysplastic (MDS) are a very heterogeneous group of myeloid disorders characterized by peripheral blood cytopenias and increased risk of transformation to acute myelogenous leukemia (AML). MDS occurs more frequently in older male and in individuals with prior exposure to cytotoxic therapy.

DIAGNOSIS: Diagnosis of MDS is based on morphological evidence of dysplasia upon visual examination of a bone marrow aspirate and biopsy. Information obtained from additional studies such as karyotype, flow cytometry, or molecular genetics is complementary but not diagnostic. RISK-STRATIFICATION: Prognosis of patients with MDS can be calculated using a number of scoring systems. In general, all these scoring systems include analysis of peripheral cytopenias, percentage of blasts in the bone marrow, and cytogenetic characteristics. The most commonly used system is the International Prognostic Scoring System. This score divides patients into a lower risk subset (low and intermediate-1) and a higher risk subset (int-2 and high). Other more modern systems have been developed that allow more precise risk calculation. RISK-ADAPTED THERAPY: Therapy is selected based on risk, transfusion needs, percent of bone marrow blasts and more recently cytogenetic profile. Goals of therapy are different in lower risk patients than in higher risk. In lower risk, the goal is to decrease transfusion needs and transformation to higher risk disease or AML. In higher risk, the goal is to prolong survival. Current available therapies include growth factor support, lenalidomide, hypomethylating agents, intensive chemotherapy, and allogeneic stem
cell transplantation. The use of lenalidomide has significant clinical activity in patients with lower risk disease, anemia, and a chromosome 5 alteration. 5-azacitidine and decitabine have activity in higher risk MDS. 5-azacitidine has been shown to improve survival in higher risk MDS. Additional supportive care measures may include the use of prophylactic antibiotics and iron chelation.

**MANAGEMENT OF PROGRESSIVE OR REFRACTORY DISEASE:** At the present time, there are no approved interventions for patients with progressive or refractory disease particularly after hypomethylating based therapy. Options include cytarabine-based therapy, transplantation, and participation on a clinical trial. Am. J. Hematol. 86:491-498, 2011. © 2011 Wiley-Liss, Inc.

PMID: 21594886 [PubMed - in process]


**Long-Term Efficacy of Deferasirox in Preventing Cardiovascular Complications in the Iron-Overloaded Gerbil.**

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Iron-induced cardiovascular disease is the leading cause of death in iron-overloaded patients. Deferasirox is a novel tridentate oral chelator that exhibits a half-life suitable for once-daily dosing; however, little is known regarding the effectiveness of this agent in preventing iron-induced cardiovascular disease. Adult male Mongolian gerbils were randomly divided into 3 groups: control, iron overload, and iron overload followed by deferasirox treatment. Iron-overloaded animals received iron dextran 100 mg/kg intraperitoneally (ip)/5 days for 10 weeks, while deferasirox was given 100 mg/kg per d orally (po) for 9 months post iron loading. Cardiac and aortic iron levels were determined by inductively coupled plasma atomic emission spectrometry. Gerbil electro- and echocardiograms were obtained in anesthetized animals at regular intervals. Compared to control animals, iron concentration was 3.3- and 2.4-fold higher in iron-overloaded heart and aorta, respectively (P < .05). Deferasirox treatment reduced cardiac and aortic iron levels by 32% and 35%, respectively (P < .05). These results were consistent with the decrease in cellular iron deposition observed with Prussian Blue iron staining. Iron-overloaded gerbils were found to exhibit frequent arrhythmias including premature ventricular contractions, supraventricular tachycardia, and recurrent ventricular tachycardia. In addition, echocardiographic assessment demonstrated
iron overload-associated increase in left ventricular dimensions including left ventricular posterior wall dimension (LVPWd: 49%), left ventricular internal dimension (LVIDd: 26%), and left ventricular septum thickness (LVSd: 42%). These parameters were significantly reduced with deferasirox treatment (LVPWd: 23%, LVIDd: 24%, and LVSd: 27%). Iron overload was also associated with reduced ejection fraction (EF: by 30%) and fractional shortening (FS: by 23%) in comparison with controls (P < .05). With deferasirox treatment, these values were higher (EF: by 30%, FS: by 28%) compared to iron-overloaded group. These findings suggest that deferasirox may be useful for attenuating iron-induced changes in cardiac structure and function.

PMID: 21593444 [PubMed - as supplied by publisher]


**Persistence and compliance of deferoxamine versus deferasirox in Medicaid patients with sickle-cell disease.**

Jordan LB, Vekeman F, Sengupta A, Corral M, Guo A, Duh MS.

