РЕЗЮМЕ НА НАУЧНИТЕ ТРУДОВЕ

НА АСИСТЕНТ Д-Р ЦВЕТЕЛИНА КОСТАДИНОВА ПОПОВА, Д.М.

УС „МЕДИЦИНСКИ ЛАБОРАНТ“, МЕДИЦИНСКИ КОЛЕЖ, МУ- ВАРНА

Представени във връзка с участие в конкурс за заемане на академична длъжност „Доцент“ в област висше образование 7. Здравеопазване и спорт, професионално направление 7.1. Медицина, по специалност **„Вирусология"**, **ДВ бр. 36/ 27.04.2018 г.**

I. РАВНОСТОЙНИ НА МОНОГРАФИЧЕН ТРУД ПУБЛИКАЦИИ:

1 Tsankova G. S., **Kostadinova Ts. P**., Todorova T. T. (2016). Seroprevalence of hepatitis B among pregnant women in Varna Region (Bulgaria). *Journal of Medical Virology*., 1-4. doi: 10.1002/jmv.24543; (IF.-1.935)

Abstract: The aim of the present study was to assess the prevalence of hepatitis B surface antigen among pregnant women in Varna Region, Bulgaria. During the period 2009-2013, an average prevalence of 2.26% (95% CI 1.75, 2.91) was measured in a total number of 2700 samples.

Analysis demonstrated that rural residence and minority ethnic origin are important risk factors for hepatitis B infection among pregnant women with relative increase in the prevalence of 2.40 (95% CI 1.46, 3.94) and 2.43 (95% CI 1.46, 4.05) when compared with urban residence and ethnic majority origin respectively.

2 Tsankova G., Todorova T. T., **Kostadinova Ts.,** Ivanova L., Ermenlieva N. (2016). Seroprevalence of Syphilis among pregnant women in Region Varna (Bulgaria), *Journal of Acta Dermatovenerologica Croatica*, 24(4):288-290; (IF 0.725), **цитирана 1 път**)

Abstract: Syphilis is a sexually transmitted disease with continuously rising rates among European countries. The vertical (mother to child) transmission is an important way of dissemination, often leading to stillbirth and permanent impairment of the newborn.

We present a retrospective cross-sectional analysis of 2702 pregnant women tested for syphilis seropositivity. During the study period (2009-2013) non-specific and specific treponemal antibodies were detected in 15 pregnant women (0.56% of sample size with CI 95% 0.28, 0.84).

Our results showed lack of correlation between syphilis seropositivity and age, ethnic origin or pregnancy trimester of the mother. The only factor found to influence syphilis seropositivity was the mother‘s place of residence – rural inhabitants had significantly higher risk for syphilis infection when compared to urban inhabitants with seropositive proportion of 1.08% versus 0.36%, respectively.

Глава от книга:

3 Liliya Ivanova, Denitza Tzaneva, Zhivka Stoykova, **Tcvetelina Kostadinova (**2015). Viral Diseases in Transplant and Immunocompromised Patients- Immunopathology and Immunomodulation. Prof. Krassimir Metodiev (Ed.) 6 глава, 101-126 ,(ISBN 978-953-51-2210-4) InTech Open

Abstract: For the last few years, the number of immunocompromised individuals is growing fast, due to more intensive antitumor therapy, transplantations and the concomitant immunosuppressive therapy, and the HIV epidemic, as well. Immunosuppressed patients very often are affected with nosocomial infections in hospitals, and with infections in the society. The defense from viral diseases depends mainly on the immune system. When there is immune deficiency, the illness is taking severely longer and has complicated outcome. Usually immunocompromised individuals have one or more defects in the defensive mechanisms and leading cause of death is infection.The viruses taking part in this process are Epstein Barr virus (EBV), Cytomegalovius (CMV), Herpes simplex viruses (HSV1, HSV2), Varicella zoster virus (VZV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Human Polyomaviruses (BKV, JC). Many viruses (HIV, CMV, EBV) are depressing the immune resistance and are leading to co-infections with other microbial agents. Some viruses (HSV1/2, HPV, CMV, EBV, BKV, JC) are at latent condition in the infected persons for life. They become activated when decline in the immunity occurs, leading to serious illnesses. For this reason, accurate screening and prompt and precise diagnosis can be performed to prevent exacerbation of diseases and provide appropriate treatment.

Глава от книга:

4 Todorova T., Tsankova G., Lodozova N., **Kostadinova Tc.** (2015). Tuberculosis and HIV – doubling the fatality, In: Immunopathology and Immunomodulation, Prof. Krassimir Metodiev (Ed.) 4 глава, 55-74.(ISBN 978-953-51-2210-4) InTech Open

Abstract: Tuberculosis (TB) and HIV/AIDS infection are one of the most ubiquitous and deadliest communicable diseases in the world. They cause millions of deaths each year and are recognized as major threats for public health worldwide. The corresponding pathogens (Mycobacterium tuberculosis and HIV) share overlapping epidemiology—they affect low-income countries and place an immense burden on their feeble health care systems. Over the last decades, the natural history of both diseases has changed; in addition to devastating single HIV and TB infections, the coinfection with both pathogens has emerged and has spread in pandemic scale. When present as dual infection in an individual, Mycobacterium tuberculosis and HIV potentiate each other and kill in cooperation the host. TB is the leading cause of death in HIV-positive patients

and in turn HIV infection is the strongest risk factor for the development of new or reactivation of dormant TB disease. Both pathogens (as single or dual infection) provoke a robust immune response in the infected host but the immune system does not achieve to eliminate the infectious agent(s). The failure of immune defense results in vulnerable immune balance between the micro- and the macroorganism and often ends up in a fatal outcome.

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Tsankova G., Todorova T., Ermenlieva N., ***Popova Tsv. K.,*** Tsankova D. (2016). Epidemiological study of hepatitis A infection in Eastern Bulgaria. Folia Medica, 59(1), 63-69, SJR фактор (SCOPUS) (ICV 2013-6.78); (SJR 2008 – 2015 0.18)

Abstract: According to the World Health Organization, clinical cases with hepatitis A account for 1,5 million each year and its spread strongly correlates with socioeconomic and cultural development of each country. Bulgaria is a region with intermediate endemicity of hepatitis A viral infection with average incidence of 27 – 80 cases per 100 000 population**.**

Aim The objective of the current study is to analyze the epidemiological data on hepatitis A in five of the largest provinces of Bulgaria, located in its eastern part – Varna, Shumen, Dobrich, Burgasand Yambol.

Methods: In the current study, we investigate all reported cases of hepatitis A in the easternmost provinces of Bulgaria for 7 year-period (2008-2014). The information was received from the Regional Health Inspections in Varna, Dobrich, Shumen (Northeast Bulgaria) and in Burgas and Yambol (Southeast Bulgaria).

Results: During the period of the study, a total of 2879 newly infected individuals was registered, but this number varied widely – from 190 cases in 2014 to 923 in 2012. Southeastern provinces (Burgas and Yambol) showed higher average incidence of HAV compared with the provinces on the North (Varna, Dobrich and Shumen) – 51,41%000 versus 16,04%000 respectively ($p < 0,0001$). In all studied provinces age group 5-9 years showed the highest incidence rate and males and females were equally affected.

Conclusion: Hepatitis A is an important social disease and it is necessary to raise the health knowledge of children and adolescent about hepatitis A and to improve the essential hygienic habits (washing hands).

II. АВТОРЕФЕРАТ НА ДИСЕРТАЦИОНЕН ТРУД:

6 **Попова Ц. К.** (2018). Сероепидемиологични и лабораторно диагностични проучвания върху разпространението и клиничната значимост на epstein-barr вирусната инфекция.

Дисертационният труд е посветен на проучване ролята на EBV в развитието на различни клинични заболявания и изработване на алгоритми за лабораторна диагностика в зависимост от имунния статус на пациентите.

Литературният обзор дава пълна информация за биологията на вируса, участието му в различни патогенетични механизми, съществуващите възможности за диагностика, профилактика и терапия.

Целта на дисертацията е дефиниране на сероепидемиологичния статус на населението в Североизточна България и установяване относителния дял на възрастово свързаното разпространение на остра Epstein-Barr вирусна инфекция. Дефиниране диагностичните възможности за доказване остра вирусна инфекция и реактивация на инфекцията при рискови пациенти.

