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Intensification of menopausal symptoms among female inhabitants of East European countries

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The objective of the study was analysis of the occurrence and intensity of menopausal symptoms in postmenopausal women from Poland, Belarus, Ukraine, Czech Republic, Slovakia and Poland. The study was conducted during the period 2014-2015 among postmenopausal women living in the areas of Poland, Belarus, Ukraine, Czech Republic and Slovakia. The degree of menopausal complaints was assessed using the Kupperman Menopausal Index and Greene Climacteric Scale. The respondents were additionally asked about age, educational level, place of residence, marital status and age at last menstrual period. Into the study were enrolled women aged 50-65, minimum 2 years after the last menstrual period, who had a generally good state of health and did not use hormone replacement therapy. The results were subjected to statistical analysis. The intensity of all menopausal symptoms measured by the Kupperman Menopausal Index and Greene Climacteric Scale was similar in Poland, Czech Republic and Slovakia. In these countries, severe, moderate and mild menopausal symptoms measured by Kupperman Menopausal Index occurred with a similar frequency. Similar results were also obtained in the subscales of psychological, somatic and vasomotor symptoms according to the Greene Climacteric Scale. Nearly a half of the women from Belarus did not report symptoms measured by Kupperman Menopausal Index. They obtained significantly lower menopausal complaints in the subscales of psychological and somatic symptoms according to the Greene Climacteric Scale, compared to the inhabitants of the remaining countries. The majority of women from the Ukraine had mild menopausal symptoms as measured by the Kupperman Menopausal Index. They had significantly more severe complaints in the subscales of psychological, somatic and vasomotor symptoms according to the Greene Climacteric Scale, compared to the inhabitants of the remaining countries in the study. The intensity of menopausal symptoms in women from Ukraine and Belarus was related with educational level, place of residence, and marital status, whereas in women from Poland, Czech Republic and Slovakia, only with marital status.

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Mitochondrial dynamics during cell cycling.

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Mitochondria are the cell's power plant that must be in a proper functional state in order to produce the energy necessary for basic cellular functions, such as proliferation. Mitochondria are 'dynamic' in that they are constantly undergoing fission and fusion to remain in a functional state throughout the cell cycle, as well as during other vital processes such as energy supply, cellular respiration and programmed cell death. The mitochondrial fission/fusion machinery is involved in generating young mitochondria, while eliminating old, damaged and non-repairable ones. As a result, the organelles change in shape, size and number throughout the cell cycle. Such precise and accurate balance is maintained by the cytoskeletal transporting system via microtubules, which deliver the mitochondrion from one location to another. During the gap phases G_1 and G_2, mitochondria form an interconnected network, whereas in mitosis and S-phase fragmentation of the mitochondrial network will take place. However, such balance is lost during neoplastic transformation and autoimmune disorders. Several proteins, such as Drp1, Fis1, Kif-family proteins, Opa1, Bax and mitofusins change in activity and might link the mitochondrial fission/ fusion events with processes such as alteration of mitochondrial membrane potential, apoptosis, necrosis, cell cycle arrest, and malignant growth. All this indicates how vital proper functioning of mitochondria is in maintaining cell integrity and preventing carcinogenesis.

Keywords: *Apoptosis; Cell cycle arrest; Drp1; Mitochondria; Mitochondrial fission and fusion; Mitophagy*

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A gene cluster for the biosynthesis of moenomycin family antibiotics in the genome of teicoplanin producer Actinoplanes teichomyceticus

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Moenomycins are phosphoglycolipid antibiotics notable for their extreme potency, unique mode of action, and proven record of use in animal nutrition without selection for resistant microflora. There is a keen interest in manipulation of structures of moenomycins in order to better understand their structure-activity relationships and to generate improved analogs. Only two almost identical moenomycin biosynthetic gene clusters are known, limiting our knowledge of

the evolution of moenomycin pathways and our ability to genetically diversify them. Here, we report a novel gene cluster (tchm) that directs production of the phosphoglycolipid teichomycin in Actinoplanes teichomyceticus. Its overall genetic architecture is significantly different from that of the moenomycin biosynthesis (moe) gene clusters of Streptomyces ghanaensis and Streptomyces clavuligerus, featuring multiple gene rearrangements and two novel structural genes. Involvement of the tchm cluster in teichomycin biosynthesis was confirmed via heterologous co-expression of amidotransferase tchmH5 and moe genes. Our work sets the background for further engineering of moenomycins and for deeper inquiries into the evolution of this fascinating biosynthetic pathway.

