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Grizelj R[1], Bojanić K[2], Pritišanac E[1], Luetić T[3], Vuković J[1], Weingarten TN[4], Schroeder DR[5], Sprung J[6]. Survival prediction of high-risk outborn neonates with congenital diaphragmatic hernia from capillary blood gases. BMC Pediatr. 2016;29.16:114.

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BACKGROUND: The extent of lung hypoplasia in neonates with congenital diaphragmatic hernia (CDH) can be assessed from gas exchange. We examined the role of preductal capillary blood gases in prognosticating outcome in patients with CDH. METHODS: We retrospectively reviewed demographic data, disease characteristics, and preductal capillary blood gases on admission and within 24 h following admission for 44 high-risk outborn neonates. All neonates were intubated after delivery due to acute respiratory distress, and were emergently transferred via ground ambulance to our unit between 1/2000 and 12/2014. The main outcome measure was survival to hospital discharge and explanatory variables of interest were preductal capillary blood gases obtained on admission and during the first 24 h following admission. RESULTS: Higher ratio of preductal partial pressure of oxygen to fraction of inspired oxygen (PcO2/FIO2) on admission predicted survival (AUC = 0.69, P = 0.04). However, some neonates substantially improve PcO2/FIO2 following initiation of treatment. Among neonates who survived at least 24 h, the highest preductal PcO2/FIO2 achieved in the initial 24 h was the strongest predictor of survival (AUC = 0.87, P = 0.002). Nonsurvivors had a mean admission preductal PcCO2 higher than survivors (91 ± 31 vs. 70 ± 25 mmHg, P = 0.02), and their PcCO2 remained high during the first 24 h of treatment. CONCLUSION: The inability to achieve adequate gas exchange within 24 h of initiation of intensive care treatment is an ominous sign in high-risk outborn neonates with CDH. We suggest that improvement of oxygenation during the first 24 h, along with other relevant clinical signs, should be used when making decisions regarding treatment options in these critically ill neonates.

Šimić I[1,2], Potočnjak I[3], Kraljičković I[2], Stanić Benić M[4], Čegec I[2], Juričić Nahal D[2], Ganoci L1,[5], Božina N[1,5]. CYP2D6 *6/*6 genotype and drug interactions as cause of haloperidol-induced extrapyramidal symptoms. Pharmacogenomics. 2016; 13:1385-9.

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A 66-year-old male Caucasian, received 1 mg of haloperidol orally and rapidly developed severe iatrogenic extrapyramidal symptoms. Treatment was immediately discontinued, and the side effects resolved. Haloperidol is mainly metabolized by Phase I CYP2D6 and to the lesser extent by CYP3A4 and by Phase II UGT2B7 enzymes. Genotyping was performed revealing CYP2D6*6/*6, CYP3A4*1/*1, and UGT2B7 -161 C/T genotypes, implicating poor, extensive and intermediate metabolism, respectively. Of the CYPs, haloperidol is metabolized by CYP2D6 and CYP3A4 primarily. It was the introduction of ciprofloxacin which was a trigger for the development of adverse drug reaction due to inhibition of CYP3A4, which was in presented patient main metabolic pathway for haloperidol since he was CYP2D6 poor metabolizer. Presented case report highlights the importance of genotyping. Pharmacogenetics testing should be considered when drug toxicity is suspected, polymorphic metabolic pathways used and drugs concomitantly applied.

Orlic L[1], Mikolasevic I[2], Crncevic-Orlic Z[3], Jakopcic I[4], Josipovic J[5], Pavlovic D[5]. Forearm bone mass predicts mortality in chronic hemodialysis patients. J Bone Miner Metab. 2016 Jul 27. [Epub ahead of print].

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We aim to determine the relationship between bone mineral density (BMD), measured by T- and Z-score, and mortality risk in hemodialysis (HD) patients. We also investigate which are the most suitable skeletal sites for predicting mortality rate. We analyzed the survival of 102 patients who had been treated with chronic HD according to BMD. Patients with a T-score ≤2.5 at the middle, ultradistal and proximal part of the forearm had a higher mortality risk than those with a T-score of -2.5 or higher. Furthermore, no statistically significant association was found between loss of bone mass at other measuring points-lumbar spine (anteroposterior orientation from L1-L4) and hip (neck, trochanter, intertrochanter, total and Ward's triangle)-and mortality risk. We were also interested in exploring the relationship between Z-score at different skeletal regions and mortality risk. We found that patients with a Z-score of -1 or lower at all three parts of the forearm had a greater mortality risk. It is also worth noting that the Z-score at all three parts of the forearm was a more apparent predictor of mortality, compared to the T-score at the same skeletal regions. This empirical analysis showed that BMD assessments should be obtained at the forearm, due to the good predictability of this skeletal site regarding mortality of HD patients. Moreover, data concerning bone density should be reported as Z-scores.

Blagojević Zagorac G[1], Mahmutefendić H[1], Maćešić S[2], Karleuša L[1], Lučin P[1]. Quantitative Analysis of Endocytic Recycling of Membrane Proteins by Monoclonal Antibody-Based Recycling Assays. J Cell Physiol. 2016 Jul 26. [Epub ahead of print].

