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9. HRVATSKI KONGRES O INFEKTIVNIM BOLESTIMA
s međunarodnim sudjelovanjem**

**12th CROATIAN CONGRESS OF CLINICAL MICROBIOLOGY
9th CROATIAN CONGRESS ON INFECTIOUS DISEASES
with international participation**



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ABSTRACT BOOK**

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SADRŽAJ / CONTENTS	Str. br. / Page no.
Plenarna predavanja / Plenary lectures PL-1 – PL-8	
Predavanja / Lectures O-1 – O-89	
Mikrobiota i gastrointestinalne infekcije <i>Microbiota and gastrointestinal infections</i>	
Zoonoze <i>Zoonoses</i>	
Multiplorezistentne bakterije <i>Multidrug resistant bacteria</i>	
HIV <i>HIV</i>	
Novosti u laboratorijskoj dijagnostici <i>Advances in laboratory diagnostics</i>	
Neriješena pitanja u virusnom hepatitisu – hepatocelularni karcinom <i>Unresolved issues in chronic hepatitis-hepatocellular carcinoma</i>	
Racionalizacija uporabe antibiotika <i>Rational antibiotic prescribing</i>	
Virusni hepatitis – na putu eliminacije <i>Viral hepatitis: on the way towards the elimination</i>	
Novosti u intenzivnom liječenju teških infektivnih bolesti <i>News in the treatment of severe infectious diseases</i>	
Infekcije povezane sa zdravstvenom zaštitom <i>Healthcare associated infections</i>	
Deset godina izvantjelesne oksigenacije u Klinici za infektivne bolesti <i>Ten years of ECMO in UHID</i>	
Urogenitalne infekcije <i>Urogenital infections</i>	
Pristup „Jedno zdravlje“ u kontroli širenja rezistencije <i>"ONE HEALTH" approach in antimicrobial resistance control</i>	
Pedijatrijske infektivne bolesti <i>Pediatric infectious diseases</i>	
Infekcije lokomotornog sustava <i>Infections of the musculoskeletal system</i>	
Respiratorne infekcije <i>Respiratory tract infections</i>	
Infekcije i upale središnjeg živčanog sustava <i>CNS infections</i>	
Putnička medicina i parazitarne bolesti <i>Travel medicine and parasitic diseases</i>	
Poster / Posters PO-1 – PO-94	
Kratice /Abbreviations: PL – plenarno predavanje / plenary lecture O – usmena predavanja / oral lecture PO – poster / poster presentation	

PLENARNA PREDAVANJA
PLENARY LECTURES

PL-1 Ongoing revolution in clinical microbiology: current status and future perspectives

Mario Poljak

Laboratory for Molecular Microbiology and Diagnostics of Hepatitis and HIV/AIDS, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

PL-2 Most important interventions in infection control – difference between endemic and outbreak situation

Alexander Friedrich

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Medical Centre Groningen, Netherlands

PL-3 Challenges in the treatment of MDR infections

Jesus Rodriguez Bano

President-Elect, European Society of Clinical Microbiology and Infectious Diseases (ESCMID)

PL-4 Antibiotic heteroresistance in *Acinetobacter baumannii*

Spyridon Pournaras

Laboratory of Clinical Microbiology ATTIKON University Hospital; Medical School, University of Athens, Greece

PL-5 Combination therapy: myths and facts

Inge Gyssens

Radboud Institute for Molecular Life Sciences, Nijmegen, Netherlands

**PL-6 Infections of the locomotor system – a modern concept in
diagnosis and treatment**

Andrej Trampuž

Infectious Diseases Research Laboratory, Charité – University Medicine in
Berlin, Berlin, Germany

PL-7 Antimicrobial stewardship approach to the treatment of community-acquired respiratory tract infections

Bojana Beović

University Medical Centre Ljubljana; Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

PL-8 Zamke i dobrobiti serološke dijagnostike lajmske borelioze iz laboratorijske perspektive

Eva Ružič-Sabljić

Zavod za mikrobiologiju i imunologiju, Medicinski fakultet, Sveučilišta u Ljubljani, Ljubljana, Slovenija

Pitfalls and benefits of serological diagnosis of Lyme borreliosis from a laboratory perspective

Eva Ružič-Sabljić

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Lyme borreliosis, dominantly presenting as erythema migrans, is the most reported vector-borne disease in Europe and North America. Different *Borrelia* species are described as its' etiological agent. In Europe, *B. afzelii*, *B. garinii*, *B. bavariensis*, *B. burgdorferi* sensu stricto, and *B. spielmanii* were isolated from human material while in North America Lyme borreliosis is exclusively related to *B. burgdorferi* sensu stricto. Borreliae are maintained in natural transmission cycles between vector ticks of the genus *Ixodes* and numerous vertebrate reservoir hosts (rodents, insectivores, birds); humans are infected incidentally.

Erythema migrans is sufficient for clinical diagnosis of borrelial infection. Many other clinical manifestations may suggest with more or less reliability borrelial infection. Herein we consider atypical skin manifestations, meningitis, meningoencephalitis, cranial nerve paresis, arthritis, chronic skin disorders, and many other signs and symptoms that appear (or not) after the tick bite; these clinical manifestations have to be confirmed by microbiological tests. Because of high exposure of inhabitants to infected ticks in endemic region, humans may undergo more than one borrelia infection in their lives.

Microbiological diagnosis is based on direct and indirect test as well as their combination. Direct microbiological tests such as culture and PCR are not widely used in laboratory diagnosis because of its low sensitivity; culture itself is requested method and implemented in specially equipped laboratories. Routinely, borrelial infection is confirming by serologic tests that are available for many laboratories. Serologic tests detect presence of antibody response that indirectly demonstrate exposure of individual to the pathogen (e.g. borrelial antigens). Factors affecting serological tests include timing of specimen collection regarding to the disease state, start of antimicrobial therapy, kinetics and maturation of antibody expansion to particular borrelial antigen as well as selection of immune-dominant proteins (antigens) in serologic test. Some pitfalls that were recorded considering borrelial infection can be listed: 1.) Slow developing immune response (up to 4 weeks for IgM, over more for IgG); 2.) Absence of immune response 3.) Antimicrobial therapy in the beginning of infection can inhibit further immune response 4.) Persistence of

specific antibodies for years (also lifelong) after getting over borrelial infection; 5.) Presence of specific antibodies for years without clinical manifestation (serological background in endemic region) suggesting more frequently undergoing infection as officially registered cases. So, results of serological tests must be considered in the context of the individual patient's illness.

In the absence of localized distinctive erythema migrans, nonspecific symptoms and signs like headache, myalgia, arthralgia, malaise, fatigue, cognitive decline, mental and psychiatric disorders, progressive skin disorders, and many other could be difficult to diagnose as borrelial infection. In these patients positive as well as negative serological background lead to misdiagnosis of borrelial infection, patients' belief of undergoing chronic Lyme borreliosis call for prolonged antimicrobial therapy, alternative laboratory methods try to confirm borrelial infection in any case, patients become vulnerable and desperate, physicians can't breakthrough magic circle. Accurate microbiological diagnosis of borrelial infection is crucial to ensure antimicrobial therapy for truly infected patients as well as not mistakenly told to patients with nonspecific symptoms that they have not borrelial infection.

MIKROBIOTA I GASTROINTESTINALNE INFEKCIJE
MICROBIOTA AND GASTROINTESTINAL INFECTIONS

O-1 Ljudska mikrobiota i upalne bolesti crijeva

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Izrazi mikrobiota i mikrobiom često se upotrebljavaju s istim značenjem. Dok mikrobiota podrazumijeva skup svih mikroorganizama u zajednici, mikrobiom predstavlja ukupnu mikrobnu zajednicu te pripadajuće gene (metagenom) i biomolekule koje proizvode (metabolom). Ljudsko tijelo sadrži 10^{14} bakterija što 10 puta premašuje broj ljudskih stanica. To je ujedno 250 puta više mikrobnih gena od gena ljudskog genoma. Prije uvođenja tehnika molekularne biologije, fokus istraživanja je bio na razumijevanju patogeneze infekcija uzrokovanih patogenim bakterijama koje se mogu kultivirati. S boljim razumijevanjem složenih interakcija mikrobiote i domaćina postalo je očito da je bolest češće rezultat neravnoteže mikrobiote negoli unosa određenog infektivnog uzročnika. Ljudska mikrobiota sadrži više od 1000 bakterijskih vrsta od kojih se mnoge mogu detektirati samo molekularnim tehnikama, a za opisivanje srodnih bakterija otkrivenih tim tehnikama koristi se operativna taksonomska jedinica (OTU). Jednom uspostavljena u ranim godinama života, crijevna mikrobiota je stabilna tijekom života, ali okolišni čimbenici poput načina života, prehrane, dobi, izloženosti antibioticima mogu pomaknuti bakterijsku populaciju izvan zone „zdravog mikrobioma“. Općenito, koljena *Firmicutes* i *Bacteroidetes* dominiraju u crijevnoj mikrobioti zdravih ljudi dok je udio proteobakterija povećan u bolesti. Zbog velikog broja redundantnih bakterijskih vrsta, zdravi mikrobiom je otporan na utjecaje iz okoliša, no kod bolesti je uočena smanjena mikrobna biološka raznolikost. U okviru projekta Hrvatske zaklade za znanost (IP-2014-09-3788) postavili smo metodu polimorfizma duljina terminalnih fragmenata restrikcije (T-RFLP) kojom uspoređujemo fekanu mikrobiotu u djece s upalnom bolesti crijeva (IBD), njihove zdrave braće i zdravih kontrola. Bolje razumijevanje uloge mikrobiote u razvoju IBD-a poboljšat će terapijske mogućnosti manipulacije mikrobiomom poput uporabe probiotika, prebiotika ili transplantacije fekalne mikrobiote.

Human microbiota and inflammatory bowel disease

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Terms microbiota and microbiome are often used interchangeably. While microbiota imply the total collection of microorganisms within a community, microbiome stands for the total microbial community, related genes (metagenome) and biomolecules (metabolome). A human body contains 10^{14} bacteria which 10-fold exceeds the number of human cells. This is also 250-fold more genes than that found in the human genome. Before the introduction of molecular biology techniques research was focused on understanding pathogenesis of infections caused by recognized pathogens that could be cultured. With our deeper understanding of complex interactions of microbiota and the host it became obvious that a disease is more often a disbalance of microbiota than the appearance of a specific infectious agent. Human microbiota contains more than 1000 bacterial species many of which can be detected by molecular techniques only and operational taxonomic unit (OTU) is used to describe closely related taxa detected by these techniques. Once established in the early years of life the intestinal microbiota is stable throughout life but environmental factors like lifestyle, diet, age, exposure to antibiotics can shift bacterial populations out of the “healthy microbiome” zone. Overall, the phyla *Firmicutes* and *Bacteroidetes* dominate in the healthy gut microbiota while Proteobacteria are increased in a disease. Due to redundant bacterial taxa the healthy microbiome is resilient to environmental perturbations but in a disease reduced microbial biodiversity is common. Within the Croatian Science Foundation project (IP-2014-09-3788) we have set up a Terminal restriction fragment length polymorphism (T-RFLP) method to compare faecal microbiota in children with inflammatory bowel disease (IBD), their healthy siblings and healthy controls. Better understanding of the role of microbiota in the development of IBD will improve microbe-based therapy approaches, such as the use of probiotics, prebiotics or faecal microbiota transplantation.

O-2 Mikrobiota, crijevni patogeni i antibiotici

Marija Tonkić

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Crijevna mikrobiota čovjeka predstavlja složen ekosustav sastavljen mahom od bakterija ali i drugih mikroorganizama koji ima veliki utjecaj na fiziološke i patološke procese u domaćinu. Mikrobiota u probavnom sustavu ima brojne funkcije a jedna od njih je ometanje naseljavanja patogenih mikroorganizama direktnom kompeticijom za receptore i hranjive tvari ali i oslobađanjem toksičnih molekula te indirektno stimulacijom imunološkog odgovora domaćina. Štoviše, pojam „mikrobna endokrinologija“ označava sposobnost mikrobiote gastrointestinalnog sustava da komunicira dvosmjerno sa središnjim živčanim sustavom domaćina lučenjem određenih neurokemijskih spojeva.

Primjena antibiotika utječe na sastav crijevene flore, uzrokujući tzv. disbiozu, što omogućava kolonizaciju patogenih mikroorganizama. Stoga je nuspojava primjene antibiotika povećana osjetljivost na čitav niz bakterijskih infekcija. Ponovno uspostavljanje normalne ravnoteže u sastavu crijevene flore smanjuje mogućnost intestinalne kolonizacije bakterijama kao što je vankomicin rezistentni enterokok ili rezistentne enterobakterije. Smatra se da su obligatni anaerobi bakterije crijevene mikrobiote koje najviše doprinose otpornosti na kolonizaciju patogenim bakterijama.

Složene interakcije crijevene mikrobiote i domaćina te poremećaji u sastavu crijevene mikrobiote imaju značaj i u nastanku raznih drugih bolesti kao što su alergijske i autoimune bolesti, maligne bolesti i oportunističke infekcije. Sve te spoznaje predstavljaju temelj za razvoj terapije temeljene upravo na korištenju mikrobiote u uspostavljanju homeostaze između mikrobiote i zdravstvenog stanja domaćina. Jedna od mjera koja svakako doprinosi toj homeostazi je i smanjeno korištenje antibiotika.

Microbiota, gastrointestinal pathogens and antibiotics

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The human gut microbiota is a complex ecosystem composed mainly of bacteria and other microorganisms, which has a great influence on the physiological and pathological processes in the host. The gut microbiota has many functions, one of which is to interfere with the pathogenic microbial population by directly competing for receptors and nutrients but also by releasing toxic molecules and, indirectly, by stimulating the host immune response. Moreover, the term "microbial endocrinology" denotes the ability of the gastrointestinal microbiota to communicate bidirectionally with the host central nervous system by secreting certain neurochemical compounds.

The use of antibiotics affects the composition of the intestinal flora, causing the so-called dysbiosis, which allows colonization of pathogenic microorganisms. Therefore, the side effect of antibiotic administration is increased susceptibility to a range of bacterial infections. Restoring normal balance in the composition of the intestinal flora reduces the possibility of intestinal colonization by bacteria such as vancomycin-resistant enterococci or resistant enterobacteria. Anaerobes are thought to be obligatory bacteria of the gut microbiota, which most contribute to resistance to colonization by pathogenic bacteria.

Complex gut microbiota-host interactions and disorders in the gut microbiota composition are also significant in the emergence of various other diseases such as allergic and autoimmune diseases, malignancies and opportunistic infections. All these insights form the basis for the development of therapy based precisely on the use of the microbiota in establishing homeostasis between the microbiota and the host's health. One of the measures that certainly contributes to this homeostasis is the reduced use of antibiotics.

O-3 Novosti u dijagnostici *Clostridioides (Clostridium) difficile* infekcija

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Clostridioides difficile infekcije (CDI) su među najčešćim bolničkim infekcijama u visoko razvijenim zemljama. Najveći izazov u dijagnostici je odabir brzog i točnog testa, visoke osjetljivosti i specifičnosti

Clostridioides difficile je oportunistički patogen te je važno razlikovati kolonizaciju od infekcije. Stoga je osnovni kriterij u dijagnostici, odabir prikladnog uzorka, tj. testiranje isključivo proljevaste stolice simptomatskih pacijenata.

Danas su dostupni brojni testovi koji koriste različite metode (imunoenzimski, imunokromatografski i molekularni testovi) i ispituju postojanje različitih dijelova bakterijske stanice ili njene produkte u uzorku stolice. Neki od testova dokazuju prisustvo specifičnog bakterijskog antigena GDH (glutamat-dehidrogenazu), a neki produkciju toksina A i/ili B ili postojanje toksigene regije u genomu bakterije.

Europsko društvo kliničkih mikrobiologa i infektologa (ESCMID) je 2009. godine objavilo prve smjernice za dijagnostiku CDI i predložilo uvođenje tzv. dvostupanjskog postupnika.

U prvom koraku se koristi probirni test visoke NPV (negativne prediktivne vrijednosti) kao što je brzi, relativno jeftini i osjetljivi imuno-enzimski test (EIA) za GDH antigen. Potom se GDH pozitivni uzorci stolice testiraju potvrdnim EIA ili molekularnim testom (engl. nucleic acid amplification test, NAAT) za dokaz slobodnih toksina A i/ili B odnosno toksigene kromosomske regije. Ponekad se rade oba testa (dokaz toksigene regije i aktivne produkcije toksina) pa govorimo o trostupanjskom algoritmu.

Nakon dijagnosticiranja CDI i uspješno provedenog liječenja (nestanak simptoma CDI), ne radi se kontrolni test (tzv. test izlječenja) jer pacijenti mogu ostati kolonizirani mjesecima.

Od uvođenja dvostupanjskog postupnika, dijagnostika CDI je poprilično standardiziran, ali različiti laboratoriji koriste testove različite osjetljivosti i specifičnosti pa je rezultate ponekad teško usporediti. Stoga su smjernice ažurirane 2016. i 2018. g., a ESCMID-ov dvo/trostupanjski postupnik, potvrđen je kao optimalni odabir u CDI dijagnostici. Prisustvo slobodnih toksina u stolici pacijenata bolje korelira sa simptomatskom CDI i lošim ishodom, dok molekularni testovi mogu otkriti i asimptomatske nositelje koji nemaju simptoma i ne zahtijevaju nikakvu intervenciju ni liječenje.

Advances in *Clostridioides (Clostridium) difficile* diagnostics

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Clostridioides difficile infections (CDI) are among the most common hospital-acquired infections in highly developed countries. The most important challenge in diagnostic is choosing the accurate test with high sensitivity and specificity. *Clostridioides difficile* is an opportunistic pathogen and it's important to distinguish colonization from infection. Therefore, only diarrheal stool from symptomatic patients should be tested.

Many different testing methods are available today (immunoenzymatic, immunochromatographic and molecular). Some tests detect specific bacterial antigen GDH (glutamate dehydrogenase), production of toxins A/B or the existence of a toxigenic region in the bacterial genome.

In 2009, the European Society of Clinical Microbiologists and Infectious Disease (ESCMID) published the first guidelines for the diagnosis of CDI and proposed the introduction of a two-step algorithm.

In the first step, screening test with high NPV (negative predictive value) is used, such as rapid immuno-enzyme assay (EIA) for GDH antigen. GDH positive specimens are then tested with a confirmatory EIA or nucleic acid amplification test (NAAT) for evidence of free toxins A/B or toxigenic chromosomal region. Sometimes both tests (evidence of toxigenic region and active toxin production) are used.

Control testing (test of cure) is not recommended as patients may be colonized for months.

Since the introduction of two-step algorithm, CDI diagnostic has been fairly standardized, but different laboratories use different tests, so it's sometimes difficult to compare results. Therefore, the guidelines were updated in 2016 and 2018, and ESCMID's two / three-step algorithm was confirmed as optimal choice in CDI diagnostics. The presence of free toxins in the stool of patients better correlates with symptomatic CDI and poor outcome, while molecular tests can detect asymptomatic carriers that have no symptoms and do not require any intervention or treatment.

O-4 Liječenje *Clostridioides difficile* infekcije; smjernice i novosti

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Temeljeno na nizu studija koje ukazuju na kliničku inferiornost liječenja peroralnim metronidazolom u odnosu na vankomicin, nove američke preporuke liječenja *Clostridioides difficile* infekcije (CDI) od strane IDSA/SHEA iz 2018. izbacuju peroralni metronidazol iz preporuka, dok je on prisutan u europskim ESCMID-ovim smjernicama iz 2014., za liječenje blagih/srednje teških prvih epizoda CDI. No, što se često zanemaruje, u potonjim se smjernicama daje prednost peroralnom vankomicinu u svih osoba s povećanim rizikom rekurencije CDI, što znatno suzuje indikacije za liječenje peroralnim metronidazolom. Dakle pri odlučivanju o liječenju potrebno je procijeniti težinu CDI (blaga/srednje teška, teška, fulminantna), utvrditi broj epizode bolesti i procijeniti rizik rekurencije.

Ne uzimajući u obzir kriterij rizika rekurencije, retrospektivna studija na populaciji 1073 bolesnika s laboratorijski potvrđenom CDI u Klinici za infektivne bolesti „Dr. Fran Mihaljević“ od 2013.-2017. je utvrdila stopu inicijalnog pridržavanja ESCMID-ovim preporukama liječenja CDI od 61%, a u subpopulaciji fulminantnih CDI svega 20.5%, što ukazuje na nepoštivanje kriterija težine bolesti. Ukupno je 29.8% bolesnika bilo subterapirano.

Zbog učinkovitosti u liječenju rekurentnih (izlječenje cca 90%) i fulminantnih CDI mnogi europski centri primjenjuju transplantaciju fekalne mikrobiote, čija je procedura regulirana preporukama Europskog konzensusa (Rim, 2017.), a objavljuju se i početna iskustva transfera sterilnih fekalnih filtrata. Studije ukazuju na podjednaku kliničku učinkovitost liječenja peroralnim vankomicinom u odnosu na fidaksomicin, no potonje rezultira značajno manjom rekurencijom. Signifikantno smanjenje stope rekurencije se postiže i jednokratnom primjenom monoklonalnih anti- toksin B protutijela (bezlotuxumab). U ispitivanju su inaktivirana, rekombinirana i komponentna cjepiva za aktivnu imunizaciju, čitav niz antiklostridijskih lijekova uskog spektra (cadazolid, ridinilazole, ACX-362E itd), nova beta-laktamaza (ribaxsamase) za profilaktičku peroralnu primjenu uz beta-laktamski antibiotik, koja bi spriječavala narušavanje crijevne flore, pripravak za jednokratnu oralni primjenu s ciljem obnove crijevne flore (CP101), itd.

Napredak u kirurškom liječenju fulminantnih CDI predstavlja tehnika „loop ileostomije“ uz lavaže kolona otopinom vankomicina, čime se može izbjeći kolektomija.

Treatment of infections caused by *Clostridioides difficile*; guidelines and news

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Based on numerous studies that have shown clinical inferiority of oral metronidazole in comparison to oral vancomycin, the new American guidelines for the treatment of infections caused by *Clostridioides difficile* (CDI), released by the IDSA/SHEA in 2018, omit oral metronidazole from the first-line treatment recommendations. Oral metronidazole is recommended by ESCMID European guidelines from 2014, for the treatment of the first episode of mild/moderate CDI, along with recommendation that in patients with high risk for disease recurrence the treatment with oral vancomycin should be preferred. Therefore, when deciding about the initial CDI treatment, the assessment of disease severity (mild/moderate, severe, fulminant), number of episode and recurrence risk is necessary.

Omitting the recurrence risk criteria assessment, a retrospective study of 1073 patients with laboratory confirmed CDI performed at the University Hospital for Infectious Diseases „Dr. Fran Mihaljević“ from 2013-2017 found that the ESCMID treatment guidelines adherence rate of the initial CDI therapy was 61%, and in a subpopulation of fulminant CDI cases it was only 20.5%, suggesting a substantial disregard of disease severity criteria. In total, 29.8% of patients were undertreated. Due to the high efficiency of treatment of recurrent (approx. 90%) and fulminant CDI, many European centers use fecal microbiota transplantation, a procedure regulated by the European consensus recommendations (Rome, 2017), and initial experiences with sterile fecal filtrate transplantations have been released. Studies have shown equal clinical efficiency of oral vancomycin in comparison to fidaxomicin, but the latter therapy has been related to a significantly lower recurrence rate. A decrease in the recurrence rate can be also achieved by one dose of monoclonal anti-toxin B antibodies (bezlotoxumab).

Under research are: inactivated recombinant and component immunisations, many narrow spectrum anti-clostridial drugs (cadazolid, ridinilazole, ACX-362E etc.), new beta-lactamase (ribaxamase) for prophylactic use along with beta-lactam antibiotics, which would preserve normal fecal microbiota, one-dose oral preparation for restoration of normal fecal microbiota (CP101), etc.

A progress in the surgical treatment of fulminant CDI presents the „loop ileostomy“ technique, with lavage of the colon with vancomycin solutions, whereby colectomy can be avoided.

O-5 Kampilobakterioze u Splitsko – dalmatinskoj županiji: epidemiološke, mikrobiološke – molekularne značajke i antimikrobna otpornost izolata

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Cilj istraživanja je bio sustavnim praćenjem podataka o svim laboratorijski potvrđenim infekcijama kampilobakterima među ambulantnim i hospitaliziranim bolesnicima u Splitsko dalmatinskoj županiji (SDŽ) od 2007. do 2012. godine procijeniti incidenciju kampilobakterioze u SDŽ i ispitati povezanost incidencije s demografskim, prostornim, klimatskim, poljoprivrednim i mikrobiološkim čimbenicima. Ispitani su i otpornost na antibiotike gradijent strip testom te genetska struktura *C. jejuni* metodom gel elektroforeze u električnom polju (PFGE). Ukupna prosječna stopa incidencije razdoblja je bila 96/100 000 stanovnika; najniža je bila u ruralnim, a najviša u urbanim područjima županije te u dobnoj skupini 0-4 godine i među muškarcima. Najveći mjesečni broj infekcija kampilobakterima je zabilježen u lipnju. Bio je umjereno povezan s višim prosječnim mjesečnim temperaturama i nižom relativnom vlažnosti zraka, a nije bio povezan s prosječnom mjesečnom količinom oborina.

Ispitivanje osjetljivosti i genotipizacija *C. jejuni* provedeni su od 1.5.2012. do 31.5.2013. testiranjem 77 uzastopnih izolata *C. jejuni* hospitaliziranih bolesnika i 77 izolata ambulantnih bolesnika, izoliranih istoga datuma kada i izolati hospitaliziranih bolesnika. Na ciprofloksacin je bilo otporno 60% izolata *C. jejuni*, a na tetraciklin 24%, od kojih je 89% bilo i korezistentno na ciprofloksacin (TcR/CipR). Otpornost *C. jejuni* na gentamicin i eritromicin je bila vrlo niska (< 0,7%). Između 2010. i 2012/13. godine zabilježen je značajan porast rezistencije na ciprofloksacin i TcR/CipR korezistencije. Porast udjela TcR/CipR korezistentnih izolata *C. jejuni* je bio povezan s naglim pojavljivanjem epidemiološki povezanih klonalnih grupa TcR/CipR izolata uz ravnomjernu dobnu raspodjelu tih izolata među bolesnicima svih dobnih skupina, što sugerira da je riječ o emergentnim sojevima na ovom području. Otpornost izolata nije bila povezana sa spolom niti s hospitalizacijom bolesnika.

Rezultati istraživanja ukazuju na nove i specifične značajke kampilobakterioze što je osnova za planiranje preventivnih mjera i optimalan izbor empirijske terapije.

Campylobacterioses in Split Dalmatian County: epidemiological, microbiological – molecular characteristics and antibiotic susceptibility

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The incidence of campylobacteriosis and number of antibiotic-resistant *Campylobacter* strains has been increasing worldwide in the last decade, contributing to the increasing public health burden of *Campylobacter* infections.

Data from population-based laboratory surveillance were used to examine the epidemiological pattern of campylobacteriosis in a sentinel site, Split-Dalmatia County (SDC), from 2007 to 2012, and to evaluate the association between disease incidence and demographic, geographical, climatic, agricultural, and microbiological factors. Antibiotic susceptibility testing and pulsed-field gel electrophoresis (PFGE) genotyping of isolates were performed.

Overall mean incidence was 96/100 000, ranging from 61/100 000 in rural to 131/100 000 in urban areas; rates were highest in the age group 0-4 years. The number of infections peaked in early summer and was correlated with higher average monthly temperature and lower humidity, but not with precipitation.

From May 2012 to May 2013, 153 consecutive *C. jejuni* isolates were collected from stool samples of all patients hospitalized with gastroenteritis (n = 76) and matched positive outpatients (by the date of laboratory submission) (n = 77). *C. jejuni* isolates were genetically highly diverse and exhibited a weak clonal structure. Approximately 60% of *C. jejuni* isolates were resistant to ciprofloxacin, whereas 24% of isolates were resistant to tetracycline; of the latter, 89% were also coresistant to ciprofloxacin. Resistance to erythromycin and gentamicin was infrequent (< 0.7%). However, the prevalence of coresistant strains increased sharply after 2010, and these coresistant strains were more prevalent in infections caused by clonal PFGE types, with distinct patterns of temporal occurrence and age distribution in infected patients, suggestive of newly identified strains. Antibiotic-resistant strains were generally not associated with the need for hospitalization; however, effective treatment options for *Campylobacter* infections may be limited. These data signal recent and new campylobacteriosis patterns, which may help formulate further preventive measures.

O-6 Epidemiologija *Helicobacter pylori* infekcije u Hrvatskoj

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CILJ: Cilj projekta bio je ustanoviti seroprevalenciju *H. pylori* infekcije na izabranim područjima Hrvatske. Prisutnost specifičnih *H. pylori* protutijela određivala se u osoba bez znakova peptične ili druge kronične bolesti.

METODA: Uzorci su prikupljeni od bolesnika koji su bili hospitalizirani na traumatološkom odjelu u pet hrvatskih bolnica iz četiri regije (Zagreb, Split, Osijek, Rijeka) u razdoblju od 2016. do 2018. godine. Svi ispitanici potpisali su informirani pristanak i ispunili upitnik s podacima o starosti, socioekonomskom statusu, gastrointestinalnim simptomima, navikama (pušenje) i obiteljskoj anamnezi. Uzorci seruma testirani su komercijalnim ELISA testom prema uputama proizvođača.

REZULTATI: Testirano je 306 seruma bolesnika; od toga 142 muškaraca i 164 žene, starosne dobi od 20-89 godina (srednje dobi 49.9). U 141 (46%) ispitanika utvrđena su specifična protutijela na *H. pylori*, od kojih su 73 muškarca (51,8%) i 68 žena (48,2%). Seroprevalencija po starosnoj dobi bila je slijedeća; 5,7% u dobi 20-29 godina, 7,9% u dobi 30-39, 18,4% u dobi 40-49, 24,1% u dobi 50-59, 24,9% u dobi od 60-69, i 12,0% u dobi od 70-79 i 7% u starosnoj dobi od 80-89 godina. Većina seropozitivnih osoba je bila u braku (62,4%), imali su završenu srednju školu (59,5%) i živjeli su u kući (64,5%). Roditelji su im bili srednjeg imovinskog statusa (66%) i obrazovanja (68,7%). Većina seropozitivnih ispitanika, njih 85 (60,2%) imalo je gastrointestinalne simptome (mučnina, povraćanje, žgaravica, bol u epigastriju).

ZAKLJUČAK: Seroprevalencija *H. pylori* infekcije na izabranim područjima Hrvatske je 46%. Stopa infekcije postupno raste s godinama starosti, nižom stopom obrazovanja (kako ispitanika, tako i njihovih roditelja), nižim socioekonomskim statusom roditelja, životom u kući u odnosu na stan, te dijeljenjem zajedničke kupaonice u djetinjstvu s više od 2 osobe.

Epidemiology of *Helicobacter pylori* infection in Croatia

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AIM: The aim of the study was to determine the seroprevalence of *H. pylori* infection in selected geographical areas of Croatia. The presence of specific *H. pylori* antibodies was determined in persons without symptoms of peptic or other chronic diseases.

MATERIAL AND METHODS: Specimens were collected from patients hospitalized in the traumatology ward of the five Croatian hospitals in four hospitals (Zagreb, Split, Osijek, Rijeka) during 2016 to 2018. All examinees signed informed consent and filled the form containing data on the age, socioeconomic status, gastrointestinal symptoms, habits (smoking) and family anamnesis. Serum samples were tested by commercial ELISA test according to the manufacturer's instructions.

RESULTS: In total 306 sera were tested: 142 from male patients and 164 from females, age ranging from 20 to 89 (average 49,9). In 141 (46%) examinees specific antibodies to *Helicobacter pylori* were found of which 73 were males (52%) and 68 females (48%). Seroprevalence according to the age was as follows: 5,7% in the age range of 20-29 years, 7,9% aging 30-39, 18,4% in the age range of 40-49, 24,1% in the age of 50-59, 24,9% in the age 60-69, 12,0% in the age of 70-79 and 7% in the age range of 80-89 years. The majority of seropositive were married (62,4%), had secondary school education (68,7%) and lived in the house (64,5%). The parents had middle property status (66%) and education (68,7%). The majority of seropositive persons, in total 85 (60,2%) had gastrointestinal symptoms (nausea, vomiting, heartburn and epigastric pain).

CONCLUSIONS: Seroprevalence of infection in selected areas of Croatia was 46%. The rate of infection increases with the age, lower education level (examinees and parents), lower socioeconomic status of parents, living in the house compared to the flat and sharing of the bathroom in the childhood with more than 2 persons.

**ZOONOZE
ZOOZOSES**

O-7 Molekularna epidemiologija West Nile infekcija na području Hrvatske

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West Nile virus (WNV) pripada porodici Flaviviridae, rodu Flavivirus. Ptice su prirodni rezervoar za WNV, vektori su komarci, dok ljude i ostale kralježnjake smatramo slučajnim domaćinima. Infekcije ljudi ovim virusom variraju u prezentaciji od asimptomatske infekcije do teške neuroinvazivne bolesti. U Hrvatskoj su WNV infekcije dokazane u konja, ptica i ljudi serološkim i molekularnim metodama. Trenutno je predloženo devet genskih loza za razvrstavanje sojeva WNV s tim da su loze 1 i 2 odgovorne za velike epidemije u životinja i ljudi. Cilj ovog rada je prikazati molekularnu epidemiologiju WNV infekcija u Hrvatskoj u sezonama prijenosa 2017. i 2018. godine. Virusna RNA je sekvencirana Sanger metodom u četiri humana uzorka iz 2017. godine te osam humanih i jednog uzorka iz uginulog jastreba (*Accipiter gentilis*) iz 2018. godine. Analizom dobivenih nukleotidnih odsječaka gena NS5 utvrđeno je da svi sojevi pripadaju genskoj lozi 2 i pokazuju veliku sličnost sa sojevima dokazanim u različitim domaćinima u drugim europskim zemljama. Uočena su grupiranja nukleotidnih sekvenci iz naše zemlje bez obzira na sezonu prijenosa, mjesto detekcije i domaćina. Ovo upućuje na vjerojatno višestruki unos ovog virusa u Hrvatsku, intenzivnu cirkulaciju, ali isto tako i lokalno prezimljavanje virusa. Za virusnu RNA iz uginulog jastreba sekvenciran je cijeli genom Sanger metodom u 12 djelomično preklapajućih segmenata. Cijeli genom pokazuje najveću sličnost (99,8%) sa sojevima dokazanim u pticama iz Njemačke iz iste godine. Unatoč velikoj sličnosti, u uzorku iz Hrvatske nađena je delecija od 8 nukleotida u 3' nekodirajućoj regiji genoma koja nije nađena niti u jednoj od dostupnih sekvenci WNV. Potrebna su daljnja istraživanja na molekularnoj razini WNV dokazanih u Hrvatskoj kako bi se dobio bolji uvid u molekularnu epidemiologiju WNV infekcija i njenu lokalnu specifičnost.

Molecular epidemiology of West Nile virus infections in Croatia

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West Nile virus (WNV) belongs to the family Flaviviridae, genus Flavivirus. Birds are natural reservoir for WNV, mosquitoes are vectors, while humans and other vertebrates are considered as accidental hosts. Infections caused by WNV in humans vary in the presentation, from asymptomatic infections to a severe neuroinvasive disease. In Croatia, WNV infections are detected in horses, birds and humans using serological and molecular methods. Currently, there are nine genetic lineages proposed for classification of WNV and the lineages 1 and 2 are responsible for extensive epidemics in animals and humans. The aim of this study was to present the molecular epidemiology of WNV infections in Croatia in the transmission seasons 2017 and 2018. Viral RNA was sequenced using Sanger method in four human samples in 2017 as well as eight human and one sample from a dead goshawk (*Accipiter gentilis*) in 2018. Analysis of the NS5 gene segment has shown that all the strains belong to the lineage 2 and show high similarity with strains detected in different hosts in other European countries. Grouping of nucleotide sequences from our country into different clusters regardless the transmission season, location and host was observed. This indicates to probably multiple introduction of the virus into Croatia, intensive circulation and local overwintering of the virus. For the viral RNA from the dead goshawk the whole genome was sequenced in 12 partially overlapping segments using Sanger method. The whole genome shows the highest similarity (99.8%) with strains detected the same year in birds from Germany. Despite the high similarity, a deletion of eight nucleotides was found in the 3' non-coding region of the genome which is not present in any of the available WNV sequences. Further studies at the molecular level of WNV detected in Croatia are needed to obtain better insight into the WNV molecular epidemiology and its local specificity

O-8 Infekcije uzrokovane Usutu virusom na području Hrvatske: pet godina poslije

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Usutu virus (USUV) je arbovirus koji pripada porodici Flaviviridae, rodu Flavivirus. U prirodnom ciklusu, glavni rezervoari virusa su ptice, a vektori komarci roda *Culex*. Iako su humane infekcije rijetko zabilježene, nedavni podaci iz Italije su pokazali da su USUV infekcije češće u odnosu na infekcije uzrokovane West Nile virusom u pojedinim područjima gdje je dokazana cirkulacija oba virusa. Cilj ovog rada je prikazati pojavnost, kliničku sliku i molekularnu epidemiologiju USUV infekcija dokazanih na području Hrvatske. USUV je potvrđen dokazom specifičnih protutijela pomoću ELISA testa i virus neutralizacijskog testa (VNT) i/ili dokazom USUV RNA pomoću RT-PCR. Uzorci s dokazanom USUV RNA su potom sekvencirani Sanger metodom. Na području Hrvatske, prva USUV seropozitivna osoba dokazana je 2012. godine. Do sada je zabilježeno šest slučajeva humane USUV neuroinvazivne infekcije. Tri su osobe oboljele tijekom epidemije 2013. godine, a tri osobe 2018. godine, pet godina nakon prvih slučajeva. U pet je bolesnika infekcija potvrđena dokazom USUV neutralizacijskih protutijela, dok je u jednog bolesnika s fatalnim ishodom USUV RNA dokazana u uzorku urina. Bolesnici su bili s područja grada Zagreba/Zagrebačke županije, Požeško-slavonske i Osječko-baranjske županije. Dva USUV seropozitivna konja opisana su 2011. godine na području Zagreba i Sisačko-moslavačke županije. Tijekom epidemije 2018. godine, USUV je prvi put dokazan u uginulom kosu (*Turdus merula*) s područja Zagrebačke županije. USUV pozitivni skupni uzorci komaraca dokazani su u sezoni prijenosa 2016. u Zagrebu (*Aedes albopictus*), 2017. u Međimurskoj županiji (*Culex pipiens*) i 2018. ponovno u Zagrebu (*Cx. pipiens*). Sekvenciranje je učinjeno za skupni uzorak komaraca prikupljen 2018. godine. Filogenetska analiza pokazala je da sojevi USUV dokazani u humanom uzorku, kosu i skupnom uzorku *Cx. pipiens* komaraca pripadaju USUV Europe 2 liniji. Naši rezultati potvrđuju prisutnost USUV na području Hrvatske. Potrebne su daljnje studije kako bi se procijenio klinički značaj i geografska rasprostranjenost ove emergentne arbovirusne infekcije.

Usutu virus infections in Croatia: five years later

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Usutu virus (USUV) is a mosquito-borne arbovirus that belongs to the family Flaviviridae, genus Flavivirus. Birds are the natural reservoirs of the virus and mosquitoes of the genus *Culex* are the main vectors. Although human clinical cases were rarely reported, recent data from Italy showed that USUV infections may be more frequent than West Nile virus infections in some regions where these viruses co-circulate. The aim of this study was to present the occurrence, clinical symptoms and molecular epidemiology of USUV infections detected in Croatia. USUV was confirmed by detection of specific antibodies using ELISA and virus neutralization test (VNT) and/or detection of USUV RNA using RT-PCR. USUV RNA positive samples were further tested using Sanger sequencing. In Croatia, the first USUV seropositive human was detected in 2012. So far, six cases of human USUV neuroinvasive disease were confirmed. Three cases were detected in 2013 and three cases in 2018 transmission season, five years after the first ones. In five patients, infection was confirmed by detection of USUV neutralizing antibodies, while in one fatal case, USUV RNA was detected in a urine sample. Patients were from Zagreb/Zagreb County, Požega-Slavonia and Osijek-Baranja County. Two USUV seropositive horses were recorded 2011 in Zagreb and Sisak-Moslavina County. During the 2018 outbreak, USUV was detected for the first time in one dead blackbird (*Turdus merula*) from Zagreb County. USUV positive mosquito pools were recorded in the season 2016 in Zagreb (*Aedes albopictus*), 2017 in Međimurje County (*Culex pipiens*) and 2018 again in Zagreb (*Cx. pipiens*). Sequence was obtained from pooled sample collected in 2018. Phylogenetic analysis showed that Croatian strains detected in human, blackbird and *Cx. pipiens* pool belong to USUV Europe 2 lineage. Our results confirm the presence of USUV in Croatia. Further studies are needed to analyze the clinical significance and distribution of this emerging arboviral infection.

O-9 Značaj kućnih ljubimaca u epidemiologiji influence

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Influenca je u veterinarskoj medicini najznačajnija i najviše istraživana u ptica, svinja i konja. Općenito virusi influence su najčešće vrsno specifični, međutim, povremeno se opisuju međuvrtni prijenosi uključivši i prijenos virusa influence sa životinja na ljude. Posljednjih godina sve značajnija postaju istraživanja epidemiologije influence u kućnih ljubimaca s obzirom na njihov blizak suživot s ljudima. Društvene pomijene modernog načina života rezultiraju sve češćim držanjem kućnih ljubimaca u domaćinstvima, uključivši i držanje novih vrsta životinja koje do sada nisu bile uobičajeni kućni ljubimci. Primjerice u posljednjih nekoliko godina pitome vretice postaju sve češći kućni ljubimci, a upravo ova vrsta se koristi desetljećima kao model za istraživanje influenza A virusa zbog njihove visoke osjetljivosti na infekciju.

Stoga je cilj ovog istraživanja bio ustanoviti učestalost infekcija virusom influence A u najčešćih kućnih ljubimaca u Hrvatskoj.

Sveukupno 667 seruma životinja kućnih ljubimaca (555 seruma pasa, 73 seruma mačaka i 39 seruma pitomih vretica), uzorkovanih tijekom sezone influence u ljudi, pretraženo je kompetitivnim ELISA testom za dokaz protutijela za nukleoprotein influenza A virusa. Protutijela za influenza A virus potvrđena su u 0,9% pasa i 1,4% mačaka, a statistički značajno viša seroprevalencija od 17,9% ustanovljena je u pitomih vretica. Pojedini ELISA pozitivni serumski dodatno su pretraženi inhibicijom hemaglutinacije uz korištenje virusa influence različitog podrijetla radi određivanja specifičnosti protutijela, a rezultati ukazuju na infekciju kućnih ljubimaca humanim sojevima.

Uvriježeno mišljenje stručne javnosti je da kućni ljubimci imaju zanemariv značaj i sporednu ulogu u epidemiologiji influence. Međutim prikazani rezultati potvrđuju infekcije različitih vrsta kućnih ljubimaca te ukazuju na vjerojatni međuvrtni prijenos virusa influence s vlasnika na njihove ljubimce. Stoga, buduća istraživanja epidemiologije influence, uz ptice, svinje i konje, svakako moraju obuhvaćati i kućne ljubimce. Sveukupno se pristup „Jedno zdravlje“ nameće kao jedini moguć u istraživanjima i ove zoonoze kako bi stekli cjelovitije spoznaje te unaprijedili nadzor i suzbijanje influence u životinja i ljudi.

The role of pet animals in influenza epidemiology

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Among animal influenza is most commonly described in birds, pigs and horses. In general, individual isolates are host-specific. However, interspecies transmissions of influenza A viruses and zoonotic transmission have been described. In recent years, role of the pet animals has become a key question because of their close co-existence with their owners. Cultural and social changes in human society led to rise in number of pet owning households as well as rise in number of some more exotic pet species. In last few years ferrets, long time known as an experimental model to study influenza because their high susceptibility to influenza virus, have become one of the most popular pets.

The aim of this study was to investigate presence of influenza A infection in different pet animal species in Croatia.

A total of 667 pet animal sera (555 dog sera, 73 cat sera and 39 ferret sera), sampled during human influenza season, were tested using competitive ELISA for the detection of anti-nucleoprotein antibodies. Influenza A antibodies were confirmed in 0,9% dog and 1,4% cat sera. Statistically significant higher seroprevalence of 17,9% was detected in ferrets. To determine HA specificity of antibodies, HI test was performed on some ELISA positive sera using influenza virus strains of different origin. Results confirmed infections with influenza viruses closely related to human strains.

It was a common belief that pet animals have minor, if any, role in influenza epidemiology. Our results have confirmed influenza A infections in pets and strongly suggest possibility of interspecies transmission between the pet animals and the owners in the households. Alongside with well-known role of birds, pigs and horses in influenza epidemiology, pet animal role requires further studies and “One Health” approach seems to be the only reasonable way to improve surveillance and control of influenza in animals and human population.

O-10 Hepatitis E u imunokompromitiranih osoba

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Infekcija virusom hepatitisa E (HEV) je emergentna bolest u brojnim europskim zemljama, pri čemu su primijećene akutne i kronične infekcije te širok raspon ekstrahepatičnih manifestacija. Kronična HEV infekcija pojavljuje se u imunokompromitiranih osoba kao što su transplantirani pacijenti, HIV-pozitivne osobe i pacijenti koji primaju kemoterapiju zbog hematoloških malignih bolesti. Do dvije trećine imunokompromitiranih osoba izloženih HEV-u razvijaju kroničnu infekciju, pri čemu se može javiti brza progresija jetrene fibroze u cirozu, jetrena dekompenzacija i smrt. Svi do sada opisani slučajevi kronične infekcije uključuju genotipove HEV3 i HEV4. U imunokompromitiranih pacijenata, imunosupresivna terapija ugrožava humoralni imunski odgovor i ograničava dijagnostičku vrijednost serologije te je zato potreban RT-PCR za dokazivanje aktivne infekcije. Ovaj sveobuhvatan pregled o HEV infekciji u imunokompromitiranih pacijenata potkrijepljen je i podacima iz različitih hrvatskih kohorti; nakon transplantacije jetre i na hemodijalizi koji su testirani na HEV IgG/IgM protutijela i HEV RNA. Prevalencija HEV IgG protutijela u transplantiranih i hemodijaliziranih pacijenata iznosila je 24,4% odnosno 27,9% i značajno je rasla s dobi bolesnika. HEV RNA nije bila dokazana. U prikazu raspravljamo njihovu visoku razinu seroprevalencije u kontekstu rizičnih čimbenika i razmatramo moguće mjere prevencije.