Keywords: *Actinoplanes; Moenomycins; Nosokomycin; Teichomycin*

Blood. 2016 Aug 4;128(5):630-7. (IF = 11.847)

Efficacy and safety of rVIII-SingleChain: results of a phase 1/3 multicenter clinical trial in severe hemophilia A

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Recombinant VIII (rVIII)-SingleChain is a novel B-domain-truncated recombinant factor VIII (rFVIII), comprised of covalently bonded factor VIII (FVIII) heavy and light chains. It was designed to have a higher binding affinity for von Willebrand factor (VWF). This phase 1/3

study investigated the efficacy and safety of rVIII-SingleChain in the treatment of bleeding episodes, routine prophylaxis, and surgical prophylaxis. Participants were ≥12 years of age, with severe hemophilia A (endogenous FVIII <1%). The participants were allocated by the investigator to receive rVIII-SingleChain in either an on-demand or prophylaxis regimen. Of the 175 patients meeting study eligibility criteria, 173 were treated with rVIII-SingleChain, prophylactically (N = 146) or on-demand (N = 27). The total cumulative exposure was 14306 exposure days (EDs), with 120 participants reaching ≥50 EDs and 52 participants having ≥100 EDs. Hemostatic efficacy was rated by the investigator as excellent or good in 93.8% of the 835 bleeds treated and assessed. Across all prophylaxis regimens, the median annualized spontaneous bleeding rate was 0.00 (Q1, Q3: 0.0, 2.4) and the median overall annualized bleeding rate (ABR) was 1.14 (Q1, Q3: 0.0, 4.2). Surgical hemostasis was rated as excellent/good in 100% of major surgeries by the investigator. No participant developed FVIII inhibitors. In conclusion, rVIII-SingleChain is a novel rFVIII molecule showing excellent hemostatic efficacy in surgery and in the control of bleeding events, low ABR in patients on prophylaxis, and a favorable safety profile in this large clinical study. This trial was registered at www.clinicaltrials.gov as #NCT01486927.

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Analysis of a distinct speech disorder seen in chronic manganese toxicity following Ephedrone abuse

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INTRODUCTION: In the last fifteen years a new cause of chronic manganese toxicity has been recognized. It follows recreational intravenous injections of Ephedrone, synthesized from a cold remedies contained pseudoephedrine. Potassium permanganate is used as an oxidant. It presents with severe parkinsonism-dystonia and a characteristic dysarthria.

OBJECTIVES: We performed a focus perceptual study of dysarthria in Ephedrone induced parkinsonism and compared the findings with the speech disorders seen in Parkinson's disease (PD) and Progressive Supranuclear Palsy (PSP).

METHODS:A digital voice recording, perceptual speech analysis (Darley, 1975) [18], serial neurological assessment and Brain Magnetic Resonance (MR) imaging were performed at the Lviv regional Clinical Hospital. The results were analysed at the Institute of Neurology in London.

RESULTS: Dysarthria developed after 8.5±3.2months of daily intravenous Ephedrone abuse and was an initial symptom in a third of cases. It was characterised by a robotic-flat prosody, whispering or continuous phonation, an inability to regulate pitch and volume, frozen lip articulation, a variable degree of dystonic tightness, difficulties in speech initiation and palladia, There was no nasality and swallowing was normal. In some patients speech deteriorated even after the discontinuation of Ephedrone. MR imaging, performed soon after drug cessation showed T1 signal hyperintesity in striatum and pallidum, especially in the Globus Pallidum interna.

CONCLUSION: Ephedrone induced chronic manganese toxicity can lead to a mixed hypokinetic-dystonic dysarthria with a distinct dystonic pattern. Perceptual speech analysis can be a helpful ancillary investigation in the differential diagnosis of parkinsonism, and may permit the recognition of chronic manganese toxicity.