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What is known and Objective: Patients with sickle-cell disease (SCD) receiving chronic transfusions of red blood cells are at risk of developing serious adverse effects. Iron chelation therapy (ICT) helps eliminate iron overload by binding with plasma iron to form a non-toxic conjugate that can be safely excreted from the body. Two iron chelating agents are currently available in the United States: Deferoxamine (DFO) is an injectable formulation, and deferasirox (Exjade®) is an oral suspension. This study compared the frequency of hospitalizations, persistence and compliance of patients with SCD from Medicaid programmes treated with DFO vs. deferasirox. Methods: Health care claims from Medicaid Florida (1998-2007), Missouri (1993-2008) and New Jersey (1996-2008) were analysed. Patients with continuous enrolment for ≥6 months prior to ICT initiation and ≥1 SCD diagnosis were included in the analysis. Patients were divided into four cohorts: patients treated with DFO (any-DFO group) and patients treated with deferasirox (any-deferasirox group); the latter was further divided into patients initiated on DFO and then switched to deferasirox (deferasirox switchers), and patients treated with deferasirox-only (deferasirox-only group). Frequency of hospitalization for crisis conditions related to SCD as well as length of stay pre- and post-ICT treatment initiation were assessed. Persistence was defined as
time to drug discontinuation with ≥1 Rx gap, using Kaplan-Meier approach. Compliance was estimated using a medication possession ratio (MPR) based on the drug exposure approach. Adjusted analyses of persistence and compliance were also conducted. Results: A total of 217 (mean age: 19.4 years, 39.2 men), 275 (20.1 years, 41.5% men), 105 (19.4 years, 42.9% men) and 166 (20.4 years, 41.6% men) patients were included in the any-DFO, any-deferasirox, deferasirox switchers and deferasirox-only groups, respectively. After ICT initiation, the any-deferasirox and deferasirox-only groups experienced a statistically significant reduction in the frequency of hospitalizations relative to pretreatment [any-deferasirox: from 0.09 to 0.06 hospitalizations per patient per month (pmpm), \( P = 0.0105 \); deferasirox-only: from 0.11 to 0.07 hospitalizations pmpm, \( P = 0.0188 \)], whereas it remained stable in the any-DFO group at 0.08 hospitalizations pmpm (\( P = 0.9483 \)). The Kaplan-Meier rates of medication persistence assessed at 6 and 12 months of follow-up were significantly lower for DFO patients (6 months: 0.34, 12 months: 0.21) as compared to all deferasirox (0.51, 0.29, \( P = 0.0002 \)), deferasirox switchers (0.56, 0.37, \( P = 0.0002 \)) and deferasirox-only (0.47, 0.24, \( P = 0.0176 \)) patients. Similarly, compliance to treatment was significantly lower for patients treated with DFO (mean MPR: 0.64) compared with any-deferasirox (0.78, \( P < 0.0001 \)), deferasirox switchers (0.75, \( P = 0.0002 \)) and deferasirox-only (0.80, \( P < 0.0001 \)) patients. Adjusted analyses of persistence and compliance yielded similar results. What is new and Conclusions: Based on a Medicaid population, patients treated with deferasirox were more compliant and persistent with their treatment than those treated with DFO. Frequency of hospitalizations was significantly reduced after treatment initiation for the any-deferasirox and deferasirox-only groups. Prospective studies controlling for potential clinical and treatment pattern differences between deferasirox and DFO patients are needed to assess whether the decreased hospitalizations after initiation of deferasirox are related to better treatment compliance.

PMID: 21592159 [PubMed - as supplied by publisher]


**Long-term safety and efficacy of deferasirox (Exjade®) for up to 5 years in transfusional iron-overloaded patients with sickle cell disease.**


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of Pediatrics, Center Hospitalier Intercommunal Créteil, Créteil, France Centro della Microcitemia, Ospedale Galliera, Genoa, Italy Louisiana State University Health Sciences Center, New Orleans, LA University of Colorado Health Sciences Center, Denver, CO Children's Hospital Boston, Boston, MA, USA Evelina Children's Hospital, Guy's and St Thomas' Hospital NHS Trust, London, UK Medical College of Georgia, Augusta, GA Children’s Healthcare of Atlanta at Egleston, Atlanta, GA Loma Linda University Medical Center, Loma Linda, CA, USA University College London, London, UK St Joseph's Children's Hospital of Tampa, Tampa, FL University of South Alabama, Mobile, AL Novartis Pharmaceuticals Corporation, East Hanover, NJ Children's Hospital Los Angeles, Los Angeles, CA, USA.

To date, there is a lack of long-term safety and efficacy data for iron chelation therapy in transfusion-dependent patients with sickle cell disease (SCD). To evaluate the long-term safety and efficacy of deferasirox (a once-daily oral iron chelator), patients with SCD completing a 1-year, Phase II, randomized, deferoxamine (DFO)-controlled study entered a 4-year extension, continuing to receive deferasirox, or switching from DFO to deferasirox. Average actual deferasirox dose was $19.4 \pm 6.3$ mg/kg per d. Of 185 patients who received at least one deferasirox dose, 33·5% completed the 5-year study. The most common reasons for discontinuation were withdrawal of consent (23·8%), lost to follow-up (9·2%) and adverse events (AEs) (7·6%). Investigator-assessed drug-related AEs were predominantly gastrointestinal [including nausea (14·6%), diarrhoea (10·8%)], mild-to-moderate and transient in nature. Creatinine clearance remained within the normal range throughout the study. Despite conservative initial dosing, serum ferritin levels in patients with ≥4 years deferasirox exposure significantly decreased by $-591$ μg/l (95% confidence intervals, $-1411$, $-280$ μg/l; $P = 0.027$; $n = 67$). Long-term deferasirox treatment for up to 5 years had a clinically acceptable safety profile, including maintenance of normal renal function, in patients with SCD. Iron burden was substantially reduced with appropriate dosing in patients treated for at least 4 years.

PMID: 21592110 [PubMed - as supplied by publisher]


**Characteristics of the arthropathy described in hereditary haemochromatosis.**

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Database: PubMed, Embase
Keywords: deferiprone, 30652-11-0, deferasiroxamine, deferoxamine, desferal, deferasirox, (iron + sickle) iron chelation, iron chelators, iron overload, thalass*, 1,2 dimethyl-3-hydroxypyridin-4-one, ICL670*, Exjade
Hereditary Haemochromatosis is a common inherited disorder, which primarily affects populations of northern European origin. Individuals homozygous for the C282Y mutation in the HFE gene product have up to a 30 percent chance of developing significant disease as a result of iron overload. Arthropathy is arguably the most disabling complication of iron overload in this disorder. Here we review the clinical and pathophysiological aspects of arthropathy in Hereditary Haemochromatosis. © 2011 by the American College of Rheumatology.