Hepatitis E in immunocompromised persons

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Hepatitis E virus (HEV) infection is an emerging disease in many European countries, where acute and chronic infection and a wide range of extrahepatic manifestations has been observed. Chronic HEV infection occurs in immunocompromised individuals such as transplanted patients, HIV-positive patients and patients receiving chemotherapy for haematological malignancies. Up to two-thirds of immunosuppressed patients who are exposed to HEV will develop a chronic infection, where rapid progression of liver fibrosis to cirrhosis, decompensation and death have been described. All reported cases of chronic infection so far have involved HEV3 or HEV4 genotypes. In immunocompromised patients, immunosuppressive therapy may compromise humoral immune response and limit the diagnostic value of serology therefore RT-PCR is required to establish an active infection. This comprehensive review on HEV infection in immunocompromised populations, we corroborate with data from different Croatian cohorts; liver transplant patients and patients on haemodialysis (HD) who were tested for HEV IgG/IgM antibodies and HEV RNA. Prevalence of HEV IgG antibodies in transplanted and HD patients were 24.4% and 27.9%, respectively and has significantly increased with age. HEV RNA was not detected. We discuss their high seroprevalence rates in the context of associated risk factors along with recommendations for preventive measures.

O-11 Emerging zoonoses in Oman: scrub typhus

Pandak Nenad

The Royal Hospital, Muscat

Scrub typhus is a potentially fatal rickettsial infection caused by *Orientia tsutsugamushi*. It is an obligate intracellular Gram-negative bacterium transmitted by the bite of infected chigger larva. The disease is distributed from Asia to the Pacific islands, and this region is known as the Tsutsugamushi Triangle.

A 28-year-old man was admitted to the Royal Hospital with a four-day history of fever, headache, rigors, anorexia, and a nonspecific macular rash. Clinical presentation, laboratory results as well as epidemiological data indicated that this might be a case of scrub typhus. Additional serology tests confirmed the presumed diagnosis, and the patient was successfully treated with empirical therapy.

Untreated scrub typhus has high mortality and early diagnosis and adequate treatment can prevent the potentially fatal outcome of the disease.

O-12 Neuroinvazivna infekcija uzrokovana Toscana virusom – zapostavljena bolest

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Toscana virus (TOSV) je arbovirus kojeg na ljude prenose flebotomi. Iako većina humanih TOSV infekcija prolazi asimptomatski ili se očituje kao nespecifična febrilna bolest, može nastati i neuroinvazivna infekcija. TOSV je endemski u mediteranskim zemljama s najvećom incidencijom tijekom ljetnih mjeseci. Na području Hrvatske, vrlo je malo podataka o kliničkim slučajevima TOSV infekcije. U ovom radu prikazujemo slučaj TOSV infekcije u bolesnika s kliničkom slikom seroznog meningitisa.

U ljeto 2018. godine, 21-godišnji bolesnik s područja srednje Dalmacije zaprimljen je u Kliniku za infektologiju drugog dana bolesti koja se očitovala vrućicom (do 38°C), glavoboljom, mučninom, povraćanjem i općom slabošću. Kod prijema, bolesnik je bio subfebrilan (T=37.6°C), urednih vitalnih znakova. Rutinske laboratorijske pretrage bile su unutar referentnih vrijednosti. Analizom cerebrospinalnog likvora (CSL) nađena je pleocitoza (175 leukocita/mm³) uz 76% limfocita, povišene vrijednosti proteina 0,447 g/L (referentne vrijednosti 0,17-0,37) te vrijednost glukoze 3,78 mmol/L (referentne vrijednosti 2,5-3,3). Kopjuterizirana tomografija mozga pokazala je uredan nalaz.

Budući da je nalaz CSL upućivao na serozni meningitis, postavljena je sumnja na arbovirusnu infekciju. Uzorci CSL i seruma testirani su na prisustnost neuroinvazivnih arbovirusa: virus krpeljnog encefalitisa, West Nile, Usutu, TOSV, Tahyna i Bhanja virus. Visok titar IgM protutijela (1000) i IgG protutijela (32000) u uzorku seruma ukazivao je na akutnu TOSV infekciju. TOSV RNA nije dokazana u uzorcima seruma i CSL. Nadalje, protutijela na ostale fleboviruse (sicilijanski, napuljski i ciparski virus papataci groznice) nisu dokazana. Bolesnik je liječen simptomatski uz potpuni oporavak tijekom pet dana.

Prikazani slučaj naglašava potrebu za uključivanjem TOSV u dijagnostičku obradu kao jednog od mogućih uzročnika seroznog meningitisa/meningoencefalitisa tijekom sezone prijenosa arbovirusa.

Neuroinvasive infection caused by Toscana virus – a neglected disease

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Toscana virus (TOSV) is an arthropod-borne virus, transmitted to humans by sandflies. Although majority of human TOSV infections are asymptomatic or presented as a non-specific febrile disease, neuroinvasive disease may also occur. TOSV is endemic in the Mediterranean countries with the highest infection rates during summer months. In Croatia, there are very few data on clinical cases of TOSV infection. We present a case report of TOSV infection detected in Croatian patient presented with aseptic meningitis.

In the summer 2018, a 21-year-old male patient from Middle Dalmatia was admitted to the Infectious Disease Department with a two-day history of fever (up to 38°C), headache, nausea, vomiting and fatigue. At admission, the patient was subfebrile (T=37.6°C) with normal vital signs.

Routine blood laboratory parameters were within normal range. Cerebrospinal fluid (CSF) analysis revealed a white blood cell count of 175 cells/mm³ with 76% lymphocytes, a protein level of 0.447 g/L (reference range 0.17-0.37) and a glucose level of 3.78 mmol/L (reference range 2.5-3.3). Brain computed tomography was normal.

Since the CSF findings were suggestive of aseptic meningitis, arboviral etiology was suspected. CSF and serum samples were tested for the presence of neuroinvasive arboviruses: tick-borne encephalitis, West Nile, Usutu, TOSV, Tahyna and Bhanja virus. High titers of both IgM (1000) and IgG (32000) to TOSV in a serum sample indicated acute TOSV infection. TOSV RNA was not detected in the CSF or serum sample. In addition, antibodies to other phleboviruses (sandfly fever Sicilian, Naples and Cyprus virus) were negative. The patient was treated with symptomatic therapy and recovered fully within five days.

The presented case highlights the need of increasing awareness of TOSV infection as a possible cause of aseptic meningitis/meningoencephalitis during the arbovirus transmission season.

O-13 Dvojna infekcija uzrokovana West Nile virusom i echovirusom 9 u bolesnice sa seroznim meningitisom

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Neuroinvazivne infekcije uzrokovane West Nile virusom (WNV) i enterovirusima imaju istu sezonsku pojavnost te slične kliničke i laboratorijske značajke bolesti. U ovom radu prikazan je slučaj dvojne infekcije uzrokovane WNV i echovirusom 9 bolesnice sa seroznim meningitisom. U kolovozu 2018. godine, 59-godišnja bolesnica je hospitalizirana u Klinici za infektologiju trećeg dana bolesti manifestirane svakodnevnim febrilitetom do 38,2°C, difuznom glavoboljom i mučninom. Pri pregledu bila je febrilna, bistre svijesti, hipodinamična, srednje teškog općeg stanja uz kočenje vrata. Rutinski laboratorijski nalazi bili su u referentnim vrijednostima. Učinjenom lumbalnom punkcijom utvrđeno je 19×10⁶/L leukocita uz 53% limfocita te blažu proteinuriju (0,412 g/L). Elektroencefalogram je bio difuzno dizritmički promijenjen. Analiza cerebrospinalnog likvora (CSL) PCR metodom na HSV 1/2, enteroviruse, CMV, EBV, B. burgdorferi i L. monocytogenes pokazala je negativan rezultat. Visok titar WNV IgM (omjer 3,36; >1,1 pozitivan) i IgG protutijela (142,81 RU/ml; pozitivan >22) niskog IgG aviditeta (indeks aviditeta 21%; <40% nizak) u serumu te graničan nalaz IgG protutijela u CSL (18,86 RU/ml) ukazivao je na WNV infekciju. RT-PCR CSL i urina bio je negativan na WNV RNA. Iz uzorka stolice izoliran je echovirus 9. U serumu su dokazana IgG protutijela na echoviruse, dok je serološki nalaz CSL bio negativan. Započeta je inicijalna antimikrobna terapija aciklovirom, ampicilinom i ceftriaksonom i.v. uz antiedematoznu i drugu suportivnu terapiju do prispjeća mikrobiološke obrade te se nastavila simptomatska terapija do otpusta kući. Od trećeg dana hospitalizacije bolesnica je afebrilna uz regresiju ranije prisutnih tegoba. Period rekonvalescencije protekao je uredno (klinički kontrolirana kroz tri mjeseca). Prikazani slučaju akutnog WNV meningitisa uz istovremenu infekciju echovirusom 9 ukazuje na moguće koinfekcije. Zbog sezonskog preklapanja, diferencijalna dijagnoza neuroinvazivnih infekcija uz WNV treba uključivati i enteroviruse.

Dual infection with West Nile virus and echovirus 9 in a patient with aseptic meningitis

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The seasonality, clinical and laboratory features of West Nile virus (WNV) neuroinvasive infection overlap with those of enteroviruses. We report a case of dual infection with WNV and echovirus 9 in a patient with aseptic meningitis. In August 2018, a 59-year-old woman with a history of arterial hypertension was hospitalized at the Clinic for Infectious Diseases on the third day of the illness. The disease was manifested by a daily fever up to 38.2°C, diffuse headaches and nausea without vomiting. On admission, her condition appeared severe. She was conscious, but she suffered from weakness and hypotonia. Neurologic examination revealed terminal neck stiffness. Routine laboratory parameters were normal. Cerebrospinal fluid (CSF) analysis showed pleocytosis (19×10⁶ cells/L) with 53% mononuclear cells and elevated protein level (0.412 g/L). Electroencephalogram showed slow diffuse dysrhythmia. PCR of CSF for HSV 1/2, enteroviruses, CMV, EBV, *B. burgdorferi* and *L. monocytogenes* were negative. High titer of both WNV IgM (ratio 3.36; >1.1 positive) and IgG antibodies (142.81 RU/ml; positive >22) of low avidity (avidity index 21%; low <40%) in serum sample as well as equivocal IgG antibodies (18.86 RU/ml) in CSF sample indicated WNV infection. RT-PCR of CSF and urine was negative for WNV RNA. Echovirus 9 was isolated from a stool sample. IgG antibodies to echoviruses were found in a serum sample, while CSF was negative. The patient was initially treated with acyclovir, ampicillin and ceftriaxone intravenously (until the completion of virology results) with a supportive (antiedematous) therapy. Third day into hospitalization, the patient was afebrile and without headache. The patient was monitored during three months and recovered fully. The presented case of acute WNV meningitis occurring concurrent with echovirus 9 infection suggest possible co-infections. Due to the overlapping seasonal activity, differential diagnosis of neuroinvasive infections should include both WNV and enteroviruses.

MULTILOREZISTENTNE BAKTERIJE
MULTIDRUG RESISTANT BACTERIA

O-14 KPC *K. pneumoniae* u Kliničkom bolničkom centru Split

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Sojevi *Klebsiella pneumoniae* rezistentni na karbapeneme zbog lučenja karbapenemaza (*Klebsiella pneumoniae* carbapenemase producing; KPC) pojavljuju se diljem svijeta. KPC sojevi *K. pneumoniae* su rezistentni ne samo na karbapeneme nego i na druge skupine antibiotika te uzrokuju teške Infekcije za koje su terapijske mogućnosti ograničene a to dovodi do značajnog rasta morbiditeta i mortaliteta. Globalnom širenju ovih sojeva pridonosi, između ostalog, smještaj gena koji kodira lučenje enzima na plazmidu te međunarodna putovanja. Iako je do značajnijih epidemija uzrokovanih KPC sojeva *K. pneumoniae* došlo u nama susjednoj Italiji još 2007. godine a infekcije su odavno zabilježene i u sjevernim područjima Hrvatske, u KBC Split do rujna 2018. godine nisu bili izolirani KPC sojevi *K. pneumoniae*. Prvi takav soj je izoliran iz uzorka bolesnika s multiplim traumom zbog saobraćajne nesreće koji je zaprimljen na Hitni kirurški prijem KBC Split i nakon toga liječen u više bolničkih odjela i klinika. Od tada se, unatoč poduzetim mjerama za sprečavanje širenja bolničkih infekcija koje se kontinuirano poduzimaju, KPC sojevi *K. pneumoniae* izoliraju iz različitih kliničkih uzoraka te iz nadzornih kultura. U ovom predavanju su prikazane najbitnije mikrobiološke, molekularne i epidemiološke značajke KPC sojeva *K. pneumoniae* izoliranih u KBC Split u razdoblju od rujna 2018. do srpnja 2019.

KPC *K. pneumoniae* in University Hospital Centre Split

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Carbapenem-resistant *Klebsiella pneumoniae* strains due to carbapenemase production (*Klebsiella pneumoniae* carbapenemase producing; KPC) are emerging worldwide.

KPC *K. pneumoniae* strains are resistant not only to carbapenems but also to other groups of antibiotics, causing severe infections for which therapeutic options are limited, leading to significant increase in morbidity and mortality. The global spread of these strains is, among other things, because of the plasmid-encoded gene and international travel.

Although significant outbreaks of KPC *K. pneumoniae* strains occurred in neighboring Italy back in 2007 and infections have long since been reported in the northern regions of Croatia, in University Hospital Centre (UHC) Split KPC *K. pneumoniae* strains have not been isolated until September 2018. The first such strain was isolated from a sample of patient with multiple traumas due to a traffic accident, which was received at the Emergency Surgical Service of UHC Split and subsequently treated at multiple hospital departments and clinics.

Since then, despite measures taken to prevent the spread of hospital-acquired infections, KPC *K. pneumoniae* strains are isolating from various clinical specimens and from surveillance cultures.

In this lecture, the most important microbiological, molecular and epidemiological characteristics of KPC *K. pneumoniae* strains isolated in UHC Split from September 2018 to July 2019 are presented.

O-15 Multirezistentani *Acinetobacter baumannii* – desetljeće endemskog klona u Hrvatskoj

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Acinetobacter baumannii zauzima posebno mjesto unutar skupine uzročnika teških infekcija, poznatije kao „ESKAPE” mikroorganizmi. Ovaj mikroorganizam postao je vodeći uzročnik hospitalnih infekcija u 21. stoljeću, te su brojna istraživanja usmjerena na epidemiologiju, rezistenciju i nadzor nad ovim patogenom. Epidemiologija i molekularna osnova rezistencije kliničkih izolata *Acinetobacter baumannii* u Hrvatskoj tijekom posljednja dva desetljeća bitno se promijenila u većini zdravstvenih ustanova, uz visoki postotak rezistencije na karbapeneme, kinolone i aminoglikozide te prisutnost multiplo-rezistentnih izolata.

Istraživanje na području rezistencije ovog mikroorganizma kao važnog bolničkog patogena započelo je u Hrvatskoj 2002. godine na izolatima iz KBC Split, gdje je molekularno istražena osnova smanjene osjetljivosti na karbapeneme. Genotipizacija prvih kliničkih izolata sa smanjenom osjetljivosti na jedan ili oba karbapenema dokazala je prisutnost Europskog klona 1 (kasnije nazvan Internacionalni IC1) u razdoblju od 2002. do 2008. Početkom 2009. godine došlo je do epidemijskog širenja novog klona koji pripada IC2. Karakteristike *A. baumannii* koji pripada novom klonu lako je otkriti u rutinskom testiranju osjetljivosti jer ovaj izolat pokazuje rezistenciju na oba karbapenemska antibiotika s visokim vrijednostima minimalnih inhibitornih koncentracija (MIK > 32 mg/L) na imipenem i meropenem. Ovaj novi klon koji pripada IC2 s potvrđenim epidemiološkim prijenosom iz susjedne Bosne i Hercegovina, u prvim publiciranim navodima označen i kao “Mostarski klon”, danas je dominantno prisutan u većini zdravstvenih ustanova u Hrvatskoj. U epidemiološkom smislu, ovaj novi klon je potpuno potisnuo izolate koji su pripadali IC1 iz 2002. godine te je postao dominantan u gotovo svim zdravstvenim ustanovama u Hrvatskoj.

Multidrug resistant *Acinetobacter baumannii* – a decade of the successful clone in Croatia

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Among the “ESKAPE” group of serious pathogens *Acinetobacter baumannii* is under a great concern worldwide. This microorganism has become a leading nosocomial pathogen of the 21st century, and numerous studies are focused on the epidemiology, resistance and control measures of this pathogen in the hospital setting. The epidemiology and molecular basis of resistance of clinical isolates of *Acinetobacter baumannii* in Croatia over the last two decades has changed significantly in most health institutions, with a high percentage of resistance to carbapenems, quinolones and aminoglycosides, and the presence of multiresistant isolates.

Research into the resistance of this microorganism as an important hospital pathogen began in Croatia in 2002. on isolates from UHC Split, where the basis of reduced susceptibility to carbapenems was studied molecularly. Genotyping of the first clinical isolates with reduced susceptibility to one or both carbapenems proved the presence of European clone 1 (later called International IC1) from 2002. to 2008. In early 2009., an epidemic spread of a new clone belonging to IC2 occurred. The characteristics of *A. baumannii* belonging to the new clone are easy to detect in routine susceptibility testing as this isolate shows resistance to both carbapenem antibiotics with high levels of minimum inhibitory concentrations (MIC > 32 mg/L) on imipenem and meropenem. This new clone belonging to IC2 with confirmed epidemiological transmission from neighboring Bosnia and Herzegovina, also referred to as the Mostar Clone in its first published citations, is today predominantly present in most healthcare institutions in Croatia. In epidemiological terms, this new clone completely suppressed isolates belonging to IC1 from 2002. and has become dominant clone in almost all health care institutions in Croatia.

O-16 Evolucija karbapenem rezistentnih enterobakterija u Hrvatskoj

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Evolution of carbapenem resistant enterobacteria in Croatia

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O-17 KPC tu, KPC tamo, KPC posvuda

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Otkako je karbapenemaza KPC prvi put opisana u SAD-u 1996. godine, u kliničkim izolatima *K. pneumoniae*, širenje enterobakterija koje proizvode karbapenemazu KPC postao je globalni zdravstveni problem. Kao jedna od klinički najznačajnijih karbapenemaza, KPC uspješno hidrolizira sve beta-laktamske antibiotike, uključujući i karbapeneme, dok plazmidni smještaj gena bla_{KPC} omogućuje horizontalni prijenos i širenje putem visoko rizičnih bakterijskih klonova. Iako je gen bla_{KPC} do sada opisan u velikom broju vrsta reda Enterobacterales, karbapenemaza KPC se prvenstveno povezuje s *K. pneumoniae* zahvaljujući širenju izrazito uspješnog epidemijskog klona ST258.

Unatoč tome što je prisutnost karbapenemaze KPC-2 po prvi puta u Hrvatskoj opisana 2011. godine u kliničkom izolatu *K. pneumoniae* klonskog tipa ST37, pojava i monoklonsko širenje klonskog tipa ST258 bili su glavni pokretač epidemijskog širenja KPC-2-producirajuće *K. pneumoniae* na području središnje i sjeverozapadne Hrvatske tijekom 2011. i 2012.

Kroz redovito djelovanje Referentnog centra za praćenje rezistencije bakterija na antibiotike Ministarstva zdravstva, u razdoblju od 1.1.2018. do 15.8.2019 godine, prikupljeno je 50 jedinstvenih izolata KPC-producirajućih enterobakterija iz 12 centara u svrhu analize molekularne epidemiologije. Iako je proizvodnja karbapenemaze KPC iz zbirke detektirana u četiri bakterijske vrste, većina je detektirana u izolatu *K. pneumoniae* (n=47, 94%). Gen bla_{KPC-2} detektiran je u većini izolata iz zbirke (n=47, 94%), dok je proizvodnja karbapenemaze KPC-3 detektirana u svega 3 izolata. Za razliku od monoklonske prirode epidemijskog širenja tijekom 2011. i 2012. godine, uočeno je da je recentno regionalno širenje KPC-producirajuće *K. pneumoniae* poliklonske prirode. U poliklonskoj genskoj pozadini zbirke analiziranih izolata najviše se ističu četiri genska klastera koji pripadaju klonskim tipovima ST15, ST258 i ST512, pri čemu je, kao dominantni klon i pokretač regionalnog širenja koje obuhvaća 7 centara, prepoznat klonski tip ST101 (n=29, 58%). Iako je prisutnost KPC-producirajuće *K. pneumoniae* na području RH od 2011. godine konstantna, molekularno-epidemiološka slika širenja se tijekom vremena bitno izmijenila.

KPC here, KPC there, KPC everywhere

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Ever since KPC carbapenemase was first reported in USA in 1996, in clinical isolates of *K. pneumoniae*, global spread of KPC-producing Enterobacterales has become an issue of great health concern. As one of the most prominent carbapenemases, KPC successfully hydrolyzes all beta-lactams, including carbapenems and plasmid nature of *bla*_{KPC} genes facilitates horizontal transfer and association with high-risk bacterial clones. Even though *bla*_{KPC} gene was reported in a variety of Enterobacterales species, KPC carbapenemase is still mostly associated with *K. pneumoniae* due to successful global spread of ST258 *K. pneumoniae*.

Although KPC-2-producing *K. pneumoniae* in Croatia was first reported in 2011, in a clinical *K. pneumoniae* isolate belonging to ST37, emergence and monoclonal spread of ST258 was recognized as the main driving force of KPC-2-producing *K. pneumoniae* epidemic spread in central and north-western Croatia during 2011 and 2012.

In a period from 1.1.2018 to 15.8.2019, a total of 50 non-duplicate KPC-producing isolates from 12 centres were referred to Croatian Reference Centre for Antibiotic Resistance Surveillance and were genotyped using methods of molecular epidemiology. Even though KPC production was observed in four species, most of KPC-producing isolates were identified as *K. pneumoniae* (n=47, 94%). *bla*_{KPC-3} gene was detected in 3 isolates but production of KPC-2 carbapenemase was the most prevalent among analyzed collection of isolates (n=47, 94%). In comparison to monoclonal nature of epidemic spread in 2011 and 2012, recent regional spread of KPC-producing *K. pneumoniae* was characterized as polyclonal. Polyclonal background of analyzed isolates is mostly comprised of four distinctive genetic clusters belonging to ST15, ST258 and ST512, but ST101 was identified as the most dominant clone responsible for regional spread of KPC-producing *K. pneumoniae* covering 7 centres (n=29, 58%). Presence of KPC-producing *K. pneumoniae* in Croatia has been constant since 2011, but nevertheless, genetic background has changed during that time.

0-18 Možemo li kontrolirati MRSA u JIL – u?

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Opća bolnica “Dr. Ivo Pedišić”, Sisak, Hrvatska

Meticilin rezistentni *Staphylococcus aureus* (MRSA) je bakterija sa eksponencijalnim potencijalom širenja i izazivanja infekcija postala je globalni (svjetski) problem. Uzrokuje multiple infekcije s opsežnim komplikacijama, visokom smrtnošću i visokim troškovima liječenja. U svrhu smanjenja incidencije i puteva širenja uveli smo u našoj OB “Dr. Ivo Pedišić” Sisak metode dekolonizacije za sve bolesnike koji ulaze u JIL. Period praćenja bolesnika u JIL – u je 01.01.2006. do 31.12. 2006. (ukupno liječenih 892). Period bez navedenog tretmana dekolonizacije tj.pristup samo sa standardnim mjerama dezinfekcije, obuhvatio je razdoblje od 01.01. do 12.06.2006. (ukupno 425 bolesnika). U tom periodu izolirali smo kod 33 bolesnika MRSA. Od 13.06. do 01.11.2006. uvode se mjere dekolonizacije. Tretirano 337 bolesnika. 0 izolata MRSA. U periodu od 01. 11. 2006. do 31.12. 2006 nastaje defektura mupirocina – 6 izolata MRSA.

ZAKLJUČAK : Mjere dekolonizacije izvrsno doprinose smanjenju incidencije i puteva širenja MRSA u JIL – u a samim tim smanjenje broja infekcija, smrtnosti i visokih troškova liječenja.

Can we control MRSA infection in ICU?

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacterium with an exponential potential to spread and cause infection has become a global (worldwide) problem. It causes multiple infections with extensive complications, high mortality and high treatment costs. In order to reduce the incidence and spread pathways, we have introduced in our OB Dr. Ivo Pedisic Sisak methods of decolonization for all patients entering the ICU. The follow-up period for patients at ICU is 01.01.2006. to 31.12. 2006 (892 in total). The period without decolonization treatment, ie access only with standard disinfection measures, covered the period from 01.01. to 12.06.2006. (425 patients in total). During this period, we isolated in 33 MRSA patients. From 13.06. do 01.11.2006. decolonization measures are introduced. 337 patients treated, 0 isolates of MRSA. In the period from 01. 11. 2006 to 31.12. 2006 mupirocin defect – 6 isolates of MRSA. CONCLUSION: Decolonization measures make an excellent contribution to reducing the incidence and pathways of spread of MRSA in JIL and thereby reducing infection rates, mortality and high treatment costs.

HIV
HIV

O-19 Primarna rezistencija HIV-1 na antiretrovirusne lijekove u Hrvatskoj

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Rezistencija HIV-a na antiretrovirusne lijekove uzrokovana je mutacijama u pol regiji genoma virusa koje dovode do promjene slijeda aminokiselina u aktivnim mjestima virusnih enzima koji su ciljne strukture lijekova. Primarna rezistencija tj. rezistencija u prethodno neliječenih osoba može predstavljati prepreku u postizanju virusološkog odgovora na antiretrovirusno liječenje. Mutacije povezane s primarnom rezistencijom HIV-a na antiretrovirusne lijekove određuju se metodom sekvenciranja pol regije genoma virusa, dok se njihova klinička značajnost analizira primjenom algoritma i preporuka WHO-a iz 2009.g. (surveillance for drug resistance mutations, SDRM). Rezultati prvog nacionalnog istraživanja o prevalenciji primarne rezistencije HIV-a na lijekove pokazali su visoku prevalenciju rezistencije na inhibitore reverzne transkriptaze (22%) u ispitanika koji su uključeni u skrb u razdoblju od 2006. do 2008.g. Rezultati novog istraživanja prevalencije primarne rezistencije HIV-a na antiretrovirusne lijekove koje je obuhvatilo novodijagnosticirane osobe uključene u skrb u razdoblju od 2014. do 2018.g. (403 ispitanika), pokazalo je prevalenciju primarne rezistencije od 16.4% (66/403). Po prvi je puta dokazana primarna rezistencija i na lijekove iz skupina inhibitora proteaze i integraze. Većina ispitanika s dokazanom primarnom rezistencijom pripadala je MSM skupini dok su rezultati filogenetske analize pokazali prisutnost transmisijskih klastera. Rezultati ovog istraživanja pokazuju da postoji potreba praćenja prevalencije primarne rezistencije HIV-a na antiretrovirusne lijekove u Hrvatskoj, posebice zbog pojave primarne rezistencije na inhibitore integraze.

Primary antiretroviral drug resistance among HIV type-1 infected persons in Croatia

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HIV resistance to antiretroviral drugs is associated with mutations in the pol region of the genome that induce change in the structure of viral enzyme active sites that are targeted by drugs. Transmitted drug resistance (TDR) or primary resistance in untreated patients can represent an obstacle to the virological success of the treatment. Mutations associated with TDR are analysed by sequencing the pol region of the viral genome. Clinical significance of mutations associated with TDR is evaluated by using the WHO recommendations in 2009 (surveillance for drug resistance mutations, SDRM). The first national study on the prevalence of TDR that included patients entering clinical care in the period 2006 to 2008 showed a high prevalence of TDR (22%). The results of the recent study that included patients entering care in the period 2014-2018 (n=403) showed a 16.4% (66/403) prevalence of TDR. This study provided the first evidence on TDR to protease and integrase inhibitors. The majority of patients with TDR belonged to the MSM group and phylogenetic analysis showed the presence of transmission clusters. The results of this study suggest that there is a need for TDR monitoring in Croatia, particularly due to the primary resistance to integrase inhibitors.

O-20 Liječenje i skrb za osobe zaražene HIV-om u Hrvatskoj

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Treatment and care for HIV-infected persons in Croatia

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O-21 Infekcije humanim papilomavirusima u osoba zaraženih HIV-om

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Infekcije humanim papilloma virusom (HPV) su najčešće virusno spolno prenosive infekcije. Svake godine otprilike 17,500 žena and 9,300 muškaraca dobiju karcinom uzorkovan HPV-om.

Otprilike 1 od 100 spolno aktivne osobe ima šiljaste kondilome. Osobe s HPV infekcijom sklonije su nastanku HIV infekcije - rizik za infekciju HIV-om u osoba s HPV infekcijom je udvostručena. HIV pozitivni bolesnici imaju povećanu prevalenciju i incidenciju HPV infekcije (posebice HPV povezanih displazija). Karcinomi povezani s HPV-om su najučestaliji karcinomi u bolesnika s HIV-om. Zbog visoke incidencije i perzistencije infekcije, HIV pozitivni bolesnici imaju povećani rizik za nastanka karcinoma povezanih s HPV-om. Incidencija analnog, orofaringealnog, karcinoma penisa i vulvovaginalnog karcinoma u HIV pozitivnih osoba je u povećanju neovisno o uvođenju HAART terapije. Incidencija cervikalnog karcinoma u HIV pozitivnih osoba je visoka, po uvođenju HAART-a ne raste, ali nema dokaza niti o smanjenoj učestalosti.

Human papillomavirus infection in HIV infected persons

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Human papilloma virus (HPV) infections are the most common viral sexual transmitted disease. Approximately 17,500 women and 9,300 men receive HPV-associated cancer every year. Persons with HPV infection are prone to HIV infection - risk of HIV infection in people with HPV infection doubled. HIV positive patients have increased prevalence and incidence for developing HPV infection (especially HPV associated dysplasia). HPV-associated carcinomas are the most common cancer in patients with HIV. Due to the high incidence and persistence of infection, HIV positive patients have increased risk for HPV-associated cancer. Incidence of anal, oropharyngeal, penile and vulvovaginal cancer in HIV-positive individuals is increasing regardless of the introduction of HAART therapy. The incidence of cervical cancer in HIV positive persons is high, with the introduction of HAART it is not growing, but there is no evidence of reduced frequency.

0-22 Radiološke karakteristike neuroloških komplikacija HIV-a u Hrvatskoj

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Ciljevi: prikazati radiološko-kliničku korelaciju spektra najčešćih bolesti središnjeg živčanog sustava (SŽS) u bolesnika zaraženih HIV-om u Hrvatskoj, liječenih u Klinici za infektivne bolesti u Zagrebu, u posljednjih pet godina (od 1. siječnja 2014. do 31. prosinca 2018.): HIV- encefalopatija, progresivna multifokalna encefalopatija, primarni limfom, metastatski limfom i toksoplazmoza.

Metode: retrospektivno prikupljanje i radiološka analiza slikovnog materijala izabranih bolesnika (kompjutorizirana tomografija-CT, magnetna rezonancija-MR), arhiviranih u digitalnoj arhivi Klinike. Retrospektivno prikupljanje epidemioloških, kliničkih i laboratorijskih podataka iz bolničkih kartona koje su obavljali infektolozi. Formiranje serije prikaza s radiološko-kliničkom korelacijom uz izdvojene, klinički relevantne podatke važne za dijagnostiku, liječenje i prognozu bolesnika.

Rezultati: diskusija o najvažnijim slikovnim karakteristikama i diferencijalnoj dijagnostici različitih bolesti SŽS-a u bolesnika zaraženih HIV-om. Prikaz i obrazloženje ograničenja pojedinih slikovnih tehnika koje mogu uzrokovati odgađanje u postavljanju ispravne dijagnoze. Navođenje važnih točaka koje radiolog mora prezentirati infektologu i neurokirurgu.

Zaključak: bez obzira na uspješnu antiretrovirusnu terapiju, bolesnici zaraženi HIV-om su u riziku za razvoj različitih oportunističkih bolesti SŽS-a. Brza slikovna dijagnostika može ograničiti oštećenja SŽS-a.

Imaging characteristics of neurological complications in HIV infection in Croatia

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Goals: to present a radiological-clinical correlation of the spectrum of the most common central nervous system (CNS) diseases in HIV-infected patients in Croatia, treated at the University Hospital for Infectious Diseases in Zagreb, Croatia, in the last five years (from January 1 2014 to December 31 2018): HIV-encephalopathy, progressive multifocal encephalopathy, primary lymphoma, metastatic lymphoma and toxoplasmosis.

Methods: a retrospective collection and analysis of selected patients' images (computed tomography-CT and magnetic resonance-MR), archived in the digital archive, performed by a radiologist. A retrospective collection of epidemiological, clinical and laboratory data from patients' medical records was performed by infectious diseases specialist. Creation of a case series was done with the radiological-clinical correlation including selected, relevant data important for patients' diagnostics, treatment and prognosis.

Results: discussion about the most important imaging presentation and differential diagnosis of different CNS diseases in HIV-infected patients. Explaining and discussing limitations of imaging techniques that may delay the correct diagnosis. Listing important points that radiologist should state to the infectious disease specialist and neurosurgeon.

Conclusion: despite a successful antiretroviral therapy, HIV-infected patients are at risk for a variety of CNS opportunistic infections. Rapid imaging evaluation may limit damage to the CNS.

O-23 Preekspozicijska profilaksa HIV infekcije

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Preexposure prophylaxis for HIV infection

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O-24 Isplativost EmERGE usluge u skrbi za osobe sa stabilnom HIV-infekcijom u Hrvatskoj

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Svrha: Izračunati isplativost oblika skrbi koji uključuje mHealth sustav, za klinički stabilne osobe koje žive s HIV-om, a koje su bolesnici Klinike za infektivne bolesti „Dr. Fran Mihaljević“, Zagreb, Hrvatska. Ovo omogućuje pojedincima da primaju informacije o liječenju HIV-a na svoj pametni telefon putem mHealth aplikacije.

Metode: 293 sudionika studije EmERGE uglavnom su koristili usluge Ambulante za HIV, što je bio fokus troškovne studije. Jedinstveni troškovi izračunati su i povezani s prosjekom korištenja HIV usluga po godini bolesnika (MPPY). Podaci o korištenju usluga prikupljeni su retrospektivno godinu dana prije i prospektivno godinu dana nakon uvođenja mHealth aplikacije, što je omogućilo procjenu godišnjih troškova pružanja HIV usluga. Godišnji troškovi kombinirani su s podacima o biomedicinskim i socijalnim ishodima – broju CD4 limfocita, viremiji, kvaliteti života (PROQOL-HIV) i samoupravljanju (PAM13), prije i nakon uvođenja aplikacije. Troškovi su izračunati u kunama.

Rezultati: Prosječni ambulantni posjeti smanjeni su sa 5,2 (95% CI: 4,9 do 5,5) na 4,75 (95% CI: 4,5 do 5,0) MPPY. Godišnji troškovi bili su prije mHealth 43.313kn (95% CI 42.933 – 43.708kn) i 42.063kn (95% CI 41.747 – 42.397kn); ART je činila 82-84% godišnjih troškova, testovi 10%. Nisu primijećene značajne razlike u broju CD4 limfocita, a prosječna viremija je ostala nemjerljiva između razdoblja. PROQOL-HIV i PAM13 rezultati ostali su visoki i nisu se statistički razlikovali tijekom 12 mjeseci korištenja aplikacije.

Zaključak: Godišnji troškovi prije i nakon uvođenja mHealth sustava smanjeni su za 1%, učinkovita intervencija; ART je glavni izvor troškova. Sudionici su nakon uvođenja mHealth sustava u skrb ostali klinički stabilni, kao i njihova kvaliteta života i sposobnost samoupravljanja. Može se očekivati i buduća učinkovitost uvođenjem mHealth sustava kroz Kliniku. Dodatne analize uključivat će troškove za bolesnike.

The Cost-effectiveness of the EmERGE Pathway of Care for Stable Croatian People Living with HIV

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Purpose: To calculate the cost-effectiveness of an mHealth supported Pathway of Care for clinically stable people living with HIV managed at the Klinika za Infektivne Bolesti Dr.Fran Mihaljevic, Zagreb Croatia. This enables individuals to receive HIV treatment information on their smart-phone via the mHealth App.

Methods: The 293 study participants of the EmERGE study mainly used HIV outpatient services, the focus of the costing study. Unit costs were calculated and linked to mean per patient year (MPPY) use of HIV services. Data on use of services were collected retrospectively one-year before and prospectively one-year after the introduction of the mHealth App, enabling annual cost of HIV service provision to be estimated. Annual costs were combined with biomedical and social outcome data – CD4 count, Viral Load, quality of life (PROQOL-HIV), self-management (PAM13) respectively, before or after the introduction of the App. Costs were calculated in Kuna.

Results: Mean outpatient visits decreased from 5.2 (95%CI:4.9 to 5.5) to 4.75 (95%CI: 4.5 to 5.0) MPPY. Annual costs were 43,313 KN (95%CI 42,933 – 43,708 KN) pre-mHealth and 42,063KN (95%CI 41,747 – 42,397) post-mHealth; ARVs comprised 82-84% of annual costs, tests 10%. No significant differences in CD4 counts were observed and average viral load remained undetectable between periods. PROQOL-HIV and PAM13 scores remained high and did not differ statistically over the 12 months since using the App.

O-25 Istraživanje Positives Perspectives – koji su izazovi i potrebe osoba koje žive s HIV-om?

Ana Slavikovski

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Međunarodno Istraživanje Positives Perspectives je anketa koju je provela kompanija ViiV Healthcare u suradnji s međunarodnim, multidisciplinarnim odborom koji je uključivao liječnike te osobe koje žive sa HIV-om (PLHIV). Cilj ankete bio je razumijevanje perspektiva i stavova ljudi koji žive s HIV-om, kao i njihovih partnera. Prvi podaci iz istraživanja objavljeni su 2017, a u međuvremenu je obuhvaćeno mišljenje 1.111 PLHIV-a o raznim temama kao što su stigma, potpora koju imaju ili pružaju svojim pozitivnim partnerima za HIV, ulogu koju imaju u donošenju odluka o liječenju i izazovi s kojima se suočavaju. Istraživanjem se nastojalo zabilježiti iskustva i mišljenja velike i raznolike međunarodne skupine PLHIV-a, o temama psihosocijalnih aspekata življenja s HIV-om, dijaloga između bolesnika i pružatelja zdravstvene skrbi te s trenutnim antiretrovirusnim terapijama. Predavanje će kratko pokriti ključne uvide o izazovima sa stigmom i diskriminacijom, emocionalnoj podršci koju PLHIV ima i kome se obraća za potporu; otkrivanju HIV statusa; Iskustvima s liječenjem te načinu komunikacije između PLHIV-a i njihovog liječnika.

“Positives Perspectives” survey – tackling challenges and needs of PLHIV

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The Positive Perspectives survey is an international survey conducted by ViiV Healthcare in collaboration with an international, multi-disciplinary Steering Committee that included HIV physicians, PLHIV and patient group representatives. The aim of the survey was to understand the perspectives and attitudes of people living with HIV and their partners.

First Data from the Positive Perspective survey was announced in 2017, exploring the perspective of partners or significant others (1,111 PLHIV surveyed) on the support they provide to their HIV positive partner, the role they play in treatment decision-making and the challenges they may face associated with their partner's HIV. The Positive Perspectives survey sought to capture the experiences and opinions of a large and diverse international group of PLHIV, on the topics of the psychosocial aspects of living with the virus, dialogues between patient and healthcare provider and satisfaction with current antiretroviral therapies. Lecture will briefly cover key insights on The emotional support/guidance PLHIV received at diagnosis and where they turn to for support now; How open PLHIV are about disclosing their status; Experiences with stigma and treatment; communications between PLHIV and their doctor.

NOVOSTI U LABORATORIJSKOJ DIJAGNOSTICI
ADVANCES IN LABORATORY DIAGNOSTICS

O-26 Current approaches to rapid pathogen detection in septic patients

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Blood culture is the gold standard for detection of bloodstream infections. Its major limitations are the delay before results become available, poor sensitivity for slow-growing and fastidious organisms and decrease of sensitivity after initiation of antimicrobial therapy. These limitations can be partially overcome by using emerging technologies such as mass spectrometry, hybridization methods, microarrays and different variants of polymerase chain reaction which shorten the time to pathogen identification.

Technologies for rapid identification of bloodstream pathogens can be separated into two categories based on sample type: either positive blood cultures or blood samples.

Blood culture remains an indispensable method for identification of bloodstream pathogens, which can be supplemented with a variety of technologies for rapid microbial identification. When combined with antibiotic stewardship programs, these approaches may provide clinical benefits for the management of patients with sepsis.

O-27 Novosti u dijagnostici invazivnih gljivičnih infekcija

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Kultura gljiva iz primarno sterilnih uzoraka odnosno samog mjesta zahvaćenog infekcijom te bronhoalveolarnih lavata (BAL) uz histopatološki dokaz invazije tkiva predstavljaju zlatni standard i smatraju se dokazom invazivne gljivične infekcije. Problem predstavlja dobivanje invazivnog uzorka te niska osjetljivost i trajanje kultivacije. Rani početak primjene antifungalne terapije utječe na preživljenje bolesnika zbog čega se u dijagnostici koriste i druge dijagnostičke metode uključujući fungalne biomarkere, molekularne metode, te u novije vrijeme imunokromatografski testovi. Određivanje fungalnih biomarkera (galaktomanana i beta-D-glukana) radi se većinom pomoću imunoenzimske odnosno kolorimetrijske metode što zahtijeva prikupljanje dovoljnog broja uzoraka radi bolje iskoristivosti testa. To može biti problem u laboratorijima koji obrađuju uzorke manjeg broja bolesnika zbog čega vrijeme do izdavanja rezultata može biti predugo da bi imalo utjecaj na kliničku odluku o liječenju. Ovaj problem pokušava se riješiti razvojem novih metoda.

Za određivanje beta-D-glukana odnedavno je na raspolaganju turbidimetrijska metoda koja omogućuje testiranje pojedinačnih uzoraka ali vjerojatno niže osjetljivosti te graničnih vrijednosti koje se trenutno još uvijek definiraju. Za određivanje galaktomanana postoji imunokromatografski test za ispitivanje uzoraka seruma i BAL-a pri čemu osjetljivost i specifičnost kod uzoraka seruma zahtijeva daljnju evaluaciju.

Molekularni testovi koriste se prvenstveno za detekciju *Aspergillus* spp i *Pneumocystis jirovecii* te postoje brojne *in-house* metode i *real-time* PCR komercijalni testovi od kojih neki omogućuju i otkrivanje rezistencije na azole. Novosti u brzom dijagnostici kandidemije je T2 magnetska rezonanca s PCR-om koja omogućuje otkrivanje klinički najvažnijih vrsta *Candida* spp direktno u uzorcima krvi.

U fazi istraživanja su elektronski nos i analiza hlapivih komponenti u izdahnutom zraku pomoću koje se stvara fingerprint složenih mirisa i metabolički profil jedinstven za invazivnu aspergilozu. U dijagnostici invazivne aspergiloze pokušava se koristiti i otkrivanje siderofora (triacetilfuzarinin) u serumu i urinu te interpretacija fungalnih biomarkera u kontekstu inflamatornih markera (IL-8).

New insights into laboratory diagnosis of invasive fungal infections

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Cultivation from primary sterile samples or infected site and bronchoalveolar lavage (BAL) with histopathological proof of tissue invasion is a gold standard for invasive fungal infection diagnosis. Problem is to obtain invasive sample and low sensitivity and duration of cultivation as well. Early start of antifungal treatment influences patient survival. Recently, additional diagnostic methods including fungal biomarkers, molecular methods and immunochromatographic assays are also used. Fungal biomarkers (galactomannan and beta-D-glucan) are determined with immunoenzymatic and colorimetric methods demanding collection of adequate number of samples for better test usability. It poses a problem in labs with lower number of patient samples leading to long turn-around-time with no influence of results on clinical decision.

Recently, for determining of beta-D-glucan there is turbidimetric method available that enables single sample testing but with possibly lower sensitivity and cut-off values still to be defined. Immunochromatographic tests for determining of galactomannan in serum and BAL samples is also available, but sensitivity and specificity for serum samples still in evaluation.

Molecular methods are mainly used for detection of *Aspergillus* spp i *Pneumocystis jirovecii* with numerous *in-house* methods and *real-time* PCR commercial tests, some also enabling detection of azole resistance. New methods in fast candidemia diagnostics is T2 magnetic resonance with PCR enabling detection of clinically important *Candida* spp directly from blood samples.

Under investigation is electronic nose and analysis of volatile compounds in expired air in which metabolic profile unique for invasive aspergillosis is defined. For diagnostics of invasive aspergillosis there are also attempts to use siderophores (triacetilfusarinin) in serum and urine and interpretation of fungal biomarkers in the context of inflammatory markers (IL-8).