Keywords: *Dysarthria; Globus pallidum; Manganism; Parkinsonism*

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Bevacizumab plus paclitaxel versus placebo plus paclitaxel as first-line therapy for HER2-negative metastatic breast cancer (MERiDiAN): A double-blind placebo-controlled randomised phase III trial with prospective biomarker evaluation

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AIM: MERiDiAN evaluated plasma vascular endothelial growth factor-A (pVEGF-A) prospectively as a predictive biomarker for bevacizumab efficacy in metastatic breast cancer (mBC).

METHODS: In this double-blind placebo-controlled randomised phase III trial, eligible patients had HER2-negative mBC previously untreated with chemotherapy. pVEGF-A was measured before

randomisation to paclitaxel 90 mg/m^2 on days 1, 8 and 15 with either placebo or bevacizumab 10 mg/kg on days 1 and 15, repeated every 4 weeks until disease progression, unacceptable toxicity or consent withdrawal. Stratification factors were baseline pVEGF-A, prior adjuvant chemotherapy, hormone receptor status and geographic region. Co-primary end-points were investigator-assessed progression-free survival (PFS) in the intent-to-treat and pVEGF-A$_{high}$ populations.

RESULTS:Of 481 patients randomised (242 placebo-paclitaxel; 239 bevacizumab-paclitaxel), 471 received study treatment. The stratified PFS hazard ratio was 0.68 (99% confidence interval, 0.51-0.91; log-rank p = 0.0007) in the intent-to-treat population (median 8.8 months with placebo-paclitaxel versus 11.0 months with bevacizumab-paclitaxel) and 0.64 (96% confidence interval, 0.47-0.88; log-rank p = 0.0038) in the pVEGF-A$_{high}$ subgroup. The PFS treatment-by-VEGF-A interaction p value (secondary end-point) was 0.4619. Bevacizumab was associated with increased incidences of bleeding (all grades: 45% versus 27% with placebo), neutropenia (all grades: 39% versus 29%; grade ≥3: 25% versus 13%) and hypertension (all grades: 31% versus 13%; grade ≥3: 11% versus 4%).

CONCLUSION:The significant PFS improvement with bevacizumab is consistent with previous placebo-controlled first-line trials in mBC. Results do not support using baseline pVEGF-A to identify patients benefitting most from bevacizumab.

CLINICAL TRIALS REGISTRATION:ClinicalTrials.gov NCT01663727.

Keywords:*Bevacizumab; Biomarker; Double-blind; Metastatic breast cancer; Predictive; Prospective; VEGF-A; Weekly paclitaxel*

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A rare clinical case of the isolated primary frontal bone osteoma

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AIM: To study a rare clinical case of isolated primary osteoma localized in the frontal bone, provide its detailed clinical and pathomorphological analysis, and evaluate statistical indicators of occurrence frequency and localization of facial skeleton osteomas during 2006-2015.

MATERIALS AND METHODS: The retrospective case records analysis of patients undergoing treatment in the ma-xillofacial department of Lviv Regional Clinical Hospital and suffering from facial skeleton osteomas was conducted. The clinical examination was carried out in accordance with the inspection protocol required for the examination of patients diagnosed with tumors and tumor-like neoplasms in a particular clinical case. Frontal and lateral views were used in the course of X-ray imaging. Histological studies included macroscopy and microscopy.

RESULTS: According to the retrospective case record analysis made over the last 10 years 346 cases of facial bone osteoma were revealed and proved histologically comprising 3.7% of all benign osteogeneous maxillofacial tumors. For the first time in 10 years osteoma localized in the frontal bone had been revealed and thoroughly studied. Macroscopically - a semi-spherical and immovable neoformation 7 cm in diameter of hard consistency, splaying out at 4 cm and being adherent with the frontal bone. Roentgenologically - homogeneous intense shadowing of a round form with relatively distinct outlines complying with clinical sizes. According to the histological

data, the tumor consists mostly of the solid osseous tissue and the spongy osseous tissue with the evident thickened trabeculas of the bone located in different directions.

CONCLUSION: The analysis of historical data demonstrated extremely rare localization of primary osteoma of the frontal bone, and indicated the uniqueness of the case and significant clinical importance of its detailed study.