За постигане на целта са поставени 3 големи основни **задачи:** Да се установи серопревалентността на населението в Североизточна България за периода 2010 г. - 2016 г.; Да се разработи диагностичен алгоритъм за подобряване лабораторната диагностика на острата EBV – инфекция; Да се проучи ролята на EBV при имуносупресирани пациенти и пациенти с различни видове лимфоми, и възможностите на специфичните лабораторни методи за дефиниране на реактивация. В ретроспективното проучване анализирахме 5957 изследвания, за да установим разпространението на EBV-инфекцията сред населението в Североизточна България за периода 2010 г. - 2016 г., да установим възрастовото начало на първична EBV инфекция и да анализираме най-честите заболявания. Проспективно изследвахме 126 серумни/празмени проби за различни антитела и по различни методи, за да създадем диагностичен алгоритъм за установяване на EBV инфекция. Също проспективно изследвахме 169 плазмени проби на пациенти с Ходжкинови и неходжкинови лимфоми, с първична инфекция и други имуносупресирани в Real time PCR, за да определим риска от реактивиране на EBV, което би помогнало за създаване на работещи практически диагностични алгоритми за контролиране и управление на вирусната инфекция и реактивация.

Резултати: Направено е широкомащабно сероепидемиологично проучване върху разпространение на EBV сред населението в Североизточна България, като се анализираха тенденциите в разпространението на вирусната инфекция за 7 годишен период. Дефинирано е влиянието на възрастта и пола върху началото на първичната инфекция. Проучена е ролята

на различни комерсиални ELISA-базирани серологични маркери при пациенти с различни профили в имунния отговор при първична EBV инфекция. Дефинирани са възможностите за разширяване набора от серологични маркери за изследване в зависимост от първичните серологични профили на пациентите, възрастта и клиничната диагноза. Приложен Real time PCR метод в диагностиката на EBV при пациенти с първична инфекция, болест на Ходжкин, Неходжкинови лимфоми и други имуносупресирани пациенти. Изработен е диагностичен алгоритъм от серологични възможности за установяване и потвърждаване на инфекция с EBV, който може да се използва от всички лаборатории в страната.

III. НАУЧНИ ПУБЛИКАЦИИ, СВЪРЗАНИ С ПРИДОБИВАНЕ НА ОНС „ДОКТОР”

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Ц. Костадинова (2015). Лабораторна диагностика на EBV. *Варненски медицински форум*, 4 (3):460-465. (ISSN 2367-5519)

Резюме: EBV е широко разпространен представител на семейство Herpesviridae. Първичната инфекция е безсимптомна при заразяване в ранното детство или протича с клиника на инфекциозна мононуклеоза при повече от 50% от случаите на инфектиране в юношеството и в зряла възраст. Основното социално значение на EBV инфекцията обаче се дължи на връзката му с развитие на злокачествени заболявания като лимфом на Бъркит, назофарингеален карцином, болест на Ходжкин, лимфоми при имунокомпрометирани пациенти, вкл. и след органна трансплантация и др., както и автоимунни заболявания. Познаване на EBV инфекцията и възможностите за нейната диагностика и проследяването ѝ може да бъде решаващ прогностичен фактор. Цел: Да се представят възможностите за диагностика на EBV инфекцията на базата на световния опит.

Материали и методи: Систематична литературна справка на публикации от чуждестранни източници за основните методи за диагностика и интерпретация на резултатите на EBV инфекция.

Изводи: 1. За диагностика на EBV се използват основно серологични методи (ELISA, IFA, Western blot) и PCR. Наличието на IgG и IgM към антигени от репликативния цикъл на вируса (VCA, EA-D), в комбинация с липса на антитела към ядрени антигени (EBNA 1), е показателно за първична EBV инфекция. За оценка на серостатуса се използват anti-VCA IgG, които остават до живот. 2. Определяне на риска от развитие на EBV-асоциирани туморни заболявания и проследяване хода на терапията изискват в комбинация със серологичните методи да се извършват по-чувствителни и специфични лабораторни изследвания (PCR). 3. При имунокомпрометирани пациенти средство на избор е определяне на EBV DNA.

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Ц. Костадинова, Л. Иванова, Т. Райков (2015). Роля на EBV в човешката патология. *Варненски медицински форум,* ,4 (3):466-475. (ISSN 2367-5519)

Резюме: EBV (Epstein-Barr) или HHV-4 (Humsn herpesviruses - 4) е представител на семейство Herpesviridae, подсемейство Gammaherpesvirinae и род Lymphocryptovirus. Той е повсеместно разпространен, като по литературни данни над 90% от населението в света е инфектирано с него. В България по данни от различни проучвания серопозитивност е установена при 6079% от населението чрез определяне на anti-EBV (VCA) IgG антитела по метода ELISA. Преобладава при лицата от мъжки пол (57,6%) в съответствие със световните тенденции и най-висок процент серопозитивност (80%) при лицата между 40 и 60 г., следвани от 12 и 18-годишните (14,9%). EBV се асоциира най-често с инфекциозна мононуклеоза, която обикновено се развива при инфектиране в периода на юношеството. Той е доказан причинител на злокачествени тумори основно от В-клетъчен или епителен произход – лимфом на Бъркит, Ходжкинов и не-Ходжкинов лимфом, пострансплантационни лимфопролиферативни заболявания (PTLD), назофарингеален карцином (NPC), орална влакнеста левкоплакия, СПИН-свързани лимфоми. Освен това вирусът се асоциира с чернодробен карцином и карцином на стомаха, както и с автоимунни заболявания – ревматоиден артрит, системен лупус еритематодес, автоимунен хепатит, множествена склероза.

Цел: Проучване на литературни източници за ролята на EBV при развитието на заболявания при хората.

Материали и методи: Систематична литературна справка на публикации от български и чуждестранни автори.

Изводи: EBV е широко разпространен и има отношение към развитие на редица злокачествени заболявания. Проследяването на EBV инфекцията при определени групи лица може да има прогностично значение за развитие на лимфоми.

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Ts. Kostadinova, L. Ivanova, T. Raykov, Z. Stojkova, G.Tsankova (2016). Seroprevalence of Epstein-Barr Virus in North-Eastern Bulgaria. *Acta Microbiologica Bulgarica,* ,32: 33-38 (ISSN 0204-8809)

Abstract: Epstein-Barr Virus (EBV) is a widely spread member of the Herpesviridae family. Data show that in more than 90% of the adult population, specific anti-EBV can be found. In different Bulgarian studies the seroprevalence was set between 60% and 80%. The primary infection early in life is often asymptomatic or with nonspecific clinical symptoms, while in teenagers infectious mononucleosis develops. EBV is a proven agent of malignant, autoimmune

and lymphoproliferative diseases, especially in immunocompromised patients. Tracking and analyzing the seroepidemiological status of the population in every region is of utmost importance.

In our study, 5016 single serum samples from patients referred for EBV testing for various reasons were analyzed for the period 2010-2015. People aged between 1 month and 89 years old were divided into sixteen age groups. The samples were tested using indirect enzyme-linked immunosorbent assay (ELISA) for detection of anti-EBV (VCA) IgM and IgG. The proportion of EBV seropositive individuals and their corresponding confidence intervals (CI), chi-squared distributions and p-values were calculated.

Our data indicated high, age-dependent EBV (VCA) IgG dissemination with 90% seroprevalence after age 26. Primary infections detected by anti-EBV (VCA) IgM occur in a bimodal model with peaks in age groups 1 – 5 and 11 - 20 years old.

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Ts. Popova, T. Todorova, G.Tsankova, L. Ivanova, T. Raykov, N. Ermenlieva, E.Georgieva. (2016). Epstein-Barr virus – molecular basis for malignant transformation. *Scripta Scientifica Medica*. 48(1) 11-15. (ISSN 1314-6408, **цитирана 1 път**)

Abstract: Epstein-Barr (EBV) is a widespread virus which can be detected in more than 90% of world population. Primary EBV infection during adolescence and adulthood results in infectious mononucleosis, while in children it is usually asymptomatic. EBV is responsible for different malignant forms of B-cell or epithelial cancers, such as Hodgkin's and non-Hodgkin's lymphoma, Burkitt's lymphoma, post-transplant lymphoproliferative disorders, nasopharyngeal carcinoma, hairy leukoplakia and HIV-associated lymphomas. Evidence exists that an infection with EBV is also linked with a higher risk of hepatocellular and gastric cancers, as well as autoimmune diseases.

EBV shows two alternative life cycles – latent and lytic. After the primary infection, the virus remains in the B lymphocytes in latency, while the lytic infection takes place predominantly in the epithelial cells and can last for months with constant virus release in saliva and nasopharyngeal secretion. Unlike other herpes viruses, the development of oncological diseases is linked with the latent cycle, as a result of the immune response failure to control latently infected cells.

With the present work we try to concisely review the current knowledge about mechanisms of EBV pathogenesis in humans and to summarize recent findings in the field.