O-28 Ispitivanje osjetljivosti na antifungike

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Ispitivanje osjetljivosti na antifungike uzročnika invazivnih gljivičnih infekcija (IGI) je izuzetno važno i utječe na ishod bolesnika oboljelih od ovih infekcija. Danas postoje dva internacionalno prihvaćena standarda ispitivanja osjetljivosti na antifungike Clinical and Laboratory Standards Institute (CLSI) i European Committee on Antimicrobial Susceptibility Testing (EUCAST). Referentna metoda u oba standarda je mikrodilucija koja je tehnički zahtjevnija za izvođenje, ali i za očitavanje testa. Ovi standardi omogućavaju kategorizaciju izolata u osjetljive, intermedijarne i rezistentne i time daju odgovor na pitanje kliničara koji antifungik primjeniti u liječenju. Standardi za interpretaciju postoje samo za neke gljivične izolate, ali ne za sve koje svakodnevno susrećemo kao uzročnike IGI. Kod testiranja uzročnika za koje ne postoje granične vrijednosti za interpretaciju osjetljivosti koriste se epidemiološke granične vrijednosti (ECV, ECOFF) koje govore o tome koja je gornja granica raspona MIK-ova za divlji soj. U nedostatku graničnih vrijednosti za interpretaciju osjetljivosti na antifungik ukoliko su viši MIK-ovi od uobičajenih moguć je loš klinički odgovor na antifungik.

U području ispitivanja osjetljivosti na antifungike javlja se sve više komercijalnih metoda koje su obično jednostavnije za izvođenje i očitavanje u laboratoriju. Neke od komercijalnih metoda dobro koreliraju s referentnim standardiziranim metodama, no neke komercijalne metode imaju lošu korelaciju pa je potreban oprez pri odabiru metode kako bi se olakšao izbor odgovarajućeg antifungalnog lijeka.

Razvijaju se i nove tehnologije za ispitivanje osjetljivosti na antifungike npr platforma za detekciju rezistencije na ehinokandine, koje se baziraju na nukleinskim kiselinama, što je posebno značajno kod izolata *Candida glabrata*. *Candida glabrata* sve je češće rezistentna na ehinokandine, koji su prvi izbor liječenja infekcija izazvanih ovim uzročnikom.

MALDI-TOF-MS metode za detekciju rezistencije na ehinokandine ili azole potrebno je još dalje istraživati u svrhu standardizacije.

Antifungal susceptibility testing

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Antifungal susceptibility testing of fungi causing invasive fungal infections (IFI) is extremely important and it has important impact on patient outcome. Today we have two internationally accepted standards of antifungal susceptibility testing: Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST). Referent method in both standards is microdilution and it is technically demanding for performing but also reading the results. However those standards enable categorization of isolates in categories: susceptible, intermediate and resistant and provide the answer to question what antifungal drug should be used. Standards for interpretation don't have breakpoints for all fungal isolates that can cause IFI. In case of infection caused with such fungi epidemiological cut-off values (ECV, ECOFF) are used. Epidemiological cut-off values define the upper limit of "wild" type MIC distributions. In case of MIC-s that are higher than upper limit of "wild" type MIC-s there is possibility of poor clinical outcome.

More commercial methods are available in the field of antifungal susceptibility testing. These methods have usually simpler performance than reference standard. Some of those commercial methods showed good correlation with reference method results. On the other hand, some of them have poor correlation with reference method results. Thus, it is very important which method is used in order to improve selection of appropriate antifungal drug for treatment.

New approaches to antifungal susceptibility testing will enhance its clinical usefulness in the near future. Very important is development of platforms based on molecular methods for echinocandins resistance detection. Those platforms are especially important in *Candida glabrata*. *Candida glabrata* resistance to echinocandins is increasing.

MALDI-TOF-MS methods for resistance detection to echinocandins and fluconazole should further be evaluated in order to standardization.

O-29 Prenosivi instrumenti za molekularnu dijagnostiku: trenutno stanje i izazovi

Snježana Židovec Lepej

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Prenosivi instrumenti za molekularnu dijagnostiku infektivnih bolesti imaju važnu ulogu u mobilnoj mikrobiologiji. Cilj ove prezentacije je analizirati tehničke karakteristike prenosivih instrumenata za molekularnu dijagnostiku s posebnim naglaskom na okolišne čimbenike te prikazati rezultate novih validacijskih studija molekularnih testova koji se izvode na ovim instrumentima. Nekoliko prenosivih instrumenata za molekularnu dijagnostiku koji su odobreni za kliničku primjenu zadovoljavaju zahtjeve izazova mobilne mikrobiologije. Molekularna dijagnostika dostupna na prenosivim instrumentima najčešće omogućuje ranu dijagnozu HIV-1/2 infekcije u djece zaraženih majki kao i brzu detekciju HCV RNA i DNA *M. tuberculosis*. Iako nekoliko prenosivih instrumenata za molekularnu dijagnostiku zadovoljava tehničke preduvjete za rad u mobilnim laboratorijima, potrebno je naglasiti da postoje značajna ograničenja u njihovoj primjeni, prvenstveno zbog vrlo ograničenog broja molekularnih testova koji su dostupni na pojedinim platformama kao i zbog relativno velikog postotka analitički neadekvatnih rezultata.

Portable instruments in molecular diagnostics: current status and challenges

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Portable instruments for molecular diagnostics of infectious diseases play an important role in mobile microbiology. The aim of this presentation is to discuss technical features and environmental requirements of portable molecular diagnostics instruments as well as recent data on validation studies. Several portable molecular diagnostics instruments approved for clinical diagnostics are suitable for mobile microbiology laboratories. The majority of instruments provide a limited number of assays with a particular emphasis of early infant diagnosis of HIV as well as rapid detection of HCV RNA and DNA of *M. tuberculosis*. Although several portable instruments for molecular diagnostics available on the market fulfill technical requirements for field work, important limitations of these instruments, including a limited range of assays per platform and relatively high frequency of invalid results, have been identified.

NERIJEŠENA PITANJA U VIRUSNOM HEPATITISU – HEPATOCELULARNI KARCINOM
UNRESOLVED ISSUES IN CHRONIC HEPATITIS-HEPATOCELLULAR CARCINOMA

O-30 Trendovi u pojavnosti hepatocelularnog karcinoma u Hrvatskoj

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Cilj: Prikazati epidemiološku situaciju i trendove pojavnosti hepatocelularnog karcinoma u svijetu i Hrvatskoj.

Materijali i metode: Epidemiologija hepatocelularnog karcinoma u Hrvatskoj prikazat će se deskriptivnom metodom temeljem podataka registra za rak Hrvatskog zavoda za javno zdravstvo (HZJZ) i pregleda literature.

Rezultati i zaključak: U svijetu je 2018. godine bilo 841 080 novooboljelih od raka jetre, a umrlo ih je 781 631, od kojih je u Europi bilo oko 10 % slučajeva raka jetre i smrti od raka jetre. Najveće stope incidencije i mortaliteta od raka jetre (oko 70 % svih slučajeva) bilježe se u Aziji. Prema dobno-standardiziranoj stopi incidencije (9,3/100.000) rak jetre je globalno na sedmom mjestu po pojavnosti među karcinomima. U Europi je procijenjena stopa incidencije raka jetre 5,1, a smrtnosti 4,4 na 100.000 stanovnika, što rak jetre svrstava na 18. mjesto po pojavnosti među karcinomima (GLOBOCAN 2018). Prema podacima GLOBOCAN-a procjena dobno-standardizirane stope incidencije raka jetre u Hrvatskoj u 2018. godini je 6,3/100 000, što ga svrstava na 18. mjesto po učestalosti među zloćudnim bolestima, a procjena stopa mortaliteta 5,2 /100.000, (9. mjesto po smrtnosti). Stopa smrtnosti od ukupnog raka jetre u razdoblju 2000.-2016. godine u Hrvatskoj nešto je viša od prosjeka zemalja članica EU (Health for all, WHO, 2019).

Prema podacima registra za rak posljednjih godina (2012.-2016.) prosječno se godišnje bilježi više od 500 oboljelih od raka jetre, od kojih je oko 260 oboljelih od hepatocelularnog karcinoma (raspon 233-304), a godišnje se prosječno bilježi nešto više od 500 smrtnih ishoda od raka jetre. Rak jetre češće se bilježi među muškarcima i on je na 10. mjestu po učestalosti te čini udio od 3 % svih sijela karcinoma u muškaraca. Češće se otkrije u starijoj dobi, najveći broj slučajeva dijagnosticiranih u razdoblju 2001.-2016. zabilježen je u dobnim skupinama 60-79 (64 %). Trendovi incidencije i smrtnosti od raka jetre (ukupno) i hepatocelularnog karcinoma u razdoblju 2001.-2016. su u kontinuiranom blagom porastu. S obzirom na način prikupljanja podataka o incidenciji i mortalitetu i ograničenja svakog od tih sustava, podatke o incidenciji i mortalitetu je potrebno tumačiti oprezno, kao i neprestano raditi na unapređenju kvalitete.

Ključne riječi: rak jetre, hepatocelularni karcinom, trend pojavnosti, Hrvatska

Trends in hepatocellular carcinoma in Croatia

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Aim: To present the epidemiological situation and incidence trends for hepatocellular carcinoma in Croatia and worldwide.

Materials and methods: The epidemiology of hepatocellular carcinoma in Croatia will be presented with descriptive method based on data obtained from the cancer registry of the Croatian Institute of Public Health (CIPH) and the reviewed literature.

Results and conclusion In 2018 there were 841 080 new cases of liver cancer with 781 631 deaths worldwide, of which about 10% of cases and deaths from liver cancer were in Europe. The highest incidence and mortality rates of liver cancer (about 70% of all cases) were recorded in Asia. According to age-standardized incidence rate (9.3/100.000) liver cancer ranks seventh among cancers worldwide. The estimated incidence rate of liver cancer in Europe is 5.1 and mortality rate is 4.4 per 100 000 inhabitants, ranking liver cancer eighteenth in terms of incidence among all cancers (GLOBOCAN 2018).

According to GLOBOCAN the estimated age-standardized incidence rate of liver cancer for Croatia in 2018 is 6.3/100 000, ranking it eighteenth in terms of incidence among malignant diseases, with estimated mortality rate of 5.2/100 000 (ranking ninth in terms of mortality). Liver cancer mortality rate between 2000 and 2016 in Croatia was slightly above average for EU member states (Health for all, WHO, 2019).

According to the cancer registry in recent years (2012-2016) more than 500 new cases of liver cancer are recorded annually, with about 260 cases of hepatocellular carcinoma (range 233-304), and over 500 deaths from liver cancer. Liver cancer is more common in males, ranking tenth in terms of incidence and accounting for 3% of all carcinoma sites in males. It is more frequently diagnosed in advanced age, with highest number of cases between 2001 and 2016 diagnosed in age group 60-79 (64%). Incidence and mortality trends for liver cancer (in general) and hepatocellular carcinoma between 2001 and 2016 are on continuous slight increase. With respect to the type of data collection on incidence and mortality, and limitations of each of these systems, the data on incidence and mortality should be interpreted cautiously. Continuous work on advancement of data quality is also necessary.

Key words: liver cancer, hepatocellular carcinoma, incidence trend, Croatia

O-31 Virusni hepatitis i karcinogeneza

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Viral hepatitis and carcinogenesis

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O-32 Što se događa u jetri nakon eliminacije virusa?

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What happens to the liver after viral clearance?

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O-33 Liječenje HCV-om uzrokovanog HCC-a

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Treatment of HCV-related HCC

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RACIONALIZACIJA UPORABE ANTIBIOTIKA
RATIONAL ANTIBIOTIC PRESCRIBING

O-34 Novosti o radu AMS tima u OB Koprivnica

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Rastući problem antimikrobne rezistencije doveo je do kompleksnijeg propisivanja antimikrobne terapije. Propisivanje prikladne antimikrobne terapije više ne uključuje jednostavan odabir empirijskog ili terapijskog antibiotika koji će prikladno djelovati na uzročnika kod odgovarajućeg pacijenta, već podrazumijeva skup kompleksnih postupaka za što je potrebno uključenje čitavog tima za antimikrobno upravljanje (A-tim). Uslijed navedenog u Hrvatskoj je osnovan prvi A-tim 1.rujna 2017. godine koji je dokazao uspjeh imlementacije kod propisivanja posebne skupine antibiotika koji se daju u zadnjoj liniji liječenja kada drugi antibiotici više ne djeluju (tzv.antibiotici rezerve). A-tim se sastoji od infektologa kao vođe A-tima, kliničkog mikrobiologa i kliničkog farmaceuta. Međutim, studije pokazuju kako je potreban kontinuirani rad A-tima kako bi se održao njihov učinak. U tu svrhu A-tim je nastavio s radom te su vidljivi rezultati u 3 polugodišnja intervala (poput održavanje smanjenja potrošnje antibiotika rezerve ili smanjenja bolničkih infekcija uzrokovanih *Cl.dificile*). Također će se prikazati bazične infektološke, ali i farmaceutske intervencije, ali i prepreke s kojima se svakodnevno susreće A-tim.

Advances in the AMS team activities in GH Koprivnica

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The growing problem of antimicrobial resistance has led to more complex prescribing of antimicrobial therapy. Prescribing of suitable antimicrobial therapy no longer involves a simple selection of an empirical or therapeutic antibiotic that will suitably affect the cause of the appropriate patient, but it involves a complex set of procedures that requires the involvement of the entire antimicrobial stewardship team (A-team). As a result of this, in Croatia, the first A-team was established on 1st July 2017, which proved the success of implementation in prescribing of the special groups of antibiotics that are given as the last line of treatment when other antibiotics no longer work (the so-called reserve antibiotics). The A-team consists of an infectious disease specialist as the leader, a clinical microbiologist and a clinical pharmacist. However, studies show that continuous work of A-team is needed to maintain their positive effect. For this purpose, the A-team has continued its work and the latest results can be seen from 3 six-months periods (such as maintaining reduction of reserve antibiotics consumption or hospital-acquired *Cl.dificile* infections). Also basic infectology and pharmacist' interventions will be shown, together with everyday obstacles of A-team.

O-35 Upravljanje uporabom antimikrobnih lijekova u KBC Split: dosadašnja iskustva

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Nekritična uporaba antimikrobnih lijekova ima brojne negativne posljedice, među ostalim i rastuću rezistenciju mikroorganizama. Upravljanje uporabom antimikrobnih lijekova jedan je od ključnih temelja u nadvladavanju razvoja rezistencije, a uključuje implementaciju niza koraka kojima se postiže pažljiva i odgovorna primjena antimikrobnih lijekova.

Izbor strategija programa za upravljanje uporabom antimikrobnih lijekova ovisi o lokalnim potrebama i problemima, kao i dostupnosti infrastrukture, stručnog kadra i drugih resursa. Nedostatak potonjeg dovodi do problema koji lako mogu obeshrabriti provedbu programa. Ipak, i u takvoj situaciji je moguće postići pozitivne promjene, primjerice uvođenjem lakših i manje skupih pristupa.

Takvi pristupi uključuju, među ostalim, ograničavanje dostupnosti određenih antimikrobnih lijekova i formulare kojima se zahtijeva i obrazlaže razloge primjene određenog rezervnog lijeka, uvođenje lokalnih smjernica za primjenu antimikrobnih lijekova u liječenju i kirurškoj profilaksi, bržu mikrobiološku dijagnostiku i bolju komunikaciju s mikrobiološkim laboratorijem, uvođenje tzv. antibiotskih vizita i revizije antimikrobnog liječenja s naglascima na deeskalaciju (illi po potrebi eskalaciju) terapije, racionalno skraćivanje dužine terapije, optimizaciju farmakokinetike i farmakodinamike, konverziju načina primjene lijeka s parenteralnog na peroralni put, procjenu potrebe za kombiniranom terapijom itd. Posebnu važnost ima kontinuirana edukacija svih zdravstvenih djelatnika koji sudjeluju u propisivanju antimikrobnih lijekova.

Jeftin, praktičan i učinkovit alat za procjenu kvalitete propisivanja antibiotika su studije prevalencije propisivanja antimikrobnih lijekova, pogotovo u nedostatku elektronske umreženosti. One pomažu identificirati ciljeve koji zahtijevaju poboljšanje kvalitete, te u nedostatku ljudskog kadra i drugih resursa olakšavaju usmjeravanje intervencije na najaktualniji problem. Također olakšavaju praćenje učinkovitosti intervencija.

Iako je KBC Split i ranije imao određene mjere kontrole propisivanja antimikrobnih lijekova, od 2015. godine se, pod vodstvom Povjerenstva za kvalitetu, započelo s intenzivnijim mjerama upravljanja uporabom antimikrobnih lijekova, i to provođenjem studija prevalencije propisivanja antibiotika i postepenim uvođenjem intervencija prema zadanim mogućnostima. Postignuti uspjeh u provođenju intervencija daje entuzijazam kojim se lakše suočavati s novim, složenijim izazovima.

Antimicrobial stewardship in UHC Split: experience to date

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The irrational use of antimicrobial agents has a number of negative consequences, including the growing resistance of microorganisms. Antimicrobial stewardship is one of the key foundations in overcoming the development of resistance, and involves the implementation of a series of steps to achieve the careful and responsible administration of antimicrobials.

The choice of strategies for antimicrobial stewardship depends on local needs and problems, as well as the availability of infrastructure, expertise and other resources. The lack of the latter leads to problems that can easily discourage program implementation. However, even in such a situation, positive changes can be achieved, for example by introducing easier and less expensive approaches.

Such approaches include, among others, restricting availability of certain antimicrobials and formulary restrictions requiring an explanation of the reasons for using a particular drug, introducing local guidelines for the use of antimicrobials in treatment and surgical prophylaxis, faster microbiological diagnostics and better communication with the microbiological laboratory, the introduction of so-called 'antibiotic visits' and revisions of antimicrobial treatment with emphasis on de-escalation (or escalation if necessary) of therapy, rational reduction of therapy length, optimization of pharmacokinetics and pharmacodynamics, intravenous to oral conversion, assessment of the need for combination therapy, etc. Of particular importance is the continuing education of all healthcare professionals involved in prescribing antimicrobials.

An inexpensive, practical and effective tool for assessing the quality of antibiotic prescribing are point prevalence studies of antimicrobial prescribing, especially in the absence of adequate electronic networking system. They help to identify goals that require quality improvement, and make easier to focus on the interventions that are of most need in the absence of human and other resources.

Although UHC Split has previously had some control measures in the prescribing of antimicrobials, more intensive measures under the guidance of the Quality Committee have been taken since 2015, primarily by conducting point prevalence studies of prescribed antibiotics and gradually introducing interventions according to the given possibilities.

The success of implementing the interventions gives the enthusiasm that helps easier to face new, more complex challenges.

O-36 Praćenje infekcija i potrošnje antimikrobnih lijekova u domovima za starije i nemoćne u Hrvatskoj

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Surveillance of infections and antibiotic consumption in Croatian nursing homes

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O-37 Restriktivno izdavanje nalaza

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Restrictive reporting

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VIRUSNI HEPATITISI – NA PUTU ELIMINACIJE
VIRAL HEPATITIS: ON THE WAY TOWARDS THE ELIMINATION

O-38 Eliminacija virusnih hepatitisa – gdje se nalazimo?

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Elimination of viral hepatitis, where are we now?

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O-39 Na putu prema eradikaciji hepatitisa C: Hrvatski nacionalni akcijski plan

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On the road to eradicate hepatitis C: Croatian national action plan

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In May 2016, the World Health Assembly endorsed the first Global Health Sector Strategy on viral hepatitis which calls for elimination of viral hepatitis as a public health threat by 2030 through implementation of national strategies. Elimination is defined as a 90% reduction in new infections and a 65% reduction in mortality. Countries are urged to develop national strategies or action plans appropriate to their local epidemiological circumstances and health system capacities.

Croatia has developed a national action plan for prevention and control of viral hepatitis 2019-2030 according to WHO published guidance and based on national epidemiological and disease burden data collected in 2017. National strategy defines aims, long-term goals (2030), short-term goals (2021), core indicators, activities, responsible groups, monitoring and evaluation systems and financial framework.

The initial assessment of the existing data has shown that hepatitis B and C still pose a significant public health burden with an estimated 25,000 persons chronically infected with HBV and about 40,000 anti-HCV positive persons. People who inject drugs (PWIDs) have the highest risk for HCV infection with prevalence of 30-40%.

The national action plan focuses on 5 long-term goals: 1. Raising the awareness of general population and key populations on risks and protection from viral hepatitis 2. Monitoring health sector response to hepatitis 3. Reducing new infections with viral hepatitis by 90% 4. Strengthening the hepatitis A surveillance 5. Reducing the mortality from chronic hepatitis by 65%.

The main objective of the goal 1 is to increase education of primary care physicians in screening people at-risk.

To achieve the goal 2 estimates of morbidity and mortality due to chronic hepatitis B and C have to be defined and every case of cirrhosis and hepatocellular carcinoma has to be attributed to a cause.

The main objective for the goal 3 is to decrease HCV incidence among PWID by strengthening the harm reduction programmes, increasing testing and linkage to care. In order to reduce the mortality by 65% at least 500 patients with hepatitis C have to be treated annually.

By implementation of national action plan Croatia as a small country has a reasonable chance to eliminate the viral hepatitis by 2030.

O-40 Uloga nacionalnog osiguravatelja u ostvarenju akcijskog plana

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The role of national health insurance fund in the implementation of viral hepatitis action plan

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O-41 Trendovi mortaliteta i morbiditeta kroničnih virusnih hepatitisa u Hrvatskoj

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Cilj: Prikazati epidemiološku situaciju kroničnih virusnih hepatitisa B i C u Hrvatskoj. Materijali i metode: Epidemiologija virusnih hepatitisa prikazat će se deskriptivnom metodom temeljem podataka registra za zarazne bolesti, javnozdravstvenog registra uzroka smrti Hrvatskog zavoda za javno zdravstvo (HZJZ).

Rezultati i zaključak: Hrvatska ima nisku prevalenciju infekcije virusom hepatitisa B (HBV) i hepatitisa C (HCV) u općoj populaciji. Prema rezultatima seroepidemioloških studija, oko 0,2 % - 0,7 % opće populacije ima kronični hepatitis B, a 0,5 % - 0,9 % anti-HCV protutijela, dok osobe s povećanim rizikom za zarazu imaju značajno višu prevalenciju (osobe koje injektiraju droge čine glavnu rizičnu skupinu za infekciju HCV-om s prevalencijom od 29 % - 65 %). Procjenjuje se da oko 25.000 osoba ima kroničnu infekciju HBV, a oko 40.000 osoba nosioci su anti-HCV protutijela. Prema podacima registra zaraznih bolesti HZJZ-a u posljednjih pet godina prosječno se godišnje zabilježi 115 oboljelih od hepatitisa B i 181 oboljelih od hepatitisa C, što pokazuje stabilan trend pojavnosti hepatitisa B i C u Hrvatskoj. Prema podacima iz baze hospitalizacija HZJZ-a, u promatranom petogodišnjem razdoblju je zbog kroničnih virusnih hepatitisa B i C bilo prosječno godišnje 2.060 hospitalizacija u stacionarnom dijelu i dnevnim bolnicama. Prema podacima javnozdravstvenog registra uzroka smrti HZJZ-a u razdoblju 2009.-2018. godine prosječno je bilo godišnje zabilježeno 95 smrtnih ishoda od kroničnih virusnih hepatitisa B i C. U svrhu poboljšanja kvalitete podataka i razumijevanja epidemiološke situacije i rizičnih čimbenika povezanih s pojavnosti virusnih hepatitisa, za oboljele u 2018. godini prikupljeni su anketni upitnici za 62 % oboljelih od hepatitisa B i 21 % oboljelih od hepatitisa C, što je za prvu godinu dodatnog praćenja razmjerno dobar udio prikupljenih dodatnih epidemioloških i kliničkih podataka, no zahtijeva ulaganje dodatnog napora u poboljšanje praćenja virusnih hepatitisa.

Ključne riječi: virusni hepatitisi, epidemiološka situacija, morbiditet, mortalitet, Hrvatska

Trends in mortality and morbidity from chronic hepatitis in Croatia

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Aim: To present the epidemiological situation of chronic viral hepatitis B and C in Croatia.

Materials and methods: Epidemiology of viral hepatitis will be presented using descriptive method and will be based on data obtained from the communicable diseases registry and causes of death registry of the Croatian Institute of Public Health (CIPH).

Results and conclusion: Croatia has low prevalence of hepatitis B (HBV) and hepatitis C (HCV) virus infection in the general population. According to seroepidemiological studies, about 0.2% - 0.7% of the general population has chronic hepatitis B and 0.5%-0.9% has anti-HCV antibodies, with significantly higher prevalence in people at high risk for infection with HBV or HCV (people who inject drugs are the group with the highest risk of contracting HCV, with prevalence of 29%-65%). It is estimated that about 25 000 people have chronic HBV infection, and about 40 000 people are carriers of anti-HCV antibodies. According to communicable diseases registry of the Croatian Institute of Public Health for the past five years, an average of 115 new cases of hepatitis B and 181 cases of hepatitis C is recorded annually. This indicates a steady incidence trend of hepatitis B and C in Croatia. According to the hospitalisation database of CIPH for the past five years, an average of 2.060 hospitalizations due to chronic viral hepatitis B and C is recorded annually for patients hospitalized in inpatient hospital wards and in day-care hospitals. According to the causes of death registry of CIPH between 2009 and 2018, the average annual number of deaths from chronic viral hepatitis B and C was 95. With the purpose of improving the quality of data and understanding the epidemiological situation and risk factors associated with viral hepatitis, in 2018 we compiled questionnaires from 62% of patients with hepatitis B and 21% of patients with hepatitis C. This is a relatively valuable amount of additional epidemiological and clinical data for the first year of added monitoring. However, additional efforts are needed to improve the monitoring of viral hepatitis.

Key words: viral hepatitis, epidemiological situation, morbidity, mortality, Croatia

O-42 Uloga programa u zajednici u postizanju eliminacije hepatitisa C

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Infekcija hepatitis C virusom (HCV) je vrlo važan javnozdravstveni problem, kako u Splitsko-dalmatinskoj županiji (SDŽ), tako i u Hrvatskoj. Zbog tihog kliničkog tijeka većina bolesnika s hepatitisom C uopće ne zna da su zaraženi pa stoga ne budu na vrijeme prepoznati i liječeni, te predstavljaju izvor infekcije za druge ljude. Nacionalna strategija za kontrolu virusnih hepatitisa, uz ostalo, uključuje edukaciju liječnika primarne zdravstvene zaštite o HCV infekciji, ali isto tako potiče povećanje aktivnosti u pronalaženju novih bolesnika u tzv. „screening“ programima. Od 1993.-2015. godine u SDŽ prijavljeno je 1434 osobe s HCV infekcijom. Budući da je procjena da u SDŽ ima barem još 3000 osoba sa HCV infekcijom koje nisu prijavljene, poduzet je aktivniji pristup u pronalaženju ovih bolesnika. Sastavljen je tim koji se sastoji od različitih zdravstvenih i nezdravstvenih djelatnika radnika, te je poduzet niz aktivnosti koje su usmjerene prema skupinama s višom incidencijom HCV infekcije. Unutar terapijskih zajednica za prevenciju i liječenje bolesti ovisnosti proveden je „screening“ HCV infekcije, a fibroelastografijom su otkrivene ugroženije skupine bolesnika, koje su po ubrzanijem postupku pripremljene za liječenje. Slične aktivnosti poduzete su i u udrugama veterana domovinskog rata, u kojima su testirani branitelji koji u anamnezi imaju podatke o ranjavanju, operacijama i primanju krvi i krvnih pripravaka do 1993. godine. Kao rezultat ovih aktivnosti od 2015. godine povećan je broj novootkrivenih HCV infekcija u stanovnika SDŽ, te je mnogima skraćen put do liječenja. Već spomenuti tim je kroz zadnje četiri godine imao 36 izlazaka na teren tijekom kojih su testirane 652 osobe oralnim brzim testom na C virus i napravljena im je fibroelastografija kojim je utvrđen stupanj oštećenja jetrenog parenhima. Iste aktivnosti planiraju se provesti i u lokalnoj navijačkoj udruzi te u zatvorima u SDŽ među osobama lišenim slobode.

The role of outreach programmes in achieving goals for hepatitis C elimination

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The HCV infection is a serious public health problem, both in Split Dalmatia County (SDC), and in Croatia. Due to a rather silent course of disease, most patients with hepatitis C don't even know they have been infected. Therefore they are neither recognized nor treated on time, and are a source of infection for other people. From 1993 to 2015, there were 1,434 reported cases of HCV infection in SDC. Since it is estimated that there are at least 3,000 persons with HCV infection in the SDC who are not registered, a more active approach in identifying these patients has been initiated. A multidisciplinary team has been established to initiate a number of activities aimed at groups with higher incidence of HCV. Screening for HCV infection was implemented within the therapeutic communities for the prevention and treatment of addiction. Using fibroelastography high-risk patient groups were identified. These patients were enrolled into an urgent treatment program. Similar activities have been taken within the war veterans associations for those that were wounded, had a surgery or received blood transfusion until 1993. As a result of these activities, the number of newly diagnosed HCV infections in the population of SDC has increased since 2015, and many have received their therapy faster. The aforementioned team has had thirty-six field trips over the last four years, during which time 652 people were tested by oral rapid C virus test and fibroelastography was performed to determine the extent of liver parenchyma damage. The same activities are planned in the local fan club associations, as well as in SDC prisons.

NOVOSTI U INTENZIVNOM LIJEČENJU TEŠKIH INFektivNIH BOLESTI
NEWS IN THE TREATMENT OF SEVERE INFECTIOUS DISEASES

O-43 Sepsa i septički šok – epidemiologija, rizični čimbenici i rano prepoznavanje

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Sepsis and septic shock – epidemiology, risk factors and early recognition

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O-44 Apsorpcija citokina u teškim infekcijama

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Cytokine absorption in severe infections

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O-45 Immunoglobulins in sepsis

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Sepsis represents a major cause of morbidity and mortality in critically ill patients. The early diagnosis and appropriate treatment have a crucial influence on survival. Despite of advances in diagnosis and treatment the overall mortality remain unacceptably high. Incidence of sepsis has increased over years, probably due to aging of population, the existence of more comorbidities, aggressive surgical and diagnostic interventions, immunosuppressive treatment and the emergence of resistant bacteria due to non-critical use of antibiotics. Mortality in patients with sepsis varies between 20% and 50% and in patients with septic shock is frequently over 50%. In addition to early hemodynamic stabilization of the patient and antimicrobial treatment, modulation of the immune system and the host response may be an effective therapeutic approach. It has been shown that serum immunoglobulin levels are usually low in severe infections and low IgM and IgG concentrations in septic patients are accompanied with higher mortality rate.

Intravenous immunoglobulins (IVIg) can modulate the host immune response. The mechanism of action is likely multifaceted and include antibacterial or anti-endotoxin activities, reducing the expression of inflammation markers, scavenging these molecules and other immunomodulatory effects. IVIg have been used in septic patients for many years as an adjunctive treatment. However, the recent revision of the Surviving Sepsis Guidelines does not suggest using IVIg in adults with sepsis and septic shock due to low certainty of evidence. Most studies are small, and some have a high risk of bias. The only prospective randomised trial with an adequate sample size found no benefit to the 28-day mortality rate after treatment with polyclonal IgG. On the other hand, several meta-analyses were showing that the adjunctive treatment with IVIg could have beneficial effects for patients with sepsis and there are differences between the effects of different types of immunoglobulins. The reduction in mortality was greater in septic patients treated with IgM enriched IVIg compared to standard IVIg preparations containing only IgG. However, there are several unresolved issues, such as optimal timing of administration, the appropriate dose, and who gets the most from immunoglobulins.

The clinical practice is different, in some countries IVIg are used as a salvage treatment in septic shock patients when standard treatment fails. According to German local guidelines the use of IgM enriched IVIg may be considered for treatment of adult patients with sepsis or septic shock. Some experts use IVIg, usually IgM enriched preparations only in specific clinical situations such as meningococcal sepsis, toxic shock syndrome, overwhelming post splenectomy infection, and necrotizing fasciitis.

The exact role of IVIg in patients with sepsis is still unclear and which subgroup of them will benefit most remains to be shown. Further research is needed to clarify the clinical usefulness of immunoglobulins in patients with sepsis.

O-46 Kortikosteroidi u teškoj pneumoniji

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Pneumonija iz opće populacije i dalje je uzrok značajnog morbiditeta i mortaliteta usprkos efikasnoj antimikrobnoj terapiji. U industrijaliziranim zemljama Europe i Sjeverne Amerike mortalitet hospitaliziranih bolesnika s pneumonijom i dalje je 5-10%, a u jedinicama intenzivne skrbi i do 30%. Smatra se da je neuspjeh liječenja često bar djelomično uzrokovan pretjeranim lokalnim i sistemskim upalnim odgovorom na infekciju. Kortikosteroidi su se pokazali djelotvornima u smirivanju upale i poboljšanju ishoda liječenja nekoliko infektivnih bolesti (pneumokokni meningitis, tuberkulozni meningoencefalitis, P.jiroveci pneumonija). Korisnost imunomodulatornog i protuupalnog djelovanja u liječenju pneumonije potvrđena je u više studija u kojima je imunomodulatorno djelovanje makrolida dovelo do boljeg preživljenja bolesnika s pneumonijom. Stoga su, s obzirom na poznato imunomodulatorno djelovanje kortikosteroida, u posljednjih desetak godina provedene brojne studije kojima se pokušalo utvrditi utjecaj dodavanja kortikosteroida na ishod liječenja bolesnika s pneumonijom iz opće populacije. Iako je većina studija pokazala pozitivan efekt u smislu bržeg postizanja kliničke stabilnosti, skraćenja trajanja antimikrobne terapije ili skraćenja trajanja hospitalizacije, u većini nije nađena statistički značajna razlika u smrtnosti. U većini studija također je zabilježeno da su najviše koristi od kortikosteroida imali bolesnici s teškom pneumonijom. Od nuspojava najčešće je zabilježena hiperglikemija, dok su ozbiljnije nuspojave bila izrazito rijetke. Od 2017. do danas objavljene su dvije velike metaanalize od strane IDSA i Cochrane Library koje su uvelike utjecale na preporuke o korištenju kortikosteroida u novim smjernicama iz 2019. za liječenje pneumonije (IDSA I NICE). Iako se ni u jednim smjernicama ne preporučuje rutinsko davanje kortikosteroida bolesnicima s pneumonijom iz opće populacije, neki ih stručnjaci ipak preporučuju kao opciju u liječenju isključivo teške pneumonije, uz napomenu da su potrebne daljnje studije kako bi se, između ostalog, pobliže utvrdilo koje će skupine bolesnika imati najviše koristi od kortikosteroida te koja je optimalna doza i trajanje liječenja.

Corticosteroids in severe pneumonia

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Community acquired pneumonia (CAP) remains a significant cause of morbidity and mortality despite appropriate antimicrobial treatment. In the industrialized countries of Europe and North America mortality rates of hospitalized patients with CAP are still 5-10%, and in the ICU up to 30%. It is a widely held view that frequent treatment failure is at least in part caused by an excessive inflammatory response to infection. Corticosteroids have been proven effective in suppressing excessive inflammation and thus improving treatment outcomes in several infectious diseases (pneumococcal meningitis, tuberculous meningoencephalitis, *P. jirovecii* pneumonia). The immunomodulatory effect of macrolides has been shown as beneficial in treatment of CAP. With this rationale, many studies have been conducted in order to assess whether the immunomodulatory and anti-inflammatory effect of steroids would be beneficial in treatment of CAP. Although many studies did show a positive effect in terms of shorter time to clinical stability, shorter antimicrobial treatment, and shorter hospitalization, most failed to show a statistically significant survival benefit. Also, most studies showed that the greatest benefit is to be expected with patients with severe pneumonia. The most common side effect of steroids was hyperglycemia, with more serious side effects being extremely uncommon. Since 2017 there were two major meta-analyses published by IDSA and Cochrane Library that influenced the recommendations for corticosteroid use in the most recent guidelines for treatment of CAP, published in 2019 by IDSA and NICE, respectively. Although both guidelines generally recommend not to use corticosteroids routinely in treatment of CAP, some experts still recommend their use in case of severe CAP, while admitting that further studies are needed in order to determine which groups of patients are most likely to benefit from corticosteroids and what is the optimal dose and duration of corticosteroid treatment.

O-47 Sepsa i endokarditis tim

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Usprkos suvremenom liječenju, sepsa i infektivni endokarditis (IE) još uvijek su stanja visokog morbiditeta i mortaliteta. Kompleksnost bolesnika s ovim bolestima, u kojim odgovarajuće postupanje podrazumijeva više komponenti (kao hemokulture, hemodinamski monitoring i terapijske intervencije npr. kirurško liječenje), zahtijeva ranu dijagnozu i odgovarajuće liječenje kako bi se povećale šanse za preživljenje. Bez obzira koliko smo učinkoviti kao individualni liječnici, liječnik pojedinac ne može sam adekvatno zbrinjavati bolesnika s nekom od spomenutih bolesti.

Nekoliko istraživanja je pokazalo da tim liječnika za sepsu (ST) može doprinijeti ishod bolesnika s težim oblicima sepse i da je nužna podrška u razvoju ovakvih timova, osobito u hitnim službama i jedinicama intenzivnog liječenja (JIL). Sepsa tim bi trebao biti dostupan 24 sata tjedno i odgovoran za stabilizaciju i rano liječenje bolesnika s težim oblicima sepse.

Infektivni endokarditis je rijetka, ali važna bolest jer se ponekad teško dijagnosticira, liječi i obavezno smrtonosna ako se neadekvatno liječi. Bolesnici s IE najčešće se liječe u bolnici 4-6 tjedana, a otprilike polovica ih treba kardiokirurško liječenje. S obzirom da je IE uobičajeno septičko stanje praćeno brojnim kardijalnim i nekardijalnim komplikacijama, ovi bolesnici se često liječe i monitoriraju u JIL. Ishod se može poboljšati pravovremenom dijagnozom i odgovarajućim antibiotskim liječenjem i ranim kirurškim zahvatom kad postoji indikacija. Usprkos navedenom, može se kasniti s dijagnozom, griješi se s izborom, trajanjem i dozom antibiotika ili se antibiotik (obično ambulantno) primijeni prije uzorkovanja hemokultura. Bolesnici se često upućuju specijalisti tek u uznapredovaloj fazi bolesti ili se ne primjenjuje kardiokirurško liječenje usprkos postojanju indikacije. Kako bi se ubrzalo i poboljšalo kompleksno odlučivanje, multidisciplinarni timski pristup može pomoći u postupanju s bolesnikom s IE. Takvi timovi su široko prihvaćeni za druga srčana oboljenja, ali nisu još uobičajena praksa za bolesnike s IE usprkos specifičnim preporukama. Uloga endokarditis tima je održavanje redovitih sastanaka s ciljem postavljanja promptne dijagnoze, odabira vrste i trajanja antibiotika i ubrzanja ranog kirurškog liječenja u bolesnika s jasnom indikacijom.

Sepsis and endocarditis team

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Despite modern treatment, sepsis and infective endocarditis (IE) are still conditions with high morbidity and mortality. The complexity of patients with these diseases, in whom appropriate management involves multiple components (like blood cultures, hemodynamic monitoring and therapeutic interventions like surgery), requires early diagnosis and appropriate treatment to maximize chances of survival. No matter how efficient we are as individual doctors, a single doctor simply cannot adequately manage a patient with one of these conditions.

Several studies have now demonstrated that sepsis teams (STs) can improve outcomes for patients with severe sepsis and we must encourage their development, especially in emergency department and intensive care unit (ICU). The ST should be available 24/7 and responsible for stabilization and early treatment of all patients with severe sepsis.

Infective endocarditis is uncommon but important disease because it is sometimes difficult to diagnose, manage and universally fatal unless appropriately treated. Patients with IE remain in hospital for a median of 4–6 weeks and approximately a half requires inpatient cardiac surgery. Since the IE is commonly septic condition followed with cardiac and non-cardiac complications, these patients are often treated and monitored in ICUs. The outcome can be improved by prompt diagnosis and antibiotic therapy and by early surgery when indicated. Despite this, the diagnosis may be delayed, mistakes may be made in the type, duration or dose of antibiotic or the antibiotic may be started (usually ambulatory) before blood cultures are obtained. Patients are still frequently referred to a specialist only at an advanced stage of disease or may not receive surgery even when indicated. To facilitate and improve complex decision-making, a multidisciplinary team approach may support the management of patients with IE. Such teams are widely accepted for other heart conditions, but are not yet common for IE despite being specifically recommended. The role of the ET includes regular meetings in order to make prompt diagnoses, choose the type and duration of antibiotic therapy and to facilitate early surgery in those patients with a clear indication.

INFEKCIJE POVEZANE SA ZDRAVSTVENOM ZAŠTITOM
HEALTHCARE ASSOCIATED INFECTIONS

O-48 Dezinficijensi, rezistencija bakterija i utjecaj na razvoj antimikrobne rezistencije

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Disinfectants, resistance in bacteria and its impact on antimicrobial resistance development

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O-49 U potrazi za multirezistentnim uzročnicima – kada, gdje i zašto?

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Infekcije uzrokovane multirezistentnim (MR) uzročnicima povezane su s lošijim ishodom za bolesnika uključujući povećani morbiditet, mortalitet, troškove liječenja i duže trajanje hospitalizacije u usporedbi s infekcijama uzrokovanim s osjetljivim uzročnicima. Meticilin-rezistentni *Staphylococcus aureus* (MRSA), vancomicin-rezistentni *Enterococcus* spp. (VRE), and multirezistentne Gram-negativne bakterije uključujući enterobakterije koje produciraju beta-laktamaze proširenog spektra (ESBL) karbapenem-rezistentne enterobakterije (KRE), multirezistentni *Pseudomonas aeruginosa* i multirezistentni *Acinetobacter baumannii* glavni su multirezistentni uzročnici u bolničkoj sredini.

Bolesnici mogu biti kolonizirani ovim uzročnicima bez prisutnosti infekcije i istraživanja su pokazala da vrlo često kolonizacija ovim bakterijama prethodi razvoju infekcije. Primjenom prakse da se identificiraju i izoliraju samo bolesnici koji imaju infekciju uzrokovanu s multirezistentnim uzročnicima, ne otkriva se puno veća populacija bolesnika koji su asimptomatski kolonizirani.

Kada se otkrije multirezistentna infekcija ili kolonizacija kod hospitaliziranih bolesnika, većina međunarodnih smjernica preporučuje primjenu mjera kontaktne izolacije kako bi se spriječilo širenje u bolničkoj sredini. Otkrivanje kolonizacije omogućuje i bolji odabir empirijskog antimikrobnog liječenja prilikom razvoja febriliteta i ranu primjenu adekvatne terapije. Dekolonizacija se pokazala učinkovitom u smanjenju morbiditeta i mortaliteta kod infekcija uzrokovanih s MRSA.

Nadzorne kulture predstavljaju izazov za mikrobiološki laboratorij s obzirom na izbor metode (osjetljivost, vrijeme do izdavanja rezultata, složenost), financijske troškove i povećano radno opterećenje laboratorijskih djelatnika. Odluka o uzimanju nadzornih kultura treba se temeljiti na lokalnoj epidemiologiji i rizičnosti bolesnika. Primjena nadzornih kultura ima smisla samo uz istovremeno striktno pridržavanje ostalih mjera prevencije i kontrole infekcija uključujući kontaktnu izolaciju i higijenu ruku.

Searching for multiply resistant organisms – when, where and why?

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Infections caused by multidrug-resistant (MDR) pathogens are associated with worse patient outcomes including increased morbidity, mortality, healthcare costs, and increased hospital lengths of stay when compared to infections by more drug-sensitive pathogens. Methicillin-resistant *Staphylococcus aureus* [MRSA], vancomycin-resistant *Enterococcus spp.* (VRE), and multidrug-resistant Gram-negative bacteria including extended spectrum beta-lactamase producing *Enterobacteriaceae* (ESBL), carbapenem-resistant *Enterobacteriaceae* (CRE), MDR *Pseudomonas aeruginosa*, and MDR *Acinetobacter baumannii* have been mainly responsible for most drug-resistant infections that occur in healthcare settings.

Patients can be also colonized with these pathogens without developing infection, and studies have shown that most often colonization by these bacteria precedes development of infection. The present practice of identifying and isolating patients who develop an infection with antimicrobial-resistant microorganisms fails to identify the far larger population of patients asymptomatically colonized. Once MDR-bacteria infection or carriage is detected in hospitalized patients, most international guidelines recommend the application of contact precautions to these patients to prevent hospital spread. Identifying bacterial colonization may allow to better select empiric antibiotic treatment at the onset of fever or infection, and early adequate therapy obtains a better response in MDR infections. Decolonization has been an effective tool for reduction of morbidity and mortality from infections due to MRSA.

Surveillance cultures present a challenge for microbiology lab regarding the choice of method (sensitivity, turn-around-time, complexity), financial costs and increased laboratory workload. Decision on obtaining surveillance cultures should be made based on local epidemiology and patient risk. Implementation of surveillance cultures has sense only with appropriate adherence to other infection prevention and control measures including contact isolation and hand hygiene.