PMID: 21584944  [PubMed - as supplied by publisher]


Reduced transverse relaxation rate (RR2) for improved sensitivity in monitoring myocardial iron in thalassemia.


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PURPOSE: To evaluate the reduced transverse relaxation rate (RR2), a new relaxation index which has been shown recently to be primarily sensitive to intracellular ferritin iron, as a means of detecting short-term changes in myocardial storage iron produced by iron-chelating therapy in transfusion-dependent thalassemia patients.

MATERIALS AND METHODS: A single-breathhold multi-echo fast spin-echo sequence was implemented at 3 Tesla (T) to estimate RR2 by acquiring signal decays with interecho times of 5, 9 and 13 ms. Transfusion-dependent thalassemia patients (N = 8) were examined immediately before suspending iron-chelating therapy for 1 week (Day 0), after a 1-week suspension of chelation (Day 7), and after a 1-week resumption of chelation (Day 14).

RESULTS: The mean percent changes in RR2, R2, and R2* off chelation (between Day 0 and 7) were 11.9 ± 8.9%, 5.4 ± 7.7% and -4.4 ± 25.0%; and, after resuming chelation (between Day 7 and 14), -10.6 ± 13.9%, -8.9 ± 8.0% and -8.5 ± 24.3%, respectively. Significant differences in R2 and RR2 were observed between Day 0 and 7, and between Day 7 and 14, with the greatest proportional changes in RR2. No significant differences in R2* were found.
CONCLUSION: These initial results demonstrate that significant differences in RR2 are detectable after a single week of changes in iron-chelating therapy, likely as a result of superior sensitivity to soluble ferritin iron, which is in close equilibrium with the chelatable cytosolic iron pool. RR2 measurement may provide a new means of monitoring the short-term effectiveness of iron-chelating agents in patients with myocardial iron overload. J. Magn. Reson. Imaging 2011;33:1510-1516. © 2011 Wiley-Liss, Inc.

PMID: 21591022 [PubMed - in process]


Comparison of the Region-Based and Pixel-Wise Methods for Cardiac T2* analysis in 50 Transfusion-Dependent Thai Thalassemia Patients.

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PURPOSE:: To compare the observer variability of the conventional region-based (RB) to the typical and proposed pixel-wise (PW) methods for cardiac T2* analysis in thalassemia patients. DESIGN AND METHODS:: Fifty thalassemia major patients were enrolled for the study. Short-axis bright- and black-blood sequences were acquired and analyzed using the RB and PW methods. Regions were defined using the whole septum (WS) or partial septum (PS). From the same PS region, results were reported by mean (PS-PW) and median (MPS-PW). Intraobserver and interobserver variabilities were investigated on all data set by 2 independent observers blinded to the result. RESULTS:: The T2* values from the PS-PW and MPS-PW methods were comparable to the conventional WS-RB method on both scanning techniques. When comparing the interobserver variability from the WS-RB to the PS-PW method, the coefficient of variation of the PS-PW method was equivalent (4.5% vs 4.7%, P = NS) for the bright-blood technique but 31% lower (4.0% vs 2.8%, P = 0.21) for the black-blood technique. The proposed MPS-PW method performed even better with respect to the conventional WS-RB method, decreasing interobserver coefficient of variation by 24% (4.5% vs 3.5%, P = 0.08) and 42% (4.0% vs 2.4%, P = 0.02), respectively. Intraobserver reproducibility followed the same trend.
CONCLUSIONS: The proposed PW method using the median of T2* values calculated from partial interventricular septum region provided lower intraobserver and interobserver variabilities compared with the conventional RB or typical PW methods.

PMID: 21586934 [PubMed - as supplied by publisher]


[Protective effect and mechanism of hepcidin in rats with alcoholic liver damage.]

[Article in Chinese]

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To study the mechanism of how iron-regulatory protein (hepcidin) affect iron overload in alcoholic liver disease (ALD). Thirty male wistar rats were randomly divided into 3 groups: Lieber-DeCarli liquid without alcohol group (control group), Lieber-DeCarli liquid with alcohol (alcohol group) and hepcidin intraperitoneally injected group (hepcidin group), each rat was fed for 6 weeks. The Serum concentration of Alanine Aminotransferase (ALT), Aspartate Amino Transferase (AST), Iron, Total Iron Binding capacity (TIBC), Ferritin, Malonyl Dialdehyde (MDA) and Hepcidin were determined. Hepatic tissue was examined by hematoxylin and eosin staining, prussian blue iron staining and immunohistochemistry staining. (1) Serum concentration of ALT in control group, alcohol group and hepcidin group were (25.2+/-4.6) U/L, (37.9+/-14.3) U/L and (40.9+/-14.1) U/L (F = 4.907, P less than 0.05), respectively. Serum AST among three groups were (32.3+/-13.4) U/L, (55.0+/-18.6) U/L and (48.3+/-26.0) U/L (F = 3.742, P less than 0.05), respectively. The secretions of ferritin were (224.72+/-85.49) ng/ml, (345.59+/-124.75) ng/ml and (339.47+/-138.47) ng/ml (F = 3.539, P less than 0.05). The serum concentrations of TIBC were (147.30+/-31.98)mumol/L,(148.04+/-58.74)mumol/L and (143.28+/-37.38)mumol/L (F = 1.209, P more than 0.05), respectively. The serum concentrations of iron were (55.64+/-13.32)mumol/L, (60.37+/-25.89)mumol/L and (49.77+/-17.64)mumol/L (F = 0.651, P more than 0.05), respectively. The serum concentration of MDA were (5.84+/-2.17) nmol/ml, (6.51+/-2.23) nmol/ml and (4.27+/-2.68) nmol/ml (F = 2.782, P more than 0.05), respectively. The serum concentration of Hepcidin were (155.96+/-44.91)ng/ml, (124.11+/-31.98) ng/ml and (114.96+/-25.81) ng/ml (F =
3.839, P less than 0.05), respectively. (2) Significant fat change observed in the liver of alcohol group. The positive granulationes of iron staining were (0.8+/-1.0), (1.2+/-1.6) and (1.1+/-1.1) (F = 0.254, P more than 0.05), respectively. No differences found of liver iron express among the three groups. Intraperitoneal injection of hepcidin increased hepcidin expression in liver which was inhibited by alcohol (F = 4.139, P less than 0.05). ALD rats with lower hepcidin expression in liver can result in iron metabolism disorder. Ectogenic hepcidin can protect liver against alcohol damage by inhibiting lipid peroxidation.