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In this report, we present an analysis of several recycling protocols based on labeling of membrane proteins with specific monoclonal antibodies (mAbs). We analyzed recycling of membrane proteins that are internalized by clathrin-dependent endocytosis, represented by the transferrin receptor, and by clathrin-independent endocytosis, represented by the Major Histocompatibility Class I molecules. Cell surface membrane proteins were labeled with mAbs and recycling of mAb:protein complexes was determined by several approaches. Our study demonstrates that direct and indirect detection of recycled mAb:protein complexes at the cell surface underestimate the recycling pool, especially for clathrin-dependent membrane proteins that are rapidly reinternalized after recycling. Recycling protocols based on the capture of recycled mAb:protein complexes require the use of the Alexa Fluor 488 conjugated secondary antibodies or FITC-conjugated secondary antibodies in combination with inhibitors of endosomal acidification and degradation. Finally, protocols based on the capture of recycled proteins that are labeled with Al-

exa Fluor 488 conjugated primary antibodies and quenching of fluorescence by the anti-Alexa Fluor 488 displayed the same quantitative assessment of recycling as the antibody-capture protocols. This article is protected by copyright. All rights reserved.

Lucijanic M[1], Livun A[2], Tomasovic-Loncaric C[3], Stoos-Veic T[4], Pejsa V[5], Jaksic O[5], Prka Z[6], Kusec R[5]. Canonical Wnt/β-Catenin Signaling Pathway Is Dysregulated in Patients With Primary and Secondary Myelofibrosis. Clin Lymphoma Myeloma Leuk. 2016 Jun 8. pii: S2152-2650(16)30109-4.

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INTRODUCTION: β-Catenin is a central effector molecule of the canonical wingless-related integration site (Wnt) signaling pathway. It is important for maintenance of stem cell homeostasis and its aberrant activation has been implicated in a wide array of malignant hematological disorders. There are few reports suggesting its dysregulation in Philadelphia chromosome-negative (Ph-) myeloproliferative neoplasms (MPNs). PATIENTS AND METHODS: We analyzed β-catenin mRNA expression in bone marrow (BM) aspirates of 29 patients with primary (PMF) and 4 patients with secondary, post Ph- MPN, myelofibrosis (SMF) using quantitative real-time polymerase chain reaction (qRT PCR). The control group consisted of 16 BM aspirates from patients with limited-stage aggressive non-Hodgkin lymphoma without BM involvement. We compared relative gene expression with clinical and hematological parameters. RESULTS: Relative expression of β-catenin differed significantly among groups (P = .0002), it was significantly higher in patients with PMF and SMF than in the control group, but did not differ between patients with PMF and SMF. A negative correlation was found regarding hemoglobin level in PMF (P = .017). No association according to Janus kinase 2 (JAK2) V617F mutational status or JAK2 V617F allele burden was detected. CONCLUSION: Our results show for the first time that β-catenin mRNA expression is increased in patients with PMF and SMF and its upregulation might potentiate anemia. A number of inflammatory cytokines associated with PMF are capable of mediating their effects through increased β-catenin expression. Accordingly, β-catenin can induce expression of a number of genes implicated in processes of cell cycle control, fibrosis, and angiogenesis, which are central to the PMF pathogenesis. Therefore, β-catenin might represent an interesting new therapeutic target in these diseases.

Dobrivojević M[1], Špiranec K[2], Gorup D[1], Erjavec I[3], Habek N[4], Radmilović M[5], Unfirer S[6], Ćosić A[7], Drenjančević I[8], Gajović S[9], Sinđić A[10]. Urodilatin reverses the detrimental influence of bradykinin in acute ischemic stroke. Exp Neurol. 2016;6;284(Pt A):1-10.

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Occlusion of cerebral arteries leads to ischemic stroke accompanied by subsequent brain edema. Bradykinin (BK) is involved in the formation of cerebral edema, and natriuretic peptides (NPs) potentially have beneficial effects

on brain edema formation via a still unknown mechanism. The aim of this study was clarifying the mechanisms of action of NPs on BK signaling, and their interactive effects after ischemic brain injury. We used a mouse model for stroke, the middle cerebral artery (MCA) occlusion. Brain lesion and edema were measured by microcomputerized tomography volumetric measurements. To determine the effects of NPs on the BK signaling pathway in the MCAs we measured changes in vessel diameter and membrane potentials in endothelial cells. To determine the effects of NPs on BK signaling pathway in isolated astrocytes and neurons, membrane potentials and intercellular Ca2+ concentrations were measured. Urodilatin inhibited and when applied together with BK, reduced the formation of the ischemic lesion via activation of G-Protein-Signaling Protein Type 4 at the cellular (atrocities, neurons) and blood vessel (endothelial cells and isolated MCA) level as well as in in vivo experiments. The results of this study show the existence of a natural antagonist of BK in the brain, and the possible use of NPs in the treatment of stroke.