O-50 Učestalost infekcija kirurške rane i utjecaj različitih perioperativnih protokola

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Incidence of surgical site infections and impact of various perioperative protocols

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O-51 Strategije za prevenciju i liječenje biofilm infekcija

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Metode za prevenciju stvaranja biofilma još se široko ne primjenjuju, a uobičajene metode liječenja i dalje najčešće uključuju kombiniranu primjenu antimikrobnih lijekova i eksplantaciju inficiranih protetskih materijala. Budući da su mikroorganizmi unutar biofilma do tisuću puta rezistentniji na antibiotike, odavno je jasno da bi se isti trebali primjenjivati u maksimalnim podnošljivim dozama te da su njihove kombinacije učinkovitije od monoterapije. Pritom je važno birati antibiotike koji učinkovito prodiru u biofilm te imaju niske minimalne inhibitorne i baktericidne koncentracije u samom biofilmu, a ne samo u populaciji planktonskih mikroorganizama. Također, kad god je moguće, uputno je kombinirati sistemsku antimikrobnu terapiju s lokalnom kao što je, primjerice, inhalacijska antimikrobna terapija kod plućnih biofilm infekcija. Međutim, odavno je jasno da samo primjena antibiotika nije učinkovita u liječenju infekcija povezanih s biofilmom, a ni eksplantacija protetskih materijala nije optimalna terapija jer oba pristupa pridonose povećanju troškova liječenja te psihofizičkoj neugodi pacijenta i njegovom produljenom oporavku. S obzirom na to, važno je napore usmjeriti ka sprječavanju nastanka biofilma. Većina metoda prevencije još je u eksperimentalnoj fazi, no neke su u kliničkoj primjeni. U kliničkoj primjeni su implantati proizvedeni od materijala koji smanjuju adheziju mikroorganizama te koji su obloženi antimikrobnim lijekovima ili nanočesticama iona poput srebra te je tako sve češća primjena kirurških proteza i konaca obloženih antibiotcima te primjena obloga s ionskim srebrom. Obećavajuća su i istraživanja molekula koje ometaju detekciju kvoruma blokadom receptora mikroorganizama. Primjenom fizikalnih metoda poput struje, ultrazvuka, elektromagnetskih polja i lasera u kombinaciji s antimikrobnim lijekovima postiže se sinergistički učinak koji sprječava stvaranje te učinkovito pridonosi disperziji biofilma. Ključan korak u prevenciji i liječenju biofilm-infekcija odigrat će i pronalazak efikasnih metoda detekcije biofilma in vivo, kao i testiranje antimikrobne osjetljivosti u laboratorijskom modelu sličnijem biofilmu, a ne ekstrapoliranje rezultata antimikrobne osjetljivosti planktonskih mikroorganizama.

Strategies for the prevention and treatment of biofilm infections

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Biofilm prevention methods are not widely used in practice yet, and the most common therapeutic approach still consists of combined antimicrobial treatment and removal of infected prosthetic material. Microorganisms within the biofilm are up to thousand times more resistant to antimicrobial treatment, therefore a preferable pharmacological approach includes a combination of antimicrobials given in maximal doses tolerated by the patient. It is important to carefully select antibiotics which efficiently penetrate the biofilm and have low minimal inhibitory and bactericidal biofilm concentration, rather than just low inhibitory and bactericidal concentrations measured on planktonic microorganisms. In addition, it is prudent to combine systemic therapy with locally applied antibiotics, such as antibiotic inhalation in cases of biofilm-related pulmonary infections. However, administration of antimicrobials and removal of implants are not optimal therapeutic solutions because both amount to higher healthcare costs and contribute to patients' psychophysical discomfort and prolonged recovery. Therefore, it is crucial to direct our efforts toward biofilm prevention. Most prevention methods are still experimental, but some have entered clinical setting. Implants, sutures and wound dressings made of materials that lessen microbial adhesion and/or are coated with antibiotics or silver nanoparticles are ever more common in clinical practice. Experiments with molecules that interfere with quorum sensing by receptor blockade are also promising. Application of physical methods such as electrical current, ultrasound, electromagnetic fields and lasers combined with antibiotics show a synergistic effect on preventing biofilm formation and enhance dispersion. A key role in improved approach to biofilm-related infections is going to be a better biofilm detection in vivo, as well as the new laboratory approach to antimicrobial sensitivity testing (AST). Rather than just extrapolating AST results obtained from planktonic populations, it is crucial to implement such an AST method which would better mimic biofilm conditions and make the results more clinically relevant.

O-52 Uloga kliničkog mikrobiologa u praćenju hematoloških bolesnika

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Nitko u medicinskoj skrbi o pacijentima ne razumije i ne zna patogenezu, otkrivanje i identifikaciju, osjetljivost na antimikrobne lijekove te javnozdravstveni problem uzročnika zaraznih bolesti ljudi bolje od medicinskog mikrobiologa koji radi u laboratoriju kliničke mikrobiologije.

Klinički mikrobiolog pomaže u postavljanju diferencijalne dijagnoze, predlaže koje uzorke pacijenata poslati u laboratorij i kojim metodama se služiti u otkrivanju uzročnika u cilju što ranijeg postavljanja točne dijagnoze. Što se prije otkrije patogen, veća je šansa da se pacijent izliječi. Kako bi se u potpunosti iskoristile sve prednosti laboratorijske dijagnostike, mikrobiolog i kliničar trebaju izravno komunicirati. Klinički mikrobiolozi interpretiraju dobivene rezultate, savjetuju o mogućnostima i potrebi daljnjih ispitivanja osjetljivosti uzročnika i liječenja antibioticima. U slučajevima kada je potrebno liječenje antimikrobnim lijekovima, oni daju savjet o izboru takvih lijekova i trajanju liječenja.

U našoj bolnici klinički mikrobiolozi redovito sudjeluju u multidisciplinarnim sastancima s kolegama, drugim specijalistima, koji imaju veliki broj pacijenata sklonih infekcijama, s odjela poput pedijatrije, intenzivne njege i hematologije. Također svakodnevno komuniciraju i s osobljem zaduženim za suzbijanje i kontrolu infekcija kako bi smanjili rizik prijenosa uzročnika među pacijentima.

Hematološki pacijenti izloženi su velikom riziku razvoja teških i smrtonosnih bakterijskih infekcija. Hematološki odjeli imaju veliku potrošnju antibiotika te visoku učestalost multirezistentnih mikroorganizama i članovi našeg mikrobiološkog tima svakodnevno posjećuju (i/ili zovu) ove odjele. Cilj ovog predavanja je rasvijetliti ulogu i odgovornosti kliničkog mikrobiologa u praćenju hematoloških bolesnika.

Clinical microbiologist on hematology ward

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No one in medical care knows and understands the pathogenesis, detection and identification, antimicrobial response, and public health dangers of agents of human infectious diseases better than the medical microbiologist who works in the clinical microbiology laboratory.

Clinical microbiologist can offer advice concerning the differential diagnosis, sampling techniques and detection methods to facilitate diagnosis. The sooner a pathogen is detected the better chance the patient has of getting cured. To fully exploit the benefits of laboratory diagnoses, the microbiologist and clinician should interact directly. Clinical microbiologists provide advice regarding the interpretation of results and the appropriateness of further investigations and antibiotic treatment. In cases where antimicrobial drugs are required, they provide advice concerning the choice of such drugs and the duration of treatment.

In our hospital clinical microbiologists regularly attend multidisciplinary meetings with colleagues from specialties that deal with large numbers of patients with infections, such as pediatrics, intensive care and hematology units. They also communicate daily with hospital-infection-control staff to minimise the risks of cross-infection between patients.

Hematology patients are at high risk for severe life threatening bacterial infection. Hematology units have high rates of antibiotic use and the high incidence of multiresistant microorganisms and members of our microbiology team visit these units (and/or call) on a daily basis. Aim of this lecture is to elucidate the role and responsibilities of clinical microbiologist on hematology ward.

DESET GODINA IZVANTJELESNE OKSIGENACIJE U KLINICI ZA INFektivNE BOLESTI
TEN YEARS OF ECMO IN UHID

O-53 Razvoj respiratornog ECMO centra u Klinici za infektivne bolesti „Dr. Fran Mihaljević“ u Zagrebu

Marko Kutleša

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Development of ECMO at UHID

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O-54 Teška influenza pneumonija: gdje i zašto griješimo?

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Upala pluća je glavna komplikacija influence, a pojavljuje se najčešće u određenih skupina bolesnika s kroničnim bolestima koji se klasificiraju kao skupine visokog rizika. Primarna influenza pneumonija (PIP) nastaje kad virus influence izravno ošteti pluća i obično uzrokuje klinički tešku pneumoniju. Ova bolest ima visoku smrtnost tijekom pandemije i to ne samo u imunosuprimiranih bolesnika i u bolesnika s komorbiditetima, već i u mladih, prethodno zdravih osoba.

Kiničari moraju imati visok indeks sumnje za ovu dijagnozu u bolesnika sa simptomima influence koji brzo (tijekom 2-5 dana) progrediraju do respiratornog distresa (visoka temperatura, otežano disanje, cijanoza). Ključni postupci u liječenju su osiguravanje odgovarajuće osigenacije i ventilacije i pravovremeno antivirusno liječenje. Osobe s težim oblicima bolesti (oni koje je potrebno hospitalizirati ili s dokazom zahvaćenosti donjeg dišnog sustava) ili s visokim rizikom razvoja komplikacija treba liječiti antivirusnim lijekom. Antivirusno liječenje potrebno je primijeniti što je prije moguće s obzirom da je korist takvog liječenja najveća ako se započne u prvih 48 sati od prvih simptoma. Liječenje ne treba odgađati do pristizanja rezultata dijagnostičkog testiranja niti ga ne primijeniti u bolesnika s indikacijom za liječenje koji se prezentiraju >48 sati nakon početka simptoma, osobito onih koji su hospitalizirani. U zimskim mjesecima, tijekom sezone influence važno je razlikovati PIP od sekundarne bakterijske pneumonije s obzirom da liječenje antibioticima neće pomoći bolesnicima s PIP-om.

Američka i Europska stručna društva preporučuju cijepljenje protiv influence za sve osobe starije od 6 mjeseci. Osobe visokog rizika, njihovi bliski kontakti i zdravstveni djelatnici trebaju ostati visoko prioritetne skupine tijekom cijepljene kampanje. Međutim, s obzirom da H1N1 virus još uvijek cirkulira u populaciji u Hrvatskoj (i odgovoran je za PIP), važno je promovirati cijepljenje ne samo za visokorizične skupine, već i za sve starije od šest mjeseci.

Severe influenza pneumonia: where and why we make mistakes?

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The major complication of influenza is pneumonia, which occurs most frequently in certain groups of patients with underlying chronic illnesses who are classified as high risk. Primary influenza pneumonia (PIP) occurs when influenza virus infection directly involves the lung, typically producing a severe pneumonia. It has a high mortality rate during pandemics, not only in immunocompromised individuals and with comorbidities, but also in young healthy adults.

Clinicians should maintain a high index of suspicion for the diagnosis in patients with symptoms of influenza that progress quickly (2-5 days) to respiratory distress (high fever, dyspnea, cyanosis). Ensuring an appropriate oxygenation and ventilation strategy, as well as prompt initiation of antiviral therapy, is essential in management. Individuals with severe disease (requiring hospitalization or with evidence of lower respiratory tract infection) or at high risk for complications should receive antiviral therapy. Antiviral therapy should be initiated as soon as possible since antiviral therapy is most likely to provide benefit when initiated within the first 48 hours of illness. Treatment should not be delayed while awaiting the results of diagnostic testing, nor should it be withheld in patients with indications for therapy who present >48 hours after the onset of symptoms, particularly among patients requiring hospitalization. In the winter months, during influenza season it is important to distinguish PIP and secondary bacterial pneumonia since treatment with antibiotics will not help patients with PIP.

American and European professional societies recommends influenza vaccination for all individuals six months of age and older. High-risk individuals, their close contacts, and health care workers should remain high-priority populations in vaccination campaigns. However, since H1N1 virus still circulates in population in Croatia (and is responsible for PIP) it is important to promote vaccination not only for high risk groups but for all individuals six months of age and older.

O-55 Gljivične koinfekcije u teškoj influenci

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Fungal co-infection in severe influenza – who is at risk?

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Incidence of fungal superinfection during severe influenza is being increasingly reported in literature over last decade, especially in patients treated with VV ECMO. Invasive pulmonary aspergilosis (IPA) is usually seen in immunocompromised patients, however over past years numbers patients with flu and IPA as superinfection is increasing, while data on candida superinfection and its significance is scarce. During 2018/2019 seasonal flu epidemics fungal superinfection during was demonstrated in 27% of patient, *Aspergillus fumigatus* and *Candida albicans* being predominant species. Fungal superfection with *Aspergillus* and *Candida* was associated with increased mortality in influenza patients. Use of systemic corticosteroids was shown to be associated with increased fungal infection rate. Patients on regular therapy with inhaled inhalation corticosteroids was don't seem to have increased increased incidence of fungal superinfection. Further investigation is warranted in order to better understand fungal superinfection in influenza patients.

O-56 VV-ECMO kao terapija premoštenja do transplantacije pluća

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VV-ECMO as a bridge therapy to lung transplantation

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O-57 VV-ECMO i antibiotici

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VV-ECMO and antibiotics

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UROGENITALNE INFEKCIJE
UROGENITAL INFECTIONS

O-58 Mikrobiota spolnoga sustava žena

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Sastav mikrobiote spolnoga sustava značajno se mijenja tijekom života žene. Perinatalno, rezidualni estrogen majke izaziva zadebljanje epitela vagine i taloženje glikogena u stanicama epitela. Stoga, u to doba života vaginalnu mikrobiotu čine mikroorganizmi koji fermentiraju glukozu (prevladavaju laktobacili). Tijekom djetinjstva, majčin estrogen se metabolizira, što rezultira stanjivanjem sluznice, smanjenjem količine bakterija koje fermentiraju glukozu, te prevladavanjem aeroba i fakultativnih anaeroba u vagini. Mala količina laktobacila tipična je za prepupertet. S početkom puberteta, pod utjecajem estrogena, epitel vagine se opet zadebljava, a vaginalna mikrobiota postaje tipična za odrasle žene, te ponovo dominiraju mikroorganizmi koji fermentiraju glukozu poput laktobacila. Tijekom menopauze, usprkos padu estrogena, mikrobiom je sličan stanju u premenopauzi i takav ostaje stabilan. Većinu životnog ciklusa žene u vaginalnoj mikrobioti dominira *Lactobacillus spp.*, a manjak ovih bakterija povezan je s raznim neželjenim komplikacijama kao i s povećanim rizikom od prijenosa spolno prenosivih infekcija. Laktobacili su u stanju inhibirati patogene stvaranjem aktivnih komponenti, poput bakteriocina, mliječne kiseline i vodikovog peroksida. Također, čuvaju epitel potičući stvaranje sluzi i modulirajući imunološki odgovor. Prisutnost laktobacila pokazatelj je zdrave ravnoteže vaginalnog mikrobioma. Smatra se da na nastanak vaginalne disbioze utječe sposobnost nekih bakterija da formiraju gusti prijanjajući biofilm. Infekcije bakterijama koje su povezane sa stvaranjem biofilma, poput *Gardnerella vaginalis* i *Atopobium vaginae*, imaju visoku stopu recidiva i teško ih je liječiti. Unatoč uvjerenju da se razmnožavanje odvija u aseptičnom okruženju, današnja su istraživanja pokazala da gornji dijelovi spolnoga sustava nisu sterilni kako se ranije smatralo. Identificirani su mikroorganizmi u jajnicima, jajovodima i endometriju. Prema novim otkrićima, mikrobiota ženskoga spolnog sustava moguće ima ulogu tijekom oplodnje, implantacije i gestacije.

The microbiota of the female reproductive tract

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The composition of the vaginal microbiota changes remarkably over a woman's lifecycle. Perinatally, residual maternal estrogen induces thickening of the vaginal epithelium and the deposition of glycogen in the epithelial cells, with domination of glucose fermenting microorganisms (mainly lactobacilli). During childhood, the maternal estrogen is metabolized, resulting in thinning of the mucosa, reduction in glucose fermenting bacteria and selection for a wide range of aerobes and facultative anaerobes. Typical for prepuberty is the low abundance of lactobacilli. With the beginning of puberty, under estrogenic control, once again vaginal epithelium thickens, and vaginal microbiota becomes typical for adult women, with glucose fermenting microorganisms, such as lactobacilli as dominated bacteria. During menopause, despite the decline in estrogen, microbiome is similar to the premenopausal state and it remains stable. Most of the woman's lifecycle, vaginal microbiome is dominated by *Lactobacillus* spp., and deficiency of these bacteria is associated with important adverse conditions, with increased risk for transmission of sexually transmitted infections. Lactobacilli are able to inhibit pathogens by producing active components, such as bacteriocins, lactic acid, hydrogen peroxide. Also, they preserve epithelium by stimulating mucus production and modulating the immune response. The presence of lactobacilli is an indicator of a healthy balance of vaginal microbiome. It is considered that the ability of some bacteria to form a thick adherent biofilm affects the onset of vaginal dysbiosis. Biofilm associated bacteria, such as *Gardnerella vaginalis* and *Atopobium vaginae*, have a high recurrence rate and they are difficult to treat. Despite the belief that reproduction takes place in an aseptic environment, nowadays investigations have proved that the upper parts of the genital tract are not sterile as previously though. Microorganisms in the ovaries, Fallopian tubes, and endometrium have been identified. According to new findings, the female microbiota may play a role during fertilization, implantation and gestation.

O-59 Rezistencija mikoplazmi na antibiotike: razlog za zabrinutost?

Edita Sušić

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Mikoplazme i ureaplazme su najmanje samostalno živuće bakterije s visokom specifičnošću za nositelja. Svim vrstama mikoplazmi zajedničko je da imaju tkivni tropizam prema dišnom sustavu, spolnomokračnom sustavu i zglobovima. Za ljude su patogene *Mycoplasma pneumoniae*, uzročnik infekcija dišnoga sustava, te *Mycoplasma genitalium*, *Mycoplasma hominis* i *Ureaplasma* spp., koje mogu uzrokovati različite kliničke sindrome, od uobičajenih infekcija spolnoga sustava do rijetkih manifestacija poput Reiterova sindroma. Te genitalne mikoplazme mogu se prenijeti direktnim kontaktom, najčešće genito-genitalnim ili genito-oralnim. Mikoplazme su intrinzički rezistentne na antibiotike koji djeluju na staničnu stijenku (β -laktamski antibiotici, fosfomicin, glikopeptidi), na sulfonamide, prvu generaciju kinolona, trimetoprim, polimiksin i rifampicin. Makrolidi i njima srodni antibiotici, fluorokinoloni i tetraciklini, koriste se za terapiju infekcija uzrokovanih mikoplazmama. Rezistencija na te antibiotike varira ovisno o vrsti mikoplazme. *M.hominis* je rezistentna na eritromicin i druge 14- i 15-eročlane (azitromicin) makrolide, ali je osjetljiva na 16-eročlane makrolide (josamicin) i klindamicin. Za razliku od *M.hominis*, koja pokazuje dobru osjetljivost na doksiciklin, kod infekcija uzrokovanih *M.genitalium* doksiciklin pokazuje slabu djelotvornost u rasponu 30-40%. Uz *C.trachomatis*, *M.genitalium* vodeći je uzročnik negonokoknog (NG) uretritisa muškaraca i značajan uzročnik NG cervicitisa žena. Prvi lijek izbora za terapiju tih infekcija je azitromicin. Nažalost, prevalencija rezistencije *M.genitalium* na makrolide visoka je diljem svijeta: u Velikoj Britaniji prevalencija je 41%, Njemačkoj 57%, Norveškoj 56%, Kanadi 58% i Sjedinjenim Američkim Državama 48%. Stoga bi se kod pozitivnog testa na *M.genitalium* trebala testirati i rezistencija na makrolide. Ukoliko rezistencija nije prisutna, azitromicin je prvi lijek izbora, produženi dozni režim od 1,5 grama tijekom 5 dana. Kod dokazane rezistencije na makrolide za liječenje se koristi moksifloksacin. Zabrinjavajući je porast rezistencije *M.genitalium* na kinolone, i porast dvostruke rezistencije na makrolide i kinolone zbog čega su nam terapijske mogućnosti ograničene, osobito ako se radi o infekcijama tijekom trudnoće i u novorođenčadi.

***Mycoplasma* resistance to antimicrobials: cause for concern?**

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Mycoplasmas and ureaplasmas are the smallest free-living bacteria with high host specificity. Tissue tropism to the respiratory tract, urogenital tract and joints is common for all species. In humans, pathogens are *Mycoplasma pneumoniae*, causing respiratory infections, and *Mycoplasma genitalium*, *Mycoplasma hominis* and *Ureaplasma* spp., which can cause a plethora of clinical syndroms, ranging from common genital tract infections to rare manifestations such as Reiter syndrome. Genital mycoplasmas can be transmitted by direct contact, most commonly through genital-genital or genital-oral contact. Mycoplasmas are intrinsically resistant to antimicrobials targeting the cell wall (β -lactams, fosfomicin, glycopeptides), sulfonamides, first-generation quinolones, trimetoprim, polymixin, and rifampicin. Macrolides and related antibiotics, fluoroquinolones and tetracyclines are used to treat mycoplasma-induced infections. Resistance to those antibiotics varies according to species. *M.hominis* is resistant to erythromycin and other 14- and 15-membered (azithromycin) macrolides but susceptible to 16- membered macrolides (josamycin) and clindamycin. Unlike *M.hominis*, which shows good susceptibility to doxycycline, in infections caused by *M. genitalium* doxycycline shows poor response rates ranging 30-40%. In addition to *C.trachomatis*, *M.genitalium* is a leading causative agent of non-gonococcal (NG) urethritis in men and a significant causative agent of NG cervicitis in women. The first drug of choice for the treatment of these infections is azithromycin. Unfortunately, there is a high prevalence of *M.genitalium* resistance to macrolides worldwide: the prevalence in the UK is 41%, Germany 57%, Norway 56%, Canada 58% and the United States 48%. Therefore, all cases with *M.genitalium*-positive test should be tested for macrolide resistance. In the absence of macrolide resistance, azithromycin is the first drug of choice, an extended-dose regimen of 1.5 grams for 5 days. With a proven macrolide resistance, moxifloxacin is used for treatment. The increase in *M.genitalium* resistance to quinolones and dual class resistance to macrolides and quinolones are cause great concern, resulting in limited therapeutic, especially for infections in pregnancy and in newborns.

O-60 Praćenje BHS B kod trudnica – potreba za nacionalnim smjernicama

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Streptococcus β haemolyticus serološke grupe B (BHS B) ili S. agalactiae nastanjuje gastrointestinalni i genitourinarni trakt kod ljudi. Prema nekim istraživanjima do 40% žena je u trudnoći kolonizirano s BHS B. Vertikalnim prijenosom BHS B kolonizirane majke na dijete tijekom poroda može doći do invazivne bolesti kod djeteta kao što su sepsa, meningitis, pneumonija. BHS B se povezuje s prijevremenim rođenjem djeteta te mrtvorođenjem.

Prenatalnim probirom trudnica između 35. i 37. tjedna trudnoće otkrivaju se kolonizirane trudnice s BHS B, kod kojih bi trebalo provesti intrapartalnu antibiotsku profilaksu.

Stavovi stručnjaka u pogledu probira na BHS B i profilakse nisu jedinstveni. Razlikuju se dva pristupa, „univerzalni pristup“, tj. testiranje svih trudnica u 35.-37. tjednu trudnoće te „ciljani probir“ pristup temeljen na rizičnim faktorima, odnosno primjena antibiotka prilikom porođaja ako su prisutni jedan ili više faktora rizika: novorođenče s BHS B sepsom nakon prethodnog poroda, svaki prijevremeni porod, curenje plodove vode dulje od 18 sati, laboratorijski nalazi koji sugeriraju sindrom intraamnijske infekcije (SIAI), povišena tjelesna temperatura tijekom poroda (380C), nalaz BHS B-a u cervikalnom brisu ili urinokulturi tijekom trudnoće, bez obzira na kontrolni nalaz liječenja.

Prema dostupnim podacima, antibiotska profilaksa se ordinira u oko 30% žena na osnovu mikrobiološkog probira, dok se na temelju rizičnih čimbenika ona ordinira u oko 17-20% trudnica.

U Hrvatskoj, do sada, postoje nacionalne preporuke Hrvatskog društva za perinatalnu medicinu HLZ-a, no ne i nacionalne smjernice pisane u skladu s AGREE (eng. Appraisal of Guidelines for Research and Evaluation) metodologijom, prema standardima na dokazima zasnivane medicine i kao rezultat konsenzusa svih zainteresiranih stručnih društava, recenzirane od strane internacionalnih konzultanata i pilotirane u praksi.

Prema provedenoj anketi u mikrobiološkim laboratorijima u Hrvatskoj 2015. godine probir na BHS B ne rade svi laboratoriji. Metoda probira koja se koristi u mikrobiološkim laboratorijima nije ujednačena.

Bolesti koje uzrokuje BHS B kod novorođenčadi su potencijalno smrtonosne, ali se uspješno mogu prevenirati.

Vrijeme je za donošenje nacionalnih smjernica za probir na BHS B i prevenciju rane infekcije s BHS B u novorođenčadi temeljenih na nacionalnim smjernicama u skladu s AGREE metodologijom.

Screening pregnant women for GBS – need for national guidelines?

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Streptococcus β haemolyticus serological group B (GBS) or *S. agalactiae* inhabits human gastrointestinal and genitourinary tract. According to some research up to 40% of women are colonised with GBS in pregnancy. Vertical transmission from mother to a child during labour can lead to invasive sicknesses in a child, such as sepsis, meningitis and pneumonia. GBS is associated with premature birth and stillbirth as well.

Prenatal screening of women in 35th – 37th week of pregnancy reveals those colonized with GBS, who require intrapartum antibiotic prophylaxis.

Expert views on GBS screening and prophylaxis vary. There are two approaches: a “universal approach” i.e. testing of all women in 35th – 37th week of pregnancy and “focused screening” based on risk factors, which implies the use of antibiotics during labour if one or more risk factors are present: an infant with GBS sepsis following a previous labour, each premature labour, leakage of amniotic fluid for more than 18 hours, laboratory test results suggesting intraamniotic infection syndrome (SIAI), increased body temperature during labour (38°C), presence of GBS in cervical smear or urinoculture during pregnancy, regardless of the treatment results.

According to the data available, antibiotic prophylaxis is prescribed to 30% of women on the basis of microbiological screening and to 17 – 20% of women based on risk factors.

In Croatia, so far, there are national recommendations by Croatian Association for Perinatal Medicine, but there are no national guidelines written in accordance with AGREE methodology, following the standards of evidence – based medicine and resulting from the consensus of all interested professional associations, reviewed by international consultants and piloted in practice.

According to the survey conducted in microbiological laboratories in Croatia in 2015, GBS screening is not performed in all of them. Moreover, the screening method used in those that do it is not uniform either.

Diseases caused by GBS in infants are potentially lethal but can be successfully prevented.

It is time to set national guidelines for screening and prevention of early GBS infections in infants based on national guidelines following AGREE methodology.

O-61 Akutne i kronične bubrežne infekcije

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Acute and chronic urinary tract infections

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O-62 Procjena neodgovarajuće uporabe antibiotika i pridržavanje smjernica za infekcije urinarnog trakta

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CILJ: procijeniti kvalitetu propisivanja antimikrobnih lijekova za infekcije urinarnog trakta u primarnoj zdravstvenoj zaštiti u Hrvatskoj, koristeći setove indikatora kvalitete, uključujući stupanj potrošnje pojedinih J01 skupina prema DDD/TSD metodologiji i stupanj adhezencije s postojećim nacionalnim i međunarodnim smjernicama u izboru terapije.

METODE: analizirani su podaci o izvanbolničkoj potrošnji antimikrobnih lijekova (ATK: J01) za 2013. i 2014.g. iz elektroničke baze Hrvatskog zavoda za zdravstveno osiguranje (3.512.053 recepata za 2013.g. i 3.536.652 recepata za 2014.g.) za svih 20 županijskih ureda u Hrvatskoj.

REZULTATI: analizom recepata liječnika primarne zdravstvene zaštite (PZZ) u Hrvatskoj u 2013. i 2014. liječeno je 17.626 pacijenata zbog akutnog pijelonefritisa, 394.533 pacijenata zbog akutnog cistitisa i 4.555 pacijenata zbog akutnog prostatitisa. Za akutni pijelonefritis, 89,20% pacijenata je dobilo antimikrobni lijek prema tada aktualnim nacionalnim smjernicama (kombinacija penicilina sa beta-laktamaza inhibitorom ili 2. ili 3. generaciju cefalosporina ili kinolon). Amoksicilin je propisan samo u 1,38% pacijenata, a sulfonamidi s trimetoprimom u 6,48%. Za akutni cistitis, 47,30% je dobilo nitrofurantoin ili kombinaciju penicilina sa beta-laktamaza inhibitorom ili 1.generaciju cefalosporina. Ampicilin je propisan u 2,77% pacijenata, a sulfonamidi s trimetoprimom u 23,67%. Za akutni prostatitis, 76,20% pacijenata je dobilo kinolon ili sulfonamid s trimetoprimom. Ampicilin je propisan u 1,69% pacijenata.

ZAKLJUČAK: većina liječnika u PZZ propisuje antibiotike u skladu sa smjernicama za liječenje pijelonefritisa i prostatitisa, ali većina liječnika ne propisuje antibiotike u skladu sa smjernicama za cistitis. Pozitivno je što većini pacijenata nije propisan amoksicilin i sulfometoksazol s trimetoprimom empirijski. Prema aktualnim ISKRA hrvatskim nacionalnim smjernicama, za akutne nekomplicirane IMS donjeg urotrakta žena kao lijek prvog izbora preporučeno je nitrofurantoin ili fosfomicin zbog niske rezistencije. Antibiotici s rezistencijom od 10-20% ne bi se trebali davati u empirijskoj primjeni.

Assessment of inappropriate antibiotic use and guideline adherence for urinary tract infections

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OBJECTIVES: evaluate the quality of the consumption of antibacterials for urinary tract infections in primary health care in Croatia, using a set of performance indicators, including the degree of consumption of different J01 groups according to the DDD / TID methodology and the degree of adherence to the existing national and international guidelines for the choice of therapy

METHODS: data on outpatient consumption of antibacterial drugs (ATC: J01) for the years 2013. and 2014. were obtained from the electronic database of the Croatian Health Insurance Fund (3,512,053 prescriptions for 2013. and 3.536.652 prescriptions for 2014.), for all 20 regional offices in Croatia.

RESULTS: by analyzing the prescriptions of primary health care physicians in Croatia in 2013 and 2014, 17,626 patients were treated for acute pyelonephritis, 394,533 for acute cystitis and 4,555 for acute prostatitis. For acute pyelonephritis, 89.20% of patients received an antimicrobial drug according to the current national guidelines (a combination of penicillin with beta-lactamase inhibitor or 2nd or 3rd generation cephalosporin or quinolone). Amoxicillin is prescribed only in 1.38% of patients and sulfonamide with trimethoprim in 6.48% of patients. For acute cystitis, 47.30% of patients received nitrofurantoin or combination of penicillin with beta-lactamase inhibitor or 1. generation of cephalosporin. Ampicillin is prescribed in 2.77% of patients and sulfonamide with trimethoprim in 23.67%. For acute prostatitis, 76.20% of patients received quinolone or sulfonamide with trimethoprim. Ampicillin was prescribed in 1.69% of patients.

CONCLUSION: Most primary health care physicians prescribe antibiotics in accordance with guidelines for the treatment of acute pyelonephritis and prostatitis, but most physicians do not prescribe antibiotics in accordance with the guidelines for acute cystitis. It is positive that amoxicillin and sulfamethoxazole with trimethoprim were not prescribed empirically for most patients. According to current ISKRA Croatian National Guidelines, nitrofurantoin or fosfomycin is recommended as the first drug choice for the acute uncomplicated UTI because it's low resistance. Antibiotics with a resistance of 10-20% should not be given empirically.

**PRISTUP „JEDNO ZDRAVLJE“ U KONTROLI ŠIRENJA REZISTENCIJE
"ONE HEALTH" APPROACH IN ANTIMICROBIAL RESISTANCE CONTROL**

O-63 Molekularna karakterizacija *Acinetobacter baumannii* iz uređaja za pročišćavanje otpadnih voda Zagreba

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Ciljevi: urbane otpadne vode grada Zagreba koje sadrže udio sirovih bolničkih voda obrađuju se u uređaju za pročišćavanje otpadnih voda drugog stupnja (WWTP). Karakterizirani su izolati *Acinetobacter baumannii* izdvojeni tijekom jednogodišnjeg praćenja (2015-16) iz glavnih stupnjeva WWTP kako bi se dobio uvid u učinkovitost uklanjanja ovog emergentnog patogena.

Metode: Izolacija *A. baumannii* provedena je na pločama CHROMagar Acinetobacter. Izolati su identificirani pomoću MALDI-TOF MS. Profil antibiotske rezistencije učinjen je i interpretiran prema EUCAST kriterijima za kliničke izolate *A. baumannii*. Molekularna karakterizacija provedena je WGS i cgMLST.

Rezultati: *A. baumannii* su kontinuirano izdvajani iz različitih stupnjeva pročišćavanja: ulazna voda, aktivni mulj, digestirani mulj, izlazna voda, osim iz vapnom tretiranog otpadnog mulja. Izolati rezistentni na karbapeneme i fluorokinolone (CFQR) dominirali su (82%) u svim stupnjevima WWTP, ali u suživotu s 14% osjetljivih izolata. Sveopće rezistentni (PDR) izolati (3%) zabilježeni su u aktivnom mulju i izlaznoj vodi. Većina CFQR i PDR izolata pripadala je IC2 (ST-195Oxford/ST-2Pasteur), a manjina IC1, dok su osjetljivi izolati bili neklonski. Rezistencija na karbapeneme bila je posredovana stećenim blaOXA-23 u izolata IC2 i blaOXA-72 u izolata IC1. CFQR i PDR *A. baumannii* koji su pripadali ST-195 su prethodno nađeni u istom periodu praćenja (2015-16) u bolničkih pacijenata, bolničkim vodama te rijeci Savi. Njihova visoka sličnost s izolatima izdvojenim iz zagrebačkog WWTP ukazuje na širenje klinički značajnih *A. baumannii* iz pacijenata, preko netretiranih bolničkih voda, urbanih otpadnih voda i WWTP u rijeku Savu.

Zaključak: Klinički značajni *A. baumannii* opstaju u WWTP i šire se putem izlazne vode u rijeku Savu. Alkalni tretman vapnom osigurava otpadni mulj bez vijabilnih *A. baumannii*. Potrebna je dezinfekcija izlazne vode WWTP prije ispuštanja u prirodni recipijent kako bi se izbjegao mogući javnozdravstveni rizik.

Molecular characterization of *Acinetobacter baumannii* from Zagreb wastewater treatment plant

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Objectives: Urban wastewater from the City of Zagreb, containing a fraction of raw hospital wastewaters, is treated at the secondary wastewater treatment plant (WWTP). *Acinetobacter baumannii* recovered during one-year monitoring (2015-16) at the main stages of the WWTP were characterized to elucidate the efficiency of WWTP in removal of this emerging hospital pathogen.

Methods: Recovery of *A. baumannii* was performed on CHROMagar *Acinetobacter* plates. Isolates were identified by MALDI-TOF MS. Antimicrobial susceptibility testing was performed and interpreted according to EUCAST breakpoints for clinical *A. baumannii* isolates. Molecular characterization was performed by WGS and cgMLST.

Results: *A. baumannii* isolates were continuously recovered from different stages of the WWTP: influent wastewater, activated sludge, digested sludge, effluent wastewater, except from lime-treated waste sludge. Isolates resistant to carbapenems and fluoroquinolones (CFQR) dominated (82%) in all stages of WWTP, but coexisted with 14% of susceptible isolates. Pan-drug resistant (PDR) isolates (3%) were detected in activated sludge and effluent wastewater. The majority of CFQR and PDR isolates belonged to IC2 (ST-195Oxford/ST-2Pasteur), and a minority to IC1, while susceptible isolates were unclustered. Carbapenem resistance was mediated by acquired blaOXA-23 in IC2 isolates and blaOXA-72 in IC1 isolates. The CFQR and PDR *A. baumannii* belonging to ST-195 were previously reported in the same period of monitoring (2015-16) from hospitalised patients, hospital wastewater, and the Sava River. Close relatedness with isolates recovered from Zagreb WWTP suggests dissemination of *A. baumannii* of clinical significance from patients, via untreated hospital wastewater, urban sewage, and WWTP to the Sava River.

Conclusion: Clinically relevant *A. baumannii* persist in secondary WWTP and are emitted via effluent to the Sava River. Alkaline lime-treatment renders the waste sludge free of viable *A. baumannii*. However, additional disinfection of effluent prior to its discharge into the natural recipient is needed to avoid the possible public-health risk.

O-64 Rezultati pilot studije molekularne karakterizacije MDR kliničkih izolata *Acinetobacter baumannii* iz susjednih zemalja

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Acinetobacter baumannii jedan je od najčešćih bolničkih mikroorganizama koji uzrokuje infekcije u svijetu. Ovaj mikroorganizam izaziva infekcije kod imunokompromitiranih bolesnika u jedinicama intenzivnog liječenja koji u anamnezi imaju traumu, podvrgnuti su kirurškom zahvatu ili imaju potrebu za mehaničkom potpornom ventilacijom. MDR klinički izolati *A. baumannii* predstavljaju vodeći problem u epidemiološkom i terapijskom smislu, te je liječenje ovih infekcija ujedno i izazov za kliničare. Nadzor nad izolatima *A. baumannii* koji su otporni na karbapeneme (u pravilu i multirezistentni) u Hrvatskoj se kontinuirano prati, budući da je u posljednjem desetljeću postotak izolata dosegao 97%. Pored Hrvatske, Bosna i Hercegovina i Srbija također su zabilježile značajan porast incidencije i prevalencije klinički relevantnih izolata *A. baumannii* otpornih na karbapenem. Cilj ove pilot studije bio je genotipizirati i molekularno usporediti mehanizam rezistencije 12 kliničkih izolata *A. baumannii* otpornih na karbapeneme, prikupljenih iz tri različite bolnice u susjednim zemljama u regiji jugoistočne Europe. Prvi rezultati predstavljeni su na 12. Simpoziju o biologiji Acinetobacteria u Frankfurtu tijekom rujna 2019. godine.

Results of the pilot study on molecular characterization of MDR clinical *Acinetobacter baumannii* isolates from neighbouring countries

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Acinetobacter baumannii has emerged as one of the most common nosocomial pathogens worldwide. This organism mostly targets the susceptible immunocompromised patients in ICUs where natural barriers are breached by trauma, surgery or mechanical support ventilation. MDR clinical isolates represent a major problem in the epidemiological and therapeutic sense and challenge for clinicians. Surveillance of carbapenem resistant isolates (which are also multiresistant) of *A. baumannii* in Croatia is continually monitored since in the last decade the percentage of carbapenem resistant isolates reached 97%. In addition to Croatia, Bosnia and Herzegovina and Serbia also recorded a significant increase in the incidence and prevalence in carbapenem resistant clinically relevant isolates of *A. baumannii*. The aim of this pilot study was to compare the genotype resemblance and resistance mechanism of 12 isolates of carbapenem resistant *A. baumannii* collected from three different hospitals in neighbouring countries in region of south-eastern Europe. First results of pilot study were presented on 12th Symposium on the biology of *Acinetobacter* in Frankfurt during September 2019.

O-65 Pristup „ONE HEALTH“ i antimikrobna rezistencija u vanbolničkoj populaciji

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U današnje vrijeme, otpornost bakterija na antibiotike /antimikrobna rezistencija (AMR) ozbiljna je prijetnja javnom zdravlju koja sve više uzima zamah. Unatoč akcijama koje se poduzimaju, uključujući Svjetsku zdravstvenu organizaciju (SZO), pobol i smrtnost u vezi s AMR stalno rastu. Prema literaturnim podacima AMR bi mogla do 2050. godine, postati uzročnik smrtnosti broj 1. Stoga se u zemljama EU, pristupilo Projektu – zajedničkoj akciji – o AMR i infekcijama udruženim sa zdravstvenom njegom (engl. Joint action on antimicrobial resistance and health care associated infections – JA AMR and HCAI). RH se pridružila projektu kroz djelovanje Službe za mikrobiologiju HZJZ 2017. god. JA AMR je u skladu s Akcijskim planom EU-a i Zaključcima Europskog Vijeća o AMR-u (usvojenom 17. lipnja 2016.) i Globalnim akcijskim planom SZO. Glavni cilj Zajedničke akcije AMR-HCAI je kako osigurati da se politika utemeljena na dokazima za kontrolu AMR usvoji i provodi u svim zemljama članicama EU na koordiniran način, poštujući nacionalne specifičnosti u skladu sa smjernicama i preporukama ECDC-a i SZO, te svim drugim europskim inicijativama. Metodologija i ciljevi projekta su kako odabrati osnovne pokazatelje nadzora antimikrobne potrošnje u vanbolničkoj populaciji kroz podatke iz ordinacija liječnika primarne zdravstvene zaštite (PZZ) o: ukupno potrošenim antimikrobnim lijekovima, potrošnji amoksicilin-klavulanata, cefalosporina 3. generacije, kinolona i makrolida, ukupnom broju patogena: enterobakterija koje proizvode karbapenemaze, ESBL E. coli, ESBL K. pneumoniae meticilin-rezistentnih S. aureus (MRSA)). Učestalost svih izvještaja je kvartalna, a nakon završetka svakog kvartala slijedi učitavanje podataka na web-stranice. Također, potrebno je ostvariti suradnju s postojećim mrežama: EARS i ESAC. Obzirom na kompleksnost problema AMR i različite državne, europske i internacionalne inicijative koje su se pojavile u posljednjem desetljeću, osnovna korist koja se očekuje od Projekta, jest, da svi sudionici udruže snage da bi se izbjeglo nepotrebno preklapanje te da se osigura bolja povezanost unutar svjetskog pokreta borbe protiv AMR.

"ONE HEALTH" approach and antimicrobial resistance in outpatient population

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Incidence and morbidity caused by resistant bacteria have been growing steadily despite the actions being undertaken by political world authorities, including the World Health Organization (WHO). Therefore, in the EU countries was established the Project – Joint Action on Antimicrobial resistance (AMR) and health care associated infections (JA AMR &HCAI). The Republic of Croatia joined the project through the activities of the Croatian Institute of Public Health, Department of Microbiology in 2017. Project is in line with the EU Action Plan and the Conclusions of the European Council on AMR (adopted on 17 June 2016) and the Global Action Plan WHO. The main objective of project is to ensure that policy based on evidence of AMR control is adopted and implemented in all EU member states in a coordinated manner, respecting national specificities in accordance with ECDC and WHO guidelines and recommendations and all other European initiatives. Objectives of the project are: to select the basic indicators of antimicrobial consumption monitoring in the primary health care facilities – total antimicrobial drugs consumed and consumption of amoxicillin-clavulanate, 3rd generation cephalosporins, quinolone and macrolide. Also, to find out total number of: carbapenemases produced Enterobacteria, ESBL Escherichia coli, ESBL Klebsiella pneumoniae, meticillin-resistant Staphylococcus aureus. Other objectives are: to enhance existing local monitoring systems to get the information available as soon as possible and cooperate with existing networks: EARS, ESAC. Frequency of the report is quarterly. Data managers will have a two-month period after the end of each quarter to upload the data to the webpage of project. Given the complexity of the AMR problem and the various state, European and international initiatives that have emerged in the last decade, the basic result and benefits expected from the Project is, that all participants join forces to avoid unnecessary overlap and to ensure better interconnection within the World Movement to fight the AMR.

O-66 Pojavnost multirezistentnih rezistentnih uzročnika bakterijskih spolno prenosivih infekcija kao javno zdravstveni problem

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Spolno prenosive infekcije (SPI) proglašene su globalnim javnozdravstvenim problemom. Povećane migracije ljudi, različite seksualne navike, tendencija porasta spolnih odnosa muškaraca s muškarcima (MSM) te stupanje u seksualne odnose u ranijoj životnoj dobi, uzroci su povećane incidencije SPI, a time i prijenosa uzročnika SPI rezistentnih na antibiotike. Prema podacima Svjetske zdravstvene organizacije (SZO) svake godine pojavi se 357 milijuna novih slučajeva SPI od kojih prednjače: trihomonijaza, klamidijaza, gonoreja i sifilis. Pojava antimikrobne rezistencije u bakterija znatno ugrožava liječenje, ali i kontrolu širenja spolno prenosivih bolesti. Posebice zabrinjava mogućnost da bakterijski uzročnici SPI *Neisseria gonorrhoeae* (NG) i *Mycoplasma genitalium* (MG), zbog ograničenog izbora antimikrobnih lijekova i sposobnosti razvoja mehanizma rezistencije, evaluiraju u višestruko ili potpuno rezistentne bakterije. Rezistencija NG na antibiotike zaslužuje posebnu pažnju. Naime, SZO je 2017. godine uvrstila ovu bakteriju među 12 patogena koji predstavljaju prijetnju zdravlju ljudi i zahtijevaju prioritet u nastojanjima razvoja novih antibiotika. Prvi soj NG visoko rezistentan na ceftriakson i cefiksime bio je izoliran 2009. godine u Japanu. Ozbiljnu zabrinutost izazivaju podaci iz Velike Britanije i Australije u 2018. godini, gdje su izolirane NG s visokom rezistencijom na ceftriakson i u kombinaciji s azitromicinom. Infekcija gonokokom je u zemljama zapadne Europe u porastu, a problem AMR sve izraženiji. Stoga je u EU pokrenut program Euro GASP za kontrolu praćenja gonokokne AMR, u kojem sudjeluje i Hrvatski zavod za javno zdravstvo (HZJZ).

Zabrinjavajuća je i antimikrobna rezistencija MG na tetracikline i makrolide. Naime, tetraciklini pokazuju klinički nisku stopu eradikacije usprkos relativnoj učinkovitosti *in vitro*, a učinkovitost azitromicina se drastično smanjuje.

U konačnici, problemu AMR kao i prijenosu rezistentnih sojeva uzročnika SPI-a možemo doskočiti primjenjujući sveobuhvatni pristup promicanja znanja o adekvatnoj uporabi antibiotika, praćenjem kretanja rezistentnih sojeva i suzbijanjem njihovog daljnjeg širenja unutar populacije. Također, neophodno je jačanje suradljivosti lokalnih i državnih zdravstvenih institucija, prijavljivanje SPI, umrežavanje podataka kao i svakodnevno promicanje i savjetovanje seksualnog obrazovanja prilagođeno određenoj populaciji (adolescenti, MSM, heteroseksualci, itd.).