PMID: 21586231 [PubMed - as supplied by publisher]


**Human Parvovirus B19: General considerations and impact on patients with sickle cell disease and thalassemia as well as on blood transfusions.**

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Human Parvovirus B19 (B19V) is a small (22-24 nm) non-enveloped DNA virus, belonging to the genus Erythrovirus (family Parvoviridae). Although, it causes generally self-limiting conditions in healthy people, B19V infection could have different outcome in patients with inherited hemolytic anemias. In such high-risk individuals, the high-titer replication may result in bone marrow suppression triggering life-threatening drop of the hemoglobin values (profound anemia, aplastic crisis). Nevertheless, up to day does not exist a consensus B19V screening program neither for the blood donations used in the hemotherapy, nor for high-risk patients. Moreover, questions like molecular mechanisms by which B19V produces latency and persistent replication, primary site (sites) of B19V infection and B19V immunopathology are far from being known. This review summarizes general aspects of B19V molecular characteristics, pathogenesis, and diagnostic approaches as well as it accentuates the role of this pathogen in blood transfusions and in patients with some hemoglobinopathies (sickle-cell disease, thalassemia).

PMID: 21585562 [PubMed - as supplied by publisher]

**Evidence for a Proatherogenic Biochemical Phenotype in Beta Thalassemia Minor and Intermedia.**

Lai ME, Vacquer S, Carta MP, Spiga A, Cocco P, Abete C, Dessì S, Mandas A.

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The purpose of this study was to focus on pathophysiological mechanisms linking β-thalassemia intermedia (β-TI) and minor (β-TMI) with cardiovascular risk. Iron status, prooxidant-antioxidant balance and lipid profiles in serum, and lipid content in peripheral blood mononuclear cells (PBMCs) were evaluated in 20 β-TMI subjects, 22 β-TI patients and in 30 nontalassemic blood donors. The mRNA levels of some genes involved in the regulation of iron and cholesterol metabolism were also determined. In β-TI and in β-TMI, serum iron, prooxidant-antioxidant ratio, transferrin saturation and erythropoietin levels were higher, while transferrin and hepcidin were lower compared to controls. Hepcidin and interleukin-1α mRNA levels were found to be reduced in β-TI- and β-TMI-PBMCs, while those of tumor necrosis factor alpha were increased. A reduction in high-density lipoprotein cholesterol in serum and an accumulation of neutral lipids coupled with increased mRNA levels of acetyl-coenzyme A:cholesterol acyltransferase and decreased neutral cholesterol ester hydrolase in PBMCs were also observed in β-TI and β-TMI compared to controls. Taken together, these findings provide experimental support for the idea that not only β-TI patients but also β-TMI have a proatherogenic biochemical phenotype which may contribute to increase their cardiovascular disease risk.

PMID: 21576933 [PubMed - as supplied by publisher]


**Deferasirox protects against iron-induced hepatic injury in Mongolian gerbil.**


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Iron overload is associated with an increased risk of liver complications.
including fibrosis, cirrhosis, and hepatocellular carcinoma. Deferasirox is a new oral chelator with high iron-binding potency and selectivity. Here we investigate the ability of deferasirox to remove excessive hepatic iron and prevent iron-induced hepatic injury. Adult male Mongolian gerbils were divided into 3 groups (n = 5/group)-control, iron overload (100 mg iron-dextran / kg body weight / 5 days; intraperitoneal for 10 weeks), and iron overload followed by deferasirox treatment (100 mg deferasirox / kg body weight / d; pulse oral for 1 or 3 months). Compared with the nontreated iron overload group, deferasirox reduced hepatic iron concentration by 44% after 3 months of treatment (P < 0.05). Histological analysis of hepatic tissue from the iron overloaded group detected frequent iron deposition, evidence of hepatic damage, and an accumulation of lipid vacuoles. Iron deposition was significantly diminished with deferasirox treatment, and no evidence of lipid accumulation was observed. Immunoblotting demonstrated that iron overload caused approximately 2-fold increase in hepatic ferritin expression (P < 0.05), which was 48% lower after 3 months of deferasirox treatment (P < 0.05). Deferasirox treatment also was associated with reduced hepatic protein oxidation, superoxide abundance, and cell death. The percentage of terminal deoxynucleotidyl transferase dUTP nick end labeling positive cells in the deferasirox-treated livers was 41% lower than that of iron overloaded group (P < 0.05). Similarly, an iron-related increase in the expression of Bax/Bcl2, Bad, and caspase-3 were significantly lower after deferasirox treatment. These findings suggest that deferasirox may confer protection against iron-induced hepatic toxicity.