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Neutrophil Extracellular Traps Form a Barrier between Necrotic and Viable Areas in Acute Abdominal Inflammation

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Neutrophils form neutrophil extracellular traps (NETs) of decondensed DNA and histones that trap and immobilize particulate matter and microbial pathogens like bacteria. NET aggregates reportedly surround and isolate large objects like monosodium urate crystals, which cannot be sufficiently cleared from tissues. In the setting of acute necrotizing pancreatitis, massive tissue necrosis occurs, which is organized as pancreatic pseudocysts (1). In contrast to regular cysts, these pseudocysts are not surrounded by epithelial layers. We hypothesize that, instead, the necrotic areas observed in necrotizing pancreatitis are isolated from the surrounding healthy tissues by aggregated NETs. These may form an alternative, putatively transient barrier, separating necrotic areas from viable tissue. To test this hypothesis, we investigated histological samples from the necropsy material of internal organs of two patients with necrotizing pancreatitis and peritonitis accompanied by multiple organ failure. Tissues including the inflammatory zone were stained with hematoxylin and eosin and evaluated for signs of inflammation. Infiltrating neutrophils and NETs were detected by immunohistochemistry for DNA, neutrophil elastase (NE), and citrullinated histone H3. Interestingly, in severely affected areas of pancreatic necrosis or peritonitis, chromatin stained positive for NE and citrullinated histone H3, and may, therefore, be considered NET-derived. These NET structures formed a layer, which separated the necrotic core from the areas of viable tissue remains. A condensed layer of aggregated NETs, thus, spatially shields and isolates the site of necrosis, thereby limiting the spread of necrosis-associated proinflammatory mediators. We propose that necrotic debris may initiate and/or facilitate the formation of the NET-based surrogate barrier.

Keywords: *inflammation; neutrophil elastase; neutrophil extracellular traps; neutrophils; sepsis*

Genet Res (Camb). 2016 Oct 11;98:e13. (IF = 0.743)

Identification of FBN1 gene mutations in Ukrainian Marfan syndrome patients

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Marfan syndrome is an autosomal dominant connective tissue disorder, predominantly affecting the ocular, skeletal and cardiovascular systems. Here, we present the results of the first genetic testing in 40 Ukrainian Marfan (-like) patients and 10 relatives. We applied a targeted next generation sequencing panel comprising FBN1 and 13 thoracic aortic aneurysm genes. We identified 27 causal mutations in FBN1, obtaining a mutation yield of 67·5%. A significant difference in age at aortic surgery between mutation positive and negative patients was observed. Thus, we conclude that genetic testing is important to identify patients at higher risk for developing life-threatening cardiovascular complications.

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Limits of application of initiated chemiluminescence in monitoring of oncological process of mucous membrane of mouth and larynx

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Investigation into the limits of application of chemiluminescence (CL) methods in oncology still attracts the attention of researchers. In the present work we analyze the screening and monitoring of oncological processes (OP) in the mucous membrane of the mouth and larynx by initiated CL (ICL). Chemiluminescence has already been used by stomatologists to define the start of OP, but methods that reflect the metabolic changes in organism under cancer diagnostics still have not found their place. This work presents results of ICL on blood serum (BS) of patients with oncological diseases at different stages of medical treatment compared with those of healthy people. We found an essential metabolic difference only in types of OP that are characterized by two maxima on chemiluminograms. These OP represent only 12.81% of groups of patients with oncological diseases. The possibility to apply ICL methods to monitor operation quality and control medical treatment at different stages when the two ICL maxima are present is established. At present, the chemiluminograms with the two maxima are mostly informative, but this does not exclude the quantitative analysis of other ICL kinetic methods and is encouraging for their investigation. Any OP introduces changes in organism function and these should be reflected in the ICL. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: *blood serum; chemiluminescence; oral cancer; second maximum*

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Sweet but dangerous - the role of immunoglobulin G glycosylation in autoimmunity and inflammation

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Glycosylation is well-known to modulate the functional capabilities of immunoglobulin G (IgG)-mediated cellular and humoral responses. Indeed, highly sialylated and desialylated IgG is endowed with anti- and pro-inflammatory activities, respectively, whereas fully deglycosylated IgG is a rather lame duck, with no effector function besides toxin neutralization. Recently, several studies revealed the impact of different glycosylation patterns on the Fc part and Fab fragment of IgG in several autoimmune diseases, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Here, we provide a synoptic update summarizing the most important aspects of antibody glycosylation, and the current progress in this field. We also discuss the therapeutic options generated by the modification of the glycosylation of IgG in a potential treatment for chronic inflammatory diseases.