The incidence of multidrug resistance in bacterial STD as a public health problem

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Sexually transmitted infections (STIs), became the global public health problem. Increased migration of people, different sexual habits, tendency of men who have sex with men (MSM) and the initiation of sex at an earlier age, the causes of the increased incidence of STIs, and thus the transmission of pathogens SPI resistant to antibiotics. According to the World Health Organization (WHO), every year there are 357 million new cases of STIs, of which the lead: trichomoniasis, chlamydiasis, gonorrhoea and syphilis. The emergence of antimicrobial resistance in bacteria significantly jeopardizes treatment, and control the spread of sexually transmitted diseases. Of particular concern is the possibility that STI bacterial pathogens *Neisseria gonorrhoeae* (NG) and *Mycoplasma genitalium* (MG), the limited selection of antimicrobial agents and the ability to develop resistance mechanisms, to evaluate multiple or completely resistant bacteria. Resistance to antibiotics NG deserves special attention. The WHO in 2017 ranked among the 12 the bacteria pathogens that pose a threat to human health and require priority in efforts to develop new antibiotics. The first strain NG highly resistant to ceftriaxone and cefixime was isolated in 2009 in Japan.

Serious concern cause data from the UK and Australia in 2018, where they isolated the NG with high resistance to ceftriaxone and in combination with azithromycin. The infection gonococcal is in Western Europe on the rise, and AMR problem more pronounced. Therefore, the EU launched a program Euro GASP control monitoring gonococcal AMR, with the participation of the Croatian Nacional Institute of Public Health (CIPH).

The serious concern is antimicrobial resistance MG to tetracyclines and macrolides. The tetracyclines show a clinically low level of eradication in spite of the relative effectiveness of in vitro efficacy of azithromycin is drastically reduced. Ultimately, the problem of AMR and transmission of resistant strains of pathogens SPI can be remedied by applying a comprehensive approach to promoting knowledge about the adequate use of antibiotics, following the movement of resistant strains and the suppression of their further spread within the population. Also, it is necessary to strengthen the cooperation of local and national health institutions, reporting SPI, data networking as well as the daily promotion and counseling of sexual education adapted to a specific population (adolescents, MSM, heterosexuals, etc.).

PEDIJATRIJSKE INFektivNE BOLESTI
PEDIATRIC INFECTIOUS DISEASES

O-67 Kawasaki disease

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Kawasaki disease (KD) is an acute vasculitis, presenting as self-limited febrile illness of unknown cause that predominantly affects children <5 years of age.

In the absence of pathognomonic tests, the diagnosis continues to rest on the identification of principal clinical findings and the exclusion of similar entities with known causes. Complete KD is characterized by fever, rash, extremity changes, conjunctivitis, oral changes and cervical lymphadenopathy. Other common findings include extreme irritability, hepatitis, gallbladder hydrops, arthralgia, arthritis, sterile pyuria and aseptic meningitis. The diagnosis of incomplete KD is made when there is ongoing fever but less than four clinical features. KD should be considered in patients with prolonged unexplained fever and the following: (1) irritability; (2) aseptic meningitis; (3) unexplained or culture-negative shock; (4) cervical lymphadenitis unresponsive to antibiotics; (5) retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotics. Children with incomplete KD do not have milder form of the disease, rather the rate of coronary and non-coronary complications may be higher as the diagnosis often gets delayed.

The vasculitis has a predilection for coronary arteries, but other medium sized arteries can also be involved. A recently proposed model of KD arteriopathy identified the following pathological processes: necrotizing arteritis in the acute phase causing aneurysms and subacute/chronic vasculitis with luminal myofibroblastic proliferation causing progressive arterial stenosis. Low grade myocarditis occurs in 50-70% and can lead to KD shock syndrome in 5%.

The mainstay of initial treatment for both complete and incomplete KD is a single high dose of intravenous immunoglobulin (IVIG) together with acetylsalicylic acid. Timely initiation of treatment has reduced the incidence of CAA from 25% to ≈4%. Approximately 10-20% of patients are refractory to primary IVIG and may benefit from adjunctive therapy with corticosteroids and infliximab. The long-term prognosis is determined by the level of coronary artery involvement.

O-68 Kingella kingae kao uzročnik osteoartikularnih infekcija u djece

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Kingella kingae as a cause of osteoarticular infections in children

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O-69 Konatalna CMV infekcija

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Conatal CMV infection

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O-70 Bokavirusne infekcije u djece

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Ljudski bokavirus (hBoV) otkriven je 2005. godine u djece s respiratornom infekcijom. Poznata su četiri genotipa (1-4), od kojih 1 i 2 uzrokuju infekcije dišnih putova. Iako se u početku smatralo da hBoV ne uzrokuje teže respiratorne infekcije, u literaturi je opisano više slučajeva težih infekcija u djece i odraslih, neki čak i sa smrtnim ishodom.

Proveli smo retrospektivno istraživanje među djecom liječenom u Klinici za infektivne bolesti „Dr Fran Mihaljević“ u periodu od 1.11.2016. do 1.3. 2017. zbog respiratorne infekcije u kojih je iz respiratornih uzoraka dokazan hBoV. Analizirane su demografske, kliničke i laboratorijske osobine.

U navedenom je periodu u 36 djece s respiratornom infekcijom dokazan hBoV, od kojih je 18 (50%) imalo koinfekciju s drugim virusom, većinom respiratornim sincicijskim virusom (RSV). Najviše oboljelih (17) bilo je u siječnju. Djevojčica je bilo 19 (53%), a dječaka 17 (47%). Dob se kretala od 27 dana do 39 mjeseci, a medijan je bio 18 mjeseci. Sva su djeca imala infekciju donjih dišnih putova, od toga 25 (69%) pneumoniju, a 11 (31%) bronhiolitis. Najčešći simptomi bili su kašalj (svi bolesnici) i vrućica (83%). Desetero djece je hospitalizirano (28%), dok su ostali liječeni u dnevnoj bolnici. Dvoje je djece mehanički ventilirano, oboje su imali koinfekciju s RSV-om. Jedno od njih je umrlo.

Ljudski bokavirus uzrokuje infekcije dišnih putova u djece tijekom hladnih mjeseci. Iako su sva analizirana djeca imala infekciju donjih dišnih putova, bolest je bila blaga i samoograničavajuća ukoliko je hBoV bio jedini uzročnik.

Infection by human bocavirus in children

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Human bocavirus (hBoV) was discovered in 2005 in children with respiratory infection. Out of four genotypes (1-4) described, genotype 1 and 2 are associated with respiratory tract infections. Although initially considered responsible only for mild respiratory infections, there is increasing body of evidence that hBoV can cause severe respiratory infection and even death in children and adults.

We conducted a retrospective study among children aged < 18 years treated for PCR-confirmed hBoV respiratory tract infection at the University Hospital for Infectious Diseases “Dr. Fran Mihaljević” between November 1, 2016 and March 1, 2017. Demographic, clinical and laboratory data were further analyzed.

During the study period hBoV was discovered in 36 children with respiratory tract infection. Among them 18 (50%) were co-infected with another virus, mostly respiratory syncytial virus (RSV). Majority of the cases (17) were treated during January. There were 19 girls (53%) and 17 boys (47%). The mean age was 18 months, the youngest being 27 days and the oldest 39 months old. All children were diagnosed with low respiratory tract infection, 25 with pneumonia (69%) and 11 with bronchiolitis (31%). Predominant symptoms were cough (100%) and fever (83%). Ten children were admitted to hospital (28%) while others were treated as outpatients. Mechanical ventilation was performed in two patients, both co-infected with RSV of whom one died.

Human bocavirus is a causative agent of respiratory tract infection in children during winter season. All the analyzed children suffered from low respiratory tract infection, but the course of the disease was mild and self-limiting in children with hBoV as a single causative agent.

INFEKCIJE LOKOMOTORNOG SUSTAVA
INFECTIONS OF THE MUSCULOSKELETAL SYSTEM

O-71 Radiološke osobitosti infekcija lokomotornog sustava

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Cilj: prikazati niz slikovnih karakteristika probranih bolesnika s infekcijama koje zahvaćaju različite segmente lokomotornog sustava, prikupljenih u razdoblju od pet godina (od 2015. do 2019. godine) u Klinici za infektivne bolesti "Dr. Fran Mihaljević" u Zagrebu.

Metode: radiološko-klinička korelacija niza slikovnih prikaza bolesnika sa celulitisom, fasciitisom, apscesima mekih česti i piomiozitisom, dijagnosticiranih različitim slikovnim tehnikama: radiografijom, ultrazvukom, kompjutoriziranom tomografijom(CT) i magnetnom rezonancijom (MR).

Rezultati: naglasiti prednosti i ograničenja različitih slikovnih metoda u ranoj detekciji infekcija lokomotornog sustava.

Zaključak: infekcije lokomotornog sustava prezentiraju se različitim slikovnim prikazima, ovisno o dubini i opsegu zahvaćenosti tkiva. Slikovni prikaz je važan u brzom i detaljnoj dijagnostici koja je značajna za rano prepoznavanje infekcije, prognozu razvoja bolesti i odgovarajući terapijski postupak.

Imaging characteristics of musculoskeletal infections

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Goals: to represent a review of the imaging characteristics of selected patients with infections involving various segments of musculoskeletal tissues, collected over the period of five years (from 2015 to 2019) at the University Hospital for Infectious Diseases in Zagreb, Croatia.

Methods: a radiological-clinical correlation of series of images of patients with cellulitis, fasciitis, soft-tissues abscesses and pyomyositis diagnosed with different imaging techniques: radiography, ultrasound, computed tomography (CT) and magnetic resonance (MR).

Results: emphasizing the advantages and disadvantages of different imaging methods in the early detection of musculoskeletal infections.

Conclusion: musculoskeletal infections present with different imaging appearances, depending on the depth and extent of tissue involvement. Imaging is important in a rapid and accurate diagnosis which is crucial in the early recognition of infection, prognosis and adequate treatment.

O-72 Konzervativni pristup pacijentu sa spondilodiscitisom – naša iskustva

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Incidencija spondilodiscitisa zadnjih nekoliko desetljeća je u porastu zbog poboljšanih dijagnostičkih tehnika i povećanja prosječnog životnog vijeka. Klinička prezentacija spondilodiscitisa općenito je nespecifična, a dijagnoza često odgođena. Laboratorijski testovi su neuvjerljivi za dijagnozu spondilodiscitisa. Radiološke metode su ključne u procjeni točne dijagnoze, a mikrobiološka dijagnostika je temelj za optimalno liječenje spondilodiscitisa. Iako su tijekom i posljedice bolesti dobro upoznate, optimalni tretman je još kontradiktoran, a precizne preporuke oskudne. Standardni konzervativni tretman uključuje proširenu parenteralnu antibiotsku terapiju (u većini slučajeva 6 tjedana je dovoljno) u kombinaciji s imobilizacijom ortozom ako se uoče manje nestabilnosti kralježnice.

U ovom predavanju ću raspravljati o patogenezi, kliničkoj manifestaciji, dijagnozi i konzervativnom liječenju spondilodiscitisa na temelju naših hospitaliziranih pacijenata.

Conservative approach to patient with spondylodiscitis –our experience

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The incidence of spondylodiscitis has been rising over the past several decades, due to the more sensitive diagnostic techniques, the increase of the average lifetime. Clinical presentation of spondylodiscitis is generally non-specific and diagnosis is frequently delayed. Laboratory tests are usually inconclusive in diagnosing spondylodiscitis. Imaging plays a crucial role in defining the correct diagnosis and microbiological diagnosis is the cornerstone for the optimal management of spondylodiscitis. Although the course and the consequences of the disease are well recognized, optimal treatment is still controversial and precise recommendations are few. The typical conservative management includes extended parenteral antibiotic therapy (6 weeks is sufficient in most cases), coupled with orthotic immobilization if minor spinal instability is observed.

This lecture will discuss pathogenesis, clinical manifestation, diagnosis and conservative treatment of spondylodiscitis, based on our hospitalized patients.

O-73 Infekcije umjetnih ugrađenih proteza

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Prosthetic joint infections

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O-74 Kirurško liječenje spondilodiscitisa

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Spondilodiscitis se u većini slučajeva može liječiti konzervativno, ali kompliciraniji slučajevi koji uključuju prijeteci ili postojeći neurološki ispad, nestabilnost i deformitet kralježnice, jake bolove, epiduralni apsces i neuspjeh konzervativnog liječenja zahtijevaju kirurško liječenje. Ciljevi operativnog liječenja spondilodiscitisa su odstranjenje nekrotičnog tkiva i dekompresija neuralnih struktura, uzimanje tkiva za patohistološku dijagnozu i mikrobiološku potvrdu uzročnika, stabilizacija kralježnice, te rana mobilizacija pacijenta. Moderna kirurška tehnika koristi stražnji pristup, prednji pristup i kombinirani pristup u jednom ili dva stupnja, a kirurg je vođen lokalizacijom spondilodiscitisa i individualnim pristupom pacijentu. Stabilnost kralježnice se postiže transpedikularnom fiksacijom titanskim vijcima i stupićima, a prednja kolumna torakolumbalne kralježnice se nakon odstranjenja nekrotičnog tkiva rekonstruira trikortikalnim koštanim presatkom iz zdjelice ili titanskim kavezima ispunjenim spongioznom kosti. U kirurškom liječenju spondilodiscitisa vratne kralježnice stabilnost se postiže prednjim pločama sa zaključanim vijcima i/ili stražnjom stabilizacijom vratne kralježnice. Korist stabilizacije kralježnice titanskim implantatima nadilazi manjkavost implantacije stranog materijala na mjestu upale.

Surgical Treatment of Spondylodiscitis

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In most cases spondylodiscitis can be treated conservatively, though complicated cases with pending or already existent neurological deficit, focal instability or deformity of the spine with acute pain have to be treated by surgical correction and instrumentation. Surgery is absolutely indicated in cases with epidural abscess formation and in cases in which conservative treatment have given no success. Goals of surgical treatment of spondylodiscitis are debridement of necrotic and infected tissues, decompression of neural structures, obtaining specimens for bacteriological and pathohistological diagnostics, and obtainment of spine stability, making possible early mobilization of the patient. Anterior, posterior or combined approaches can be utilized, being performed in single stage or staged procedure. Leading facts determining surgeon's tactics being localisation of inflammatory process and individual approach to the patient. Stability of the spine is achieved by transpedicular fixation by screws and longitudinal rods, and by reconstruction of anterior column by means of cancellous bone filled titanium cages or by autologous structural bone grafting. In cervical spine surgical stability is achieved by anterior locking plates, and/or by posterior screw and rod system instrumentation. Benefit given by stabilized spine outpaces the risk of implanting metal implants in potentially contaminated area.

RESPIRATORNE INFEKCIJE
RESPIRATORY TRACT INFECTIONS

O-75 Dijagnostika infekcija donjih dišnih puteva

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Respiratorni sustav je široko otvoren prema mikroorganizmima u okolini te je daleko skloniji infekciji od ostalih organskih sustava. Zbog toga su respiratorne infekcije prisutne u različitim populacijama bolesnika, uzrokovane su velikim brojem različitih patogena sa, često, sezonskom distribucijom i različitom težinom kliničke prezentacije. Infekcija donjeg dijela dišnog sustava obuhvaća niz različitih bolesti, uključujući bronhitis, upalu pluća i egzacerbacije kronične bolesti pluća. Klinički mikrobiološki laboratorij ima vitalnu ulogu u dijagnozi ovih infekcija, ali se suočava s brojnim izazovima zbog njihove složenosti, kvalitete i raznolikosti kliničkih uzoraka, kontaminacije uzoraka orofaringealnom mikrobiotom i niza različitih uzročnika. Na odjelu intenzivne njege, dijagnoza infekcija donjeg dišnog sustava posebno je kompleksna zbog učestalosti neinfektivnih upalnih stanja sa sličnim kliničkim znakovima i simptomima. Rano i točno određivanje etiologije infekcija donjeg dišnog sustava presudno je za provođenje učinkovite antimikrobne terapije, ali može biti nedostatno zbog ograničenja trenutno dostupnih mikrobioloških postupaka u smislu osjetljivosti, brzine i spektra ciljnih patogena. Razvoj i rutinska primjena molekularnih dijagnostičkih testova, uključujući i multipleksnu tehnologiju, predstavlja jedan od značajnijih pomaka u mikrobiološkoj dijagnostici infekcija donjeg dišnog sustava.

U ovom predavanju raspravlja se o ulozi kliničkog mikrobiološkog laboratorija u etiološkoj dijagnozi infekcija donjeg dišnog sustava, posebno pneumonije. Naglasak je na praktičnoj primjeni sadašnjih Smjernica za bakteriološku dijagnozu respiratornih infekcija Hrvatskog društva za kliničku mikrobiologiju, kao problemima s kojima se susreće klinički mikrobiološki laboratorij. Također, naglašena je potreba suradnje mikrobiologa i kliničara budući da je neophodna za pravilno iskorištavanje laboratorijskih kapaciteta u etiološkoj dijagnostici infekcija donjih dišnih putova.

Diagnostics of the lower respiratory tract infections

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The respiratory tract is far more prone to infection than other organ systems, as it frequently comes into contact with numerous pathogens present throughout the environment. This may explain why respiratory infections affect different patient populations, and are caused by a wide variety of microorganisms with, often, seasonal distribution and varying degrees of disease severity. Lower respiratory tract infection (LRTI) is a broad term that involves a number of different diseases, including bronchitis, pneumonia and exacerbations of chronic lung disease. The clinical microbiology laboratory plays a vital role in the diagnosis of these infections but faces numerous challenges due to the complexity of LRTIs, specimen quality and diversity, contamination of specimens with oropharyngeal microbiota, and a diverse pathogen population. In the intensive care unit (ICU), LRTI diagnosis is particularly complex due to a high prevalence of noninfectious inflammatory conditions with overlapping clinical features. Early and accurate determination of LRTI etiology is crucial for implementing effective antimicrobial therapies but may be flawed due to the limitations of current microbiologic tests in terms of sensitivity, speed, and spectrum of available assay targets. The development and implementation of molecular diagnostic tests for pneumonia has been a major advance in the microbiological diagnosis of respiratory pathogens in recent years. In this lecture, the role of the clinical microbiology laboratory in the etiologic diagnosis of LRTIs, especially pneumonia, is discussed. Emphasis is placed on the practical application of the current Guidelines for bacteriological diagnosis of respiratory infections of the Croatian Society for Clinical Microbiology, as well as the problems encountered by the clinical microbiology laboratory. The need for collaboration between the microbiologist and the clinician is also highlighted as it is required if the laboratory's facilities are to be properly exploited for the etiological diagnosis of respiratory tract infections.

O-76 Q – groznica ili infekcija uzrokovana bakterijom *Coxiella burnetii* – suvremene mogućnosti laboratorijske dijagnostike

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Q-groznica (QF) opisana je četrdesetih godina prošlog stoljeća, a zbog netipične kliničke prezentacije i u početku nejasne etiologije nazvana je "Querry" (nejasna, neodređena). Vrlo brzo otkirven je uzročnik *Coxiella burnetii*. *C.burnetii* pokazuje specifične karakteristike antigenske varijabilnosti što joj omogućava izbjegavanje imunskog odgovora i razvoj kroničnog oblika bolesti, te sporulaciju. *C.burnetii* je jako virulentna i minimalna količina bakterija uzrokuje bolest, a sporulacija osigurava preživljavanje u vanjskoj sredini. Akutna QF često je samoizlječiva ili blaga nalik gripi, no moguća je teža pneumonija i hepatitis, kao i neurološke manifestacije. Infekcija *C.burnetii* može perzistirati i progredirati u kroničnu bolest. Bez specifične dijagnostike nije moguće utvrditi etološku dijagnozu.

Cilj prikaza je ukazati na potrebu postavljanja dijagnoze akutne Q-groznice i praćenja bolesnika posebno s kardio-vaskularnim bolestima, radi moguće perzistentne infekcije. Budući da je uzročnik poznat, umjesto pojma kronična QF preporuča se definiranje lokalizirane perzistentne infekcije *C.burnetii* uz označavanje zahvaćenog organa.

Dijagnostika se temelji na serološkim testovima i određivanju protutijela IgM i IgG na antigene faze II koji se pojavljuju u akutnoj QF te IgG i IgA na antigene faze I koji su pokazatelj kronične infekcije *C.burnetii*. Kultivacija nije jednostavna i zahtijeva uvjete BSL-3. PCR se radi iz krvi, srčanih valvula ili uzoraka tkiva.

Od 2013-2018. godine u Klinici za infektivne bolesti u Zagrebu QF je serološki testirana iz 2528 seruma od 2176 osoba metodom ELISA. Akutna QF dijagnosticirana je u 209 (9.6%), kronična u 25 (1.2%), a prošla QF detektirana je u 57 (2.6%) ispitanika. Serološko praćenje bolesnika bilo je sporadično.

Nakon akutne QF novi algoritmi sugeriraju praćenje bolesnika tijekom najmanje 2 godine posebno radi ranog otkrivanja endokarditisa. Preporuča se napraviti PET/CT, ehokardiogram, odrediti antifosfolipidna protutijela i serološki pratiti kretanje protutijela na antigene faze I i faze II.

Q fever or *Coxiella burnetii* infection – current tools for laboratory diagnosis

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Q-fever (QF) was described in the 1940s and was called "Query" (unclear, unspecified) because of its atypical clinical presentation and initially obscure etiology. The causative agent *Coxiella burnetii* was discovered very quickly. *C.burnetii* shows specific features of the antigenic variability which enables avoidance of immune responses, development of chronic disease and sporulation. *C.burnetii* is highly virulent and minimal amount of bacteria causing disease while sporulation ensures survival in the environment. Acute QF is often self-limiting or mild, although more severe pneumonia and hepatitis are possible as well as neurological manifestations. *C.burnetii* infection can persist and progress to chronic disease. Without specific diagnostics, it is not possible to establish the ethiological diagnosis.

The aim of the presentation is to point out the need to diagnose acute QF and to monitor patients especially with cardio-vascular diseases for possible persistent infection. As the causative agent is known, instead of the term chronic QF, it is recommended to define localized persistent *C.burnetii* infection with the affected organ identification.

Diagnosis is based on serology and determination of IgM/ IgG antibodies to phase II developing in acute QF, and IgG/IgA to phase I antigens indicative for chronic *C.burnetii* infection. Cultivation is difficult and requires BSL-3 conditions. PCR is done from blood, cardiac valves or tissue samples.

From 2013-2018 at the Clinical Hospital for Infectious Diseases, Zagreb, QF was serologically tested by ELISA in 2528 sera out of 2176 persons. Acute, chronic and past QF was diagnosed in 209 (9.6%), 25 (1.2%), and 57 (2.6%) individuals, respectively. Serological monitoring of patients was sporadic.

New algorithms suggest monitoring patients for at least 2 years after acute QF, especially for early detection of endocarditis. It is recommended to perform a PET/CT scan, echocardiogram, determine antiphospholipid antibodies, and monitor serological kinetics of antibodies against phase I and phase II antigens.

O-77 Novi i zapostavljeni uzročnici virusnih infekcija dišnog sustava

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Akutne infekcije dišnog sustava (ARI) najčešće su infekcije ljudi svih dobnih skupina, a kako su većinom uzrokovane virusima, najčešći su razlog nepotrebnog propisivanja antibiotika. Virusne ARI od bakterioloških nije moguće razlučiti bez specifične virološke dijagnostike. Razvoj pak molekularnih metoda dijagnostike doveo je do otkrića novih virusnih uzročnika ARI (bokavirus, novi koronavirusi), ali i omogućio detekciju mnogih do sada teško dokazivih i zbog toga zapostavljenih uzročnika (parehovirusi, rinovirusi).

U sklopu projekta Hrvatske zaklade za znanost, tijekom dvogodišnjeg razdoblja, testirano je 593 djece na 15 respiratornih virusa zaprimljenih u Klinici za dječje bolesti Zagreb i Općoj bolnici Karlovac sa simptomima ARI i sumnjom na virusnu infekciju. Za detekciju uzročnika prikupljen je obrisak nazofarinksa i ždrijela zajedno u istu transportnu podlogu, a virusi su detektirani pomoću multipleks PCR metode. Ukupno je bilo 348 dječaka i 245 djevojčica. Jedan ili više respiratornih virusa detektirani su u 453 (76,4%) bolesnika, od čega jedan virus u 316 (69,7%), a dva ili više virusa u 137 (30,3%) slučajeva. Najčešće detektiran virus bio je rinovirus (198; 43,7%), te su redom slijedili: respiratorni sincicijski virus tipa A i B (112; 24,7%), adenovirus (92; 20,3%), virusi parainfluence tipa 1, 2, 3 i 4 (58; 12,8%), virusi influence tipa A i B (45; 9,9%), koronavirusi OC43 i 229E/NL63 (42; 9,3%), humani bokavirus (31; 6,8%), enterovirus (26; 5,7%) i humani metapneumovirus (18; 4,0%). Rezultati ove studije pokazuju na potrebu za sveobuhvatnijom dijagnostikom respiratornih virusa koji uključuju dijagnostički zapostavljene patogene kao što je rinovirus, odnosno novootkrivene virusne uzročnike – bokavirus. Suvremena, brza i učinkovita dijagnostika kao što je multipleks PCR doprinosi kvaliteti zdravstvene skrbi jer omogućuje izbjegavanje uzimanja nepotrebnih i suvišnih antimikrobnih lijekova, a time i nepoželjnih nuspojava odnosno dugoročno prevenira razvoj bakterijske rezistencije.

New and neglected respiratory viruses

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Acute respiratory infections (ARIs) are the most common infections in humans of all ages, and although viruses cause the majority of ARIs, they are the main reason for overuse of the antibiotics. Without specific viral diagnostics, it is not possible to distinguish between viral and bacterial ARI. Rapid advance of laboratory methods has led to the discovery of new viruses (bocavirus, new coronaviruses), and has enabled diagnosis of laboratory demanding and thus neglected viruses (parechovirus, rhinovirus).

As a part of Croatian foundation project, for two years period, a total of 593 children admitted to the Children's hospital Zagreb and General hospital Karlovac with symptoms of ARI and suspected viral aetiology were tested for 15 respiratory viruses. Nasopharyngeal and pharyngeal swabs were collected and combined in viral transport medium and tested using multiplex PCR. There was 348 boys and 245 girls. Respiratory viruses were detected in 453 (76.4%) patients, in 316 (69.7%) cases as single pathogen detected and in 137 (30.3%) cases in co-detection with other respiratory viruses. The most commonly detected virus was rhinovirus (198; 43.7%), followed by respiratory syncytial virus type A and B (112; 24.7%), adenovirus (92; 20.3%), parainfluenza viruses types 1, 2, 3 and 4 (58; 12.8%), influenza viruses types A and B (45; 9.9%), coronaviruses OC43 and 229E/NL63 (42; 9.3%), human bocavirus (31; 6.8%), enterovirus (26; 5.7%), and human metapneumovirus (18; 4.0%).

The results of this study demonstrate the need for more comprehensive diagnosis of respiratory viruses that include diagnostically neglected pathogens such as rhinovirus, or newly discovered viral pathogens – bocavirus. Rapid and sensitive diagnostics such as multiplex PCR contribute to the quality of health care because it makes possible to avoid prescribing unnecessary antimicrobial drugs and thus avoiding undesirable side effects as well as the development of bacterial resistance.

O-78 Pristup antimikrobnom liječenju akutnog pogoršanja kronične opstruktivne plućne bolesti

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Kronična opstruktivna plućna bolest (KOPB) je u osnovi kronična upalna bolest malih dišnih. Oko 2/3 svih akutnih pogoršanja (AP) KOPB uzrokuju infekcije pri čemu je dokazivih 50%-70%, a pojava gnojnog sputa s velikom pouzdanošću govori da se upravo o tome i radi. Najčešći uzročnici su H.influenzae, S.pneumoniae i Moraxella catarrhalis, a znatno rjeđe Gram-negativne i druge bakterije. Gram negativne bakterije se nešto češće javljaju u težim AP KOPB, osobito ako je FEV1 manji od 50% od očekivanog. Virusi vjerojatno i sami mogu dovesti do AP KOPB, a sasvim je izvjesno da utiru put za 40%-50% bakterijskih pogoršanja KOPB. Uglavnom se radi o Rhinovirusim, RSV, Coronavirusima, te Parainfluenza i Influenza virusu.

Većina upalnih biljega nema zadovoljavajući osjetljivost i/ili specifičnost da bi sa sigurnošću mogli razlučiti bakterijskom infekcijom uzrokovano pogoršanje od onog koje je neinfekcijske prirode. Ako u sputumu osobe koja ima kriterije AP KOPB prevladavaju neutrofilni leukociti, tada je pogoršanje u 83% slučajeva uzrokovano bakterijskom infekcijom i bez primjene antibiotika najvjerojatnije neće doći do poboljšanja. Prokalcitonin (PCT) je pouzdaniji pokazatelj moguće bakterijske etiologije AP KOPB nego CRP. Što je teža ataka pogoršanja KOPB i što više komorbidnih stanja bolesnik ima, s više slobode se odlučuje za antibiotsku terapiju i širi je njen antimikrobni spektar. Primjena antibiotika u AP KOPB, bez obzira na njihov izbor, smanje rizik od terapijskog neuspjeha za 55%, rizik od smrti za 77% i gnojnost sputuma za 44%. I ovo sve usprkos brojnim studijama koje pokazuju da statistički mjerljiv povoljni učinak antibiotika vidi jedino u slučajevima teških, ali ne i u blagim ili umjerenim pogoršanja KOPB. Svim bolesnicima s KOPB preporuča se redovito sezonsko cijepljenje protiv gripe i pneumokoka. Dostupno je i cijepljenje oralnom primjenom lizata bakterija (npr.Broncho-Vax: H.influenzae, S.pneumoniae, K.pneumoniae, K.ozenae, S.aureus, S.pyogenes, S.viridans i Moraxella catarrhalis) radi stvaranje sekretornih IgA. U kliničkim istraživanjima ovako imunizirane osobe u većem broju imaju poboljšanje simptoma KOPB, pogoršanja KOPB im traju kraće kao i hospitalizacija zbog pogoršanja. Međutim, statistička značajnost ovih razlika prema neimuniziranim nije dokazana.

Antimicrobial treatment of acute exacerbation of chronic obstructive pulmonary disease

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Basically, chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the small airways. About 2/3 of all acute exacerbations (AE) COPD are caused by infections, of which 50%-70% can be proven, and appearance of purulent sputum indicates that it is exactly the case. The most common agents are H.influenzae, S.pneumoniae and Moraxella catarrhalis, while Gram-negative and other bacteria are much less frequently involved. Gram-negative bacteria are somewhat more frequently found in more severe AE COPD, especially if FEV1 is below 50% of the expected value. Probably viruses alone can lead to AE COPD, and it is quite certain that they predispose 40% -50% of bacterial exacerbations of COPD. Rhinoviruses, RSVs, Coronaviruses, and Parainfluenza and Influenza viruses are most commonly involved. Most inflammatory markers lack sufficient sensitivity and / or specificity to reliably distinguish exacerbations that are caused by bacterial infection from those that are of non-infectious nature. If neutrophilic leukocytes prevail in the sputum of a person who fulfills the AE COPD criteria, then in 83% of cases exacerbation is caused by bacterial infection, and without the use of antibiotics most likely will not improve. Procalcitonin (PCT) is a more reliable indicator of possible bacterial etiology of AE COPD than CRP. The more severe is exacerbation of COPD and the more comorbidities patient has, the introduction of antibiotic therapy is more liberal and broader is its antimicrobial spectrum. The use of antibiotics in AE COPD, regardless of their choice, reduces the risk of therapeutic failure by 55%, the risk of death by 77%, and sputum purulence by 44%. And all this is true despite numerous studies that show statistically measurable beneficial effect of antibiotics only in severe but not in mild or moderate worsening of COPD. Pneumococcal vaccine and regular seasonal vaccination against flu are recommended for all patients with COPD. Vaccination by oral application of bacterial lysates that induce production of secretory IgA (eg Broncho-Vax: H.influenzae, S.pneumoniae, K.pneumoniae, K.ozenae, S.aureus, S.pyogenes, S.viridans and Moraxella catarrhalis) is also available. In clinical trials such immunized person were more likely to improve in symptoms of COPD and to have shorter duration of exacerbation of COPD, as well as of hospitalization. However, the statistical significance of these differences compared to the unimmunised persons has not been demonstrated.

O-79 Legionarska bolest u hrvatskim bolnicama

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UVOD: Bolnički stečena pneumonija vodeći je uzrok smrtnosti među pacijentima s bolničkom infekcijom (smrtnost veća od 50% među pacijentima u intenzivnoj skrbi). Najčešći etiološki uzročnici su *Klebsiella spp.*, *Enterobacteriaceae*, *S. aureus*, *anaerobes*, *S. pneumoniae*, *P. aeruginosa* i *Legionella*, te razni virusi (*Influenza*, *RSV* i *Adenovirus*). Procjenjuje se da 2-10% ukupnog broja pneumonija stečenih u bolnici uzrokuju bakterije roda *Legionella*.

CILJ: odrediti pojavnost legionarske bolesti kao bolničke infekcije i mjere za minimiziranje rizika obolijevanja od legionarske bolesti među pacijentima i osobljem bolnice.

MATERIJALI I METODE: Analizirali smo podatke dobivene iz Registra za legionelu Hrvatskog zavoda za javno zdravstvo u Zagrebu od 2007.-2016. godine te prikazali i evaluirali mjere vezane uz pojavnost legionela u vodovodnoj vodi Opće bolnice Zadar.

REZULTATI: Od ukupnog broja prijavljenih infekcija legionelama u Hrvatskoj u promatranom razdoblju od 2% (2014. godina) do 11, 3% (2010. godine) pripada onima koje su stečene u bolnici. Godine 2008. i 2016. nisu zabilježene infekcije legionelama stečene u bolnici.

ZAKLJUČAK: pojavnost infekcija uzrokovanih legionelama, naročito među imunokompromitiranom populacijom, te kompleksnost bolničkih vodoopskrbnih sustava, nameće nužnost kontinuiranog provođenja mjera za smanjivanje rizika od ovih infekcija unutar bolnica.

KLJUČNE RIJEČI: legionarska bolest, bolnička infekcija, preventivne mjere

Legionnaires' disease in Croatian hospitals

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Introduction: Hospital-acquired pneumonia is the leading cause of mortality among patients with hospital-acquired infections (mortality greater than 50% among patients in intensive care). The most frequent etiologic agents are *Klebsiella spp.*, *Enterobacteriaceae*, *S. aureus*, *anaerobes*, *S. pneumoniae*, *P. aeruginosa* and *Legionella*, and various viruses (*Influenza*, *RSV* and *Adenovirus*). It is estimated that bacteria of *Legionella* genus causes 2 - 10% of the total pneumonia acquired in hospitals.

AIM: To determine the incidence of Legionnaires' disease as a hospital infection and measures to minimize the risk of Legionnaires' disease among patients and hospital staff.

MATERIALS AND METHODS: We analyzed data received from the Legionella Register of the Croatian Public Health Care in Zagreb from 2007 -2016 and presented the evaluated measures related to the occurrence of *Legionella* in the tap water of Zadar General Hospital.

RESULTS: In the observed periods from 2% (year 2014) to 11.3% (year 2010) of the total number of reported *Legionella* infections in Croatia belonged to those acquired at the hospital. No hospital acquired legionella infections were reported in 2008 and 2016.

CONCLUSION: The incidence of infections caused by *Legionella*, especially among immunocompromised populations, and the complexity of hospital water systems, imposes the need for continuous implementation of measures to reduce the risk of these infections within hospitals.

KEY WORDS: Legionnaires' disease, hospital infection, preventive measures

O-80 Infekcija rotavirusom A u hospitalizirane djece u Hrvatskoj tijekom sezone 2018/2019: pojava emergentnih G3P[8] reasortanata sličnih konjskim sojevima i G1P[8] reasortanata između različitih genogrupa

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Rotavirus A (RVA) je najznačajniji uzročnik virusnog gastroenteritisa u djece i mladih životinja diljem svijeta. Molekularna epidemiologija se bazira na genotipiziranju VP7 i VP4 genomskih segmenata koja rezultira binarnom klasifikacijom (genotipovi G i P). Molekularna raznolikost RVA sojeva kod ljudi je visoka, a neki sojevi imaju i zoonotsko podrijetlo. Tijekom sezone 2018/2019 testirali smo 188 uzoraka fecesa od hospitaliziranih pacijenata (većinom djece do 5 godina starosti, uključujući i 22 novorođenčadi) u Zagrebu, Osijeku i Splitu. Svi pacijenti su bili pozitivni na prisutnost RVA imunokromatografskim testom. Primijenili smo „semi-nested“ multiplex PCR protokol za VP7 i VP4 genotipiziranje u kombinaciji sa Sanger sekvenciranjem VP7, VP4 i VP6 RT-PCR odsječaka. Genotip G ili P utvrđen je u 187 uzoraka, a G/P genotipska kombinacija u 169 uzoraka. Najučestaliji genotipovi G bili su G3 (55,1%), G1 (12,9%), G2 (6,4%), G9 (2,7%), G4 (1,6%), G10 (1,1%), miješani genotipovi G (16%) i neuspješno tipizirani genotipovi G (4,8%). Od genotipova P dominantan je bio genotip P[8] (86,1%), te potom genotip P[4] (4,8%), P[9] (0,5%), miješani genotipovi P (3,7%) i neuspješno tipizirani genotipovi P (4,8%). Ukupno smo utvrdili devet G/P kombinacija; G3P[8], G1P[8], G2P[4], G4P[8], G9P[8] i manje učestale G10P[8], G2P[8], G9P[4] i G3P[9]. Među sojevima genotipa G3, 48,5% su bili emergentni, konjskim sojevima slični, G3 reasortanti s "DS-1-like" genotipskom konstelacijom. Iznimno je važno spomenuti i prvi dokaz G1P[8] reasortanata između različitih genogrupa s netipičnom „DS-1-like“ genotipskom konstelacijom u Europi. Sojevi genotipa G10 dokazanih u djece iz istočnog dijela Hrvatske moguće imaju zoonotsko, goveđe podrijetlo. Međutim ostali genotipovi G zajednički ljudima i životinjama u Hrvatskoj (G2, G4 i G9) pokazuju drugačiji evolucijski smjer. Prostorno-vremenska molekularno-epidemiološka istraživanja RVA sojeva u ekosustavu Hrvatske koja se trenutno provode, povećat će znanje i omogućiti korisnu bazu podataka kod razmatranja mogućeg uvođenja rotavirusnog cjepiva u nacionalni imunizacijski program.

Rotavirus A infection in hospitalized children in Croatia during season 2018/2019: the emergence of equine-like G3P[8] and G1P[8] intergenogroup reassortant strains

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Rotavirus A (RVA) is the main causative agent of viral gastroenteritis in children and young animals worldwide. Molecular epidemiology is primarily based on genotyping the VP7 and VP4 genome segments which gives a binary classification (G and P genotypes). Molecular diversity of RVA strains in humans is high and some of those strains have zoonotic origin. During season 2018/2019 we have tested 188 faecal samples from hospitalized patients (mostly children under the age of five years, among which 22 newborns) in Zagreb, Osijek and Split. All patients were positive for RVA by immunochromatographic assay. Semi-nested multiplex PCR for VP7 and VP4 RVA genotyping coupled with Sanger sequencing of amplified VP7, VP4 and VP6 RT-PCR fragments were applied. The G or P genotype was determined in 187 samples and G/P genotype combination in 169 samples. The most common G genotypes were G3 (55.1%), G1 (12.9%), G2 (6.4%), G9 (2.7%), G4 (1.6%), G10 (1.1%), mixed G genotypes (16%) and untypeable G genotype (4.8%). The P genotypes were predominantly P[8] (86.1%), followed by P[4] (4.8%), P[9] (0.5%), mixed P genotypes (3.7%) and untypeable P genotype (4.8%). In total there were nine G/P combinations; G3P[8], G1P[8], G2P[4], G4P[8], G9P[8] and less common G10P[8], G2P[8], G9P[4] and G3P[9]. Among G3 strains 48.5% were the emerging G3 equine-like intergenogroup reassortant RVA strains. Another notable finding is the first detection of unusual DS-1-like G1P[8] intergenogroup reassortant strains in Europe. G10 strains detected in children from eastern Croatia are possibly having the zoonotic bovine origin. However, other G genotypes shared between humans and animals in Croatia (G2, G4, G9) show different evolutionary direction. The ongoing studies on spatio-temporal molecular epidemiology of RVA strains in Croatian ecosystem will fill the knowledge gaps and provide useful database when considering the potential introduction of RVA vaccines in national immunisation program.

INFEKCIJE I UPALE SREDIŠNEG ŽIVČANOG SUSTAVA
CNS INFECTIONS

O-81 Kliničke značajke i dugoročni ishod liječenja bolesnika dječje dobi s akutnim diseminiranim encefalomijelitisom

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Clinical features and long-term outcomes of ADEM in paediatric population

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O-82 Klinički aspekti i dijagnostika tuberkuloze središnjeg živčanog sustava

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Tuberkuloza i danas predstavlja iznimno važan javnozdravstveni problem. U 2017. godini od tuberkuloze je u Svijetu oboljelo oko 10 milijuna ljudi, a 1,3 milijuna ljudi je umrlo od ove zarazne bolesti. S obzirom da se bacili prenose aerosolom, najčešće sijelo tuberkuloze su pluća. Izvanplućni oblici bolesti većinom se javljaju prilikom hematogenog rasapa bacila iz plućnog žarišta. Bacili tako mogu uzrokovati tuberkulozu pleure, urinarnog trakta, limfnih čvorova, središnjeg živčanog sustava (SŽS), kosti i drugo. Klinička prezentacija izvanplućne tuberkuloze ovisi o samom sijelu infekcije i reflektira zahvaćenost pojedinih organskih sustava. Izvanplućne manifestacije, kao što je tuberkuloza SŽS, osobito su česte kod HIV pozitivnih bolesnika te u male djece. Tuberkuloza SŽS-a jedna je od najtežih oblika bolesti koju često karakterizira nespecifična klinička slika te posljedično kasno prepoznavanje bolesti i visoki mortalitet. Tuberkuloza SŽS može se pojaviti u tri klinička entiteta: tuberkulozni meningitis, intrakranijski tuberkulom i spinalni tuberkulozni arahnoiditis. Sve tri kliničke prezentacije prisutne su u zemljama s visokom incidencijom tuberkuloze, dok u zemljama s niskom incidencijom, poput Hrvatske, većinom se susreće tuberkulozni meningitis. Definitivna dijagnoza tuberkuloznog meningitisa uključuje izolaciju *M. tuberculosis* iz uzorka likvora. Rutinski se radi mikroskopski pregled razmaza likvora te kultivacija na tekuće i krute podloge. U brzom dijagnostici veliku pomoć pružaju molekularni testovi koji se rade direktno iz uzorka, poput GeneXpert Ultra testa. Liječenje tuberkuloze SŽS je dugotrajno te uključuje istovremenu primjenu više antituberkulotika.

Clinical aspects and diagnostics of neurotuberculosis

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Tuberculosis is still today an extremely important public health problem. In 2017, about 10 million people were affected by tuberculosis, and 1.3 million people died from this infectious disease. Since the bacilli are usually transmitted by inhalation of infected aerosol, tuberculosis most commonly affects the lungs. Extrapulmonary manifestations of tuberculosis mostly occur via haematogenous spread from the primary site. The disease can present as tuberculosis of pleura, urinary tract, lymph nodes, central nervous system (CNS), bones, and other sites of the body. The clinical presentation of extrapulmonary tuberculosis depends on the affected site and reflects the involvement of different organic systems. Extrapulmonary manifestations, such as tuberculosis of the CNS, are particularly common in HIV positive patients and in young children. Tuberculosis of the CNS is one of the most severe forms of the disease, which is often characterized by a non-specific clinical picture, and consequent late detection of the disease and high mortality. Tuberculosis of the CNS can present as three clinical entities: tuberculous meningitis, intracranial tuberculosis, and spinal tuberculous arachnoiditis. All three clinical presentations are encountered frequently in countries with high incidence of tuberculosis, while in countries with low incidence, such as Croatia, tuberculous meningitis predominates. A definitive diagnosis of tuberculous meningitis requires the isolation of *M. tuberculosis* from the patient's spinal fluid. Microscopic examination of the spinal fluid for acid-fast bacilli and cultivation of the sample on liquid and solid media are routinely performed in clinical laboratories. Moreover, molecular tests performed directly from the sample, such as the GeneXpert Ultra test, can be used for the rapid diagnostics of neurotuberculosis. The treatment of neurotuberculosis is long lasting and involves the simultaneous administration of several antituberculous drugs.

O-83 Neuroinvazivna WNV infekcija u jedinici intenzivnog liječenja

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Neuroinvazivna West Nile virusna (NIWNV) bolest predstavlja rijetko, ali teško očitovanje WNV infekcije. Rizični čimbenici su starija dob, komorbiditeti (arterijska hipertenzija, šećerna bolest) te imunosupresija. Kako je u Hrvatskoj 2018. godine zabilježena najveća epidemija do sada, u ovom radu želimo prezentirati značajke najtežih bolesnika s NIWNV infekcijom liječene u Zavodu za intenzivno liječenje i neuroinfektologiju Klinike za infektivne bolesti „Dr. Fran Mihaljević“, Zagreb, od 2013. do 2018. god. Liječena su 23 bolesnika, 18 muškaraca (78%), medijan dobi 72 godine (minimum 33, maksimum 84). Deset bolesnika bili su iz Grada Zagreba, pet iz Zagrebačke županije, te po jedan bolesnik iz drugih kontinentalnih županija. Liječena su i dva pacijenta iz inozemstva, iz Mađarske i SAD-a. Većina bolesnika imali su komorbiditete, najčešće arterijsku hipertenziju (19/23) i šećernu bolest (9/23). Trojica bolesnika su imali transplantiran bubreg. Najčešća očitovanja bolesti bila su encefalitis s akutnom flakcidnom paralizom (9/23) i encefalitis (13/23). Tijekom liječenja u intenzivnoj jedinici 12 bolesnika su mehanički ventilirani, medijan mehaničke ventilacije bio je 12 dana (minimum 5, maksimum 73). Medijan trajanja hospitalizacije u JIL-u iznosio je 19 dana (minimum 5, maksimum 73), dok je medijan trajanja ukupne hospitalizacije iznosio 34 dana (minimum 7, maksimum 97). Dva bolesnika su preminula tijekom liječenja u JIL-u, a 15 bolesnika su kod otpusta imali modified Rankin Scale 3-5 (umjerena do teška nesposobnost). Kontrola svih liječenih obavljena je telefonskom anketom u srpnju 2019. god. Anketi je bilo dostupno 19/21 bolesnika. Do srpnja 2019. god. preminulo je dodatnih 5 bolesnika, a mRS 3-5 imalo je 5 bolesnika. Poboljšan mRS zabilježen je u 11 preživjelih (47%). Zaključno, NIWNV bolest je rijetka i pogađa starije osobe s komorbiditetima, većinom muškarce. Ovi bolesnici često trebaju produženo intenzivno liječenje. Poboljšanje se bilježi nakon više mjeseci u polovici bolesnika.