PMID: 21575921 [PubMed - in process]


**Enzymatic synthesis of catechol and hydroxyl-carboxic acid functionalized chitosan microspheres for iron overload therapy.**

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Excess "free" iron which occurs under certain physiological conditions participates in the formation of toxic reactive oxygen species via the "fenton" chemistry. The reactive oxygen species oxidize biomolecules and have been implicated in many oxidative stress-related diseases. However, the ideal therapy for treating iron overload problems in humans has not yet been developed. In this study, the phenolic molecules catechol, caffeic acid, and 2,5-dihydroxybenzoic acid were successfully coupled to glucosamine as model substrate in a 1:1 ratio.
using laccase. Furthermore, coupling of these molecules onto chitosans of different sizes was demonstrated, resulting in decrease in -NH(2) groups as quantified via derivatization. A concomitant increase in iron-chelating capacity from below 3% to up to 70% upon phenolic functionalization was measured for the chitosans based on reduced ferrozine/Fe(2+) complex formation. Interesting these phenolic compounds seems to also participate as cross-linkers in producing characteristic microspheres. This work therefore opens-up new strategies aimed at developing a new generation of iron-chelating biomedical polymers.

PMID: 21575720 [PubMed - as supplied by publisher]


Estimation of liver T*2 in transfusion-related iron overload in patients with weighted least squares T*2 IDEAL.

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MRI imaging of hepatic iron overload can be achieved by estimating T(2)* values using multiple-echo sequences. The purpose of this work is to develop and clinically evaluate a weighted least squares algorithm based on T(2)* Iterative Decomposition of water and fat with Echo Asymmetry and Least-squares estimation (IDEAL) technique for volumetric estimation of hepatic T(2)* in the setting of iron overload. The weighted least squares T(2)* IDEAL technique improves T(2)* estimation by automatically decreasing the impact of later, noise-dominated echoes. The technique was evaluated in 37 patients with iron overload. Each patient underwent (i) a standard 2D multiple-echo gradient echo sequence for T(2)* assessment with nonlinear exponential fitting, and (ii) a 3D T(2)* IDEAL technique, with and without a weighted least squares fit. Regression and Bland-Altman analysis demonstrated strong correlation between conventional 2D and T(2)* IDEAL estimation. In cases of severe iron overload, T(2)* IDEAL without weighted least squares reconstruction resulted in a relative overestimation of T(2)* compared with weighted least squares. Magn Reson Med, 2011. © 2011 Wiley-Liss, Inc.

PMID: 21574184 [PubMed - as supplied by publisher]

**Prevalence and specificities of red cell alloantibodies among blood recipients in the Malaysian state of Kelantan.**

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**BACKGROUND:** Red blood cell (RBC) alloantibodies may be formed following exposure to RBC antigens. In most cases, the alloimmunization develops during pregnancy or from previous blood transfusions. The RBC antigens and their alloantibodies vary among different human populations and ethnic groups, and they do have a clinical significance for their adverse immunological reactions.

**AIMS:** This study aimed at studying the prevalence of RBC alloantibodies at the Blood Transfusion Unit of Hospital Raja Perempuan Zainab II in Kota Bharu, Malaysia.

**PATIENTS AND METHODS:** A cross-sectional study was performed utilizing data obtained in the years 2007 and 2008. Data of antibody screening tests from 5719 patients were examined.

**RESULTS AND DISCUSSION:** The overall prevalence of alloimmunization was 65 (1.13%). The majority of these had a single alloantibody (76.9%), whereas the remaining 23.1% had multiple antibodies. The anti-E antibody comprised the most common alloantibody (24.6%) followed by the anti-Lewis (a) antibodies (18.5%) and the anti-M antibody (13.8%). There were more female recipients than males.

**CONCLUSIONS:** It was concluded that the findings of this work have been comparable with other published works, and that the main factors associated with alloantibody formation were multiple transfusions and pregnancies. The study also emphasizes the necessity for carrying out immunohematology studies prior to every blood transfusion especially in cases that require multiple transfusions for a long period of time such as in thalassemia patients.

PMCID: PMC3082716
PMID: 21572715 [PubMed - in process]


**d-Amphetamine-induced cytotoxicity and oxidative stress in isolated rat hepatocytes.**

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Amphetamines (AMP) are potent psychostimulants and commonly used drugs of abuse. Its chronic administration creates tolerance and addiction and also associated with neurotoxicity and hepatocellular damage through oxidative stress. The present study was designed to evaluate the cytotoxic effects as well as the oxidative stress induced by d-amphetamines in isolated rat hepatocytes. Hepatocytes were isolated by collagenase perfusion technique and were exposed to different concentrations of AMP (0.2, 0.4, 0.8 and 1.6mM) in a time-course experiment for up to 2h. AMP exposure induced a significant decrease in cell viability and a significant increase in the leakage of hepatic enzymes (lactate dehydrogenase (LDH), alanine aminotransferase (ALT) and asparate aminotransferase (AST)} in a concentration and time-related manner. In the same experiment, GSH content and thiobarbituric acid reactive substances (TBARS) generation were determined as indices of oxidative stress and lipid peroxidation respectively. AMP exposure results in a significant decrease in cellular GSH content as well as a significant enhancement of TBARS accumulation in a concentration and time-related manners. The obtained results suggested that 2-h exposure of hepatocytes to AMP (0.8mM) was accompanied by submaximal responses. Therefore, a subsequent dose-response experiment was designed to evaluate the role of GSH modulation and oxidative stress in AMP toxicity in hepatocytes at 2h. LDH release and TBARS generation were used as indicators in this experiment. Pretreatment with the GSH-depleting agents, chlorodinitrobenzene (CDNB), buthionine sulfoximine (BSO), or bis(chloroethyl)-nitrosurea (BCNU) enhanced the cytotoxicity of AMP. Conversely, pretreatment with GSH or sulhydryl compounds such as methionine (MT), cysteine (CYS) or dithiothreitol (DTT) attenuated AMP toxicity. Similarly, co-incubation with enzymatic antioxidants, superoxide dismutase (SOD) or catalase (CAT) or iron chelator, desferroxamine (DFO) or the hydroxyl radical scavengers, dimethylsulfoxide (DMSO) exhibited significant protection against AMP cytotoxicity. The present results indicate that AMP has a potential cytotoxic effect in isolated rat hepatocytes. AMP cytotoxicity is concentration-dependent. GSH depletion and oxidative stress play an important role in enhancing hepatotoxic potential of AMP in isolated rat hepatocyte. Thiol group-donors, antioxidants, free radical scavengers and iron chelators can play a critical role against AMP-induced cellular damage.