Keywords: *Fc fragment; Glycosylation; autoantibody; autoimmunity; fucosylation; galactosylation; inflammation; sialylation*

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Highly purified calf hemodialysate (Actovegin®) may improve endothelial function by activation of proteasomes: A hypothesis explaining the possible mechanisms of action

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Highly purified calf hemodialysate (HPCH) known as Actovegin® or Solcoseryl® is one of the most controversial drugs currently marketed worldwide. It is not registered as drug in some countries and therefore its medical use there is illegal, while in others it is often among the top

10 of the best-selling medications. It could be also found in the list of the «most useless drugs» and was banned for short time by World Anti-Doping Agency as performance enhancer. However, the degree of its usefulness or uselessness remains unclear and there is not enough convincing data to make reliable conclusions. HPCH is claimed to have wound/muscular injuries healing, neuroprotective and antioxidant properties, to enhance glucose uptake and oxygen consumption, and possibly to improve performance of athletes. Since HPCH consists of over 200 naturally occurring substances which potentially may exert some pharmacological effects, it is extremely difficult to perform pharmacokinetic and pharmacodynamical studies. In this paper we have analyzed the available literature concerning clinical evidence, in vitro, ex vivo and in vivo effects of HPCH. Based on these data we suggest that the main target of the drug may be endothelium and improvement of endothelial function may be responsible for numerous largely nonspecific effects. We also propose the improvement of protein quality control by the means of activation of ubiquitin-proteasomal system as the most important biochemical mechanism responsible for its effects. The role of sphingolipids as potential proteasome-activators is extensively discussed. The effects of HPCH may also include direct or indirect ones on NF-kB-, Nrf2- and FOXO-mediated regulation of metabolic processes in the cells, which result in improved protein quality control, enhanced energy metabolism and increased resistance to oxidative stress.

Keywords: *Actovegin; Endothelial function; Mechanism of action; Proteasomes; Solcoseryl; Sphingolipids*

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Experimental Investigation of Electrical Conductivity and Permittivity of SC-TiO 2 -EG Nanofluids

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The paper presents experimental studies of dielectric properties of nanofluids based on ethylene glycol and SC-TiO2 nanoparticles with average size of 15-40 nm with various mass concentrations. The dielectric permittivity both real part and imaginary part as a function of temperature and frequency were measured. Also, dependence ac conductivity on frequency, temperature, and mass concentration were investigated. Based on the curves of ac conductivity, dc conductivity was calculated, and 400 % enhancement in dc conductivity was exposed.

Keywords: *Dielectric properties; Nanofluids; Titanium oxide*

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A European Spectrum of Pharmacogenomic Biomarkers: Implications for Clinical Pharmacogenomics

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Pharmacogenomics aims to correlate inter-individual differences of drug efficacy and/or toxicity with the underlying genetic composition, particularly in genes encoding for protein factors and enzymes involved in drug metabolism and transport. In several European populations, particularly in countries with lower income, information related to the prevalence of pharmacogenomic biomarkers is incomplete or lacking. Here, we have implemented the microattribution approach to assess the pharmacogenomic biomarkers allelic spectrum in 18 European populations, mostly from developing European countries, by analyzing 1,931 pharmacogenomics biomarkers in 231 genes. Our data show significant inter-population pharmacogenomic biomarker allele frequency differences, particularly in 7 clinically actionable pharmacogenomic biomarkers in 7 European populations, affecting drug efficacy and/or toxicity of 51 medication treatment modalities. These data also reflect on the differences observed in the prevalence of high-risk genotypes in these populations, as far as common markers in the CYP2C9, CYP2C19, CYP3A5, VKORC1, SLCO1B1 and TPMT pharmacogenes are concerned. Also, our data demonstrate notable differences in predicted genotype-based warfarin dosing among these populations. Our findings can be exploited not only to develop guidelines for medical prioritization, but most importantly to facilitate integration of pharmacogenomics and to support pre-emptive pharmacogenomic testing. This may subsequently contribute towards significant cost-savings in the overall healthcare expenditure in the participating countries, where pharmacogenomics implementation proves to be cost-effective.