IV. ПЪЛНОТЕКТОВИ СТАТИИ, ПУБЛИКУВАНИ В НАУЧНИ СПИСАНИЯ С ISSN И ISBN:

11 Todorova T., Tsankova G., Tsankova D., **Kostadinova Ts**., Lodozova N. (2015). Knowledge and attitude towards hepatitis B and hepatitis C among Dental Medicine students. *Journal of IMAB*. 21(3),810-813. (ISSN 1312-773X; **цитирана 5 път**)

Summary: Background: Hepatitis B (HBV) and hepatitis C viruses (HCV) are highly contagious and important occupational hazard for health workers. Dental practice often includes direct contact with patients' body fluids and exposure at high degree to potentially HBV and HCV infected materials and instruments.

Purpose: The purpose of this study is to investigate the level of knowledge about hepatitis B and C infections and the attitude towards hepatitis B virus vaccination among Dental Medicine students.

Materials and Methods: A cross-sectional survey was conducted among 96 students of Faculty of Dental Medicine, Medical University of Varna in March, 2015. The questionnaire contained 22 questions divided into 4 major sections. SPSS ver.16 software package was used for statistical data processing.

Results: Most of the participants (82,3 %) considered hepatitis B and C as serious diseases and had positive attitude towards HBV vaccination (75 %). Almost 90 % considered that dental practice could enhance the risk of infection with HBV and HCV. Unfortunately, only 57,4 % of students knew their vaccination status and 13,9 % had checked HBV antibodies' level.

Conclusions: The majority of respondents demonstrated a high level of knowledge of HBV and HCV infections. All participants were aware about the risk of potential HBV and HCV transmission in their future practice and anticipated applying preventive measures at work. However, deeper information about HBV vaccination and checking anti HBs titer is still needed among dental students, as well continuous target education in the field.

12

Zhivka Stoykova, Liliya Iv. Ivanova, Tatina T. Todorova, **Tsvetelina Kostadinova,** Denitsa Tsaneva-Damyanova (2016). Seroprevalence of Cytomegalovirus in the North-Eastern Bulgarian Population, 2003-2015. *Acta Microbiologica Bulgarica*, ,32: 27-32 . (ISSN 0204-8809)

Abstract: The prevalence of cytomegalovirus (CMV) infections is between 50% and 85% in adults in different parts of the world. Its epidemiology varies on socioeconomic and age groups. The present retrospective study has been performed to determine the seroprevalence of CMV among the population in North-Eastern Bulgaria.

For the period 2003–2015, the prevalence of individuals with antibodies to CMV was estimated, using indirect enzyme-linked immunosorbent assay (ELISA) to detect virus-specific IgG and IgM. The population sample included 7879 randomly chosen hospitalized patients of both sexes and different ages.

The total seroprevalence of CMV was determined to be 78.4% (CI 95% 77.5; 79.3), and the relative proportion of acute CMV infections 22.9% (CI 95% 21.9; 23.7). The proportion of CMV IgG and IgM by sex and by age was also analysed. The results of the study reveal that CMV infection is highly prevalent among the population and occurs mainly in the first years of life.

13

Ermenlieva N., Bliznakova D., Tsankova G., **Popova T.**, Georgieva E., Todorova T. (2016). Pediatric urinary infections, caused by extended-spertum beta-lactamase-producing microorganisms in Varna, Bulgaria. *Journal of IMAB.* 22(2),1132-1135. (ISSN 1312-773X)

Abstract: Extended-spectrum beta-lactamase (ESBLs) producing bacteria are microorganisms which have the ability to hydrolyze β-lactame ring of a large part of the antibiotics, commonly used to treat bacterial infections including urinary tract infections. Purpose: The aim of this study is present the epidemiology of childhood urinary tract infections caused by ESBL-producing strains in Varna, Bulgaria.

Material/methods: A total of 3895 urine samples of children patients (aged 0 to 18 years) were examined during the period 2010-2012 for presence of ESBL-producing bacteria.

Results: Six percent of the tested urinary samples were positive for ESBL production. All of the isolates were resistant to ampicillin, piperacillin, cephalothin, cefprozil, cefuroxime, ceftriaxone, ceftazidime, levofloxacin, cefaclor, but were were sensitive to meropenem and imipenem.

Conclusions: Cephalosporins and penicillins are the most used antibiotics in Bulgaria, but they should be very precisely prescribed in medical practice, because otherwise preconditions for maintaining high share of ESBLs are created.

14 Ermenlieva N., Todorova T., Tsankova G., **Popova T**., Georgieva E. (2016). Effectiveness of MRSA detection methods in the laboratory practice – a brief review. *Journal of IMAB*. 22(2), 1157-1159 ((ISSN 1312-773X, **цитирана 1 път**)

Abstract: Methicillin-resistant Staphylococcus aureus (MRSA) are bacteria, responsible for severe and hard-to-manage infections in human. They are resistant to beta-lactam antibiotics - penicillins (methicillin, dicloxacillin, nafcillin, and oxacillin), cephalosporins and carbapenems, but can also be resistant to the new-generation MRSA-active cephalosporins (such as ceftaroline) or other groups of antibiotics, including aminoglycosides, macrolides, clindamycin, amphenicols, quinolones and tetracyclines. MRSA bacteria are pandemic and are often isolated in medical practice and nosocomial infections. The MRSA detection is a challenge to any clinical microbiology laboratory and demands implementation of strict protocols for active screening. While more expensive molecular techniques have the potential of offering highly sensitive and rapid results, the cultural methods require longer time but can achieve a comparable sensitivity for lower price.

15 Denitsa Tsaneva-Damyanova, Liliya Ivanova, Trifon Chervenkov, Tatina Todorova, Zhivka Stoikova, **Tsvetelina Kostadinova** (2017). Virological responses evaluated during antiviral therapy in chronically infected HBV and HDV patients. *Acta Microbiologica Bulgarica*, ,33 (4): 157-166. (ISSN 0204-8809).

Abstract: The aim of thisinvestigation was to evaluate the various virological responses at several time points of therapy in chronically infected patients with dual HBV and HDV infection.

A total of 23 patients, 8 (34.8%) women and 15 (65.2%) men with serologically proved chronic HBV and HDV infection, at the Gastroenterology Department of the University Hospital St. Marina, Varna, Bulgaria, were investigated in the hospital's laboratories of Clinical Virology and Clinical Immunology. Quantitative determination of HBV DNA and HDV RNA was performed by Real-time PCR, on several occasions during and after therapy from 2012 to 2017.

HBV viremia ranged from 1.0x10 2 to 1.6x106 cps/ml. HDV viremia ranged from 2.5x102 to 9.6x106 cps/ml. HDV replication dominated in 16 patients (69.6%), accompanied by low HBV viremia. HDV-RNA and HBV-DNA levels showed no direct inverse correlation in the less part of the investigated patients, although higher HDV levels were accompanied by lower HBV viremia. HBV DNA correlates positively with HBeAg positivity. IFN is efficient in reducing transaminanses (ALT), decreasing HDV RNA levels at some point, but it is not operative in HDV RNA clearance. Lamivudine alone is a potent inhibitor of HBV DNA replication but does not improve disease activity or lower HDV RNA levels in patients with chronic delta hepatitis. It did not increase sustained virological response when combined with IFN. When virological breakthrough during Lamivudine therapy occurs, Tenofovir is a means of choice for treatment. Biochemical parameters did not accurately indicate the stage and grade of liver disease in chronic HDV patients as they often fluctuate over time.

16 Georgieva E., Milev M., Ermenlieva N., Laleva K., **Popova Ts**. (2017). Medico-laboratory services in outpatient care in Northeastern Bulgaria – state and prospects. *Journal of IMAB*. 23(4), 1742-1746. (ISSN 1312-773X)

Abstract: The aim of this article is to study the satisfaction of patients with laboratory services in outpatient care in Northeastern Bulgaria regarding access and quality of service. Study design: Prospective cohort study.

Material and methods: The survey was carried out on the territory of Northeastern Bulgaria and covered the districts of Varna, Dobrich and Shumen and thirty municipalities. The following methods were applied in the study: sociological method by applied direct anonymous questionnaire, documentary method and statistical methods for analysis and interpretation of the data in order to reveal the nature of the observed phenomena and their interrelations.

Results: The research data show that 24,4% of the respondents live at a distance of more than ten kilometres from the nearest medico-diagnostic laboratory. The larger share of this patients are residents of small settlements in Northeastern Bulgaria. More than half (55%) of the respondents are not satisfied with their provision of laboratory services, but the majority of patients claim that the location of the selected laboratory is accessible (69,4%) and the quality of the laboratory service is high (83,7%).