PMID: 21571509 [PubMed - as supplied by publisher]

**Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG).**


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Comment in


**BACKGROUND:** Sickle-cell anaemia is associated with substantial morbidity from acute complications and organ dysfunction beginning in the first year of life. Hydroxycarbamide substantially reduces episodes of pain and acute chest syndrome, admissions to hospital, and transfusions in adults with sickle-cell anaemia. We assessed the effect of hydroxycarbamide therapy on organ dysfunction and clinical complications, and examined laboratory findings and toxic effects.

**METHODS:** This randomised trial was undertaken in 13 centres in the USA between October, 2003, and September, 2009. Eligible participants had haemoglobin SS (HbSS) or haemoglobin Sβ(0)thalassaemia, were aged 9-18 months at randomisation, and were not selected for clinical severity. Participants received liquid hydroxycarbamide, 20 mg/kg per day, or placebo for 2 years. Randomisation assignments were generated by the medical coordinating centre by a pre-decided schedule. Identical appearing and tasting formulations were used for hydroxycarbamide and placebo. Patients, caregivers, and coordinating centre staff were masked to treatment allocation. Primary study endpoints were splenic function (qualitative uptake on (99)Tc spleen scan) and renal function (glomerular filtration rate by (99m)Tc-DTPA clearance). Additional assessments
included blood counts, fetal haemoglobin concentration, chemistry profiles, spleen function biomarkers, urine osmolality, neurodevelopment, transcranial Doppler ultrasonography, growth, and mutagenicity. Study visits occurred every 2-4 weeks. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00006400.

**FINDINGS:** 96 patients received hydroxycarbamide and 97 placebo, of whom 83 patients in the hydroxycarbamide group and 84 in the placebo group completed the study. Significant differences were not seen between groups for the primary endpoints (19 of 70 patients with decreased spleen function at exit in the hydroxycarbamide group vs 28 of 74 patients in the placebo group, \( p=0.21 \); and a difference in the mean increase in DTPA glomerular filtration rate in the hydroxycarbamide group versus the placebo group of 2 mL/min per 1.73 m\(^2\), \( p=0.84 \)). Hydroxycarbamide significantly decreased pain (177 events in 62 patients vs 375 events in 75 patients in the placebo group, \( p=0.002 \) and dactylitis (24 events in 14 patients vs 123 events in 42 patients in the placebo group, \( p<0.0001 \)), with some evidence for decreased acute chest syndrome, hospitalisation rates, and transfusion. Hydroxyurea increased haemoglobin and fetal haemoglobin, and decreased white blood-cell count. Toxicity was limited to mild-to-moderate neutropenia.

**INTERPRETATION:** On the basis of the safety and efficacy data from this trial, hydroxycarbamide can now be considered for all very young children with sickle-cell anaemia.

**FUNDING:** The US National Heart, Lung, and Blood Institute; and the National Institute of Child Health and Human Development.

PMID: 21571150  [PubMed - in process]


[Molecular and prenatal diagnosis for a Chinese pregnant woman with a novel mutation of β thalassemia.]  

[Article in Chinese]

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OBJECTIVE: To conduct molecular and prenatal diagnosis for a couple with β thalassemia. METHODS: Blood routine examination and hemoglobin analysis were used for screening of thalassemia. Seventeen common Chinese mutations of β thalassemia were detected for the carriers with β thalassemia using PCR/RDB. The unknown
mutation of β thalassemia was identified by DNA sequencing and DHPLC analysis.

RESULTS: The husband was heterozygote of CD41/42 (-TCTT). The wife carried a mutation IVS-I-110 (G→A) of β thalassemia having not been reported in Chinese so far. The fetus was a double mutated heterozygote of IVS-I-110 (G→A) and CD41/42 (-TCTT). The pregnancy was terminated. CONCLUSION: Mutation IVS-I-110 (G→A) of β thalassemia in Chinese is of importance to the genetic counseling and prenatal diagnosis of thalassemia.

PMID: 21569707  [PubMed - as supplied by publisher]


[Epidemiological study on thalassemia among the children of 0 - 7 years old among the six ethnic groups in Xishuangbanna and Dehong of Yunnan province.]

[Article in Chinese]


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OBJECTIVE: To investigate the prevalence rate of thalassemia among children of 0 - 7 years old, from six ethnic groups in Xishuangbanna and Dehong, Yunnan province. METHODS: 4973 blood samples from children under 7 years old were automatically undergone blood cell count, red cell osmotic fragility and hemoglobin electrophoresis testings. RESULTS: The incidence rates of thalassaemia, β-thalassemia was 37.4%, and α-thalassaemia were 22.6% and 14.7% respectively. The thalassaemia incidence rates were significantly different among age groups but not in gender. The incidence of α-thalassaemia was decreasing along with the increase of age, while the incidence of β-thalassaemia was increasing along with the increase of age. Xishuangbanna had the higher incidence than in Dehong and the differences were significant between counties, The incidence of thalassemia of Mengla ranked the first (52.2%) in Xishuangbanna, The differences between different regions and different nationalities were significant, with β-thalassemia of Achang ranked the first (40.6%), The incidence of α-thalassemia among Han ranked the first as 45.5% while α-thalassaemia and β-thalassemia were different in regions. α-thalassaemia and β-thalassemia were significantly different between different ethnic people in the same regions. Multiple factor analysis showed that region seemed to be a risk factor and the mother's ethnicity was a protective factor and dependent variable on thalassaemia. CONCLUSION: The incidence of thalassaemia in Yunnan Xishuangbanna and Dehong was high among children under the age of 7 and were related to ethnic and regional differences in the areas. Specific genes were proliferated along
with the extension of time. Our data provided valuable information on prevention and genetic studies on thalassaemia in the minorities of Xishuangbanna and Dehong in Yunnan province.