Neuroinvasive WNV infections in ICU

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Neuroinvasive West Nile virus (NIWNV) disease is a rare, but difficult manifestation of WNV infection. Risk factors include older age, comorbidities (arterial hypertension, diabetes) and immunosuppression. As the largest outbreak in Croatia was recorded in 2018, we want to present the characteristics of patients with severe NIWNV infection, treated at the Department for Intensive Care Medicine and Neuroinfectology, University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb, from 2013 to 2018. Twenty-three patients, 18 men (78%), with a median age of 72 years (minimum 33, maximum 84) were treated. Ten patients were from the City of Zagreb, five were from Zagreb County, and other continental counties were represented by one patient each. Two patients from abroad, from Hungary and the USA, were also treated. Most patients reported comorbidities, most commonly arterial hypertension (19/23) and diabetes (9/23). Three patients had a kidney transplant. The most common manifestations of the disease were encephalitis with acute flaccid paralysis (9/23) and encephalitis (13/23). Twelve patients were mechanically ventilated (MV), the median duration of 12 days (minimum 5, maximum 73). The median ICU stay was 19 days (minimum 5, maximum 73), while median hospital stay was 34 days (minimum 7, maximum 97). Two patients died during ICU treatment and 15 patients at discharge had moderate to severe disability, evaluated by modified Rankin Scale (mRS), score 3-5. The follow-up of was performed in July 2019. Nineteen of 21 patients were available. Additional 5 patients died and 5 patients had moderate to severe disability. An improvement, according to mRS, was reported in 11 patients (47%). In conclusion, NIWNV disease occurs rarely and affects the elderly with comorbidities, mostly male. These patients often need prolonged intensive treatment. Improvement is noted after several months in half of the patients.

O-84 Molekularna epidemiologija neuroinvazivnih infekcija uzrokovanih echovirusom 30 u Hrvatskoj

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Echovirus 30 (E30) je humani enterovirus (EV) B iz porodice Picornaviridae. Enterovirusi obično uzrokuju asimptomatske infekcije, ali ponekad mogu uzrokovati i teške infekcije koje se klinički prezentiraju kao meningitis ili encefalitis. E30 je važan uzročnik meningitisa u djece i odraslih osoba. Na temelju VP1 gena E30 izolati se dijele u dva genotipa te zbog učestalih mutacija, u više genskih linija. E30 uzrokuje epidemije koje se pojavljuju svakih 3-6 godina. Jedan takav je zabilježen 2018. godine u Hrvatskoj te u nekoliko europskih zemalja. Stoga smo analizirali epidemiološke karakteristike epidemije E30 meningitisa te molekularne karakteristike izoliranih E30 u Hrvatskoj tijekom 2018. godine.

Analizirano je ukupno 128 kliničkih materijala, 81 stolica i 47 cerebrospinalnih likvora (CSL) u kojima je prisutnost EV dokazana izolacijom u staničnoj kulturi i/ili RT-PCR-om. Tip izoliranih EV određen je pomoću neutralizacijskog testa i/ili monoklonalnih protutijela metodom izravne imunofluorescence. Za sve E30 izolate provedena je i filogenetska analiza za kompletnu nukleotidnu sekvencu VP1 gena.

U razdoblju od travnja do listopada 2018. godine, udio EV izolata iz CSL, odnosno stolice bila je 4/47 (8,5%) odnosno 17/81 (21%). Tipizacijom EV izolata nađeno je da je prevladavajući virus bio E30 (7/17; 41,2%), a dokazani su i Coxsackie B (7/17; 41,2%), E9 (2/17; 11,7%), te E11 (1/17; 5,9%). Većina bolesnika s dokazanom E30 infekcijom bila je iz Slavonije (5/7; 71,2%): Osiječko-baranjske županije (3), Vukovarsko-srijemske (1) i Brodsko-posavske županija (1). Filogenetska analiza izolata iz Hrvatske ukazala je na značajnu promjenu u molekularnoj epidemiologiji E30 infekcija na globalnoj razini. Svi izolati, osim jednog, pripadali su liniji IIBF, zajedno s nedavnim izolatima iz Turske, SAD-a i Argentine.

Ovi rezultati pokazuju važnost nadzora non-polio EV infekcija te detekcije i molekularne karakterizacije EV izolata što doprinosi epidemiološkim spoznajama o ovim, često dijagnostički nedokazanim virusnim infekcijama.

Molecular epidemiology of aseptic meningitis due to Echovirus 30 in Croatia

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Echovirus 30 (E30) is a human enterovirus (EV) B in the Picornaviridae family. Enterovirus infections are generally asymptomatic, but occasionally leads to severe disorders such as meningitis or encephalitis. E30 is a major cause of meningitis in both children and adults. Based on VP1 gene sequence E30 isolates are divided into two genotypes and several lineages due to high mutation rate. Infections with E30 are usually described as epidemic waves every 3-6 years. One of such has been recorded in Croatia and several European countries in 2018. Therefore, we analysed epidemiological characteristics of E30 meningitis outbreak and molecular characteristics of circulating E30 strains in Croatia during 2018.

In total, 128 clinical specimens, 81 stools and 47 cerebrospinal fluid (CSF), were examined for EV presence using virus isolation in cell culture and/or RT-PCR. HEV strains were typed by neutralization and/or direct immunofluorescence assay. Phylogenetic analysis was carried out on E30 strains using whole coding sequence of the VP1 gene.

From April to October 2018, EV detection rate in CSF and faecal samples was 4/47 (8.5%) and 17/81 (21%) respectively. EV typing revealed predominance of E30 (7/17; 41.2%) and circulation of Coxsackie B (7/17; 41.2%), E9 (2/17; 11.7%), and E11 (1/17; 5.9%). Most of patients with confirmed E30 infection (5/7; 71.2%) were from Slavonia region: Osijek-Baranja County (3), Vukovar-Srijem (1) and Brod-Posavina County (1). Phylogenetic analysis of Croatian isolates showed striking shift in epidemiology of E30 infections on a global level. All isolates, except one, were members of IIBF lineage together with recent isolates from Turkey, USA and Argentina.

Our results highlight the importance of surveillance, detection and molecular characterization of non-polio EV infections and thus get more comprehensive epidemiological information of this often underdiagnosed viral infection.

O-85 Herpes zoster kroz dva desetljeća

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Herpes zoster over two decades

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PUTNIČKA MEDICINA I PARAZITARNE BOLESTI
TRAVEL MEDICINE AND PARASITIC DISEASES

O-86 Putnik povrtanik iz Južne Amerike

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Returning traveler from South America

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O-87 Primjena preporuka za liječenje parazitarnih infekcija u RH

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Implementation of parasitic infections treatment guidelines in Croatia

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O-88 Nešto staro, nešto novo – salinična provokacija

Suzana Bukovski

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Something old, something new – salinic provocation

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O-89 Ugrizi i ozljede zadane od majmuna u razdoblju od 2009. do 2018. godine u antirabičnoj ambulanti Referentnog centra za bjesnoću u gradu Zagrebu

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Cilj. Prikazati ugrize i ozljede majmuna u razdoblju od 2009. do 2018. godine koji su obrađeni u antirabičnoj ambulanti Referentnog centra za bjesnoću pri Nastavnom zavodu za javno zdravstvo „Dr. Andrija Štampar“, Mirogojska cesta 16, u Zagrebu.

Metode. U radu su korišteni podaci službenog registra pacijenata ugrizanih osoba antirabične ambulante Referentnog centra za bjesnoću pri Nastavnom zavodu za javno zdravstvo „Dr. Andrija Štampar“. Podaci su prikazani tabelarno i grafički.

Rezultati. U promatranom razdoblju, registrirano je ukupno 41 osoba koje su zadobile ugrize odnosno ozljede od majmuna, što u postotku iznosi 0,70 % od ukupnog broja pregledanih osoba. 33 osobe primile su postekspozicijsku antirabičnu profilaksu (PEP) bilo cjepivom protiv bjesnoće bilo u kombinaciji s cjepivom protiv bjesnoće i antirabičnim imunoglobulinom, dok u 8 slučajeva to nije učinjeno. U slučajevima ne primjene PEP-a, u 7 slučajeva radilo se o ugrizu majmuna u Zoološkom vrtu grada Zagreba prilikom njegovanja i hranjenja (profesionalni djelatnici), a u jednom slučaju, radilo se o ugrizu majmuna kućnog ljubimca.

Sve osobe su u antirabičnu ambulantu dolazile na nastavak PEP-a koja je bila započeta u zemljama i državama gdje se dogodio ugriz. Najviše ih je bilo iz Tajlanda (17) i Indonezije (9), Zagreba (8), a slijedili su ih slučajevi iz Ukrajine (2), Indije (2), te pojedinačni slučajevi iz Nepala, Maroka i Kambodže.

Svi slučajevi dogodili su se prilikom diranja/hranjenja majmuna, odnosno odbijanja davanje hrane istima. U niti jedne od obrađenih osoba u navedenom periodu, nije došlo do pojave humane bjesnoće.

Zaključak. Ugrizi majmuna relativno su rijetka pojava u svakodnevnom radu antirabične ambulante, a svaki takav slučaj potrebno je pažljivo obraditi. Prilikom putovanja u destinacije gdje se može doći u kontakt s majmunima, putnici trebaju dobro proučiti upute/upozorenja kako se ponašati u njihovoj blizini, a u slučaju ozljede/ugriza, javiti se u najbližu medicinsku ustanovu radi obrade rane te PEP-a.

Monkey bites and injuries in Antirabies Clinic of the Referral Centre for Rabies in Zagreb in period from 2009 to 2018

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Aim. To present the monkey bites/injuries of the patients who have been examined at Antirabies Clinic of the Referral Centre for Rabies in Zagreb at Dr. Andrija Štampar Teaching Institute of Public Health, Mirogojska street 16.

Objectives. All data were collected from the Official patients registry of Antirabies Clinic of the Referral Centre for Rabies. Data are presented in tables and diagrams.

Results. In the observed period, 41 persons were registered to have been injured from monkeys, which represents 0,70% from all the number of the examined people at Antirabies Clinic. 33 persons received postexposure rabies prophylaxis (PEP), with antirabies vaccine or with antirabies vaccine and rabies immune globuline. 8 persons did not receive PEP at all. In 7 cases, professional ZOO employees were injured from monkeys in Zagreb Zoo, during feeding and nursing them. In the last case, a person got an injury from his pet monkey. Persons who received PEP came to Zagreb Antirabies Clinic for continuation of PEP treatment which was initially commenced in the countries where monkey bites/injuries occurred. They were from Thailand (17), Indonesia (9), Zagreb (8), Ukraine (2), India (2), Nepal (1), Morocco (1) and Cambodia (1).

All injuries happened when patients tried to pet or feed the monkeys, or refused to give them food. None of these patients contracted rabies.

Conclusion. Monkey bites/injuries are very rare and they do not pose any serious threat in routine job of Antirabies Clinic in Zagreb. Therefore, every such case need to be treated with special care. Before travelling to locations in which persons can get monkey bites/injuries, one must thoroughly study instructions and warnings how to behave in their presence, while in case of afflicting any monkey bite/injury, search for the nearest medical facility for wound tretment and PEP.

POSTERI
POSTERS

PO-1 Neurološke komplikacije povezane s influencom u djece: iskustva jednog centra (2014.-2019.)

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CILJEVI: Neurološke komplikacije influence su rijetke, ali potencijalno letalne manifestacije bolesti. Opisan je cijeli niz različitih akutnih neuroloških komplikacija influence među kojima su najčešće konvulzije i encefalopatija, a obično se događaju u dječjoj dobi. Premda veliki dio bolesnika ima blažu kliničku sliku, neki razvijaju teže komplikacije koje dovode do trajnih neuroloških oštećenja ili smrti.

Cilj ovog istraživanja je prikazati spektar neuroloških komplikacija influence u djece liječene u tercijarnom bolničkom centru i opisati kliničku prezentaciju, neuroradiološke karakteristike i nalaze cerebrospinalnog likvora bolesnika.

METODE: Proveli smo retrospektivno istraživanje među djecom mlađom od 18 godina koja su hospitalizirana zbog PCR-om dokazane (u respiratornim uzorcima i/ili CSL-u) infekcije influencom i neuroloških komplikacija u Klinici za infektivne bolesti "Dr. Fran Mihaljević" od 1. siječnja 2014.g. do 30. svibnja 2019. g. Analizirane su demografske, kliničke i neuroradiološke (CT i MR mozga) karakteristike i likvorski nalazi bolesnika.

REZULTATI: Među 382 djece hospitalizirane zbog influence, 33 (9%) je imalo neurološke komplikacije influence. Među njima najčešće su bile konvulzije (61%) i encefalopatija (52%). Prethodna kronična neurološka bolest zabilježena je u 21% bolesnika. Nitko od oboljelih nije cijepljen protiv influence. Najveći broj slučajeva (88%) uzrokovan je influenza A virusom. Likvorski nalaz pokazao je pleocitozu u 4 bolesnika, dok je samo jedan bolesnik imao abnormalan neuroradiološki nalaz. U većine bolesnika (76%) započeto je empirijsko liječenje oseltamivrom pri primitku. Dvoje bolesnika je umrlo zbog teškog edema mozga, dok preostali nisu imali neuroloških posljedica kod otpusta.

ZAKLJUČAK: Težina neuroloških komplikacija influence je varijabilna. U manjem broju slučajeva klinička prezentacija je teška, s mogućim letalnim ishodom. Brojni dijagnostički postupci, uključujući analizu likvora i neuroradiološke pretrage, ne mogu sa sigurnošću razlučiti influencu od drugih infekcija. Stoga bi liječnici trebali razmišljati o influenci u diferencijalnoj dijagnozi vrućice s neurološkim simptomima tijekom sezone influence.

Neurologic Complications Associated with Influenza Infection in Children: A Single-Centre Experience (2014-2019)

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AIMS: Neurologic complications are rare, but potentially fatal manifestations of influenza infection. A wide variety of acute neurological presentations of influenza have been reported, of which seizures and encephalopathy are the most common ones and usually occur in children. Although the majority of patients has relatively minor symptoms, some of them experience serious complications, resulting in permanent neurologic sequelae or death.

Here we report the spectrum of neurologic complications of influenza infection in children from the Croatian tertiary hospital centre and describe clinical characteristics, brain imaging and cerebrospinal fluid (CSF) findings.

METHODS: We conducted a retrospective study among children aged < 18 years hospitalized with PCR-confirmed (from respiratory and/or CSF samples) influenza infection and neurologic complications at the University Hospital for Infectious Diseases “Dr. Fran Mihaljević” between January 1, 2014 and May 30, 2019. Demographic, clinical, brain imaging (brain CT and MRI) and CSF findings were further analysed.

RESULTS: Among 382 children hospitalized for influenza, 33 (9%) had neurologic complications of influenza. The most common ones were seizures (61%) and encephalopathy (52%). Pre-existing neurological condition was reported in 21% of the patients. None of the children had received the influenza vaccine. Influenza A virus caused the majority (88%) of cases. CSF analysis showed pleocytosis in 4 patients, and only one patient had brain imaging abnormalities. The majority of patients (76%) were empirically treated with oseltamivir. Two patients died due to the severe brain oedema and the remaining had no neurologic sequelae on discharge.

CONCLUSIONS: Severity of neurologic complications of influenza is variable. Clinical presentation can be severe, sometimes with lethal outcome. Many diagnostic tests, including CSF and radiologic studies usually cannot distinguish influenza from other CNS infections. Therefore, physicians should consider influenza in differential diagnosis of febrile illness with neurologic symptoms during the influenza season.

PO-2 Karakteristike infekcija *Bartonella henselae* u dječjoj dobi

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Cilj: Cilj istraživanja je prikazati epidemiološke, kliničke i laboratorijske karakteristike *B.henselae* infekcije u djece liječene u Klinici za infektivne bolesti "Dr. Fran Mihaljević", Zagreb, u razdoblju od siječnja 2014. do lipnja 2019. godine.

Materijali i metode: Retrospektivno smo istražili kliničke karakteristike, epidemiologiju i laboratorijske parametre u bolesnika mlađih od 18 godina kod kojih je infekcija potvrđena indirektnim imunoflorescentnim testom za IgM i IgG na *B.henselae* ili detekcijom *B.henselae* lančanom reakcijom polimerazom (PCR) iz punktata limfnog čvora.

Rezultati: Od ukupno 104 bolesnika, 47 (45,1%) je bilo ženskog i 57 (54,8%) muškog spola. Medijan dobi iznosio je 9,7 godina (raspon, 1,1 do 17,3 godina). Kontakt s mačkom zabilježen je u 101 bolesnika (97,1%). Infekcija je potvrđena serološki u 87 (83,6%), metodom PCR-a u 5 (4,8%), a kombinacijom obje metode u 12 (11,5%) bolesnika. Najčešća manifestacija infekcije bila je regionalna limfadenopatija u 92 (88,4%) bolesnika, a slijede diseminirani oblik bolesti u 5 (4,8%), neurološke manifestacije koje su uključivale encefalitis, meningoencefalitis ili encefalopatiju u 4 (3,8%) i vrućica nepoznatog porijekla u 3 (2,8%) bolesnika. U 53,6% bolesnika limfadenopatija nije bila praćena vrućicom. U 12 (13%) bolesnika s limfadenopatijom došlo je do razvoja supurativne upale koja je potvrđena citološki. Uz limfadenopatiju u 5 bolesnika (5,4%) uočena je hepatosplenomegalija te u jednog bolesnika (1,08%) Parinaudov sindrom. Ukupan broj leukocita prosječno je iznosio $9,9 \times 10^9/L$, dok je prosječna vrijednosti C-reaktivnog proteina bila 23,02 mg/L. Liječenje azitomicinom provedeno je u 77 (74,0%), a kombinacija azitromicina, rifampicina i doksiciklina u 11 (10,5%) bolesnika. U 10 (9,6%) bolesnika učinjena je drenaža limfnog čvora. U 100 (96,1%) bolesnika došlo je do izlječenja.

Zaključak: Infekcija *B.henselae* u djece najčešće je blaga bolest koja se manifestira regionalnom limfadenopatijom. Serologija i PCR metode su izbora za dijagnozu bolesti. Duljina liječenja i izbor terapije ovise o kliničkoj manifestaciji infekcije uz vrlo visoku stopu izlječenja.

Clinical manifestation of *Bartonella henselae* infection among children

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Objectives: The aim of this study was to analyze clinical manifestation, epidemiology and laboratory parameters of *B.henselae* infection among children treated at the University Hospital for Infectious Diseases, Zagreb from January 2014 until June 2019

Materials and methods: We retrospectively analyzed the epidemiology, clinical and laboratory characteristics among children with positive indirect immunofluorescence assay for *B. henselae* IgM and IgG or positive *B.henselae* polymerase chain reaction (PCR) from lymph node aspirate.

Results: Total of 104 patients, 47 (45,1%) female and 57 (54,8%) male were enrolled. The median age was 9,7 (range, 1,1 to 17,3 years). A history of cat contact was present in 101 (97,1%) children. Acute infection was serologically confirmed in 87 (83,6%), in 5 (4,8%) with PCR while both methods were positive in 12 (11,5%) patients. The infection were presented with regional lymphadenopathy in 92 (88,2%) patients, disseminated disease in 5 (4,8%), neurologic manifestations such as encephalitis, meningoencephalitis and encephalopathy in 4 (3,8%) and fever of unknown origin in 3 (2,8%) patients. Lymphadenopathy without fever were presented in 51 (53,6%) patients. Suppurative inflammation was the most common complication in patients with lymphadenopathy (n=12, 13%). Along with lymphadenopathy, hepatosplenomegaly was found in 5 (5,4%) and Parinaud's syndrom in 1 (1,08%) patient. The average white blood cell count was 9,9 x 10⁹/L, while average value of C-reactive protein was 23,02 mg/L. Azithromycin was the most commonly prescribed antibiotic (74%, n=77). In 11 (10,5%) patients rifampicin and doxycycline were added. Surgical drainage of the lymph node were performed in 10 (10,5%) patients. Full recovery was the most frequent outcome (96,1%, n=100).

Conclusion: *B.hensellae* infection among children is usually mild disease presented as regional lymphadenopathy. Serology and PCR are useful tests for its diagnosis. Treatment duration and choice of therapy depend on clinical manifestation of infection with full recovery in most cases.

PO-3 Može li krvni pripravak biti uzrokom infekcije? Bakterijska kontaminacija krvnih pripravaka - rezultati praćenja u HZTM za period 2008.-2017.

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Cilj: Infekcija je jedan od najznačajnijih rizika transfuzijskog liječenja. Rizik prijenosa bakterija procjenjuje se i do 1000 puta većim od udruženog rizika prijenosa HIV, HBV, HCV i HTL-a. Krv i krvni pripravci (KP) su idealno hranilište za bakterije. Podložni su bakterijskoj kontaminaciji, a transfuzija kontaminiranog pripravka može uzrokovati niz komplikacija, uključujući sepsu i smrt. Cilj rada je prikazati učestalost i najčešće uzročnike kontaminacije KP proizvedenih u HZTM u periodu 2008.-2017.

Metode: U HZTM provodi se statistička kontrola KP prema preporukama Paul-Ehrlich u odnosu na broj proizvedenih KP. Uzorci krvnih pripravaka nasijavaju se u aerobne i anaerobne bočice (10 mL u svaku) i inkubiraju u Bact/ALERT sustavu do 7 dana. Po signalizaciji pozitiviteta uzorak se subkultivira i identificira mikroskopskim preparatom te biokemijskim testovima.

Rezultati: U periodu od 10 godina (2008.-2017.) testirano je 17.582 KP od čega 5.040 koncentrata trombocita (KT), 7.248 koncentrata eritrocita (KE), 3.641 svježe smrznute plazme (SSP) i 1.653 krioprecipitata (Kryo). Kontaminacija je dokazana u 24 KP (0,14%) od čega u 10/5.040 KT (0,2%), 9/7.248 KE(0,12%), 4/3.641 SSP (0,11%) i 1/1.653 Kryo (0,06%). Najčešći izolat (71%) bio je *Propionibacterium acnes* (17/24). Izolirani su i *S. epidermidis* 1/24 (4%) i drugi koagulaza negativni stafilokoki 2/24 (9%), *S. aureus* 1/24 (4%), *Bacillus spp.* 2/24 (9%) te *Enterobacter cloacae* 1/24 (4%).

Zaključak: Svi KP podložni su bakterijskoj kontaminaciji, a najviše KT obzirom na uvjete skladištenja (22°C). Najčešće kontaminante KP u HZTM bili su komenzali kože (21/24) (*Propionibacterium acnes*, *S. epidermidis*, koagulaza negativni stafilokoki, *S. aureus*). Bakterije gastrointestinalne flore, koje mogu uzrokovati ozbiljne i češće fatalne poslije-transfuzijske komplikacije, rijetki su izolati (1/24). Važno je provoditi bakterijski skrining krvnih pripravaka i svaku sumnju na bakterijsku infekciju u bolesnika temeljito ispitati.

Can blood components cause infections? Bacterial contamination of blood components - monitoring results in CITM 2008-2017.

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Goals: Infection is one of the most significant risks of transfusion treatment. The risk of bacterial transmission is estimated to be up to 1000 times higher than the cumulative risk of HIV, HBV, HCV and HTLV transmission. Blood and blood components (BC) are ideal medium for bacterial growth. They are susceptible to bacterial contamination, and transfusion of contaminated BC can cause many complications, including sepsis and death. The aim of this paper is to present the frequency of BC contamination and the most common contaminants of BC produced at CITM in the period 2008-2017.

Methods: Statistical control of BC is performed at CITM according to Paul-Ehrlich recommendations, based on the number of BC produced. BC samples are inoculated into aerobic and anaerobic bottles (10 mL each) and incubated in the Bact/ALERT system for 7 days. Upon signaling a positive result, the samples are subcultured and bacterial identification is performed by microscopic examination and biochemical tests.

Results: Over a 10-year period (2008-2017), 17,582 BC were tested, of which 5,040 platelet concentrates (PC), 7,248 red cell concentrates (RCC), 3,641 fresh frozen plasma (FFP) and 1,653 cryoprecipitate (Cryo). Contamination was found in 24 BC (0.14%) of which 10/5,040 PC (0.2%), 9/7,248 RCC (0.12%), 4/3,641 FFP (0.11%) and 1/1,653 Cryo (0.06%). The most common isolate (71%) was *Propionibacterium acnes* (17/24). *S. epidermidis* 1/24 (4%) and other coagulase negative staphylococci 2/24 (9%), *S. aureus* 1/24 (4%), *Bacillus spp.* 2/24 (9%) and *Enterobacter cloacae* 1/24 (4%) were also isolated.

Conclusion: All BC are susceptible to bacterial contamination. PC have the highest risk of contamination due to storage conditions (22°C). The most common BC contaminants at CITM were skin commensals (21/24) (*Propionibacterium acnes*, *S. epidermidis*, coagulase negative staphylococci, *S. aureus*). Bacteria from the gastrointestinal flora, which can cause serious and more often fatal post-transfusion complications, are rare isolates (1/24). It is important to carry out bacterial screening of BC and thoroughly examine any suspected transfusion-transmitted bacterial infection.

PO-4 Nealkoholna masna bolest jetre kao faktor rizika za infekciju *Clostridioides difficile* u hospitaliziranih starijih bolesnika liječenih parenteralnom antimikrobnom terapijom

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UVOD: Nealkoholna masna bolest jetre (engl. „nonalcoholic fatty liver disease“ (NAFLD)) najčešća je kronična bolest jetre, povezana s metaboličkim sindromom i promjenama mikrobioma crijeva. Infekcija s *Clostridioides difficile* (CDI) vodeći je uzrok proljeva povezanog s zdravstvenom skrbi, s rastućom prevalencijom i mortalitetom. Cilj ovoga istraživanja je utvrditi povećava li NAFLD podložnost *C. difficile* infekciji.

METODE: Retrospektivna, kohortna studija obuhvatila je bolesnike ≥ 65 godina, liječene antimikrobnom terapijom ≥ 24 sata i hospitalizirane ≥ 72 sata u razdoblju od 24 mjeseca. Izuzeti su bolesnici kojima je CDI dijagnosticiran u prvih 48 sati hospitalizacije. Na temelju rezultata ultrazvuka abdomena, bolesnici su podijeljeni u dvije skupine: sa i bez NAFLD-a.

REZULTATI: Uključeno je 314 bolesnika; 83 (26.4%) s NAFLD-om (59.0% muškaraca; medijan 74, IQR 68-79 godina) i 231 (73.6%) u kontrolnoj skupini (52.4% muškaraca, 76, 69-83 godine). Osim šećerne bolesti, koja je bila učestalija u skupini s NAFLD-om (37.4% naspram 25.1%), nije bilo razlika u ostalim komorbiditetima, hospitalizaciji ili antimikrobnoj terapiji unutar 3 mjeseca. Skupina s NAFLD-om češće je primala PPI/H2RA (48.2% naspram 33.3%), a u kontrolnoj skupini češće je postavljena nazogastrična sonda (9.6% naspram 30.3%). Nije bilo razlika u broju klasa antibiotika korištenih po bolesniku, trajanju terapije ili tipu antibiotika, osim penicilina (20.5% naspram 8.7%) koji su češće propisivani u skupini s NAFLD-om. 14 (16.9%) pacijenata s NAFLD-om i 17 (7.4%) u kontrolnoj skupini razvilo je CDI za vrijeme hospitalizacije. Logistička regresijska analiza pokazala je da su Charlson Age-Comorbidity Index >6 (OR 4.3, 95% CI 1.4-13.6), hospitalizacija unutar 3 mjeseca (OR 7.1, 95% CI 2.3-21.8), serumski albumini <28 g/L (OR 3.2, 95%CI 1.4-9.5), steatoza jetre (OR 3.3, 95%CI 1.0-10.6), eGFR <40 (OR 4.9, 95%CI 1.6-14.9), liječenje piperacilin/tazobaktamom (OR 4.7, 95%CI 1.6-14.8) i karbapenemima (OR 4.0, 95%CI 1.3-12.4) povezani s CDI.

ZAKLJUČAK: Naše je istraživanje pokazalo da je steatoza jetre neovisan prediktor razvoja CDI.

Nonalcoholic fatty liver disease as a risk factor for *Clostridioides difficile* infection in hospitalized elderly patients treated with systemic antimicrobial therapy

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BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease associated with metabolic syndrome and changes in gut microbiome. *Clostridioides difficile* infection (CDI) is the leading cause of healthcare-associated diarrhea with increasing prevalence and mortality. The aim of this study was to determine whether NAFLD increases the susceptibility to CDI.

METHODS: A retrospective, cohort study included patients ≥ 65 years, treated with antimicrobial therapy ≥ 24 hours and hospitalized ≥ 72 hours in a 24-month period. Excluded were patients diagnosed with CDI within the first 48 hours of hospitalization. Based upon the results of abdominal ultrasound, patients were divided into two groups: with and without NAFLD.

RESULTS: 314 patients were included; 83 (26.4%) with NAFLD (59.0% males; median 74, IQR 68-79 years) and 231 (73.6%) controls (52.4% males, 76, 69-83 years). Except for diabetes mellitus, which was more frequent in NAFLD group (37.4% vs 25.1%), there were no differences in other comorbidities, hospital admission or antibiotic therapy within 3 months. NAFLD group received PPI/H2RA more commonly (48.2% vs 33.3%), while the controls had more nasogastric tube placements (9.6% vs 30.3%). There were no differences in number of antibiotic classes used per patient, duration of therapy or antibiotic prescription, except for penicillins (20.5% vs. 8.7%) that were more frequently prescribed in NAFLD group. 14 (16.9%) NAFLD patients and 17 (7.4%) in control group developed in-hospital CDI. Logistic regression analysis showed that Charlson Age-Comorbidity Index >6 (OR 4.3, 95%CI 1.4-13.6), hospital admission within 3 months (OR 7.14, 95%CI 2.3-21.8), serum albumins $<28\text{g/L}$ (OR 3.2, 95% CI 1.4-9.5), liver steatosis (OR 3.3, 95%CI 1.0-10.6), eGFR <40 (OR 4.9, 95% CI 1.6-14.9), treatment with piperacillin/tazobactam (OR 4.7, 95%CI 1.6-14.8) and carbapenems (OR 4.0, 95% CI 1.3-12.4) were associated with CDI.

CONCLUSION: Our study identified liver steatosis as an independent predictor of CDI.

PO-5 Sonikacija u dijagnostici periprotetičkih infekcija

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Periprotetičke infekcije nakon ugradnje umjetnog globa nisu česte, ali predstavljaju komplikacije povezane s velikim pobolom. Obično su potrebne dodatne operacije, dugo i skupo liječenje antibioticima te implantacija nove proteze. Stoga je za uspjeh liječenja važna precizna dijagnoza infekcije.

Cilj ove studije bio je usporediti rezultate standardne mikrobiološke obrade uzoraka periprotetičkog tkiva i ultrazvučne obrade ekstrahiranih implantata u dijagnosticiranju periprotetičke infekcije.

Metode: Tijekom razdoblja od jedne godine (od 1. srpnja 2018. do 30. lipnja 2019.) u Klinici za ortopediju Lovran, Hrvatska, ukupno 72 pacijenata je operirano i liječeno zbog sumnje na periprotetičku infekciju. U svih bolesnika uzeti su uzorci tkiva za mikrobiološku analizu, a metalni dijelovi proteza poslani su na sonikaciju. Sonikati za mikrobiološku analizu prikupljeni su korištenjem ultrazvučne vodene kupelji.

Rezultati: Od 72 liječenih bolesnika, mikroorganizam je izoliran u 46 bolesnika i potvrđena je dijagnoza periprotetičke infekcije. Kod 82% bolesnika bile su pozitivne kulture tkiva, dok su kulture sonikata bile pozitivne u 89% bolesnika. Tamo gdje su i kulture tkiva i kulture sonikata bile pozitivne, u 12 slučajeva izoliran je različiti ili dodatni mikroorganizam.

Zaključci: Sonikacija je postala važna dijagnostička metoda u dijagnozi periprotetičkih infekcija. Sonikacija je omogućila otkrivanje mikroorganizma koji je prouzročio infekciju i u pacijenata kod kojih se sumnjalo samo na mehaničko razlabavljenje proteze, a time su poboljšani daljnji terapijski postupci i liječenje tih bolesnika.

Sonication in periprosthetic joint infections diagnostics

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Periprosthetic joint infections (PJI) after arthroplasty are not frequent, but they represent complications associated with high morbidity. Usually there is a need for additional surgery, long and expensive antibiotic treatment and implantation of a new prosthetic joint. Therefore a need for a precise diagnosis of PJI is important for the treatment success.

The aim of this study was to compare results of standard microbiological processing of periprosthetic tissue samples and sonication of extracted implants in diagnosing periprosthetic infection.

Method: During the one year period (July 1st 2018 till June 30th 2019) in the Ortophaedic Clinic Lovran, Croatia, altogether 72 patients were operated and treated because of suspected PJI. In all patients tissue samples were taken for microbiological analysis, and the metal parts of prosthesis were sent to sonication. The sonication fluid for microbiological analysis was collected using ultrasonic water bath.

Results: Out of the 72 patients treated, a microorganism was isolated in 46 patients and the diagnosis of periprosthetic infection was confirmed. In 82% of patients were positive tissue cultures, while sonication fluid cultures were positive in 89% of patients. Where both tissue cultures and sonication fluid cultures were positive, in 12 cases a different or additional microorganism was cultured using sonication.

Conclusions: Sonication has become an essential diagnostic tool in the diagnosis of PJI. Sonication enabled the detection of a microorganism which had caused infection also in the cases where only mechanical loosening had been suspected and thus further therapeutic procedures and treatment of these patients were improved. mechanical loosening had been suspected and thus further therapeutic procedures and treatment of these patients were improved.

PO-6 RESIST – 4 O.K.N.V. test za brzu detekciju karbapenemaza – naše iskustvo

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Uvod: Brza i točna detekcija enterobakterija koje stvaraju karbapenamaze od najvećeg je značenja za sprečavanje njihovog širenja i brzu primjenu mjera kontrole bolničkih infekcija. Molekularna metoda detekcije, iako „zlatni standard“, nije dostupna svim laboratorijima, te je uvođenje brzih testova, koji ne zahtijevaju posebnu opremu i educirano osoblje, od velikog značenja za brzu detekciju karbapenemaza. Resist-4 O.K.N.V. (Coris BioConcept, Gembloux, Belgija) je novi, brzi imunokromatografski test koji omogućuje brzu identifikaciju OXA-48, KPC, NDM i VIM karbapenemaza u porasloj kulturi.

Cilj: U ovom radu prikazat ćemo naše prve rezultate detekcije OXA-48, KPC, NDM i VIM karbapenemaza pomoću Resist-4 O.K.N.V. testa.

Metode: U radu smo koristili izolate enterobakterija koje su porasle iz kliničkih uzoraka. Identifikacija je napravljena Maldi-tof metodom, a antibiogram metodom disk-difuzije prema EUCAST standardima. Izolate enterobakterija koji su u antibiogramu pokazivali smanjenu osjetljivost na bilo koji od karbapenema ispitali smo pomoću Resist-4 O.K.N.V. testa. Test smo radili prema preporuci proizvođača. Rezultate Resist-4 O.K.N.V. testa potvrdili smo „in house“ PCR metodom koju radimo rutinski u našem laboratoriju.

Rezultati: Ukupno smo s obje metode testirali 80 izolata enterobakterija. Brzim testom, OXA-48 detektirana je u 31-nom izolatu *Klebsiella pneumoniae*, u jednom izolatu *Klebsiella oxytoca*, *Escherichia coli* i *Serratia marcescens*. VIM je detektiran u 3 izolata *Klebsiella oxytoca*, u jednom izolatu *Klebsiella pneumoniae* i *Klebsiella aerogenes* i u 2 izolata *Escherichia coli*, *Citrobacter freundii* i *Enterobacter cloacae*. KPC smo našli u 2 izolata *Klebsiella pneumoniae*. NDM je nađen u 4 izolata *Enterobacter cloacae* i jednom izolatu *Klebsiella pneumoniae*, *Escherichia coli* i *Citrobacter freundii*. Negativnih rezultata bilo je 26. Rezultati dobiveni PCR metodom su se 100% podudarali s rezultatima Resist-4 O.K.N.V. testa.

Zaključak: Naši rezultati su pokazali, da je Resist-4 O.K.N.V. test, brz i pouzdan za detekciju četiri najčešće karbapenemaze, te je prikladan i za manje laboratorije kojima nije dostupna molekularna dijagnostika.

RESIST – 4 O.K.N.V. test for rapid detection of carbapenemases – our experience

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Introduction: Rapid and accurate detection of carbapenemase-producing Enterobacterales are of utmost importance for preventing their spread and rapid implementation of infection control measures. Molecular tests are „gold standard“ but may be unaffordable for all laboratories. The introduction of rapid molecular tests, which do not require special equipment and trained staff, is of great importance for the rapid detection of carbapenemases. Resist-4 O.K.N.V. (Coris BioConcept, Gembloux, Belgium) is novel, rapid immunochromatographic test that enables rapid identification of OXA-48, KPC, NDM and VIM carbapenemases on colonies grown on susceptibility testing plates.

Purpose: In this paper, we would like to present our first results of OXA-48, KPC, NDM and VIM carbapenemases detection using Resist-4 O.K.N.V. test and confirming them with standard molecular test.

Methods: We used isolates of *Enterobacterales* growing from clinical specimens. MALDI tof identification and susceptibility testing (disc-diffusion method) were made according to the EUCAST standards. Isolates with reduced susceptibility to any of the carbapenems were tested with Resist-4 O.K.N.V. Test was performed according to the manufacturer's recommendations. The results of Resist-4 O.K.N.V test were confirmed with „in house“PCR test that we used routinely in our laboratory.

Results: With both methods a total of 80 isolates of *Enterobacterales* were tested. Results of Resist-4 O.K.N.V. test: OXA-48 was detected in 31 isolate of *Klebsiella pneumoniae*, in one isolate of *Klebsiella oxytoca*, *Escherichia coli* and *Serratia marcescens*. VIM was detected in 3 isolates of *Klebsiella oxytoca*, in one isolate of *Klebsiella pneumoniae* and *Klebsiella aerogenes*, as in 2 isolates of *Escherichia coli*, *Citrobacter freundii* and *Enterobacter cloacae*. KPC was found in 2 isolates of *Klebsiella pneumoniae*. NDM was found in 4 isolates of *Enterobacter cloacae*, and one isolate *Klebsiella pneumoniae*, *Escherichia coli* and *Citrobacter freundii*. There were 26 negative results. The results obtained by the PCR method were 100% consistent with Resist-4 O.K.N.V test results.

Conclusion: Our results showed that Resist-4 O.K.N.V. test, is fast and reliable for the detection of the four most common carbapenemases, and is suitable for smaller laboratories with no available molecular diagnostics.

PO-7 Raspodjela i antifungalna osjetljivost Candida vrsta izoliranih iz hemokultura

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Cilj: Studija je provedena kako bi se istražila raspodjela vrsta Candida izoliranih iz hemokultura te odredila njihova osjetljivost prema odabranim antifungicima.

Materijali i metode: Restrospektivnom analizom obuhvaćene su sve kandidate izolirane iz krvi bolesnika hospitaliziranih u Kliničkom bolničkom centru Rijeka, u razdoblju od 2013. do 2018. Relevantni podaci dobiveni su iz elektroničke arhive Kliničkog zavoda za kliničku mikrobiologiju. Izolati odgovorni za invazivne gljivične infekcije identificirani su korištenjem kromogenog agara i VITEK 2 YST identifikacijskih kartica (BioMérieux, Francuska). E-test je korišten za određivanje minimalnih inhibicijskih koncentracija za flukonazol, vorikonazol i anidulafungin u korelaciji s važećim EUCAST standardima.

Rezultati: Tijekom šestogodišnjeg razdoblja izolirano je ukupno 46 sojeva kandida od čega je *C. albicans* identificirana u 46%, a non-albicans vrste u 54% slučajeva. U skupini non-albicans vrsta najzastupljenije su *C. parapsilosis* (32%) i *C. glabrata* (28%). Svi izolati *C. albicans* bili su osjetljivi na vorikonazol i anidulafungin dok je 12% izolata bilo rezistentno prema flukonazolu. U non-albicans grupi, osjetljivost prema vorikonazolu dokazana je u 94%, a flukonazolu u 60% slučajeva, dok je svega 43% non-albicans izolata bilo osjetljivo na anidulafungin. Smanjena osjetljivost na anidulafungin u grupi non-albicans kandida uglavnom je posljedica predominacije *C. parapsilosis* u skladu s otprije poznatom smanjenom osjetljivošću ove vrste na ehinokandine.

Zaključak: *Candida albicans* i dalje je najčešći uzrok kandidemije, ali učestalost non-albicans vrsta, kao što su *C. parapsilosis* i *C. glabrata*, neprestano raste. Informacije o distribuciji vrsta i antifungalnoj rezistenciji na lokalnoj razini su neophodne za postizanje boljih kliničkih rezultata i odabir odgovarajuće i učinkovite antifungalne terapije.

Species Distribution and Antifungal Susceptibility of *Candida* isolated from blood cultures

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Aim: This study was performed to investigate the species distribution of *Candida* isolated from blood cultures, and to evaluate antifungal susceptibility during six-year period at a tertiary-care hospital.

Material and Methods: This is a retrospective review of all the *Candida* isolates recovered from blood of patients hospitalized in the Clinical Hospital Centre Rijeka, in the period from 2013 to 2018. Relevant data were obtained from the electronic microbiology laboratory database in our hospital. The isolates responsible for invasive fungal infections, grown in Bact/Alert systems, were identified using chromogenic culture media and VITEK 2 YST ID card system (BioMérieux, France). The e-test was used to determine the minimum inhibitory concentrations (MICs) of fluconazole, voriconazole and anidulafungin, and correlated with EUCAST.

Results: A total of 46 invasive *Candida* isolates were obtained from hospitalized patients during six-year period. *C. albicans* was the most common species identified in 46% of candidemia cases. In the non-*albicans* group (54% of all *Candida*), *C. parapsilosis* (32%) and *C. glabrata* (28%) were the most prevalent. All *C. albicans* were susceptible to voriconazole and anidulafungin, while 12% resistance to fluconazole was detected. On the other hand, voriconazole susceptibility was verified in 94%, and fluconazole in 60% of non-*albicans* isolates, while only 43% of non-*albicans* *Candida* were susceptible to anidulafungin. Reduced susceptibility to anidulafungin in non-*albicans* group is, in large part, due to predominance of *C. parapsilosis*.

Conclusion: *Candida albicans* is still the most frequent cause of candidemia, but the frequency of non-*albicans* species such as *C. parapsilosis* and *C. glabrata*, is steadily increasing. Information on recent trends in species distribution and antifungal resistance in local settings is essential to achieve better clinical result and to select an appropriate and effective antifungal therapy.

PO-8 Prevalencija krpeljnog encefalitisa i Lyme-borelioze u endemskim područjima kontinentalne Hrvatske (2017.-2019. godine)

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Infekcije uzrokovane virusom krpeljnog encefalitisa (TBEV) i *Borrelia burgdorferi* su široko rasprostranjene na području Europe. Koinfekcije s TBEV i borelijom također su opisane. Na području Hrvatske, TBEV je endemski u sjeverozapadnim regijama, no infekcije su zabilježene u svim kontinentalnim županijama. Borelioza ima sličnu geografsku distribuciju.

Cilj ovog rada je analizirati prevalenciju krpeljnog encefalitisa i Lyme-borelioze na području kontinentalne Hrvatske tijekom tri sezone prijenosa.

Od travnja 2017. do kolovoza 2019. godine, 362 bolesnika s područja kontinentalne Hrvatske s kliničkom slikom neuroinvazivne bolesti (meningitis, encefalitis) testirana su na TBEV i *B. burgdorferi*. Serološko testiranje uzoraka seruma i cerebrospinalnog likvora učinjeno je pomoću imunoinzimskih testova (TBEV; Euroimmun, Lübeck, Njemačka; *B. burgdorferi*; Virotech, Rüsselsheim, Njemačka). Uzorcima s pozitivnim TBEV IgM u IgG protutijelima određen je aviditet IgG protutijela (Euroimmun, Lübeck, Njemačka) u svrhu potvrde akutne/nedavne infekcije. Protutijela na *B. burgdorferi* potvrđena su pomoću imunoblot testa (Euroimmun, Lübeck, Njemačka).

Akutna TBEV infekcija potvrđena je dokazom IgM protutijela te IgG protutijela niskog aviditeta u 33 bolesnika. Sedam bolesnika imalo je IgG protutijela visokog

aviditeta što je ukazivalo na raniju TBEV infekciju. Neuroborelioza je potvrđena u četiri bolesnika, dok je 13 bolesnika imalo IgG protutijela na *B. burgdorferi*. U tri je bolesnika dokazana koinfekcija TBEV i *B. burgdorferi*. Infekcije su se pojavljivale od travnja do studenog, a najveći je broj zabilježen u svibnju/lipnju/srpnju (25/62,5%). Infekcije su dokazane u 12/21 hrvatskih županija. Najviša je prevalencija nađena u Međimurskoj (5/12,5%) i Koprivničko-križevačkoj županiji (4/10,0%). U 2019. godini zabilježena je manja epidemija sa šest slučajeva krpeljnog encefalitisa na području Gorskog kotara.