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Nanoparticles size-dependently initiate self-limiting NETosis-driven inflammation

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The critical size for strong interaction of hydrophobic particles with phospholipid bilayers has been predicted to be 10 nm. Because of the wide spreading of nonpolar nanoparticles (NPs) in the environment, we aimed to reveal the ability of living organisms to entrap NPs via formation of neutrophil extracellular traps (NETs). Upon interaction with various cell types and tissues, 10- to 40-nm-sized NPs induce fast (<20 min) damage of plasma membranes and instability of the lysosomal compartment, leading to the immediate formation of NETs. In contrast, particles sized 100-1,000 nm behaved rather inertly. Resulting NET formation (NETosis) was accompanied by an inflammatory reaction intrinsically endowed with its own resolution, demonstrated in lungs and air pouches of mice. Persistence of small NPs in joints caused unremitting arthritis and bone remodeling. Small NPs coinjected with antigen exerted adjuvant-like activity. This report demonstrates a cellular mechanism that explains how small NPs activate the NETosis pathway and drive their entrapping and resolution of the initial inflammatory response.

Keywords: *NETosis; inflammation; nanoparticles; neutrophils; size*

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The Cost of Inpatient Care of Schizophrenia and Treatment Schedules Used in German Academic Center: Kiel

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The authors aimed at analyzing the costs of inpatient care of schizophrenia in Kiel (Germany). The study was also to present treatment regimens used at the German Academic Center. Moreover, the study is a continuation and complement of the previous study conducted in Polish and Ukrainian Academic Center. Therefore, it helps increase the awareness and knowledge of residents concerning the cost of inpatient care of schizophrenia. The analysis was based on 105 hospital records of patients treated between January 2012 and June 2013. According to inclusion criteria, 50 adult patients (27 women and 23 men) were included in the study. The study was approved by the Ethics Committee of the Medicine Faculty of CAU in Kiel. The cost of schizophrenia treatment of 50 patients in Kiel was EUR 604,280.90 ([Formula: see text] = EUR 12,085.62). The duration of hospital stay was on average [Formula: see text] = 51.02 days. The patients were treated with neuroleptics of all generations. The most popular atypical neuroleptic was amisulpride and the most popular typical neuroleptic was haloperidol. Patients from Kiel were provided a comprehensive non-pharmacological treatment. Treatment regiments and evaluations of costs of schizophrenia vary between countries. The costs of inpatient care of schizophrenia are high in Kiel. Treatment of schizophrenia seems to be comprehensive in Kiel and wide range of treatment opportunities contribute to a more effective treatment confirmed by less frequent relapses of schizophrenia than in Lviv(Ukraine), for example. Comprehensive treatment should be available everywhere, because it is a right of every patient.

Keywords: *Direct costs; Inpatient care; Schizophrenia; Therapy*

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Is Localized Scleroderma Caused by Borrelia burgdorferi?

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Despite considerable achievements in the study of localized scleroderma, the etiology of the disease has not been investigated completely. Borrelia burgdorferi-the agent of Lyme disease- is suggested to be one of the possible etiological factors of localized scleroderma. However, among scientists, this hypothesis is quite controversial. We have conducted investigations of the level of IgM and IgG class antibodies to B. burgdorferi in the serum of patients with localized scleroderma. To rationally substantiate the role of B. burgdorferi in the occurrence of localized scleroderma, thirty-two patients with localized scleroderma treated at an in-patient department were examined. The level of anti-Borrelia antibodies was determined in ELISA. Diagnostic levels of IgM and/or IgG were detected in 18.8% of patients with localized scleroderma, which is more than in the population ($p < 0.01$). Positive levels of anti-Borrelia antibodies in patients with localized scleroderma confirm the borreliosis nature of the disease, requiring conduction of complex antimicrobial treatment.

Keywords: *Antibody; Lyme disease; benzyl penicillin; scleroderma*

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