PMID: 21569665 [PubMed - as supplied by publisher]


*A child with hyperferritinemia: Case report.*

Serra M, Longo F, Roetto A, Sandri A, Piga A.

ABSTRACT: Hereditary hyperferritinemia cataract syndrome (HHCS) is a rare condition caused by mutations in the gene coding for the light chain of ferritin; it does not lead to iron overload, but it is associated with the risk of developing a bilateral nuclear cataract also in childhood. On the contrary, a raise of serum ferritin levels is a common finding in pediatrics. We describe here a case of HHCS that offers some interesting clues for the daily practice. Our patient is a 6 year old Italian boy who came to our attention after some time of diagnostic uncertainties because of persistently high levels of ferritin with no apparent cause. We were guided to the suspect of this syndrome by the family history (5 members with various degrees of cataract developed in first infancy). High levels of serum ferritin and specific genetic testing (mutation A37C) confirmed the diagnosis. This case underlines the need of considering rare genetic syndromes, including hereditary hyperferritinemia cataract syndrome, in the differential diagnosis of raised serum ferritin in children and the importance of paying attention to family history in considering a patient with isolated raised levels of serum ferritin.

PMID: 21569394 [PubMed - as supplied by publisher]


**Dopamine D(2) /D(3) Agonists with Potent Iron Chelation, Antioxidant and Neuroprotective Properties: Potential Implication in Symptomatic and Neuroprotective Treatment of Parkinson's Disease.**


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PMID: 21567969  [PubMed - as supplied by publisher]


**Erythrocyte and reticulocyte parameters in iron deficiency and thalassemia.**

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Introduction: Red blood cells (RBCs) extended parameters or erythrocyte subsets are now reported by the new Sysmex XE 5000 analyzer. This study was aimed at establishing a characteristic analytical feature, including the new erythrocyte and reticulocyte parameters, in case of thalassemia trait and iron deficiency (IDA). Methods: Ninety healthy individuals, 136 β-thalassemia carriers, 121 mild IDA, and 126 severe IDA patients were analyzed. Results: The values obtained for the RBC extended parameters were significantly different (P<0.0001) in the groups; the only exception was %Hypo-He in the case of mild IDA and thalassemia (P=0.6226). %Hypo-He was considerably greater in severe IDA (23.4%) than in mild cases (12.4%), P<0.0001. %MicroR was more increased in thalassemia (38.6 %) than in the mild IDA (16.5%, P<0.001) and in severe IDA (21.6%, P<0.001). Immature reticulocyte fraction (IRF) mean values in the groups were statistically different; the thalassemia group had an intermediate value (8.7%) between healthy (4.4%) and IDA (16.7 and 12.9%). Conclusions: Erythrocytosis and severe microcytosis, together with a high percentage of microcytes and a moderate increase in IRF, is the profile of β-thalassemia carriers, whereas anisocytosis and the hypochromic subset correlates with the severity of the anemia in iron-deficient patients. *J. Clin. Lab. Anal.* 25:223-228, 2011. © 2011 Wiley-Liss, Inc.

PMID: 21567473  [PubMed - in process]


**Renal tubular dysfunction in pediatric patients with beta-thalassemia major.**

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To evaluate the prevalence of renal tubular dysfunction in children with
β-thalassemia (β-T) major, we studied the glomerular and tubular function in 140 children with β-T major and compared them to a healthy control group at our center from May 2007 to April 2008. Fresh first morning samples were collected from each patient and analyzed for sodium, potassium, calcium (Ca), protein, uric acid (UA), creatinine (Cr), urine osmolality and urinary N-acetyl-β-D-glucosaminidase (UNAG) activity. Blood samples were also collected for complete blood count, blood urea nitrogen (BUN), fasting blood sugar, serum creatinine (Scr), electrolytes, and ferritin before transfusion. Among the study patients, 72 were males, and the mean age was 11.5 (ranging 7-16) years. Scr levels were all within normal limits and all of them had normal glomerular filtration rate (GFR). The mean UNAG was 17.8 IU/L in the study patients (normal 0.15-11.5 IU/L) and 3.2 IU/L in the control group (P < 0.001). Of the 82 study patients who had elevated level of UNAG, 58 (62.4%) had high blood levels of ferritin also (r = 0.2, P < 0.001) and 13 (15.9%) patients had hypercalciuria also (UCa/UCr > 0.21) (P = 0.006). Nine (6.4%) thalassemic patients with a mean age of 12 years had proteinuria (Upr/UCr > 0.2). Sixty-nine (49.3%) out of the 140 patients and 45 (65.2%) of the patients having UNAG had uricosuria also (UUA/UCr > 0.26). Ten (7%) patients had microscopic hematuria and 10 (7%) patients with a mean age of 13.5 years had glucosuria or diabetes mellitus. We conclude that tubular dysfunction is a relative common complication of the β-T major; UNAG and its index are the best to detect renal tubular dysfunction in these patients. Currently, periodic measurement of UCa/UCr and UUA/UCr ratios as well as urinalysis are recommended.