Conclusion: The main problems in outpatient care are related to the poor provision of medico-laboratory services and specialized outpatient care in the smaller settlements in Northeastern Bulgaria.

17 Ivanova L., Stoykova Z., **Kostadinova Ts.,** Tsaneva D. (2018). HIV related laboratory and clinical manifestations. *Acta Microbiologica Bulgarica*, 33 (5). (ISSN 0204-8809).

Abstract: *Human immunodeficiency virus* **(***HIV*) is a member of the family *Retroviridae* that attacks the immune system of the infected person. The virus destroys a type of white blood cell (T helper cells or CD4+ cells) and gradually breaks down a person's immune system. As many as 37 million people worldwide are thought to be infected. In our retrospective study, we review the clinical evidences as a reason for association with *HIV* infection and the most common co-infections in patients living with *HIV*. Since 2003 we have tested 148 *HIV* infected patients (104 males and 44 females), aged between 3 months and 67 years, average age 37.3 years. Out of the patients investigated, 108 were with proven HIV-positive status (persons living with HIV), hospitalized in "St Marina" University Hospital, Clinic of Infectious, Parasitic and Dermatovenerologic Diseases and 40 patients were found with reactive results at our Virology Laboratory and confirmed as *HIV* infected at the National *HIV* Reference Laboratory in Sofia.

ELISA *HIV* Ag&Ab (DiaPro Italy), *HbsAg* (SURASE Taiwan), *Anti Hbc* (DiaPro Italy), *Anti HCV* (NANBASE Taiwan), Anti *CMV* IgM/IgG (EUROIMMUN Germany), Syphilis Ab screening (EUROIMMIN – Germany) were performed according to the manufacturer's recommendations. Out of the 40 investigated patients with diagnostic and therapeutic problems, 13 (32.5%) were with clinical diagnosis pneumonia, 6 (15%) with lymphadenoipathy, 5 (12.5%) with hepatitis, 3 (7.5%) with mononucleosis-like syndrome, 4 (10%) with wasting syndrome and chronic diarrhea, 4 (10%) with neurological sympthoms, 3 (7.5%) with dermatological manifestation including Herpes zoster, and 2 (5%) were mothers of infected children. Out of the 108 pre-defined *HIV* infected patients, we received serological data for hepatitis B in 12 (11%), hepatitis B/C co-infection in 2 (1.9%), hepatitis C in 6 (5.6%), syphilis in 24 (22.2%), CMV active infection in 21 (19.4%). The most common reason for HIV testing is the diagnosis bilateral pneumonia, unsusceptible to conventional antibacterial treatment. People living with *HIV* most often were co-infected with syphilis.

18 **Tsvetelina Kostadinova**, Liliya Ivanova, Zhivka Stoykova, Tatina Todorova, Liana Gercheva, Dobromir Staykov, Denitsa Tsaneva (2018). Investigation of immunosuppressed patients for the presence of EBV DNA in Real time PCR. *Journal of IMAB* (ISSN 1312-773X) (**Под печат)**

Abstract: Epstein-Barr virus (EBV) reactivates during immunosuppression (IS) and immune deficiency. The introduction of stem cell transplantation and the development of transplantology require compliance with criteria for assessing the risk of reactivation of latent viral infections, including EBV. There are no published EBV DNA findings in Bulgaria for such patient groups and therefore we want to assess the possible benefit of EBV PCR testing in immunosuppressed individuals.

We investigated 50 immunosuppressed patients – 28 with various haematological diseases, 17 after kidney transplantation and 5 patients with autologous stem cell transplantation (HSCT). Patients were first tested in an indirect ELISA to detect anti-VCA IgM/IgG (Euroimmun, Luebeck, Germany) and then in quantitative PCR (Sacace Biotechnologies S.r.l., Como, Italy).

We found EBV DNA in 14.0% (95% CI: 5.8% - 26.7%, n=7) of all tested patients. The Real time PCR results were in the range 100-500 copies/ml at the lower limit of the 500 copies/ml test positivity. The highest is the proportion of patients with haematological diseases (21.4%), predominantly with AML.

Conclusion: We found a relatively small proportion of IS patients with detectable EBV DNA. For HSC-transplanted patients, we anticipate probable reactivation or reinfection in one patient, who was anti-VCA IgG positive in the primary study.

19 **Tsvetelina Kostadinova**, Liliya Ivanova, Ivaylo Hristov, Tatina Todorova, Zhivka Stoykova, Denitsa Tsaneva (2018). The role of anti-EBNA1 IgG determination in EBV diagnostics. *Journal of IMAB* (ISSN1312-773X) **(Под печат)**

Abstract: In Bulgaria, the diagnosis of Epstein-Barr virus (EBV) infection is performed via ELISA testing of IgM and IgG against viral capsid antigen (anti-VCA IgM and anti-VCA IgG). With the current study, we try to answer is there any benefit of determination of IgG against the nuclear antigen of EBV (anti-EBNA-1 IgG) in the laboratory practice.

The prospective study included 82 serum/plasma samples tested for anti-VCA IgM, anti-VCA IgG, anti-EBNA1 IgG and anti-VCA IgG avidity in ELISA (Euroimmun, Luebeck, Germany). Quantitative variables were reported as mean and standard deviation (mean±SD) and the qualitative variables were reported as a number and a relative proportion (%).

Anti-EBNA1 IgG positive patients were 74.4% (95% CI: 63.6% - 83.4%) of all tested individuals. Their mean age was significantly higher (30.5; SD±20.5) of this of patients without anti-EBNA1 IgG (14.5; SD±14.1) ($p < 0.05$). The first group of patients (with infectious mononucleosis, anti-VCA Ig M negative) had the highest number of anti-EBNA1 IgG negative results. Negative for anti-EBNA 1 IgG were 12% of patients with Hodgkin's lymphoma.

Conclusion: Determination of anti-EBNA1 IgG together with anti-VCA should be considered in the initial serological testing in EBV diagnostics. As different immune responses against the EBNA1 antigen exist, clinicians should interpret the results carefully with regard to the clinical symptoms, the immune status and the laboratory markers. We found anti-EBNA1 IgG ELISA tests exceptionally useful to distinguish primary and past infections in anti-VCA IgM (+)/anti-VCA IgG (+) patients.

20 **Tsvetelina Kostadinova**, Liliya Ivanova, Milena Bozhkova, Denitsa Tsaneva, Tatina Todorova, Zhivka Stoykova (2018). Use of Immunoblot IgM in patients with serological and clinical evidence of primary EBV infection and reactivation. *Journal of IMAB* (ISSN1312-773X) **(Под печат)**

Abstract: Anti-VCA IgM is a marker for establishing primary infection with Epstein-Barr Virus (EBV), it is usually appear in combination with anti-VCA IgG. It has been shown that there is a risk of non-specific IgM reactivity due to cross-reactions, interference with rheumatoid factor or autoantibodies. These antibodies may also occur during reactivation. In these cases Immunoblot based tests may be useful to confirm the ELISA result. We compared the results of anti-VCA IgM in ELISA and Immunoblot IgM in patients with evidence of primary EBV infection (infectious mononucleosis, IM) and/or reactivation/reinfection.

We examined 32 serum samples with commercial immunoblot (Euroline Anti-EBV Profile 2 (IgM), Euroimmun, Germany). Samples were tested primarily for anti-VCA IgM/IgG in ELISA. Patients with IM were 11, and those with probable reactivation/reinfection - 21.

We found positive results at 31.3% (95% CI: 16.1% -50.0 %, n = 10) of all subjects. Patients with IM and isolated anti-VCA IgM in ELISA (81.8%) were negative in Immunoblot IgM. Positive in Immunoblot IgM were 38.1% (n = 8) of the patients with suspected reactivation. We confirmed a primary infection in three of them due to the low avidity of anti-VCA IgG and missing anti-EBNA1 IgG. In five of the patients, the presence of anti-VCA IgM may be interpreted as reactivation/reinfection.

Conclusion: Patients with IM and isolated anti-VCA IgM models in ELISA were not confirmed in the Immunoblot test. Approximately 43% of patients of possible reactivation was also negative in the test.