Prikazani rezultati ukazuju da su krpeljni encefalitis i borelioza endemski na području kontinentalnih hrvatskih županija. Sporadične infekcije i manje epidemije su kontinuirano bilježene uz izraženu sezonsku pojavnost.

Prevalence of tick-borne encephalitis and Lyme-borreliosis in endemic regions of continental Croatia (2017-2019)

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Infections caused by tick-borne encephalitis virus (TBEV) and *Borrelia burgdorferi* are widely distributed in Europe. Coinfections with TBEV and borrelia are also reported. In Croatia, TBEV is endemic in north-western regions, however infections were reported in all continental counties. Borreliosis has the similar geographic distribution.

The aim of this study was to analyze the prevalence of TBE and Lyme-borreliosis in the Croatian mainland during the three transmission seasons.

From April 2017 to August 2019, 362 patients from continental Croatian regions presented with neuroinvasive disease (meningitis, encephalitis) were tested for TBEV and *B. burgdorferi*. Serological tests of serum and cerebrospinal fluid samples were performed using enzyme-linked immunosorbent assays (TBEV; Euroimmun, Lübeck, Germany; *B. burgdorferi*; Virotech, Rüsselsheim, Germany). Samples with positive TBEV IgM and IgG antibodies were further tested for IgG avidity (Euroimmun, Lübeck, Germany) to confirm acute/recent infection. *B. burgdorferi* antibodies were confirmed using an immunoblot test (Euroimmun, Lübeck, Germany).

Acute TBEV infection was confirmed by detection of IgM and low avidity IgG antibodies in 33 patients. Seven patients showed IgG antibodies of high avidity

indicating previous TBEV infection. Neuroborreliosis was confirmed in four patients, while 13 patients showed IgG antibodies to *B. burgdorferi*. In three patients, TBEV and *B. burgdorferi* co-infection was detected. Cases occurred from April to November, with majority reported in May/June/July (25/62.5%). Infections were detected in 12/21 Croatian counties. The highest prevalence was recorded in Međimurje (5/12.5%) and Koprivnica-Križevci County (4/10.0%). In Gorski Kotar, a small outbreak with six cases of TBEV infection was reported in 2019. Presented results indicate that TBE and borreliosis are still endemic continental Croatian counties. Sporadic infections and small outbreaks are continuously detected with seasonal distribution of cases.

PO-9 Analiza transkriptoma ukazuje na ulogu monocita u patogenezi hemoragijske vrućice s bubrežnim sindromom

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Uvod i cilj: Pored endotelnih stanica, ortohantavirusi uspješno infiltriraju i neke stanice imunološkog sustava, poput monocita/makrofaga i dendritičkih stanica. Cirkulirajući monociti općenito igraju važnu ulogu u prepoznavanju virusne infekcije i inicijaciji urođenog imunološkog odgovora domaćina na virusnu infekciju. Oni mogu djelovati upalno ili protuupalno, ovisno o utjecaju različitih čimbenika iz mikro okruženja, uključujući i vrstu virusne infekcije. S druge strane, oni potencijalno mogu doprinijeti širenju virusa u tijelu i razvoju bolesti. Literaturni podaci o interakciji ortohantavirusa i urođenih imunoloških stanica tijekom infekcije vrlo su oskudni. Naša prethodna studija pokazala je regulatorne promjene na razini ekspresije gena uključenih u rani imunološki odgovor mononuklearnih stanica periferne krvi (PBMC) pacijenata s hemoragijskom vrućicom s bubrežnim sindromom (HVBS). Cilj ove studije bio je procijeniti utjecaj ortohantavirusne infekcije na stanice urođenog imunološkog sustava domaćina - ljudske monocite.

Metode: U studiju je uključeno 15 bolesnika s HVBS-om zaraženih virusom Puumala (PUUV) i 10 zdravih kontrola. Primarni monociti bili su izdvojeni iz svježe izoliranih PBMC-ova tijekom rane akutne faze HVBS-a. Izvršili smo duboko sekvenciranje mRNA (RNA-Seq) kako bismo analizirali transkripcijske ekspresijske profile u monocitima iz krvi bolesnika. Diferencijalna ekspresija analizirana je korištenjem DESeq paketa i diferencijalno eksprimirani geni rangirani su prema log₂ stupnju promjene i odgovarajućim p-vrijednostima. Također je provedena *enrichment pathway* analiza da bi se prikazale izmijenjene stanične funkcije monocita.

Rezultati: Ukupno je utvrđeno 5356 gena u monocitima sa značajno povišenom ili sniženom relativnom ekspresijom tijekom akutnog HVBS-a koji su definirani kao diferencijalno eksprimirani geni u odnosu na zdrave kontrole. *Enrichment pathway* analiza pokazala je da su funkcije povezane sa imunološkim sustavom i staničnim ciklusom najrelevantniji biološki procesi pod utjecajem ortohantavirusne infekcije u monocitima, a najznačajniji biološki putovi bili su procesiranje i prezentacija antigena posredivana molekulama MHC klase I kao i signalizacija interferonom tipa I.

Zaključak: Ova studija po prvi puta otkriva da se u monocitima u perifernom krvotoku događaju mnoge funkcionalne promjene tijekom njihove interakcije s ortohantavirusima tijekom rane faze HVBS-a.

Transcriptome analysis highlight the role of monocytes in pathogenesis of hemorrhagic fever with renal syndrome

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Introduction and objective: In addition to endothelial cells, orthohantaviruses successfully infiltrate some cells of the immune system such as monocytes/macrophages and dendritic cells. Circulating monocytes generally play an important role in the recognition of virus infection and host innate immune response to viral infection. They may act inflammatory or anti-inflammatory depending on the influence of various factors from the microenvironment, including the type of virus infection. On the other hand, they potentially may contribute to the dissemination of the virus in the body and development of the disease. Literature data on the interaction of orthohantaviruses and innate immune cells during the infection are very scarce. Our previous studies have shown regulatory changes at the expression level of genes involved in the early immune response of peripheral blood mononuclear cells of patients with hemorrhagic fever with renal syndrome (HFRS). The objective of this study was to assess the impact of orthohantavirus infection on host innate immune target cells – human monocytes.

Methods: The study enrolled 15 HFRS patients infected with Puumala virus (PUUV) and 10 healthy controls. Primary blood monocytes were depleted from freshly isolated PBMCs during the early acute phase of HFRS. We performed mRNA deep sequencing (RNA-Seq) in order to analyze transcriptomic expression profiles in blood monocytes of HFRS patients. Differential expression was analyzed using DESeq package and DEGs were ranked by log₂ fold change and corresponding p-values. The enrichment analysis was also conducted to illustrate altered monocyte cell functions.

Results: A total of 5356 genes in monocytes during the acute HFRS were determined as significantly up-/down-regulated and defined as differentially expressed genes compared to healthy controls. Pathway enrichment analysis revealed that immune- and cell cycle-related functions were most relevant biological processes affected by the orthohantavirus infection in monocytes. The most significant over-represented pathways were MHC class I mediated antigen processing and presentation as well as interferon type I signaling.

Conclusion: The study reveals that many functional alterations are happening in monocytes during their interaction with orthohantaviruses in peripheral circulation during the early phase of HFRS.

PO-10 Infekcije SŽS-a uzrokovane *Listeriom monocytogenes* u Klinici za infektologiju Kliničkog bolničkog centra Split

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Listerija je rijedak humani patogen koji može uzrokovati cijeli niz bolesti od kojih su infekcije SŽS povezane s najvećom smrtnošću. U ovom prikazu fokusirat ćemo se na spektar infekcija SŽS liječenih kroz godine u Klinici za infektologiju Kliničkog bolničkog centra Split, učestalost listerijskih infekcija u usporedbi s ostalim bakterijskim patogenima, populacijske skupine najčešće pogođene listerijskom infekcijom SŽS te na etablirane ali i neke novije spoznaje koje su nam pomogle u terapijskim i dijagnostičkim izazovima zbrinjavanja infekcija SŽS uzrokovanih *Listerijom monocytogenes*.

***Listeria monocytogenes* CNS infections in Infectology Clinic of Split University Hospital**

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Listeria is a rare human pathogen that can cause a variety of diseases with CNS infections being ones linked with highest mortality. In this review we will focus on the spectrum of listerial CNS infections treated through the years in Infectology Clinic of Split University Hospital, incidence of listerial infections compared with other bacterial pathogens, population groups most frequently affected by listerial CNS infections, and some established but also newer understandings that helped us overcome treatment and diagnostic challenges of CNS infections caused by *Listeria monocytogenes*.

PO-11 Ekološki faktori i prirodna infekcija sitnih glodavaca virusom krpeljnog meningoencefalitisa u Hrvatskoj

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U 2012. i 2013. godini uočen je nagli porast broja oboljelih od krpeljnog meningoencefalitisa (KME) na području Hrvatske u odnosu na posljednjih 20 godina. Ovim radom pokušali smo dovesti u vezu klimatske faktore, vrstu staništa i pojavnost KMEV kod sitnih glodavaca koji služe kao rezervoari ove bolesti.

Analiza je vršena na 232 prikupljena glodavca (*Apodemus spp.*, *Myodes glareolus*, *Microtus terrestris*) i jednom kukcojedu (*Sorex araneus*). Uzorci prikupljeni tijekom 2012. i 2013. godine na 4 različite lokacije gorske i kontinentalne Hrvatske testirani su na prisutnost virusne RNA KME koja je detektirana uz pomoć reverzne transkripcije i ugniježđenog PCR-a.

Od 232 testirana uzorka, virusna RNA detektirana je u 2 uzorka vrste *Apodemus flavicollis*. Izračunata stopa infekcije iznosila je 0.9% na razini ukupne prikupljene populacije dok je samo na razini populacije *Apodemusa* iznosila 1.6%. Zbog malog broja pozitivnih uzoraka jasna korelacija između klimatskih i okolišnih uvjeta i stope infektivnosti KMEV nije mogla biti uspostavljena te daljnja istraživanja trebaju biti izvršena.

Environmental factors and natural infection of small rodents by tick-borne meningoencephalitis virus in Croatia

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In the years 2012 and 2013, there was an increase in the number of tick-borne meningoencephalitis (TBE) cases in Croatia in comparison to the last 20 years. In this paper, we have tried to establish a connection between the climatic factors, habitat types and occurrence of TBEV in small rodents that serve as reservoirs of the disease.

The analysis was performed on 232 rodents (*Apodemus spp.*, *Myodes glareolus*, *Microtus terrestris*) and one insectivor (*Sorex araneus*). Samples were collected during the years 2012 and 2013 at 4 different locations in mountainous and continental Croatia and tested for the presence of viral TBE RNA which was detected using reverse transcription and nested PCR.

Of the 232 tested samples, the virus RNA was found in 2 samples of *Apodemus flavicollis*. The infection rate was 0.9% of the total population collected, while it was 1.6% in the *Apodemus* population level alone. Due to the small number of positive samples, a clear correlation between climatic and environmental conditions and tick-borne meningoencephalitis virus infection rate could not be determined and further research needs to be carried out before drawing conclusions.

PO-12 Vogt-Koyanagi-Harada sindrom – prikaz slučaja i diferencijalna dijagnoza uveitisa i meningitisa

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Uveitis je upala srednje očne ovojnice. Uzročnici mogu biti infektivne i neinfektivne prirode. Vogt-Koyanagi-Harada sindrom (VKH), čijom kliničkom slikom dominira uveitis, uzrokovan je autoimunim odgovorom na melanocite oka, a često je praćen i meningitisom. Predstavlja problem u kliničkoj praksi zbog diferencijalne dijagnoze. Prikazujemo slučaj pacijentice s navedenim sindromom i lažno pozitivnom serologijom na boreliju.

Pacijentica, 25 godina stara, dolazi u hitnu neurološku ambulantu radi dan ranije nastale mutne slike pred lijevim okom te glavobolje frontalne lokalizacije. Pregledom se ustanovljuje mutna slika na oba oka, a glavobolja regredira na terapiju ibuprofenom. Pacijentica je prethodno zdrava uz glavobolje unazad mjesec dana. Učinjen MSCT mozga opisan je kao uredan. MR obradom registrira se povišen intenzitet signala intrabulbarnog segmenta lijevog optičkog živca, a morfološke promjene upućuju na optički neuritis. Pacijentica je hospitalizirana. Ordinirana je pulsna kortikosteroidna terapija metilprednizolonom 1g iv./5 dana, uz koje se prati blaže kliničko poboljšanje. Ordinira se postupno smanjenje doze glukokortikoida. Konzilijarni oftalmolog nalazi eksudativno odignuće mrežnice oba oka čime postavlja sumnju na VKH. Serološkom obradom nalaze se pozitivna IgG i IgM protutijela (metodom ELISA) te pozitivna IgG protutijela (metodom WB) na Borreliu burgdorferi u serumu što upućuje na moguću neuroboreliozu. Bolesnica je cijelo vrijeme afebrilna. Upućena je na Kliniku za infektivne bolesti radi razrješenja značajnosti serologije na B. burgdorferi te daljnjeg isključenja infektivne prirode bolesti. Ponovljena serologija na borelije u likvoru i serumu negativna, PCR na HSV, VZV i enteroviruse u likvoru negativan. Bolesnica je anti-HIV i TPHA negativna. Isključena je infektivna priroda bolesti. Smanjenjem doze glukokortikoida zamijećeno je ponovno pogoršanje vida te pojava brujanja u ušima te je stoga doza metilprednizolona povećana na 500mg iv. dnevno. Liječena je i u konačnici se djelomično oporavila.

Diferencijalno dijagnostički, kliničku sliku uveitisa i meningitisa od infektivnih bolesti mogu dati bruceloza, CMV, leptospiroza, Q-groznica, West Nile virus, sifilis te tuberkuloza, a od neinfektivnih Behcetova bolest, sarkoidoza te VKH. Ovaj slučaj ukazuje na značaj pouzdane dijagnostike infekcija kao potencijalnog uzroka uveitisa.

Vogt-Koyanagi-Harada syndrome – a case report and differential diagnosis of uveitis and meningitis

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Uveitis is an inflammation of middle eye layer. Causes are of infectious and noninfectious. Vogt-Koyanagi-Harada syndrome (VKH), mainly clinically presented as uveitis, often is accompanied by meningitis. It is caused by an autoimmune response to melanocytes of the eye. Here we are presenting a case report of a patient with VKH and a false positive serology test to *Borrelia burgdorferi*.

Patient, female, age 25, admitted to emergency room because of 2-day long blurry vision of the left eye and frontal headache. Physical exam shows blurry vision of both eyes. Headache responded to ibuprofen. Patient is previously healthy besides experiencing a month-long headache. Brain MSCT scans were normal. MRI showed higher signal intensity of intrabulbar segment of the left optic nerve with morphological changes indicating optic neuritis. Patient is hospitalized and started on pulse corticosteroid therapy (methylprednisolon 1g i.v./5 days). Mild vision improvement was noted, leading to a slow decrease in corticosteroid dose. Ophthalmologist found exudative retinal detachment on both eyes and suspected VKH. Serum serology tests were found positive to IgG and IgM (ELISA) and positive IgG antibodies (WB) to *B.burgdorferi*, indicating possible neuroborreliosis. The patient is afebrile. She is admitted to University Hospital for Infectious Diseases to further explain the meaning of positive *Borrelia* test and to exclude other infectious etiology. Serum and CSF serology tests were repeated proving negative *Borrelia*. PCR tests to HSV, VZV and enteroviruses in CSF were also proved negative. The patient was anti HIV and TPHA negative, eliminating infectious etiology. Upon worsening vision, corticosteroid doses were elevated to 500 mg i.v./day. The patient eventually partially recovered.

Differential diagnosis of uveitis and meningitis should include infectious (brucellosis, CMV, leptospirosis, Q-fever, WNV, syphilis, TBC) and noninfectious causes (Bechet's disease, sarcoidosis, VKH). This clinical case addresses significance of reliable diagnostic tests for infectious diseases as a potential cause of uveitis.

PO-13 Bolesnik s novootkrivenom Addisonovom bolesti u infektološkoj ambulanti

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Prikaz slučaja: Bolesnik s novootkrivenom Addisonovom bolesti u infektološkoj ambulanti

Cilj: klinička i laboratorijska diferencijalna dijagnostika Addisonove bolesti i infekciozne mononukleoze.

Metode: klinički nalaz (anamneza, klinički pregled), laboratorijska dijagnostika (hematološke, biokemijske i serološke krvne pretrage), slikovne dijagnostičke pretrage (UZV abdomena).

Rezultati: u kliničkom nalazu pri prijemu subfebrilan, slabije hidriran, koža i sluznice blijede, ostali nalaz uredan. Treći dan boravka pojava tamnih makuloznih promjena po licu i difuzno sivkastije boje kože. Patološke vrijednosti nalaza: aspartat aminotransferaza (AST) 64 U/L, alanin aminotransferaza (ALT) 164 U/L, bilirubin 26 umol/L, natrij (Na) 126 mmol/L, kalij (K) 6 mmol/L, kortizol 42 nmol/L, adrenokortikotropni hormon (ACTH) 236 pmol/L, tiroidni stimulirajući hormon (TSH) 11 mIU/L, slobodni tiroksin (fT4) 13 pmol/L, antitireoperoksidazna protutijela (TpoAt) 221 kIU/L.

Zaključak: patološke vrijednosti aminotransferaza, bilirubina i sličnost kliničkih simptoma bolesti, zahtjeva uključivanje bolesnika s Addisonovom bolesti u diferencijalnu dijagnozu bolesnika s infekcijskom mononukleozom.

Ključne riječi: Addisonova bolest, infekcijska mononukleza, diferencijalna dijagnostika.

A patient with newly diagnosed Addison's disease in the Department for Infectious Diseases

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Case report: A patient with newly diagnosed Addison's disease in the department for infectious diseases

Objective: Clinical and laboratory differential diagnosis of Addison's disease and infectious mononucleosis.

Methods: Clinical findings (patient history, clinical examination), laboratory diagnostics (hematological, biochemical and serology blood tests), imaging diagnostic tests (ultrasound of the abdomen).

Results: On examination patient was subfebrile, dehydrated with pale skin and mucosae. Other clinical findings were normal. On the third day of the disease dark macular changes were noticed on the face along with greyish coloration of the skin diffusely. Pathological laboratory findings: aspartate aminotransferase (AST) 64 U/L, alanine aminotransferase (ALT) 164 U/L, bilirubin 26 umol/L, sodium (Na) 126 mmol/L, potassium (K) 6 mmol/L, cortisol 42 nmol/L, adrenocorticotrophic hormone (ACTH) 236 pmol/L, thyroid stimulating hormone (TSH) 11 mIU/L, free thyroxine (fT4) 13 pmol/L, antithyroid peroxidase antibodies (TpoAt) 221 kIU/L.

Conclusion: Pathological values of aminotransferases, bilirubin and similarity of clinical symptoms of the diseases, requires the inclusion of Addison's disease in the differential diagnosis of infectious mononucleosis.

Keywords: Addison's disease; Infectious mononucleosis; Differential diagnosis.

PO-14 Vanbolničke sepsa: epidemiologija, skorovi za sepsu, ishodi i etiologija

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Uvod: Sepsa je životno ugrožavajući sindrom s visokim mortalitetom (26% na globalnoj razini) unatoč napretku moderne medicine.

Ciljevi i metode: Cilj ovog istraživanja bio je usporediti qSOFA, SOFA skorove i SIRS zbroj, epidemiologiju, etiologiju i ishode u odraslih bolesnika hospitaliziranih u Klinici za infektivne bolesti u Zagrebu s vanbolničkom bakterijemijom u 2007. i 2016. godini.

Rezultati: U istraživanje je uključeno ukupno 420 bolesnika. Medijan dobi bio je 70 (IQR 56, 78), 54.76% bolesnika su bile žene, medijan Charlson indeksa komorbiditeta bio je 4 (IQR 2, 5). Srednje trajanje hospitalizacije bilo je 14 (IQR 11, 20), a za 10.71% bolesnika bilo je potrebno liječenje u jedinici intenzivne medicine. Osam bolesnika imalo je septički šok (1.9% svih bolesnika, 17.78% onih u jedinici intenzivne medicine). Dvadeset šest (6.19%) bolesnika umrlo je tijekom hospitalizacije. Medijan za SIRS zbroj, SOFA i qSOFA skor bio je 2 (IQR 1, 3), a 62.62%, 54,89% i 9,52% bolesnika ispunilo je dotične kriterije sepsa. Osamdeset četiri (20%) bolesnika nije ispunilo niti jedan od kriterija sepsa. Pri usporedbi skorova za sepsu, nije bilo značajne razlike u dobnoj distribuciji, spolu te komorbiditetima, ali za 47.5% bolesnika s qSOFA kriterijima bila je potrebna hospitalizacija u jedinici za intenzivnu medicinu te je 37.5% umrlo, dok su oba događaja bila puno manje zastupljena u bolesnika sa SOFA ili SIRS kriterijima. Najčešći uzrok bakterijemije bila je *E. coli*, zatim *S. aureus*, *S. pneumoniae*, β -haemolitički streptokoki, itd. Najčešći uzročnik u bolesnika koji su umrli bio je *S. aureus*.

Zaključak: Čini se da bolesnici s bakterijemijom pripadaju skupini starije životne dobi (medijan 70 godina), s gotovo izjednačenom distribucijom spola. Najčešći uzročnik je *E. coli*, ali u bolesnika s teškom sepsom, kojima je potrebno intenzivno liječenje i imaju viši mortalitet, češći je *S. aureus*. Stari i novi kriteriji za sepsu razlikuju se pri usporedbi ishoda – bolesnicima koji ispunjavaju qSOFA kriterije češće je potrebna intenzivno liječenje te imaju viši mortalitet.

Community-acquired sepsis: epidemiology, sepsis scores, outcomes and etiology

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Introduction: Sepsis is a life-threatening syndrome with high mortality (26% on global scale) despite the advance of modern medicine.

Aim and methods: The goal of this study was to compare qSOFA, SOFA score and SIRS criteria, epidemiology, etiology and outcomes in adult patients hospitalized at University Hospital for Infectious Diseases Zagreb with community-acquired bacteremia in 2007 and 2016.

Results: There was a total of 420 patients. The median age was 70 (IQR 56, 78), there were 54.76% females, the median Charlson Comorbidity Index was 4 (IQR 2, 5). The mean duration of hospital stay was 14 (IQR 11, 20), 10.71% of patients required ICU stay. Eight patients had septic shock (1.9% of all patients, 17.78% of those who required ICU stay). Twenty six (6.19%) patients died during hospital stay. The median SIRS, SOFA and qSOFA scores were all 2 (IQR 1, 3), and 62.62%, 54.89%, 9.52% patients fulfilled respective sepsis criteria. Eighty four (20%) of patients fulfilled no criteria for sepsis. When comparing sepsis scores, there was no significant difference in patient age, sex and comorbidities, but 47.5% patients with qSOFA stayed in ICU and 37.5% died, while both events were much less likely with SOFA and SIRS criteria. The most common cause of bacteremia was *E. coli*, followed by *S. aureus*, *S. pneumoniae* and beta-haemolytic streptococci, etc. The most common bacteria in those who died was *S. aureus*.

Conclusion: It seems that most patients with bacteremia belong to the old-age group (median 70 years), with an almost even sex distribution. The most common causative agent was *E. coli*, but in patients with severe sepsis, needing ICU treatment and with higher mortality, *S. aureus* is more common. The old and new criteria for sepsis differed when comparing outcomes – patients fulfilling qSOFA criteria required more ICU stay and had higher mortality.

PO-15 Kliničke karakteristike i ishod liječenja bolesnika liječenih u jedinici intenzivnog liječenja za infektivne bolesti

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UVOD: U većini država Europske Unije (EU) pacijenti oboljeli od težih oblika infektivnih bolesti najčešće se liječe u općim ili neurološkim jedinicama intenzivnog liječenja (JIL). Suprotno tomu, u pojedinim europskim državama, kao i u Zagrebu u Hrvatskoj, ovi bolesnici liječe se u specijaliziranim infektološkim jedinicama intenzivnog liječenja (IJIL). Cilj ovog istraživanja jest procijeniti kliničke i epidemiološke karakteristike pacijenata zaprimljenih u JIL-infektivnih bolesti te usporediti ishod liječenja bolesnika u IJIL s ishodom bolesnika liječenih u općim ili neurološkim s istim dijagnozama.

METODE: Istraživanje je retrospektivna analiza podataka prikupljenih od 1172 pacijenta liječenih u IJIL u Klinici za infektivne bolesti „Dr. Fran Mihaljević“ u Zagrebu u razdoblju od siječnja 2016.godine do prosinca 2018.godine.

REZULTATI: U istraživanje je uključeno 765 muških i 407 ženskih ispitanika zaprimljenih u IJIL. Medijan dobi ispitanika bio je 61 godinu. Gotovo 50% ispitanika imalo je više od jedne infektološke dijagnoze po primitku. Najčešće dijagnoze bile su sepsa (39%), neurološke infekcije (37%), upala pluća (10%), infektivni endokarditis (10%), kožne infekcije (4%), enterokolitis (3%) i egzacerbacija kronične opstruktivne plućne bolesti (1%). Približno 30% ispitanika sa sepsom imalo je i septički šok. Ukupna smrtnost ispitanika bila je 20%. Stopa smrtnosti oboljelih od sepse bila je 40%, od upale pluća 28%, endokarditisa 23%, a oboljelih od neurološke infekcije 12%.

ZAKLJUČAK: Smrtnost oboljelih od sepse u IJIL u Zagrebu bila je 40%, što odgovara smrtnosti u općim JIL koja prema literaturi iznosi 10 – 52%. Stoga, zaključujemo da tip jedinice intenzivnog liječenja nema utjecaja na ishod liječenja sepse, već da bi ishod liječenja pacijenata mogao ovisiti o karakteristikama bolesnika.

Clinical characteristics and treatment outcome in patients treated in an infectious disease intensive care unit

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Background: In most countries of the European Union patients suffering from severe forms of infectious diseases are commonly treated in general or neurological intensive care units (ICU). Diversely, in some European countries, as well as in Zagreb, Croatia, these patients are admitted to a specialized Infectious Diseases Intensive Care Unit (IDICU). The study aimed to evaluate the clinical and epidemiological features of patients admitted to the IDICU and compare the treatment outcome of the IDICU with literature data on the outcome of patients in non-IDICU.

METHODS: The research is a retrospective analysis of data collected on 1172 patients in the period between January 2016 and December 2018 treated in IDICU in tertiary hospital for infectious diseases in Zagreb, Croatia.

RESULTS: The study included 765 male and 407 female patients who were admitted to the IDICU.

Their age median was 61 years. Nearly 50% of patients had multiple infectious admitting diagnoses. The most common diagnoses were sepsis (39%), neurological infection (37%), pneumonia (10%), infective endocarditis (10%), skin infection (4%), enterocolitis (3%), chronic obstructive disease exacerbation (1%). Approximately 30% of admitted patients with sepsis had accompanied septic shock. The total mortality of admitted patients was 20%. The mortality rate of patients with sepsis was 40%, with pneumonia 28%, with IE 23% and with neuro infections was 12%.

CONCLUSION: Mortality of sepsis in IDICU Zagreb was 40%, which is in accordance with the mortality of sepsis in general ICUs, which is stated in literature as 10 - 52%. We conclude that the type of intensive care unit does not have an impact on the sepsis outcome but that it could depend on the patient characteristics.

PO-16 Karakterizacija hrvatske kolekcije meningokoknih izolata za razdoblje 2011.-2019.

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Uvod: Incidencija invazivne meningokokne bolesti (IMD) u Hrvatskoj je godinama niža od 1/100000. Većina invazivnih izolata je iz Klinike za infektivne bolesti Zagreb (KIB). Od 2012 godine ustanovljen je Nacionalni referentni centar s predstavnikom iz KIB i Hrvatskog zavoda za javno zdravstvo. NRC prima izolate od svih hrvatskih mikrobioloških laboratorija.

Materijal: Obradeni su podatci o meningokoknim izolatima koji su zaprimljeni u KIB u razdoblju od 2011. do srpnja 2019. Opisana je regionalna raspodjela, godišnja raspodjela, klinički uzorak, dob i spol bolesnika, raspodjela serogrupa *N.meningitidis* i osjetljivost meningokoknih izolata na antibiotike koji se upotrebljavaju u terapiji i profilaksi.

Rezultat: U promatranom razdoblju poslano 133 meningokokna izolata 42/133 iz Zagreba, 19 Splita, 18 Koprivnice i 17 Čakovca. Većina izolata je primljena 2016 24 od 133, 2013 21 od 133 i 2019 18 od 133. Bilo je 36/133 izolata djece do 5 godina starosti, od toga čak 21/ 133 djece mlađe od godinu dana. Zabilježen je i značajan broj izolata u osoba starijih od 45 godina 23/133. Većina izolata je bila iz krvi i likvora (48 odnosno 37). Meningokok serogrupe B je najčešće identificiran 83/133 izolata. Čak 29 od 60 testiranih izolata je bilo smanjeno osjetljivo na penicilin s MIK od 0,94 do 0,5 mg/L. Međutim 27 izolata su interpretirana kao intermedijarno osjetljivi na penicilin, a samo 2 kao rezistentni. Svi testirani izolati su bili osjetljivi na ceftriakson, rifampicin i ciprofloksacin.

Zaključak: U Hrvatskoj je najčešći izolat *Neisseria meningitidis* grupe B. Pojava meningokoka grupe Y i dobna distribucija ovih izolata trebaju se pažljivo pratiti. Obzirom na ograničene mogućnosti metode aglutinacije u razlikovanju grupe Y i W potrebno je uvesti genogrupiranje. Iako u Hrvatskoj penicilin nije lijek izbora u terapiji IMD sve učestalija pojava izolata smanjene osjetljivosti na penicilin i porast MIK-a zahtijevaju redovito praćenje antibiotskog profila penicilina. Bilo bi dobro uvesti test penA gena.

Characterization of Croatian Collection of Meningococcal Isolates for the Period 2011-2019

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Introduction: Incidence of invasive meningococcal disease (IMD) in Croatia is stable for years, being less than 1/100000. Most data about IMD isolates was obtained from University hospital for infectious diseases Zagreb. Since 2012 National reference centre for *N.meningitidis* had UHID and CIPH representatives. Isolates were received from all Croatian microbiological laboratories.

Materials: Data on meningococcal isolates received at UHID from 2011 to July 2019 have been analysed for regional distribution, yearly distribution, origin of clinical samples, age and gender distribution of patients, *N.meningitidis* serogroup distribution and antibiotic susceptibility profile.

Results: In observed period 133 isolates were received, 42/133 from Zagreb, 19 Split, 18 Koprivnica and 17 Čakovec. Most isolates were received in 2016 24/133, 21/133 in 2013 and 18/133 in 2019. From children under 5 years were 36/133 isolates, even 21/ 133 from children under 1 year of age. Significant number of isolates were recorded 23/133 in patients 45 years and older. Most isolates were isolated from blood 48 and CSF 37. Prevalent serogroup was serogroup B 83/133. Even 29/60 isolates were not susceptible to penicillin anymore having MIC range 0,94 to 0,5 mg/L. But 27 isolates were interpreted as intermediate and only 2 as resistant. All tested isolates were susceptible to ceftriaxone, rifampicin and ciprofloxacin.

Conclusion: *Neisseria meningitidis* group B prevailed in Croatia. Emerging of group Y should be followed up routinely. Therefore agglutination grouping techniques should be replaced by genogrouping. Although penicillin is not the first choice for treatment of IMD in Croatia recent decreasing of penicilline susceptibility implicated careful monitoring of penicillin profile. Introduction of penA gene could be foreseen.

PO-17 Invazivna meningokokna bolest u Splitsko-dalmatinskoj županiji – dvadesetpetogodišnji prikaz

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Cilj: Prikaz epidemioloških značajki invazivne meningokokne bolesti (IMB) u Splitsko-dalmatinskoj županiji (SDŽ) u razdoblju od siječnja 1994. do prosinca 2018. godine.

Metode: Primijenjene su metode deskriptivne epidemiologije. Pretražena je medicinska dokumentacija Klinike za infektologiju Kliničkog bolničkog centra Split, kao i Prijave zaraznih bolesti Službe za epidemiologiju zaraznih bolesti Nastavnog zavoda za javno zdravstvo SDŽ.

Rezultati: Tijekom promatranog razdoblja u SDŽ od IMB oboljele su 162 osobe, s prosječnom godišnjom stopom incidencije od 1,39/100.000 stanovnika. Udio djece u dobi od 0 do 14 godina bio je 74,1% (120 oboljelih). Najmlađa oboljela osoba imala je jedan mjesec, najstarija 83 godine, a medijan dobi je iznosio 4 godine. Tijekom četiri zimska mjeseca oboljelo je 88 (54,3%) osoba. Uzročnik je dokazan u krvi i/ili likvoru (jedan obrisak meninge) u 114 oboljelih (70,4%). Među izolatima s dokazanom serogrupom prevladavala je *N. meningitidis* serogrupe B (79,7%), potom *N. meningitidis* serogrupe C (14,9%) te *N. meningitidis* serogrupe Y/W 135 (6,8%). Serogrupa nije određena u 34,5% pozitivnih izolata. Sepsa s meningitisom je bila najčešća klinička prezentacija kod 48,8%, zatim sepsa kod 30,3%, te meningitis kod 21,0% oboljelih. Letalitet je iznosio 4,3%, a od sedam umrlih, petero ih je bilo u dobi do 4 godine. Dvije osobe su dvaput oboljele od IMB (jedna sa smrtnim ishodom). Nisu zabilježeni sekundarni slučajevi bolesti.

Zaključak: Potrebno je intenzivnije praćenje i evaluacija epidemioloških, mikrobioloških i kliničkih značajki IMB kako bi se razmotrila opravdanost šire primjene cjepiva u svrhu smanjenja pobola.

Invasive meningococcal disease in Split-Dalmatia County – a twenty five year surveillance

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OBJECTIVE: Epidemiological features for invasive meningococcal disease (IMD) in Split-Dalmatia County (SDC) in the period from January 1994 to December 2018.

METHODS: Descriptive epidemiology methods were applied. The relevant data was collected from medical histories gathered by the Clinical Department of Infectious Diseases of the Clinical Hospital Center Split as well as from infectious disease reports by the Department of Epidemiology for Infectious Disease of Public Health Institute of SDC.

RESULTS: During the observed period, a total of 162 patients was reported to have invasive meningococcal disease, yielding an average annual incidence rate of 1.39/100 000 inhabitants. The children aged 0-14 years yielding 74.1% (120 persons). The youngest person was one month old, the oldest was 83, median age was 4 years. 88 cases (54.3%) were recorded during fourth winter months. The pathogen was found in blood and/or cerebrospinal fluid (one meningeal swab) in 114 cases (70.4%). The most common serogroup was B with 79.7% out of isolates with determined serogroup, followed by serogroup C with 14.9% and serogroup Y/W 135 (6.8%). Serogroup wasn't determined in 34,5% of confirmed cases. The most common disease manifestation was sepsis with meningitis (48.8%-79 patients), followed by sepsis 30.3% and meningitis 21.0%. Case fatality rate was 4.3%, five out of seven deceased patients were under the age of four. Two persons had two IMD episodes (one of them died). Secondary cases were not recorded.

CONCLUSION: More intensive monitoring and evaluation of epidemiological, microbiological, and clinical features of disease is needed to consider the justification of wider use of the vaccine with the purpose of reducing morbidity. was 4.3%, five out of seven deceased patients were under the age of four. Two persons had two IMD episodes (one of them died). Secondary cases were not recorded.

CONCLUSION: More intensive monitoring and evaluation of epidemiological, microbiological, and clinical features of disease is needed to consider the justification of wider use of the vaccine with the purpose of reducing morbidity.

PO-18 Prikaz slučaja: meningoencefalitis uzrokovan sa *Streptococcus suis*

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Streptococcus suis najčešće u svinja uzrokuje meningitis, endokarditis ili artritis, a iako rijetko, može i u ljudi dovesti do gnojnog meningitisa, sepse, artritisa, endokarditisa i endoftalmitisa. Uz svinje, prenosioci mogu biti i mačke, psi, jeleni i konji.

Gotovo svi zabilježeni slučajevi su "profesionalno" oboljeli (klaonice, farmeri, mesnice, "klanja") nakon kontakta sa zaraženim svinjama i njihovim sirovim mesom.

Infekcije uzrokovane sa *Streptococcus suis* su rasprostranjene u cijelom svijetu, najveća pojavnost se bilježi u jugoistočnoj Aziji, gdje je bilo nekoliko epidemija, potom u sjevernoj Europi.

U prosincu 2018. god primljen je 64.godišnji muškarac s kliničkom slikom bakterijskog meningoencefalitisa. Iz likvora je izoliran *Streptococcus* spp., a 16SrDNA PCR-om se izdiferencira *Streptococcus suis*.

Započeto je liječenje ceftriaksonom uz deksametazon. Nakon tri dana terapije budan, orijentiran, ali gluh i ataktičan. Tijekom liječenja, a po ukidanju steroidne terapije, ponovno komatozan (GCS 6-8) uz razvoj lijevostrane hemipareze.

Obradom se nađe pogoršanje pleocitoze, proteinorahije, hipoglikorahije uz sterilan likvor i negativan 16SrDNA PCR. MR-om se u području srednjeg i precentralnog girusa frontalno desno opiše hiperintenzitet bijele moždane tvari – fokalno područje demjelinizacije u sklopu upalnih promjena. Liječenje se provede pulsnim dozama steroida uz zadovoljavajući oporavak.

Najčešće opisane komplikacije i posljedice meningoencefalitisa uzrokovanog *Streptococcus suis*-om su gluhoća i ataksija koje su se razvile i u ovom slučaju, a ono što je dodatno kompliciralo tijek liječenja je razvoj rijetkog sekundarnog vaskulitisa mozga.

Case report: *Streptococcus suis* meningoenkephalitis

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Streptococcus suis most often causes meningitis, endocarditis and arthritis in pigs, and can rarely cause purulent meningitis, sepsis, arthritis, endocarditis and endophthalmitis in humans.

Other than pigs, it can be transmitted by cats, dogs, deer and horses. Almost all recorded cases in humans are "professional" illnesses (slaughterhouses, butchers, farmers etc.) which happened after being in contact with an infected pig and their raw products. *Streptococcus suis* infections can be found all over the world but the highest incidence is in southeast Asia-where there were several outbreaks- and northern Europe.

In december 2018 a 64 year old men was admitted in our hospital with a bacterial meningitis. The CSF analysis isolated *Streptococcus* spp., and the 16SrDNA PCR identified *Streptococcus suis*. After 3 days of ceftriaxone and dexamethasone treatment the patient was awake, oriented, deaf and ataxic. After suspending the steroid treatment he became comatose (GCS 6-8) with a development of left-sided hemiparesis.

New analysis showed an exacerbation of pleocytosis, proteinorrhagia, hypoglycorrhachia with a sterile CSF and negative 16SrDNA PCR. MRI showed a hyperintensity of the white matter in frontal right middle and precentral gyrus and an area of demyelination as a part of inflammatory changes. He was once again treated with high doses of steroids with a satisfactory outcome.

The most commonly reported complications and consequences of meningoenkephalitis caused by *Streptococcus suis* are deafness and ataxia that have developed in this case as well. What has further complicated the course of treatment is the development of rare secondary brain vasculitis.

PO-19 Profil infekcija izazvanih invazivnim sojevima streptokoka grupe A i B kod pacijenata hospitaliziranih u Klinici za infektivne bolesti „Dr. Fran Mihaljević“ u razdoblju od 2011. do 2018. godine

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CILJ: Beta hemolitički streptokoki (BHS) su rjeđe uzročnici invazivne bolesti (IB). Očekivano BHS grupe B je češći izolat u bolesnika s IB. Međutim, u rutinskom radu posljednje vrijeme je uočeno sve više izolata BHS grupe A iz krvi. Stoga je cilj bio analizirati pojavnost i učestalost IB uzrokovane BHS grupe A i B kod bolesnika liječenih u Klinici za infektivne bolesti (KIB) u dužem periodu.

METODE: Podatci o pacijentima i BHS za razdoblje 2011.-2018. godine prikupljeni su iz elektronske baze podataka Centralnog dijagnostičkog laboratorija KIB te je učinjena podatkovna analiza.

REZULTATI: Tijekom razdoblja 2011- 2018 iz primarno sterilnih uzoraka identificirano je 151 BHS A i B. Većina izolata bila je iz krvi – 96,7%. Podjednako je bilo izolata BHS A 48,3% i BHS B 51,7%. Najviše izolata zabilježeno je 2012. i 2017. godine. BHS A izolata najviše je bilo u 2012. godini, 54% više od BHS B, a u 2016. 50% više od broja BHS B izolata. Broj oboljelih žena i muškaraca bio je podjednak (41,1% i 58,9% muškaraca kod BHSA i 50% žena i muškaraca za BHSB). U skupini djece (19,9%) najčešći izolat je BHS A 76,7%. Od 80,1% odraslih bolesnika uzrok IB bio je 41,3% BHSA i 58,7% BHS B. Većina oboljelih bili su stariji od 65 godina 44,4%. Na odjelima za intenzivno liječenje hospitalizirano je 12 djece (40% djece) i 18 odraslih (14,9% odraslih).

ZAKLJUČAK: Invazivne infekcije BHA A i B utječu na najranjivije dobne skupine, djecu i starije. U našoj studiji oboljeli su najčešće su bili bolesnici stariji od 65 godina. BHS A bio je češće uzrok IB u dječjoj skupini. Zbog karakteristika BHS A bilo bi dobro imati mogućnost upotpuniti dijagnostiku karakterizacijom BHS A izolata osobito u nadzoru promjena u virulenciji. To bi također bio doprinos u praćenju i evidenciji potencijalnih epidemija.

Profile of invasive group A and group B Streptococcal infections in patients hospitalised at the University Hospital for Infectious Diseases Dr. Fran Mihaljević during the period 2011-2018

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Goals: Beta haemolytic streptococci (BHS) rarely cause invasive disease (ID). Usually the most common cause of ID is BHS B. However, in our recent routine work higher number of BHS A isolates from blood was noted. The aim of this study was to report trends and findings by group A and group B invasive BHS causing laboratory confirmed disease from 2011 to 2018 in University Hospital for Infectious Diseases „Dr. Fran Mihaljević“(UIB).

Methods: Data on patients from the electronic database of microbiological laboratory at UIB for the period 2011-2018 was collected and analysed.

Results: During period 2011-2018, 151 BHS A and B were identified from normally sterile body sites. Most isolates were from blood cultures 96,7%. BHS A and BHS B were isolated almost equally, BHS A 48,3% and BHS B 51,7%. The highest number of isolates was recorded in 2012 (22/151) and 2017 (22/151). The number of BHS A isolates peaked in 2012, 54% more than BHS B, and 50% more in 2016. Gender distribution for BHS was also almost equally distributed, females 41,1% and males 58,9% for BHS A and 50% females and males for BHS B. Children presented 19,9% patients, mostly BHS A 76,7%. Even 80,1% patients were adults,41,3% BHS A, 58,7% BHS B.

Adults predominated in age group >65 years of age, 44,4%.

12 children (40% of children) and 18 adults (14,9% of adults) were hospitalised in intensive care unit (ICU).

Conclusion: Invasive group A and group B streptococcal infections predominantly affect most vulnerable age groups, children and elderly. In the study invasive BHS disease is most common among adults above 65 years of age. BHS A was most common cause of invasive disease among paediatric patients. Typing and characterization of BHS A isolates due to its characteristics should be foreseen as important diagnostic tool, especially to monitor changes in virulence and to prevent potential outbreaks.

PO-20 Septička tromboza gornje oftalmičke vene u bolesnice s pansinusitisom i celulitisom orbite uzrokovana viridans streptokokom – prikaz slučaja

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Tromboza gornje oftalmičke vene je rijedak klinički entitet koji se javlja u ranoj fazi tromboze kavernoznog sinusa a kao izoliran slučaj pojavljuje se izrazito rijetko. Klinički se prezentira naglo nastalom unilateralnom konjuktivalnom injekcijom, proptozom, kemozom spojnice, oftalmoplegijom i smetnjama vida najčešće kao posljedica infekcija i drugih upalnih stanja, traume i neoplazme u području orbite. Prikazujemo slučaj 76-godišnje bolesnice koja je liječena u Klinici za infektivne bolesti KBC Rijeka zbog *Streptococcus viridans*-sepsa, celulitisa desne orbite, pansinusitisa i pneumonije. Hospitalizirana je zbog febriliteta, kašlja i gnojne sekrecije iz nosa u trajanju četiri dana pred prijem. Iz hemokultura je izoliran *Streptococcus viridans*, radiogram grudnih organa prikazao je pneumonični infiltrat, a RTG snimka paranazalnih sinusa zasjenjenje desnog maksilarnog i frontalnog sinusa. MSCT- om mozga, orbita i paranazalnih sinusa verificiran je pansinusitis, proptoza očnih jabučica i suspektna tromboza desne gornje oftalmičke vene. Liječenje je započeto kombiniranom parenteralnom antimikrobnom terapijom ceftriaksonom i metronidazolom uz tromboprofilaksu niskomolekularnim heparinom te je učinjena endoskopska dekompresija desne orbite i trepanacija frontalnog sinusa po Rutenbergu. Drugog dana po operativnom zahvatu opće stanje bolesnice se pogoršalo uz vrućicu, kvalitativan poremećaj stanja svijesti te izrazitu proptozu i kemozu spojnice desnog oka. Učinjenom lumbalnom punkcijom isključena je infekcija SŽS-a. MR venografijom potvrđena je tromboza gornje oftalmičke vene desno, a bez znakova tromboze kavernoznog sinusa. Liječenje je nastavljeno meropenemom, niskomolekularnim heparinom te prednizolonom kroz četiri tjedna. Tijek liječenja bio je kompliciran razvojem enterokolitisa koji uzrokuje *Clostridium difficile*. Do otpusta je postignuta potpuna regresija svih znakova bolesti.