PMID: 21566307 [PubMed - in process]


An assay of gene copy number and its application based on heteroduplex products.


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The aim of this study was to set up a simple and efficient method for detecting gene copy number, based on heteroduplex products from single-tube PCR/DHPLC. Single-nucleotide polymorphisms (SNPs) on the α-globin gene and chromosome 21 were used as examples. And the formula for quantitative calculation of gene copy number was deduced-based on the peak heights of homoduplexes and heteroduplexes on the DHPLC pattern. 27 samples (14 normal DNA and 13 cases of trisomy-21) were
assessed with this method, and 160 samples (48 normal DNA and 112 α-thalassemia samples) were assessed with this method combined with a duplex PCR/DHPLC. Results for 184 of 187 cases were concordant with the known genotypes; three cases of trisomy-21 could not be detected because the target SNPs were homozygous. In conclusion, quantitative assessment of heteroduplex products from single-tube PCR/DHPLC is simple and rapid, and can be used to detect α-thalassemia gene deletions (α(-3.7), α(-4.2)) and trisomy-21.

PMID: 21565183  [PubMed - as supplied by publisher]


**Hepatitis C virus distribution and clearance following interferon-monotherapy among thalassaemia major and intermedia patients.**


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PMID: 21564076  [PubMed - as supplied by publisher]


**THE ASSOCIATION BETWEEN PORPHYRIA CUTANEA TARDA AND DIABETES MELLITUS.**

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Background: An association between porphyria cutanea tarda (PCT) and diabetes mellitus (DM) is widely-reported, but the pathogenetic link remains unknown.
Objective: To investigate the natural history of DM in the setting of PCT and which PCT features and risk factors may be associated with the development of DM.

Methods: This retrospective longitudinal study included 81 Spanish patients with PCT with at least 10 years of strict follow-up. Patients attended our Porphyria Unit for follow-up visits and the data were collected in the period 2004-2008. We classified patients into two groups: patients with glucose metabolism alterations (GMA) [DM or impaired fasting glucose (IFG)], and patients without. PCT features and DM risk factors were retrieved from clinical charts and compared between groups.

Results: We identified 33 patients (40.7%) with GMA, of whom 81.8% developed GMA a long time after the diagnosis of PCT (mean: 12.7 years). In the bivariate analysis, these patients had significantly higher mean serum ferritin at diagnosis (651 vs 405 ng/mL, p = 0.005), a higher prevalence of persistently-elevated serum ferritin (51.5% vs 14.6%, p < 0.001 for trend) and a higher prevalence of family history of DM (48.5% vs 18.8%, p = 0.004). In the multivariate analysis, persistently-elevated serum ferritin (OR, 10.66; 95% CI, 1.95-58.19, p = 0.006) and family history of DM (OR, 4.82; 95% CI, 1.34-17.33, p = 0.016) remained significantly associated with the presence of GMA.

Conclusion: GMA are highly prevalent in patients with PCT and mostly develop a long time after the diagnosis of PCT. Persistent hyperferritinemia seems to be a risk biomarker of GMA in PCT patients, probably in the setting of chronic iron overload and hepatic inflammation. Strict long-term monitoring of glucose metabolism and serum ferritin may be advisable in the routine follow-up of PCT patients.

PMID: 21564073 [PubMed - as supplied by publisher]
Entrez EMBASE Literature Review (1 New Article(s))


Iron availability modulates the IVS3-48C/T-mediated aberrant splicing of ferrochelatase

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Embase

Abstract
The common splice modulating single nucleotide polymorphism IVS3-48C/T of intron 3 of the ferrochelatase (FECH) gene was revealed as a major determinant of overt erythropoietic protoporphyria (EPP). Two mRNAs, the wild-type (wt) and an aberrant splice variant containing a 63-bp intron 3 insertion exist in genotypes IVS3-48T/T, C/T and C/C (Gouya L, Puy H, Robreau AM et al. The penetrance of dominant erythropoietic protoporphyria is modulated by expression of wildtype FECH. Nat Genet 2002; 30: 27-8). The ratio between the wt and aberrant spliced product, however, varies among the three genotypes: IVS3-48T (wt) shows around 20% aberrantly spliced mRNA, whereas IVS3-48C leads to around 40% aberrantly spliced product. As iron is a cofactor for ferrochelatase and is tightly regulated due to its toxicity, an influence of iron availability on ferrochelatase activity is possible. We measured the amount of correctly and aberrantly spliced FECH mRNA in a human erythroleukaemic cell line K562 (genotype IVS3-48T/T) under different iron conditions, including addition of 50-200 lmol L⁻¹ ferric ammonium citrate (FAC), 50-200 lmol L⁻¹ of the iron chelator desferrioxamine (DFO), or both. Reverse transcription-polymerase chain reaction quantification standardized on b-actin revealed a strong and dose-dependent increase in the amount of aberrantly spliced mRNA from 16.6 ± 1.2% (n = 4) to 56.3 ± 5.9% (n = 4) under iron-depleted conditions, accompanied by a decrease of the correctly spliced form. FAC addition did not change the percentage of aberrant splice product compared with controls. However, it reversed the effect of DFO, if added in an equimolar concentration. Deferiprone, another iron chelator, had an effect similar to DFO on the percentage of aberrant splice product. The effects of DFO and FAC on FECH protein were comparable with those observed on its RNA as demonstrated by Western blot analysis (n = 4). The observed effect indicates that iron availability may regulate FECH activity and thus might have a functional dimension, given the fact that both protoporphyrin-accumulating porphyrias, EPP and X-linked protoporphyria, show disturbances in iron metabolism.