Научни публикации в български списания:

21 **Костадинова Цв.,** Иванова Л, Цанкова Г, Жечев П. (2014). Разпространение на сифилис сред лица от уязвими групи и профилактично изследвани по повод на диагностично уточняване в две лаборатории в гр. Варна, Варненски медицински форум. 3(4): 53-55. (ISSN 2367-5519)

Резюме: Сексуално–предаваните инфекции (СПИ) са сериозен медицински и социален проблем. Това се дължи на голямото им разпространение в световен мащаб, доказаната им роля за развитие на усложнения при мъжете и жените, включително и на рак, големите разходи за диагностика и лечение. Във връзка със СПИ са обособени т.нар. уязвими групи, за които се приема, че са с по-висок риск. Сифилисът е типична сексуално-предавана инфекция, известна още от древността. Основно се разпространява при сексуален контакт, също и вертикално – от майка на дете и по кръвен път. Целта на нашето проучване е установяване честотата на разпространение на сифилис във Варненски регион, като се анализират изследваните проби на лица от уязвимите групи, бременни жени и изследвани профилактично и с диагностична насоченост в две големи лаборатории в гр. Варна. Обхванати са 6749 лица, разпределени в две възрастови групи. Случаите са дефинирани чрез доказване на антитела в серум от болен чрез използване на: кардиолипоидни антигенни тестове – Venereal Disease research laboratory (VDrl) и специфични трепонемни тестове – enzyme-linked immunosorbent assay (eliSa) и t.pallidum haemagglutination assay (tpHa). След анализиране на данните могат да се направят следните изводи: 1. Очаквано по-висока е серопозитивността сред лицата от уязвимите групи. 2. В нашето проучване не се установяват съществени разлики по пол по отношение на сифилис. 3. Броя на положителните проби е по-голям при лицата от по-младата възрастова група до 25г.

22 Цанкова Г., **<u>Костадинова Цв</u>**., Лодозова Н., Георгиева Е., Тодорова Т. (2014). Оценка на имунния статус на жени в детеродна възраст срещу вируса на рубеола във Варненска област. *Варненски медицински форум*. 3(S4), 317-321. (ISSN 2367-5519)

Резюме: Рубеолата е остро инфекциозно заболяване, което се причинява от Rubella virus. Характеризира се с леко протичане при децата и широко елидемично разпространение. Въпреки, че рубеолата е позната отдавна, интересът към нея и социалното й значение нарастват след 1941 г., когато офталмологът Норман Макалистър Грег установява, че вирусът може да предизвика различни увреждания на плода, известни като конгенитален рубеолен синдром (КРС). След въвеждане на противорубеолната ваксина броят на децата с конгенитален рубеолен синдром рязко намалява, но докато има страни с ендемично разпространение, той ще продължава да бъде проблем за общественото здравеопазване.

Цел: Обобщаване и анализиране на данни от проведено серологично проучване за наличие на защитни антитела към рубеолния вирус при жени в детеродна възраст в град Варна и областта.

Материал и методи: Проучването обхваща 710 жени на възраст от 18 до 40 години. Серологичното изследване е извършено с китове VIR-ELISA anti Rubella IgG за количествено определяне на рубеолни антитела от клас IgG.

Резултати: От всичките 710 изследвани лица 41 (5,8%) са серонегативни към рубеолния вирус. Възрастовото разпределение на серонегативните проби показва, че най-висок е относителният дял на незащитените (6,63%) сред жените на възраст от 21-30 години.

Изводи: Разпространението на рубеолния вирус в някои страни по света, увеличената миграция на хора, наличието на незащитена популация от жени в детеродна възраст, тежките увреждания на плода, налагат определянето на титъра на специфичните IgG антителата да се въведе като задължително изследване още при първото посещение на бременната в женската консултация.

23 Цанкова Д, Цанкова Г, **<u>Костадинова Цв</u>.,** Тодорова Т. (2015). Въздействие на меда от манука върху някои бактерии от микрофлората на устната кухина. *Варненски медицински форум*, 4(3): 456-458. (ISSN 2367-5519)

Резюме: Използваният в древната медицинска практика за лечение на рани, пептични язви, бактериални гастроентерити и офтоматологинчни инфекции, днес медът отново е въведен като средство в модерната медицина, .Той има и свойства свързани с лекуването на периодонтит и гингивит. Антимикробното действие на меда от манука се счита, че се дължи и на осмотичения ефект на високото му захарно съдържимо. Медът може да разруши биофилма на P. gingivalis .

Някои изследвания показват, че броят на P. gingivalis, L. acidophilus и S. mutans значително намалява след консумация на мед. Освен това медът не само спира разтежа на бактериите от зъбната плака, но също така намалява и количеството на произведената

киселина, което пречи на бактериите да произвеждат декстран. Друго проучване показва, че оралното приложение на прополиса намалява загубата на кост от алвеоларния израстък предизвикана от периодонтит при плъхове.

В заключение може да се каже, че медът или неговите компоненти добавени към продуктите за подържане на оралното здраве могат да имат ефект в превенцията и лечението на периодонтита.

24

Georgieva E., Todorova T., Tsankova G., Ermenlieva N., **Popova T**., Raykov T. (2016). Inequalities in the access to medical-diagnostic services in outpatient medical practice in Northeastern Bulgaria. *Scripta Scientifica Salutis Publicae*. 2(2), 29-33. . (ISSN 2367-7333)

Abstract: Territorial inequality in healthcare services is an important problem worldwide. A complete study of the correlation between the inequalities and the territorial disproportion of health services is required, as this will ensure a scientifically based model for improvement of the access to health services. The aim of the current work is to analyze the patients` satisfaction with the territorial distribution of medical diagnostic services and to prepare a cartogram of the observed differences in the Northeastern region of Bulgaria.

Between July and September, 2015 we studied 502 patients from 30 municipalities situated in Northeastern Bulgaria about their opinion for the number of accessible medical diagnostic laboratories. We also drew a visual presentation of the spatial distribution of medical diagnostic laboratories in the region.

Results: Laboratories in Northeastern Bulgaria are unequally distributed and mainly concentrated in the regional centers and larger towns. Accordingly, most of the patients living up to 3 km from a medical diagnostic laboratory were satisfied from the number of available labs, while people living 3-10 km apart thought that laboratories were not enough.

Conclusion: The main reason for health inequalities in Bulgaria is the territorial imbalance between health care units. The increased need of health care and social assistance requires new resources to provide laboratory services via mobile lab offices and home visits. A better infrastructure of the outpatient health care in Northeastern Bulgaria and new players in the lab service market will assure equal access and favorable concurrent environment.

25

Georgieva E., Todorova T., Ermenlieva N., Tsankova G., **Popova T.,** Raykov T. (2016). Preference for laboratory test results notification among different healthcare players in Northeastern Bulgaria. *Scripta Scientifica Salutis Publicae*. 2(2) 16-21. (ISSN 2367-7333)

Abstract: With the continuously growing number of people using online sources for health information and services, the concept of eHealth is progressively developing and it is a high-

priority topic for the European Union. The absence of centralized internet-based eHealth platform in Bulgaria results in deficiency in the information exchange among physicians and other healthcare providers. The question about the readiness and the attitude towards the eHealth concept among all participants in the healthcare system in Bulgaria still remains to be clarified and the purpose of the current study is to assess the opinion of healthcare providers and consumers about the electronic way of receiving laboratory test results. We also try to explore the existing preference trend in relation to the socio-demographic characteristics of the studied population. In the current work, we investigated the needs and recommendations of 1039 patients, laboratory staff and out-of-hospital general practitioners in Northeastern Bulgaria (regions of Varna, Dobrich and Shumen).

Results: The results show that laboratory results are preferred in electronic form and there is a significant need for better online communication between different participants in the healthcare system. In this context, we also summarize a model for improvement in the interaction among healthcare providers.

Conclusion: The actual opportunities for online communication provoke active participation of all players in the health service market and require a novel model of communication among healthcare providers.

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Ерменлиева Н., Цанкова Г., Тодорова Т., **Костадинова Ц.,** Георгиева Е. (2016). Детекция на полирезистентни ESBL-щамове. Едно от предизвикателствата пред съвременната медицина. *Мединфо*. 10 (ISSN 1314-0345)

Въведение: Поради простото си устройство бактериите се размножават в рамките само на няколко минути. Така те бързо се приспособяват към заобикалящата ги среда. Тези от тях, които заради промяна в генотипа (мутации) преживяват атаката с антибиотици, предават генетичните си качества на следващите поколения или могат да разменят променената си вече генетична информация с други бактериални щамове. Възникването, разпространението и селекцията на резистентни бактерии застрашават човешкото здраве, защото:

- Инфекциите с резистентни бактерии водят до нарастване на заболеваемостгта и смъртността на пациентите, както и увеличаване на продължителността на болничния престой на хоспитализираните такива.
- Антибиотичната резистентност често води до отлагане на подходяща антибиотична терапия.
- Неподходяща или отложена антибиотична терапия при пациенти с тежки инфекии може да доведе до нежелан изход.

27 Ерменлиева Н., **<u>Костадинова Цв.</u>,** Георгиева Е., Мехмед Х., Асенова В., Петрова М., Цанкова Г., Цанкова Д., Тодорова Т. Т. (2016). Препарати, съдържащи ботулинов невротоксин и приложението им за естетически цели. *Варненски медицински форум*. 5(S3),328-335. (ISSN 2367-5519)

Резюме: Ботулиновият токсин е една от най-токсичните биологични субстанции, известно на човечеството. Представлява невротоксин, продуциран от бактерии от род Clostridium, причиняващи заболяването ботулизъм. Появата на бръчки по лицето се дължи не само на стареене на кожата. Някои бръчки и неестетически изражения на лицето са резултат от свръхактивност на лицевата мускулатура. Успехът в приложението на BoNT като селективен депресор на активността на скелетната мускулатура води до широкото му приложение при изглаждането на бръчки. На световния пазар съществува разнообразие от продукти, съдържащи BoNT за козметично приложение, които са получили одобрение от регулаторните органи или са в процес на разработка. Към момента Botox® дава дял от 85% от световния пазар на продукти, съдържащи BoNT. Други продукти на световния пазар или с по-ограничено приложение са Dysport®, Xeomin®, Myobloc®, Prosigne® и други. По данни на редица изследвания приложението на BoNT се отличава с висока ефективност и безопасност. Нежеланите ефекти са рядкост и са обратими. Най-сериозните неблагоприятни ефекти са временна слабост (парализа на близката мускулатура), временна птоза на горния клепач или челото (1-3% от пациентите). Паралитичният ефект след инжектиране с BoNT е със средна продължителност три месеца. За поддържане на ефективността са необходими допълнителни приеми на BoNT- препарат на равни интервали.

28 Ж. Стойкова, Л Иванова, Д. Цанева-Дамянова, **<u>Цв. Костадинова</u>** (2017). Хепатит Е вирусна инфекция в Североизточна България.*Медицински преглед.*53 (3),30-34. (ISSN 1312-2193)

Abstract: Hepatitis E virus (HEV) is the most important cause of acute hepatitis in many countries in Asia, the Middle East and North Africa considered as endemic regions. Although most disease cases were imported from these countries, recent studies have shown that hepatitis E occurs also in patients who has never been abroad. HEV infection has not been considered a major health problem inEurope, but recent studies show that seroprevalence to HEV increases in different European countries.

The aims of our study are to investigate the possible role of HEV in causing acute hepatitis in Northeastern Bulgaria and to estimate the laboratory data of the previous infection. Single serum samples of 325 patients were tested from January 2012 to August 2016. Four of these patients had travelled to areas with high HEV endemicity.

The study population is divided into two groups. Group A includes 287 hospitalized patients with clinical data of acute hepatitis and group B – 38 outpatients with laboratory data of liver

dysfunction. Commercial ELISA test kits were performed for detection of specific IgM and IgG antibodies for hepatitis A, B, C and E, according to the manufactures recommendations. Our data indicated that 43/325 patients (13.2%, CI 95% [3.1-23.3%]) were associated with acute HEV infection as shown by positive anti-HEV IgM test. The other causes of acute hepatitis were excluded as a reason for the condition. Positive anti-HEV IgG only were 68 of all 325 tested patients (20.9%, CI 95% [11.2-30.6%]) cases, showing past infection.

Our data indicated that sporadic HEV infection is present in Northeastern Bulgaria as a cause of acute hepatitis. The preliminary data about seroprevalence to HEV is estimated as 20.9% in the investigated population.

29 Милена Божкова, Теменуга Стоева, Васил Божков, **Цветелина Попова-Костадинова**, Росен Маджов (2018). Етиологичен спектър и чувствителност към антибиотици на водещите бактериални причинители на остър холангит. *Варненски медицински форум*, 7 (1):87-93. (ISSN 2367-5519)

Резюме: Комплексният подход към диагностиката и лечението на заболяването остър холангит изисква познаване на спектъра на бактериалните причинители и тяхната чувствителност към антибактериални лекарствени средства. Настоящото проучване представя данни за бактериалните патогени, изолирани от жлъчка на пациенти с остър холангит (ОХ) и тяхната антибиотична чувствителност. Водещи причинители на заболяването са грам-отрицателни бактерии - основно E. coli, изолирани в 26.8% от всички изследвани материали. Сред грам-положителните патогени най-висок е относителният дял на ентерококите (E. feacalis и E. faecium). Най-висока е резистентността на изпитаните бактерии към аминопеницилини – 63.5%. Най-висока in vitro активност демонстрират imipenem, piperacillin / tazobactam, ciprofloxacin и gentamicin с нива на резистентност съответно 2.8%, 14.8%, 14.6% и 15.7%.

Научни публикации, публикувани в рецензиранисборници на научни звена или в сборници от проведени научни форуми в български списания

30 **Костадинова Цв.,** Лечев П Иванова Л., Ерменлиева Н., Георгиева Е. (2014). Какво е разпространението на урогениталната хламидийна инфекция във Варненска област. Сборник доклади от Юбилейна конференция „Превенция и рехабилитация за подобряване качеството на живот“. Тракийския университет. Стара Загора, 1(1),379-383.

Summry: According to the WHO urogenital chlamydial infection / UGCI / is the second most common sexually transmitted infection / STI/ worldwide. Although compulsory registration has been implemented by the Ministry of Health (Ordinance 21), there is still no accurate data on

the distribution of UGCL,s in Bulgaria. The lack of accurate data is in partq due to the prevalence of asymptomatic forms of the infection, which, according to recent literature was found to occur in 15-20 % of men and 65% of women.

The study included individuals/groups who are at high risk of contracting the infection such as intravenous drug users and individuals whose cultural beliefs put them at high risk/. These samples were tested in the laboratory of RHI. Samples from non-high risk individuals presenting with arthritic symptoms that had tested on another occasion in the laboratory of University Hospital "St. Marina" were also included. Positive Diagnosis was confirmed by the presence Chlamydia-specific IgM, IgG and IgA antibodies using ELISA. Aim of the study:

To Establish the spread of UGCI among selected groups in the Varna region for 2012-2013 Data currently available from the study shows: 1. In 2013 the frequency of UGCI was 14.5 % while in 2012 it was slightly lower 13.7%. 2. UGCI was seen to be more common among men, both in 2012 (16.9%) and in 2013 (17.2%) compared to women (11.9% and 13% respectively) 3. It is expected that the frequency of distribution is higher among vulnerable groups than among people studied in the laboratory of University Hospital "St. Marina".

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Ermenlieva N., Ivanova Ts., . Bliznakova D., **Tsankova G.,** Kostadinova Tsv., Georgieva E. (2014). Epidemiology of urinary tract infections, causedlw ESBLS, in Europe and Bulgaria (Survey), *Ecology and Environment*, 1: 203-210.

Abstract: Urinary tract infections are among the most common infections in ambulatory and hospitalized patients. It is estimated that approximately 150 million people suffer from urinary tract infections in the world annually. Primary causes of urinary tract infections are gram-negative microorganisms of the family Enterobacteriaceae - Escherichia coli, Klebsiella spp., Proteus mirabilis and others. The main antibiotics approach to treating urinary tract infections are β-lactam antibiotics - penicillins, III generation cephalosporins are widely applied fluoroquinolones. Extended spectrum-β-lactamase (ESBL)-producing organisms have been discovered in the 80s in Europe. They have the ability to hydrolyze the β-lactam ring of the majority of antibiotics in this group, commonly used to treat bacterial infections, including urinary tract infections. The main ESBL-strains are Klebsiella spp. (mainly Klebsilla pneumonia) and of E. coli. Their share is growing every year and they become serious health problem worldwide.

Objectives:The aim of the study is to characterize ESBL-enzymes produced by the family Enterobacteriaceae, by presenting their distribution in Europe and in Bulgaria, their epidemiology and their resistance to certain groups of β-lactam antibiotics.

Materials and methods: The methods for detection of ESBLs can be broadly divided into two groups: 1. *phenotypic methods*, that use non-molecular techniques, which detect the ability of the ESBL enzymes to hydrolyse different groups β-lactam antibiotics (mainly cephalosporins); 2. *genotypic methods*, which use molecular techniques to detect the gene responsible for the production of the ESBL.

Results and discussion: Most studies on the activity of ESBL-producers indicate, that the major share of antibiotics, that have the ability to hydrolyze these bacteria, are cephalosporins (mostly II-nd and III-rd generation) - ceftazidime, cefotaxime and ceftriaxone; penicillins; monobactams (aztreonam), etc. So far, carbapenems (imipenem and meropenem) carbacephems and cephamycins (type cephalosporins) - cefoxitin and cefotetan remain effective in the fight against extended-spectrum β-lactamases.

Conclusions and Recommendations: Studies submitted by different authors, both in Europe and in other continents, indicate widespread dissemination of ESBL-producers, causing urinary tract infection. They hydrolyze most of the groups and subgroups of β-lactam antibiotics. Carbapenems and carbacephems are the only effective antibiotics in the majority of studies. To contain extremely high share of ESBL-resistant strains is necessary to adjust very thorough use of penicillins and cephalosporins in medical practice, medical laboratories to specialize in the detection of extended-spectrum beta-lactamases and to reduce to a minimum the possibility of randomly self by patients with urinary tract infections.

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Михайлова Й., Георгиева Е., **Костадинова Цв.,** Цанкова Г., Ерменлиева Н. (2014). Медицинската лабораторна услуга като рефлекс на взаимодействието на лаборанта, медицинската сестра и лекаря в болнична среда. *Сборник доклади от Юбилейна конференция „Превенция и рехабилитация за подобряване качеството на живот“*. Тракийския университет. Стара Загора, 1(1) 252-256.

Abstract: The medical personnel interaction rise many significant issues within medical practice which should include not only professional competence but also provision of effective professional communication, observation and interaction. A good professional communication in the medical practice is accomplished by strictly following the rules of medical ethics. Purpose – research and analyses of the opinion of medical specialists in St. Marina University Hospital Varna in order to develop a manual for quality improvement of the laboratory service and the interaction of clinical and paraclinical units in hospital environment. Sources and methods: documentary, sociological, expert evaluation method and anonymous inquiry research. The work of the medical team in the hospital is organizes based on two level service which means that patient cares are provided by two units – the nurse and the doctor and subsequent interaction with
the laboratory personnel. Results: According to the interviewed experts, medical technicians possess the qualities typical of professional conduct that match our requirements and expectations. Respondents answered / 100% / s to which is crucial in the interaction within the team, which is the result of good work and trust built mzhdu health professionals.

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Михайлова Й., Георгиева Е., **Костадинова Цв.,** Цанкова Г., Ерменлиева Н. (2014). Методи за контрол на захарния диабет. *Сборник доклади от Юбилейна конференция „Превенция и рехабилитация за подобряване качеството на живот“*. Тракийския университет. Стара Загора, 1(1), 244-246.

Abstract: Glycated hemoglobin is a more accurate indicator of the quality assessment of the treatment and compensation of diabetes. Increasing frequency of this type of diseases in the past decades in the world as well as in our country, it poses serious challenges to search fornew diagnostic methods, an effective control and treatment of disorders in the early stage to avoidrisks of hypoglycemia, weight gain and other side effects. Glucose reacts non-enzymatically with the amino terminal of the valine residue of the beta chain. Initially it occurs labile HbA1c (aldimino-flowing form), which as a result of transformation occurs slowly became stable HbA1c (keto amine form). As the concentration of labile HbA1c has fluctuations that correspond to the instantaneous concentration of glucose in the blood, while the stable HbA1c reflects the average glucose concentration over the last 40 - 90 days, and is therefore a valuable indicator of the effectiveness of treatment in diabetic patients.

34

Ерменлиева Н., Георгиева Е., Тодорова Т., **Костадинова Цв.,** Цанкова Г. (2016). Микровълнова стерипизация и стерилизация с електронен лъч – иновативни технологии в подкрепа на конвенционалните методи за управление на медицинските отпадъци, Fourth student scientific conference „*Ecology and enviroment*“,; 3:113-120. (ISSN 2367-5209)

Резюме: Инсинерацията се е наложила като най-ефективен и рентабилен метод за обезвреждане на медицински отпадъци (МО) във всички проучени страни по света. Инсталациите са мащабни и скъпо струващи, но имат много голям капацитет, висока продуктивност, обезвреждат напълно МО и намаляват обема им до 95%. Недостатък в технологията са емисиите от диоксини, фурани и други замърсители, които се отделят като отпадни газове във въздуха при процеса на горене.

Технологичният прогрес в съвременното общество предлага някои алтернативни и по-екологосъобразни методи за надеждно обезвреждане на медицински опасни отпадъци. Микровълновата стерилизация и стерилизацията с електронни лъчи са едни най-съвременните подходи, отличаващи се с високата си ефективност. Чрез тях се постига пълно обезвреждане на инфекциозни болнични отпадъци и минимална вреда за околната среда. Добре е те да се познават добре от всички експерти в областта на третирането на опасни МО и здравните работници.

35 Ерменлиева Н., Георгиева Е., Цанкова Г., Тодорова Т., **Костадинова Цв**. (2016). Инсинерация – основен метод при третиране на медицински отпадъци, Fourth student scientific conference „*Ecology and enviroment*“, 3:122-129. (ISSN 2367-5209)

Резюме: Генерираните от лечебни и здравни заведения медицински отпадъци са потенциални носители на инфекциозни елементи. Тяхното управление е комплексен въпрос, който има голямо обществено значение за здравето на населението и благосъстоянието на околната среда.

Има различни физични, химични и включващи използването на радиация методи за стерилизация на болнични отпадъци, като всеки от тях се отличава с характерни особености и приложение. В световен мащаб изгарянето (инсинерацията) на медицинските отпадъци се е наложил като подход за третирането им с най-добри показатели – пълно обезвреждане на опасните отпадъци, намаляване на теглото и обемът им, голяма производителност. Процесите на горене, обаче, са свързани и с отделянето на емисии в околната среда и в този смисъл при експлоатацията на съоръженията е необходимо да се спазват стриктни изисквания за контрол на замърсителите и горивните процеси.

IV. ПУБЛИКУВАНИ РЕЗЮМЕТА ОТ УЧАСТИЯ В НАУЧНИ ПРОЯВИ

1 Tsankova G., Todorova T., **Kostadinova Ts**., Ivanova L., Ermenlieva N. Seroprevalence of syphilis among pregnant women in Varna (Bulgaria). 5th SEEC Chemotherapy and infection, 16-19 October, 2014, Bled, Slovenia.

Abstract: Syphilis is a sexually transmitted disease, caused by the spirochaete Treponema pallidum. During the course of pregnancy it may lead to serious fetal disorders and to intrauterine death. The study comprises 2702 pregnant women. The syphilis screening was performed on blood samples by ELISA (Enzyme Linked Immunosorbent Assay), VDRL (Veneral Disease Research Laboratory) and TPHA (T. pallidum haemagglutination assay). The specific treponemal antibody was detected in 27 pregnant women by using ELISA, in 15 pregnant women by VDRL and in 16 women by TPHA. Our results showed no significant relation between the age of the patient, pregnancy trimester and the susceptibility to the disease. In contrast, the ratio positive/negative samples was three-fold higher in the group of women from rural regions compared to these of urban origin. Serological syphilis screening with different methods is necessary for better protection and prevention of possible congenital

transmission and habitual abortions. The insufficient number of physicians in rural regions and therefore the limited accessibility to health care is pertinent for higher syphilis prevalence in less urbanized regions.

2

Stoykova Z., Ivanova L., **Kostadinova Tsv**., Tsankova G. The share of cytomegalovirus (CMV) in congenital and early postnatal infections in northeastern Bulgaria, 5th SEEC Chemotherapy and infection, 16-19 October, 2014, Bled, Slovenia.

Abstract: Background: Human cytomegalovirus (CMV) is an ubiquitous large enveloped DNA β-herpesvirus that, like other members of the herpesvirus family, establishes lifelong latency following primary infection. The virus is the most frequent cause of congenital infections, which can cause permanent disabilities such as hearing loss, vision loss and mental retardation. Aims: To asses the role of CMV in congenital and early postnatal infections in Northeastern Bulgaria.

Study population: 304 children (newborns to 3 months of age) with mental or physical retardation, neurological symptoms, hepatitis or other disabilities were studied by single serum samples. They are divided in two groups: Group A – 129 newborns and Group B - 175 children 1 – 3 months of age. Methods: Commercial ELISA test kits for detection of specific anti CMV IgM and IgG (EUROIMMUN -Germany, VIRCELL – Spane, Dia Pro - Italy, Adaltis - Italy) was performed.

Results: A total of 304 children investigated, 57 (18.75 %) were anti CMV IgM positive, 207 (68.1%) were only anti CMV IgG positive. In Group A - 11 (8.5 %) were anti CMV IgM positive. In Group B - 46 (26.2 %) were anti CMV IgM positive indicating acute infection. IgG positive results only were detected in 80.6% of Group A and 58.9% in Group B.

Conclusion: CMV is etiological agent in 8.5% of the newborns disabilities and in 26.2% of the early postnatal disorders.

3

Kostadinova Tc., Todorova T., Tsankova G., Ivanova L., Raykov T., Lodozova N., Georgieva E. Pathogenesis of Epstein-Barr virus infection. 6th Southeast European Conference on Chemotherapy and Infection, 13-15 November, 2015, Thessalonki, Greece

Abstract:Epstein-Barr (EBV) is a widespread virus which can be detected in more than 90% of world population. Primary EBV infection during adolescence and adultness results in infectious mononucleosis, while in children it is usually asymptomatic. EBV is responsible for different malignant forms of B-cell or epithelial cancers, such as Hodgkin's and nonHodgkin’s lymphoma, Burkitt's lymphoma, post-transplant lymphoproliferative disorders, nasopharyngeal

carcinoma, hairy leukoplakia and HIV-associated lymphomas. Evidence exists that infection with EBV is also linked with a higher risk of hepatocellular and gastric cancers, as well as autoimmune diseases. EBV shows two alternative life cycles – latent and lytic. After the primary infection, the virus remains in B lymphocytes (latent infection) and its genome localizes in the nucleus under the form of circular episome. The lytic infection takes place predominantly in the epithelial cells and can last for months with constant virus release in saliva and nasopharyngeal secretion. Unlike other herpes viruses, development of oncological diseases is linked with the latent cycle, as a result of immune response's failure to control latently infected cells. At least 5 viral genes are involved in the process of malignization and especially in blocking tumor-supressive cell mechanisms. With the present study we aimed to review the current knowledge in mechanisms of EBV pathogenesis in humans.

4

Raykov T., **Kostadinova Ts**., Georgieva E., Tsankova G., Todorova T., Depression and depressive symptomatics in individuals with rheumatoid arthritis and ankylosing spondylitis – correlation with disease activity, 6th Southeast European Conference on Chemotherapy and Infection, 13-15 November, 2015, Thessalonki, Greece

The objective of our study is to assess the level of depression among patients with rheumatoid arthritis and ankylosing spondylitis in Bulgaria. We also try to find the degree of correlation between depression levels and the activity and duration of the disease. A cross-sectional study among 140 people living with rheumatoid arthritis and ankylosing spondylitis was conducted from May 2015 to July 2015.

The following instruments were used: Beck Depression Inventory (BDI) and Routine Assessement of Patient Index Data3 (RAPID3). The relationship between variables was assessed using chi-square test with significance level of $p < 0.05$.

Almost 66% of all studied individuals living with rheumatoid arthritis and ankylosing spondylitis experienced some level of depression. This is directly related to the activity and duration of the disease. Depression among patients with rheumatoid arthritis and ankylosing spondylitis is a major health problem. Our study shows the need for assessment of depression levels in such patients. We also recommend conducting further studies on the prevalence of depression and depressive symptoms in people living with rheumatoid arthritis and ankylosing spondylitis and screening for the presence of comorbid depression and its timely treatment.

5 Hadzhieva N., Ermenlieva N., Tsankova G., Kolev Il., **Kostadinova Ts.,** Nedelcheva G., Todorova T. Minimal inhibitory concentration (MIC) determination of new organoiodine agent. *8-ма годишна среща SEEC*. Дурес, Албания. 12-15 Октомври 2017.

Background: One of oxidizing agents with a long history of usage as antimicrobials is iodine. Iodine is a halogen releasing agent manifesting rapid bactericidal, fungicidal, virucidal and sporicidal effects caused by inhibiting DNA synthesis and attacking amino acids, nucleotides and fatty acids.

Materials and methods: Four compounds (2-Iodoresorcinol, Riodoxol, 4-Iodosalicylic acid, Diiodoeudesmic acid)have been synthesized, and their antimicrobial activities against the nine strains of gram- negative and gram-positive bacteria and yeast were assessed.

Results and conclusion: The newly synthesized agent in the studied concentration showed antibacterial activity against Gram positive S. aureus, as well Gram negative bacteria E. coli and no detectable activity against fungi.

6 **Kostadinova Ts.**, Ivanova L., Stoykova Z., Todorova T., Ermenlieva N., Tsankova G., Tsaneva D. Relevance of avidity testing of VCA IgG in EBV diagnostics. *8-ма годишна среща SEEC*. Дурес, Албания. 12-15 Октомври 2017.

Abstract:Antibody-IgM antibodies against VCA are formed shortly after the onset of infection and are the main markers for determining acute infection. However, in some patients, they may not form, disappear quickly, not be proven by the tests used, or appear after IgG. The absence of IgM, as well as the possibility of developing a mononucleosis syndrome by other viruses, makes antibodies against VCA insufficient.
We also identified 13 patients positive for anti-EBV-CA IgM and anti-EBV-CA IgG, at an age at which primary infection and diagnoses other than infectious mononucleosis may occur. In the second group, routine serology can not answer the question whether it is a primary infection or reactivation, and by using the anti-EBV-CA IgG avidity tests, we will check to see if this marker can assist in laboratory diagnosis in these cases.

Aim:Determining the significance of anti-EBV-CA IgG avidity test in EBV diagnosis in patients diagnosed with Infectious mononucleosis and suspected reactivation.

Materials: The study includes 46 single serum samples from immunocompetent patients collected between May-2016 and May 2017, divided into two groups depending on: The serological profile of the initial study for anti-EBV-CA IgM / IgG and clinical diagnosis.The first group includes 33 patients with clinical diagnosis of IM and anti-EBV-CA IgM (-) and anti-EBV-CA IgG (+) profiles. The second group includes 13 patients with a serological profile of anti-EBV-CA IgM (+) and anti-EBV-CA IgG (+) and a diagnosis other than IM.

Methods: Serological ELISA to determine the avidity of anti-EBV-CA IgG with a test kit of EUROIMMUN-GERMANY.The serums were tested simultaneously in two wells - one untreated and one 8M treated urea for 10 minutes incubation at room temperature. We calculated the relative index (RAI%) by dividing the OD of the sample treated with urea and the OD of the sample without urea, according to the manufacturer's instructions. The values <40% were interpreted with low avidity and corresponding acute infection,> 60% high avidity and we have identified as past infection and between 40% and 60% undetectable, possibly due to advanced acute infection.

7

Ivanova L., Stoykova Z., **Kostadinova Ts.,** Tsaneva D. HIV related laboratory and clinical manifestations. 10th Balkan Congress of Microbiology, Microbiologia Balkanika 2017, Sofia-16-18.11.

Abstract: *Human immunodeficiency virus* **(***HIV*) is a member of the family *Retroviridae* that attacks the immune system of the infected person. The virus destroys a type of white blood cell (T helper cells or CD4+ cells) and gradually breaks down a person's immune system. As many as 37 million people worldwide are thought to be infected. In our retrospective study, we review the clinical evidences as a reason for association with *HIV* infection and the most common co-infections in patients living with *HIV*. Since 2003 we have tested 148 *HIV* infected patients (104 males and 44 females), aged between 3 months and 67 years, average age 37.3 years. Out of the patients investigated, 108 were with proven HIV-positive status (persons living with HIV), hospitalized in "St Marina" University Hospital, Clinic of Infectious, Parasitic and Dermatovenerologic Diseases and 40 patients were found with reactive results at our Virology Laboratory and confirmed as *HIV* infected at the National *HIV* Reference Laboratory in Sofia. ELISA *HIV* Ag&Ab (DiaPro Italy), *HbsAg* (SURASE Taiwan), *Anti Hbc* (DiaPro Italy), *Anti HCV* (NANBASE Taiwan), Anti *CMV* IgM/IgG (EUROIMMUN Germany), Syphilis Ab screening (EUROIMMIN – Germany) were performed according to the manufacturer's recommendations. Out of the 40 investigated patients with diagnostic and therapeutic problems, 13 (32.5%) were with clinical diagnosis pneumonia, 6 (15%) with lymphadenoipathy, 5 (12.5%) with hepatitis, 3 (7.5%) with mononucleosis-like syndrome, 4 (10%) with wasting syndrome and chronic diarrhea, 4 (10%) with neurological sympthoms, 3 (7.5%) with dermatological manifestation including Herpes zoster, and 2 (5%) were mothers of infected children. Out of the 108 pre-defined *HIV* infected patients, we received serological data for hepatitis B in 12 (11%), hepatitis B/C co-infection in 2 (1.9%), hepatitis C in 6 (5.6%), syphilis in 24 (22.2%), CMV active infection in 21 (19.4%). The most common reason for HIV testing is the diagnosis bilateral pneumonia, unsusceptible to conventional antibacterial treatment. People living with *HIV* most often were co-infected with syphilis.