***Streptococcus viridans* septic thrombosis of the superior ophthalmic vein in a patient with pansinusitis – case report**

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Superior ophthalmic vein thrombosis (SOVT) as isolated condition occurs very rarely, it usually presents an early sequela of cavernous sinus thrombosis. Clinical manifestations of SOVT include sudden unilateral conjunctival injection, proptosis, chemosis, ophthalmoplegia, and visual impairment as a result of orbital infections, inflammations, trauma and neoplasm.

We present a case of a 76-year-old female patient with *Streptococcus viridans* sepsis, right orbital cellulitis, pansinusitis, pneumonia and SOVT. She was hospitalized for fever, cough and purulent nasal secretion lasting for four days before admission. *Streptococcus viridans* was isolated from blood cultures, while chest X-ray confirmed pneumonia and paranasal X-ray diagnosed opacification of the right maxillary and both frontal sinuses. MSCT of the brain, orbits, and paranasal sinuses verified pansinusitis and proptosis, and revealed thrombosis of the right superior ophthalmic vein. Initial dual antimicrobial therapy (ceftriaxone, metronidazole i.v.) with thromboprophylaxis (low molecular weight heparin) was followed by endoscopic decompression of the right orbit frontal sinus trepanation according to Rutenberg. Two days after surgery, the patient's general condition worsened with fever, qualitatively altered consciousness and severe proptosis and chemosis of right eye. Lumbar puncture eliminated CNS infection. MR venography confirmed thrombosis of the right superior ophthalmic vein without signs of cavernous sinus thrombosis. Antimicrobial treatment with meropenem coupled with low molecular weight heparin and tapering prednisolone treatment was conducted for four weeks with *Clostridium difficile* colitis as a complication. At discharge the patient was with complete regression of all signs of infection.

PO-21 Probir trudnica na *Streptococcus agalactiae* u Primorsko – goranskoj županiji

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Dosadašnja istraživanja u razvijenim zemljama pokazala su da *Streptococcus agalactiae* (beta-hemolitički streptokok skupine B – BHSB) kolonizira ženski spolni sustav i perigenitalnu regiju u 5-40% žena reproduktivne dobi. *Streptococcus agalactiae* može se vertikalno prenijeti s majke na novorođenče i uzrokovati sepsu. *Streptococcus agalactiae* najčešći je bakterijski uzročnik sepse u novorođenčadi.

Ciljevi: Budući da kolonizacija sa *Streptococcus agalactiae* kod trudnica u Primorsko-goranskoj županiji do sada nije sustavno istraživana, odlučili smo: a) odrediti učestalost izolata *Streptococcus agalactiae* kod trudnica između 35. i 37. tjedna trudnoće u vremenskom periodu od 01. 06. 2017. do 31. 05. 2019.; b) istražiti osjetljivost izolata na β -laktamske antibiotike, makrolide i klindamicin.

Metode: Probirom je bilo obuhvaćeno 1938 trudnica, što predstavlja 39% od ukupno 4953 trudnica porođenih u KBC Rijeka u periodu od 01. 06. 2017. do 31. 05. 2019. U Odsjeku za dijagnostiku urogenitalnih infekcija Nastavnog zavoda za javno zdravstvo Primorsko-goranske županije metodom kultivacije koristeći TODDH-T bujon i chromIDtm Strepto B agar (Biomerieux) analizirali smo briseve anogenitalnog područja trudnica na *Streptococcus agalactiae*, a za pozitivne izolate izradili smo test osjetljivosti disk difuzijskom metodom.

Rezultati: Broj pozitivnih izolata *Streptococcus agalactiae* iz obrađenih briseva je bio 193 (9.95%). Izradom testa osjetljivosti nismo utvrdili rezistenciju na β -laktame, dok je rezistencija na makrolide i klindamicin bila podjednaka u ispitivanom razdoblju i iznosila je 24%.

Zaključak: U ovom istraživanju odredili smo učestalost kolonizacije anogenitalnog područja u 1938 trudnica u Primorsko-goranskoj županiji te dokazali odsutnost rezistencije *Streptococcus agalactiae* na β -laktame. Ti rezultati, osim što ukazuju na daljnju potrebu za probirom trudnica na *Streptococcus agalactiae* u našoj županiji, sugeriraju potrebu za našom intenzivnijom suradnjom s ginekolozima i specijalistima perinatalne medicine u primjeni odgovarajuće profilaktičke antibiotske terapije. Ovim mjerama značajno bi se mogao smanjiti broj novorođenačkih infekcija sa *Streptococcus agalactiae* u našoj županiji.

Screening for *Streptococcus agalactiae* in pregnancy in Primorsko – Goranska County

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Numerous studies in developed countries have shown that *Streptococcus agalactiae* (group B streptococcus – GBS) vaginal and perigenital colonization rate ranges between 5% and 40% in pregnancy. Neonatal GBS infections are typically the result of vertical transmission from colonized mothers and it is the leading cause of bacterial neonatal sepsis.

Aims: The burden GBS colonization among pregnant women in Primorsko-Goranska County has not previously been systematically investigated. In order to pursue this, we: a) determined GBS colonization rates among pregnant women in Primorsko-Goranska County; b) evaluated the resistance of GBS isolated from pregnant women to β -lactam antibiotics, macrolides and clindamycin.

Methods: A total of 1,938 pregnant women between the 35th and 37th gestational weeks, which represents 39% of 4,953 performed deliveries in Clinical Hospital Rijeka between June 1, 2017 and May 31, 2019, were enrolled in this study. Vaginal and perigenital specimens were incubated in Todd-Hewitt broth and chromIDtm Strepto B agar (BioMèrieux). Positive isolates underwent disk diffusion test for β -lactam antibiotics, macrolides and clindamycin. This study was conducted in the Department for Urogenital Infections, Teaching Institute of Public Health, Rijeka.

Results: GBS was isolated from 193 clinical specimens, indicating a GBS colonization rate of 9.95%. No resistance to β -lactam antibiotics has been observed, while the same percentage (24%) of the GBS isolates were resistant to macrolides and clindamycin.

Conclusion: In this study, we determined vaginal and perigenital colonization rate among 1,938 pregnant women in Primorsko-Goranska County and demonstrated the absence of the resistance of the GBS isolates to β -lactam antibiotics. The obtained results provide a valuable information on GBS colonization status in pregnant women in Primorsko-Goranska County, serving as a basis for improving GBS prevention and treatment strategies in collaboration with perinatal and gynecologic specialists that may effectively decrease GBS colonization in pregnant women and, consequently, occurrence of neonatal diseases.

PO-22 Akutni febrilni tortikolis u dječjoj dobi – prikaz serije bolesnika

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UVOD: Tortikolis ili „krivi vrat“ naziv je za nevoljni, prisilni položaj vrata. Tortikolis je posljedica različitih public podležeh stanja od kojih neka mogu biti bezazlena, a druga životno ugrožavajuća. Akutni febrilni tortikolis posljedica je upale ili infekcije koja zahvaća anatomske strukture vrata. S obzirom na to da komplikacije tih infekcija mogu biti po život opasne, potrebno je na vrijeme učiniti adekvatnu radiološku obradu te započeti liječenje.

PRIKAZ BOLESNIKA: Prikazujemo pet bolesnika u dobi od 10 mjeseci do 5,5 godina koji su hospitalizirani u Klinici za infektivne bolesti „Dr. Fran Mihaljević“ od 2015. do 2018. godine zbog akutnog febrilnog tortikolisa kao posljedice apscesa lokaliziranih u dubokim strukturama vrata. Osim tortikolisa i febriliteta, najčešći simptom bila je grlobolja (3/5), a potom otežano gutanje (2/5) i kašalj (1/5). Znakovi opstrukcije gornjeg dišnog puta i respiratornog distresa (stridor, tahidispneja, cijanoza) te medijastinitis bili su prisutni u najmlađeg, 10-mjesečnog bolesnika. Ultrazvuk vrata učinjen je kod četiri bolesnika te je samo u dva bolesnika vizualizirana gnojna kolekcija u dubokim prostorima vrata (para/retrofaringealno). Povećani limfni čvorovi vrata opisani su kod svih bolesnika. Osim ultrazvuka vrata, učinjene su kompjuterizirana tomografija (2/5) ili magnetska rezonanca (4/5) vrata kojima se u svih bolesnika vizualizirao apsces u dubokim prostorima vrata. Parafaringealni i retrofaringealni apsces imalo je dvoje djece, samo retrofaringealni također dvoje djece, a parafaringealni jedno dijete. Svi bolesnici liječeni su kombiniranom antimikrobnom terapijom i kirurški – pristup se razlikovao ovisno o lokalizaciji apscesa (transoralno ili transcervikalno). U svim slučajevima radilo se o kombiniranoj polimikrobnoj infekciji.

ZAKLJUČAK: Akutni febrilni tortikolis u dječjoj dobi može biti posljedica teških, životno ugrožavajućih upala lokaliziranih u dubokim prostorima vrata. U naših bolesnika, osjetljivost ultrazvuka iznosila je 50%. No, s obzirom na to da je ultrazvuk dostupna metoda, vjerojatno će i dalje biti tzv. „screening“ radiološka tehnika koja će se učiniti prije CT-a koji je neophodan. CT vrata nakon primjene intravenskog kontrastnog sredstva smatra se zlatnim standardom za identifikaciju apscesa u retrofaringealnoj regiji (osjetljivost 92%).

Acute febrile torticollis in children: case series

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INTRODUCTION: Torticollis or "wry neck" is a condition defined by an abnormal, asymmetrical head or neck position. Torticollis may be due to various underlying causes, of which some can be harmless, and other life threatening. Acute febrile torticollis is a result of inflammation or infection affecting neck structures. Considering the fact that complications of these infections can be life-threatening, it is imperative to do the necessary radiological examination and start the antimicrobial treatment timely.

CASE SERIES: We report 5 pediatric patients aged 10 months to 5,5 years, which were hospitalized in University Hospital for infectious diseases "Dr. Fran Mihaljević" in Zagreb during the period from 2015. to 2018., all due to acute febrile torticollis. Acute febrile torticollis in our patients was mainly consequent to deep neck structure abscesses. Beside torticollis and fever, most common symptom were sore throat (3/5), difficulty swallowing (2/5) and cough (1/5). In youngest patient (10 month old) signs of upper airway obstruction, acute respiratory distress (stridor, tachydyspnea, cyanosis) and mediastinitis were also present. Neck ultrasound was performed in 4 patients, but only in two of them purulent collection was visualized in deep neck space (para/retropharyngeal space). Enlarged lymph nodes of the neck were present in all of our patients. Besides neck ultrasound, computerized tomography (2/5) and magnetic resonance imaging (4/5) were performed in order to visualize deep neck space abscess. 2 children had both parapharyngeal and retropharyngeal abscess, 2 children had only retropharyngeal abscess, and 1 child had only parapharyngeal abscess. All patients were treated with combination of antimicrobial and surgical treatment – surgical approach depended on abscess localization (transoral or transcervical). In all cases, there was polymicrobial infection.

CONCLUSION: Acute febrile torticollis in children can be due to severe, life threatening infection localized in deep neck spaces. In our case series, neck ultrasound sensitivity was 50%. Nevertheless, since ultrasound is available, it will probably remain as "screening" method before CT, which is indispensable in these cases. Neck CT with contrast is considered as gold standard in identifying retropharyngeal abscesses (sensitivity 92%)

PO-23 Bolest mačjeg ogreba u bolesnika na biološkoj terapiji ulceroznog kolitisa

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U imunokompromitiranih bolesnika bolest mačjeg ogreba može se javiti kao diseminirana infekcija protražiranog tijeka sa opsežnom limfadenopatijom i zahvaćanjem različitih organa. U ovom prikazu slučaja, opisana je bolest mačjeg ogreba u bolesnika sa ulceroznim kolitisom, prethodno već dvije godine liječenog vedolizumabom i kortikosteroidima. Njemu je započeta terapija infliksimabom sedam dana prije pojave subfebriliteta i limfadenitisa u desnoj aksili. Tri tjedna nakon toga, zbog epidemiološke i kliničke sumnje na bolest mačjeg ogreba, započeta je antibiotska terapija uz kontrole infektologa. Zbog stalnih febriliteta i subfebriliteta, te perzistirajućih upalnih parametara unatoč antibiotskoj terapiji, hospitaliziran je na Zavodu za gastroenterologiju i hepatologiju Klinike za unutarnje bolesti KBC Split. Obradom je utvrđeno postojanje više povećanih limfnih čvorova u desnoj aksili kao i u hepatogastričnom i hepatoduodenalnom ligamentu, kao i remisija ulceroznog kolitisa. U više navrata rađena je incizija i drenaža desne aksile, te korekcija antibiotske terapije, bez kliničkog učinka. Serološki i patohistološki nalaz limfnog čvora potvrdili su klinički sumnju na dijagnozu, te se bolesnik premješta na Kliniku za infektologiju. Mijenja se antibiotska terapija, uvode kortikosteroidi, ekstirpira dodatni limfni čvor iz aksile. Kontrolni MSCT abdomena pokazuje stacionaran nalaz limfnih čvorova uz izraženiju kolikvaciju i početnu propagaciju upalnih promjena u jetru. Bolesnik je postao afebrilan, te je otpušten uz nastavak antibiotske terapije. Kontrolni nalazi nakon 5 tjedana pokazuju značajan pad upalnih parametara, a potom za 4 tjedna normalizaciju laboratorijskih vrijednosti. Zaključno: bolest mačjeg ogreba je u literaturi rijetko opisivana u bolesnika na biološkoj terapiji. Potrebna su daljnja opsežnija istraživanja kako bi se došlo do smjernica za terapiju i praćenje ove bolesti kod takvih bolesnika.

Cat scratch disease in patient on biological therapy of ulcerous colitis

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In immunodeficient patients, cat scratch disease can be manifested as disseminated prolonged infection with generalized lymphadenopathy, and different organ involvement. In this case report, we have described a case of cat scratch disease in patient suffering from ulcerous colitis who had previously been treated with steroids and vedolizumab. He started with infliximab therapy seven days before the onset of low grade fever and enlarged right axillary lymph nodes. Three weeks after, he started antibiotic treatment for possible cat scratch disease under infectologist supervision. Because of constant fever and persistent elevation of inflammatory laboratory markers despite antibiotic treatment, he was hospitalized in Gastroenterology Ward of University Hospital Split. During hospitalization, a number of enlarged lymph nodes were found in the right axilla, as well as in hepatogastric and hepatoduodenal ligament. Ulcerous colitis in patient was found to be in remission. Several incisions and drainages were performed in the right axilla, and changes were made in the antibiotic treatment, but with no clinical effect. The diagnose of cat scratch disease was confirmed by serology and pathological analysis of the extirpated lymph nodes. The patient was then admitted to the Infectology Ward where the antibiotic treatment was again changed with the addition of steroids and another lymph node was extirpated from the right axilla. Control MSCT scan showed stationary abdominal lymphadenopathy with more prominent colliquation and initial inflammatory changes in the adjacent liver parenchyma. Patient became afebrile and was discharged from hospital with continuation of antibiotic treatment. After five weeks, there was significant improvement of laboratory findings. On the next control four weeks after, the laboratory findings were normal. In conclusion, cat scratch disease is rarely described in patients on biological treatment. More extensive investigation is needed to propose guidelines for treatment and follow-up of cat scratch disease in these patients.

PO-24 *E. coli* endokarditis nativnih zalisaka

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Cilj: klinička i laboratorijska dijagnostika endokarditisa uzrokovanog rijetkim uzročnikom *E. coli* u bolesnice starije životne dobi s nativnim zaliscima.

Metode: klinički nalaz (anamneza, klinički pregled), laboratorijska dijagnostika (hematološke, biokemijske krvne pretrage), mikrobiološke pretrage (hemokulture), slikovne dijagnostičke pretrage (ehokardiografija).

Rezultati: u kliničkom nalazu febrilna, dehidrirana, nad prekordijem čujan sistolički šum 4/6. L 10.9 x10e9/L, E 3.61x10e12/L, Hb 118 g/L, Trc 147 x10e9/L, Urea 20.5 mmol/L, kreatinin 291 umol/L, CRP 233 mg/L. Urin: замуćen, u sedimentu leukocita 175, eritocita 123, masa bakterija. UK: *E. coli* (dobre osjetljivosti). HK: *E. coli* (dobre osjetljivosti). UZV srca: u području aortne i mitralne valvule vegetacije.

Zaključak: u bolesnika starije životne dobi bez poznatih kardijalnih rizičnih čimbenika s bakterijemijom i izostankom odgovarajućeg kliničkog odgovora na primjerenu empirijsku antimikrobnu terapiju indicirana je ultrazvučna pretraga srca.

Glavne riječi: endokarditis, *E. coli*

***E. coli* native valves endocarditis**

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Objective: Clinical and laboratory diagnosis of endocarditis caused by a rare pathogen *E. coli* in elderly patient with native valves.

Methods: Clinical findings (patient history, clinical examination), laboratory diagnostics (hematological, biochemical blood tests), microbiological analysis (blood cultures), imaging diagnostic tests (echocardiography).

Results: clinical findings: febrile, dehydrated, systolic heart murmur over precordium 4/6. L 10.9 x10e9/L, E 3.61x10e12/L, Hb 118 g/L, Trc 147 x10e9/L, urea 20.5 mmol/L, creatinine 291 umol/L, CRP 233 mg/L. Urine analysis: cloudy, urine sediment: 175 leukocytes, 123 erythrocytes, large amount of bacteria. Urine culture: *E. coli* (good sensitivity). Blood culture: *E. coli* (good sensitivity). Heart ultrasound: aortic and mitral valve vegetation.

Conclusion: ultrasound of the heart is indicated in elderly patients without known cardiac risk factors with bacteremia and lack of appropriate clinical response to empiric antimicrobial therapy.

Key words: endocarditis, *E. coli*

PO-25 Salmonelom induciran miokarditis u 16-godišnjeg mladića

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Sažetak: Miokarditis se rijetko javlja u dječjoj dobi i adolescenciji, ali pravu je incidenciju teško utvrditi zbog nedostatka dovoljno osjetljivih i specifičnih dijagnostičkih metoda, kao i blagih oblika bolesti koje prođu nezamijećeno. Etiologija može biti oboje infektivna i neinfektivna, ali u većini slučajeva uzrok su virusne infekcije. Bakterijski miokarditis je rijedak i najčešće se viđa tijekom teških sepsi i/ili kod imunokompromitiranih osoba. Može biti uzrokovan velikim brojem bakterija, ali miokarditisi uzrokovani netifoidnim salmonelama (NTS) dosad su opisivani samo u malom broju slučajeva.

Prikaz slučaja: Mi prikazujemo slučaj dosad zdravog 16-godišnjeg mladića s akutnim miokarditisom koji se javio tijekom *Salmonella enteritidis* infekcije. Bolesnik se javio u našu hitnu prijemnu ambulantu žaleći se na novonastalu bol u prsištu. Ostali simptomi koje je imao uključivali su vrućicu i profuzni proljev unatrag 3 dana. Mladić je prilikom prijema bio dobrog općeg stanja, supfebrilan uz uredne vitalne znakove. Laboratorijske pretrage pokazale su povišene vrijednosti CRP-a i srčanih biomarkera. Radiološki je utvrđena kardiomegalija, a ehokardiogram je pokazao smanjenu srčanu ejectivesku frakciju kao i insuficijenciju i prolaps mitralne valvule. Endomiokardijalnom biopsijom potvrđena je dijagnoza miokarditisa. *Salmonella enteritidis* dokazana je iz više uzoraka stolica, a hemokulture su ostale sterilne. Druge infektivne bolesti, lijekovi i imunološki poremećaji bili su isključeni. Započeto je liječenje ACE-inhibitorima, spironolakonom, ceftriaksonom i ibuprofenom. Njegovi gastrointestinalni i kardijalni simptomi su se povukli tijekom idućih dana i nakon 2 tjedna hospitalizacije otpušten je kući bez tegoba. Ponovljene laboratorijske pretrage prije otpusta bile su normalne, a ehokardiogram je pokazao normalizaciju prethodne srčane disfunkcije.

Zaključak: Infekcije s NTS najčešće uzrokuju dijarealnu bolest i same ekstraintestinalne manifestacije bolesti nisu česte. U rijetkim slučajevima prethodno opisanih *Salmonella* miokarditisa, smrtnost je bila visoka, kao i kod ostalih miokarditisa uzrokovanih bakterijama. S obzirom na tu činjenicu, potrebno je posumnjati na *Salmonella* miokarditis kod bolesnika koji se prezentiraju sa simptomima i znakovima miokarditisa uz gastrointestinalne simptome.

Salmonella induced myocarditis in a 16-year-old boy

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Introduction: Myocarditis is uncommon in childhood and adolescence, but the true incidence is difficult to establish given the lack of sufficiently sensitive and specific diagnostic tests and many mild cases of the disease that probably go undetected. It can be caused by both non-infectious and infectious etiologies, but the majority of cases are associated with viral infections. Bacterial myocarditis is rare and usually seen in the context of overwhelming sepsis and/or in immunocompromised hosts. A wide variety of bacterial agents were implicated in its etiology, but non-typhoidal *Salmonella* (NTS) myocarditis were reported only in a small number of cases.

Case presentation: We report a case of previously healthy 16-year-old boy with acute myocarditis following *Salmonella enteritidis* infection. The patient presented to our emergency department complaining on a recently started chest pain. His other symptoms started 3 days earlier with fever accompanied with profuse diarrhea. At admission, he was well-appearing with low-grade fever and normal vital signs. Laboratory test showed elevated CRP and cardiac biomarkers. Chest x-ray revealed mild cardiomegaly and echocardiography showed reduced ejection fraction with mitral valve prolapse and insufficiency. The diagnosis was confirmed by endomyocardial biopsy. *Salmonella enteritidis* was isolated from stool cultures, but blood cultures remained negative. Other infectious diseases, drugs and immune disorders were ruled out. Treatment with ACE-inhibitors, spironolactone, ceftriaxone and ibuprofen was initiated. In the following days his gastrointestinal and cardiac symptoms resolved and after 2 weeks he was discharged without complaints. Repeated laboratory test before discharge were normal and ECHO showed normalization of the previous dysfunction.

Conclusion: NTS infection usually causes diarrheal illness and extraintestinal manifestations are uncommon. In rare circumstances of previously reported *Salmonella* myocarditis mortality rates were high as well with other bacterial causes of this disease. Due to this fact, *Salmonella* myocarditis should be suspected in patients presenting with features of myocarditis and gastrointestinal symptoms.

PO-26 Bakterijemija uzrokovana s *Actinomyces* sp. kod desetogodišnjeg dječaka s karioznom zubalom

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CILJ: Prikazali smo slučaj bakterijemije uzrokovane s *Actinomyces* sp. kod desetogodišnjeg dječaka koji prema hetero anamnestičkim podatcima ima prethodno provedene operativne zahvate na jedanaest karioznih, mliječnih zuba. Dječak je hospitaliziran zbog ponavljajućih febriliteta i povišenih upalnih parametara pri prijemu (CRP 244,1). Osim povišene temperature i slabo izraženog kašlja, tijekom pregleda su uočeni povećani limfni čvorovi smješteni uz stražnji rub sternokleidomastoideusa, palpatorno bezbolni i pomični. Unatrag mjesec dana višekratno je dobivao peroralne antibiotike radi tonzilofaringitisa praćenog povišenom temperaturom.

METODE: Prilikom prijama uzeti su uzorci krvi za hemokulturu. Nakon 48 sati inkubacije u Bactec sustavu hemokulture (AE i AN) detektirane su kao pozitivne. Nakon nasađivanja na krute hranjive podloge i inkubacije na 35 °C/24 h/aerobno porasli su gram pozitivni stapici. Isti soj porastao je i na anaerobno kultiviranim podlogama nakon 48 h. Api-Coryne sustavom za identifikaciju, izolat je definiran kao *Arcanobacterium haemolyticum*. Budući se radi o izuzetno rijetkom uzročniku bakterijemije, izolat je radi potrebe za potvrdom dobivene identifikacije poslan u Referentni centar za kliničku mikrobiologiju na Klinici za infektivne bolesti „Dr. Fran Mihaljević“ u Zagrebu.

REZULTAT: Iako je porasli soj Api -Coryne sustavom definiran kao *Arcanobacterium haemolyticum*, 16S rDNA metodom sekvenciranja genoma izolat je definiran kao *Actinomyces* sp. Testiranje osjetljivosti na antibiotike gradijentnim (E-test) testom pokazalo je dobru osjetljivost na penicilin, piperacilin/tazobactam, amoksicilin/klavulanat i ertapenem te rezistenciju na metronidazol.

ZAKLJUČAK: Vrste roda *Actinomyces* čine dio mikrobioma oralne flore ljudi, a nalaze se u zubnim plakovima kod gingivitisa i periodontitisa. Rijetko se izoliraju kao uzročnici sepse. Budući se u navedenom slučaju radi o dječaku koji je imao višestruke operativne zahvate na zubima, smatramo da je navedeno anatomsko područje bilo ishodište bakterijemije. Obzirom da API sustavi identifikacije mogu biti nepouzdan, rijetke i neuobičajene izolate kod sistemskih infekcija i(li) bakterijemija treba identificirati pouzdanijim i modernijim sistemima ili molekularnim metodama.

Bacteremia caused by *Actinomyces* sp. in a ten year old boy with a carious teeth

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AIM: We have shown a case of bacteremia caused by *Actinomyces* sp. in a ten year old boy who according to heteroanamnestic data had a surgery on eleven carious milky teeth. The boy was hospitalized because of recurrent febrility and elevated inflammation parameters at reception (CRP 244,1). In addition to fever and poor cough, during examination, enlarged lymph nodes were found, located along the posterior margin of the sternocleidomastoid, palpatory painless and mobile. Over the past month he received repeatedly oral antibiotics for tonsilopharyngitis followed by fever.

METHODS: Blood samples for blood culture were taken at admission. After 48 hours of incubation at Bactec, blood cultures (aerobic and anaerobic) were detected as positive. After planting on solid nutrient media and incubation at 35 degrees for 24 hours aerobically increased gram positive sticks. The same strain also increased on anaerobically cultured media after 48 hours. Api-Coryne identification system defined this isolate as *Arcanobacterium haemolyticum*. Because it is an extremely rare cause of bacteremia the isolate was sent to the Reference Center for clinical microbiology at the University Hospital for Infectious Diseases „Dr. Fran Mihaljević“ to verify the identification.

RESULTS: Although the grown strain was identified as *Arcanobacterium haemolyticum* with Api-Coryne system, the 16S rDNA gene sequencing method defined the isolated strain as *Actinomyces* sp. Antibiotic sensitivity testing performed with E-tests showed good sensitivity to penicillin, piperacillin/tazobactam, amoxicillin/clavulanate and ertapenem and resistance to metronidazole.

CONCLUSION: *Actinomyces* sp. are part of the oral microbiome of humans and are found in dental plaques in gingivitis and periodontitis. They are rarely isolated as causative agents of sepsis. Since our case is about a boy who had multiple dental surgeries, we believe that this anatomical area was the origin of bacteremia. Since Api identification systems can be unreliable, rare and uncommon isolates in systemic infections and bacteremias should be identified with more reliable and modern systems or molecular methods.

PO-27 Utjecaj sastava perikoronarne mikrobiote na parametre oporavka nakon alveotomije mandibularnog umnjaka – preliminarni rezultati

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Cilj: Cilj ovog istraživanja jest analizirati utjecaj sastava perikoronarne mikrobiote na poslijeoperativne parametre oporavka – bol, trizmus i edem – kod bolesnika nakon učinjene alveotomije impaktiranog ili retiniranog mandibularnog umnjaka.

Metode: Preliminarni rezultati istraživanja dobiveni su u razdoblju od ožujka do srpnja 2019. godine. U Kliničkoj bolnici Dubrava su prilikom alveotomije uzimani uzorci iz perialveoarnog džepa papirnatim šiljcima (veličina 50). Prisutnost i sastav perikoronarne mikrobiote određivan je u Kliničkom bolničkom centru Zagreb molekularnom DNA hibridizacijskom metodom (Micro-Ident® plus 11, Hain Lifescience GmbH, Nehren, Njemačka) kojom se može detektirati 11 najčešćih periodontogenih bakterijskih vrsta. Parametri oporavka ocjenjivani su tijekom 72 sata nakon alveotomije na sljedeći način: osobni osjećaj boli na temelju skale intenziteta od 1 do 10, otekline na temelju četiri kategorije 1 do 4 ovisno o lokalizaciji unutar i van usne šupljine te trizmus u milimetrima ovisno o ograničenosti otvaranja usta.

Rezultati: U istraživanje je do sada uključeno ukupno devet bolesnika, šest ženskog i tri muškog spola. Broj otkrivenih bakterijskih vrsta kod bolesnika varirao je od jedne do osam vrsta. Najčešće bakterijske vrste prisutne kod bolesnika bile su *Fusobacterium nucleatum/periodonticum* (8/9, 88.9%), *Treponema denticola* (7/8, 87.5%), *Parvimonas micra* (6/9, 66.7%) i *Tannerella forsythia* (6/9, 66.7%). Najveći intenzitet osobnog osjećaja boli (10), otekline (kategorija 4) i trizmus (≤ 25 mm) utvrđeni su kod dva bolesnika kod kojih je otkrivena prisutnost šest bakterijskih vrsta. *Aggregatibacter actinomycetemcomitans*, inače smatran patogenom vrstom koja uzrokuje periodontitis, nije otkriven niti kod jednog bolesnika.

Zaključak: Preliminarnim rezultatima istraživanja utvrđena je prisutnost i sastav perikoronarne mikrobiote kod bolesnika nakon alveotomije mandibularnog umnjaka te dobiveni rezultati odgovaraju do sada poznatim podacima u literaturi. Preliminarni rezultati pokazali su veću različitost mikrobiote kod bolesnika s lošijim postoperativnim parametrima oporavka. Statističku značajnost ovih zapažanja bit će moguće utvrditi kada se u istraživanje uključi veći broj bolesnika.

Impact of pericorony microbiota composition on parameters of recovery after mandibular molar alveotomy – preliminary results

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Aim: The aim of this study is to analyse the impact of pericorony microbiota composition on postoperative parameters of recovery – pain, trismus and edema – in patients after alveotomy of impacted or retained mandibular third molar.

Methods: Preliminary results were obtained from March to July 2019. Samples were obtained from perialveolar pocket with paper points (size 50) during alveotomy procedure at the Clinical Hospital Dubrava. Presence and composition of pericorony microbiota was determined at the University Hospital Centre Zagreb with molecular DNA hybridization method (Micro-Ident® plus 11, Hain Lifescience GmbH, Nehren, Germany), capable of detecting 11 the most common periodontogenic bacterial species. Parameters of recovery were graded during 72 hours after alveotomy as follows: subjective pain on intensity scale from 1 to 10, swelling on category scale 1 to 4 based on localization inside or outside oral cavity, and trismus in millimetres based on reduced opening of mouth.

Results: Total of nine patients, six females and three males, were included in study so far. The number of detected bacterial species in individual patients varied from one to eight species. The most common species were *Fusobacterium nucleatum/periodonticum* (8/9, 88.9%), *Treponema denticola* (7/8, 87.5%), *Parvimonas micra* (6/9, 66.7%) and *Tannerella forsythia* (6/9, 66.7%). The highest grade of subjective pain intensity (10), swelling (category 4) and trismus (≤ 25 mm) were found in two patients with six bacterial species detected. *Aggregatibacter actinomycetemcomitans*, otherwise considered the true pathogen in periodontitis, was not detected in any of patients.

Conclusion: Preliminary results demonstrated presence and composition of pericorony microbiota in patients after alveotomy of mandibular third molar and results are in concordance with data published so far. Preliminary results showed high diversity of microbiota in patients with poor parameters of recovery. Statistical significance of this observations will be determined with additional patients included in the study.

PO-28 *Helicobacter pylori* – otpornost na antibiotike u Primorsko – goranskoj županiji

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Cilj: Niti za jednu bakterijsku infekciju ne postoji toliko različitih terapijskih opcija kao za infekciju koju uzrokuje bakterija *Helicobacter pylori* za koju još uvijek nije pronađen optimalan terapijski pristup. Preporučene terapijske sheme koje se primjenjuju u empirijskom liječenju ovise o otpornosti helikobaktera na antimikrobne lijekove u određenoj regiji. No, empirijsko liječenje infekcije uz sve veći porast otpornosti helikobaktera na antibiotike često ima za ishod terapijski neuspjeh. Cilj ovog rada bio je utvrditi proširenost i trend otpornosti helikobaktera na antibiotike na području Primorsko-goranske županije (PGŽ) u petogodišnjem razdoblju.

Metode: Statistički su obrađeni i interpretirani rezultati testiranja osjetljivosti *H. pylori* na antibiotike u razdoblju 2013-2017. godine. Podatci su dobiveni iz arhiva Kliničkog zavoda za kliničku mikrobiologiju Kliničkog bolničkog centra Rijeka te Mikrobiološkog odjela Nastavnog zavoda za javno zdravstvo PGŽ.

Rezultati: Zabilježena je visoka stopa otpornosti *H. pylori* na klaritromicin i metronidazol, niska stopa otpornosti na levofloksacin i sporadična otpornost na rifampicin i amoksisilin. U petogodišnjem razdoblju nije izoliran niti jedan soj otporan na tetraciklin.

Zaključci: Visoka stopa rezistencije na klaritromicin i metronidazol, uz dvojnju rezistencija na oba antibiotika koja je pronađena u četvrtini izolata ograničava korištenje ovih antibiotika u empirijskim terapijskim shemama. Uočena je i zabrinjavajuća pojava višestruke otpornosti na antibiotike prisutna u 10% izolata koja dodatno obajektežava izbor odgovarajuće terapije. Praćenje i poznavanje antimikrobne otpornosti lokalnih izolata *H. pylori* je neophodno radi izrade odgovarajućih terapijskih smjernica.

***Helicobacter pylori* resistance to antibiotics in Primorsko – Goranska County**

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Aim: There is no bacterial infection with so many different therapeutic options as for infection caused by *Helicobacter pylori* for which an optimal therapeutic approach has not yet been found. Recommended therapeutic schemes depend on *H. pylori* resistance to antimicrobial drugs in a particular region, however, empirical treatment of infections along with increasing resistance to antibiotics often results in a therapeutic failure. The aim of this study was to determine the trend and the prevalence of helicobacter antibiotic resistance in Primorsko-goranska county during the five-year period.

Methods: This study presents the results of *H. pylori* antimicrobial susceptibility testing from year 2013 to 2017. Data were obtained from the archives of the Department of Clinical Microbiology, Clinical Hospital Centre Rijeka and the Department of Microbiology, Teaching Institute of Public Health of Primorsko-Goranska County.

Results: High-level resistance to clarithromycin and metronidazole was noticed. Rare resistance to levofloxacin was observed whereas resistance to rifampicin and amoxicillin was found sporadically. Resistance to tetracycline was not detected.

Conclusions: The high resistance rate to metronidazole and clarithromycin as well as high dual resistance to both antibiotics observed in about a quarter clinical isolates can impair the efficacy of these antimicrobials in empirical eradication treatment. In addition, worrying appearance of multiple resistance to antibiotics in 10% of isolates was observed. Surveillance of local antimicrobial resistance is necessary in order to establish the relevant treatment guidelines.

PO-29 Raspodjela serogrupa dijarogenih *E.coli* (DEC) među ambulantnim bolesnicima u Splitsko – dalmatinskoj županiji: 2011. – 2018.

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Cilj: Akutni gastroenteritisi su značajan javnozdravstveni problem, a Dijarogene *E. coli* se smatraju čestim uzročnicima tih infekcija u djece. Određeni serotipovi su zajednički za EPEC i EHEC te se povezuju s težim kliničkim tijekom bolesti, ozbiljnim komplikacijama i mogućim fatalnim ishodom. Poznavanje serotipova, čimbenika virulencije i otpornosti u lokalnim i nacionalnim okvirima je važno jer pomaže ranom otkrivanju epidemijskih sojeva i ispravnom liječenju.

Cilj rada je prikazati raspodjelu serogrupa EPEC i rezultate testiranja čimbenika virulencije EHEC u razdoblju 2011. – 2018. godine.

Metode: Svi bolesnici u dobi do 5 god života, upućeni iz PZZ s dijagnozom akutnog gastroenteritisa, su bili obuhvaćeni pretragom na EPEC. Za izolaciju EPEC je korišten ENDO agar, a nakon identifikacije vrste kratkim biokemijskim nizom, serotipizacija izolata je obavljena metodom aglutinacije sa specifičnim antiserumima za živu, a potom i za kuhanu kulturu. Izolati serotipova suspektih na EHEC (O:26, O:103, O:104, O:111, O:145, O:157) su testirani na čimbenike virulencije (stx1,sStx2, ipaH gene) GenoType EHEC testom.

Rezultati: U sedmogodišnjem razdoblju dokazano je ukupno 188 izolata DEC u bolesnika dobi do 5 godina. Ukupno je dokazano 17 serogrupa, a najčešće EPEC serogrupe su bile: O:126, O:128, O:127, O:26 i O:55. Molekularna analiza čimbenika virulencije EHEC je rađena na malom broju izolata (31), a rezultati su bili negativni.

Zaključak: EPEC je još uvijek značajna u etiologiji akutnog gastroenteritisa u djece do 5 godina na području Splitsko-dalmatinske županije, dok EHEC nije dokazana među izolatima sa suspektim serotipovima. Međutim, klasična metoda kultivacije sa serotipizacijom i dokazom čimbenika virulencije s kulture je nedovoljno osjetljiva u detekciji EHEC. Primjena molekularnih metoda detekcije EHEC izravno iz uzorka stolice doprinjela bi boljem poznavanju epidemiologije i kliničkog značaja ovih uzročnika.

Distribution of Diarrheagenic E.coli (DEC) serogroups among outpatients in Split – Dalmatia County: 2011-2018

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Aim: Acute gastroenteritis is a major public health problem and Diarrheagenic *E. coli* (DEC) are considered the common cause of these infections in children. Certain serotypes are common to EPEC and EHEC and are associated with serious complications and a possible fatal outcome. The aim of the study was to examine the distribution of EPEC serogroups and to present the results of the EHEC virulence factors testing in Split-Dalmatia County (SDC) during the period 2011 – 2018.

Methods: All outpatients from SDC up to 5 years of age with acute gastroenteritis were included in the EPEC screening. After cultivation at the ENDO agar, DEC isolates were confirmed by standard biochemical tests and further characterized by O:H serotyping using agglutination of live and boiled DEC culture. Isolates with EHEC associated serotypes (O: 26, O: 103, O: 104, O: 111, O: 145, O: 157) were subsequent tested on EHEC virulence factors (stx1, stx2, and ipaH gene) by the GenoType EHEC test.

Results: During the seven-year period, a total of 188 DEC were isolated in outpatients up to 5 years of age. A total of 17 serogroups were confirmed and the most common serogroups were: O: 126, O: 128, O: 127, O: 26 and O: 55. Molecular analyzes of EHEC virulence factors were performed on a small number of isolates with EHEC associated serotypes (31) and the results were negative.

Conclusion: EPEC is still an important cause of acute gastroenteritis in children up to 5 years in the Split-Dalmatia County, while EHEC has not been confirmed among isolates with EHEC associated serogroups. However, the classical cultivation method with serotyping and with subsequent culture testing for the EHEC virulence factors is not sensitive enough for EHEC detection. Molecular testing for Shiga toxins directly in stool samples would be more effective in diagnosing EHEC infections.

PO-30 Pojavnost i karakteristike *Clostridioides difficile* infekcija (CDI) u Kliničkom bolničkom centru (KBC) Split

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Cilj: Odrediti mikrobiološke i epidemiološke karakteristike *Clostridioides difficile* infekcija (CDI) u Kliničkom bolničkom centru Split.

Metode: Retrospektivno su analizirani podatci pismohrane Kliničkog zavoda za mikrobiologiju i parazitologiju KBC-a Split u razdoblju od 1. siječnja do 31. prosinca 2017. Uključeni su svi pacijenti s prvom epizodom CDI kojima je dokazan toksigeni soj *C. difficile* u uzorku stolice. Analizirani su demografski podatci pacijenata i mikrobiološke osobitosti toksigenih sojeva *C. difficile*. U dijagnostici CDI korišten je dvostupanjski postupnik. U prvom koraku, imunoenzimskim testom, određivani su glutamat dehidrogenaza (GDH) i slobodni toksini A/B (CoproStrip *C. difficile* GDH + Toxin A + Toxin B SavyonDiagnostic, Izrael). Svi uzorci s pozitivnim GDH i negativnim toksinima, dodatno su testirani molekularnom metodom (Illumigene Meridien Bioscience, Italija).

Rezultati: Tijekom 2017., zaprimljeno je 4126 uzoraka stolice sa sumnjom na bakterijsku infekciju. Od 519 dokazanih patogena, *C. difficile* je bio najučestaliji (71%), a slijede ga *Campylobacter species* (13%), enteropatogena *Escherichia coli* (9%) te *Salmonella enterica* (7%). Primarnu CDI je imalo 370 pacijenata, od kojih je 15% razvilo rekurentnu infekciju. U trenutku dijagnosticiranja CDI, 236 (64%) pacijenata je liječeno u bolnici (od toga na Internoj klinici 40%, u jedinicama intenzivnog liječenja 28% i Infektološkoj klinici 17%). Žena je bilo 218 (59%), a većina pacijenata je bila starija od 65 godina (222 pacijenta, 62%). Aktivna proizvodnja toksina je dokazana u 291 od 370 primarnih CDI. Od toga je u 32 (9%) uzorka dokazan samo toksin A, u 18 (5%) uzoraka samo toksin B, dok je u 241 (65%) uzorku dokazana proizvodnja oba toksina. U preostalih 79 uzoraka (21%), dokazan je toksigeni soj *C. difficile* bez aktivne produkcije toksina.

Zaključak: *Clostridioides difficile* je najčešći bakterijski uzročnik gastroenteritisa u KBC-u Split i najčešće stvara oba toksina (A i B). CDI je najčešća u bolničkih pacijenata starijih od 65 godina, a žene oboljevaju češće od muškaraca.

Occurrence and characterization of *Clostridioides difficile* infection (CDI) in a University Hospital Center Split (UHC)

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Aim of the study: Epidemiological and microbiological characterization of *Clostridioides difficile* infection (CDI) in a University Hospital of Split.

Methods: During the study period (January to December 2017), data base of the Department of Clinical Microbiology was retrospectively examined. All patients with a first episode of CDI were enrolled in the study. Demographic data and microbiological characteristics of *C. difficile* were analyzed. For CDI diagnostic, two-step algorithm was used. Stool samples were tested for the presence of glutamate dehydrogenase (GDH) and toxins A/B, using immunoassay card (CoproStrip *C. difficile* GDH + Toxin A/B, Savyon Diagnostics, Israel). GDH positive, ToxinA/B negative strains were further tested with molecular tests (Illumigene MeridianBioscience, Italy).

Results: A total of 4126 stool samples were tested for a bacterial infection and 519 pathogens were found. Among them, *C. difficile* was the most frequent (71%), following with *Campylobacter species* (13%), enteropathogenic *Escherichia coli* (9%) and *Salmonella enterica* (7%). Primary *C. difficile* infection occurred in 370 patients, while recurrent infection had 15% of them. Majority of infections (64%) had hospital occurrence. Among hospitalized patients, majority were located at the Department for internal medicine (40%), Intensive care units (28%) and Department for infectious diseases (17%). Proportion of female patients (59%) was significantly higher in comparison to male. Significantly more patients were older than 65 years (62%). Active toxin production was recorded in 291 samples (only toxin A in 9%, only toxin B in 5%, and both toxins in 65%). In the remaining 21% of positive samples, toxigenic *C. difficile* strain without active production of toxins was detected.

Conclusion: *Clostridioides difficile* is the most common bacterial cause of diarrhea in University Hospital of Split. CDI occurred mostly among hospitalized patients older than 65 and female patients were far more affected. Majority of CDI were caused by strains with active toxin production.

PO-31 Mikrobiološka dijagnostika pacijentice s brucelozom

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Cilj je prikazati mikrobiološko dijagnosticiranje bruceloze kod pacijentice.

Metode: Zaprimili smo 3 seta hemokultura 47 godišnje pacijentice, upućene iz hitne infektološke ambulante OB "Dr. Ivo Pedišić"(OBS). Nakon 72 sata zvonile su aeorobne bočice sva tri seta. U direktnom preparatu vidimo sitne gram negativne kokobacile. Hemokultura je nasadena na krvni agrar obogaćen s 5% defibrinirane ovčje krvi i čokoladni agar. Nakon 48 sati inkubacije na 37°C u atmosferi s 5% CO₂ porasle su nam sitne kolonije. Od kliničara doznajemo da je pacijentica visoko febrilna (do 39°C) zadnjih mjesec dana, te povremeno ima makulopapulozni osip po koži ekstremiteta i trupa, koji ne svrbi i anemizira na pritisak. Također potvrđen joj je asimptomatski perikardijalni izljev. Epidemiološki doznajemo da je u skorije vrijeme boravila u Cazinu (BIH). S obzirom da je diferencijalno dijagnostički u obzir dolazila bruceloza, a uzgojen soj i direktan preparat odgovarali bruceli, soj šaljemo na Kliniku za infektivne bolesti "Dr. Fran Mihaljević" (KIB) i Hrvatski Veterinarski institut (HVI).

Rezultati: S HVI stigli su pozitivni nalazi na brucelu Rose Bengal testom (RBT) i reakcijom vezanja komplementa (RVK), te molekularnom metodom Bruceladder utvrđeno je da se radi o vrsti *Brucella melitensis*. S KIB stigla je potvrda *Brucella* spp, dokazana molekularnom metodom sekvencioniranja gena za 16 S RNA. Istodobno, uzgojeni soj identificirali smo na Vitek 2, karticom za gram negativne bakterije, te dobivamo rezultat *Brucella melitensis*.

Zaključak: Pacijentica je liječena 6 tjedana doksiciklinom i rifampicinom. Od 14. dana boravka u bolnici je afebrilna, a 19. dana otpuštena kući uz potpunu regresiju makulopapuloznog osipa. Kontrolni nalaz Uzv srca nakon 4 tjedana pokazuje potpunu regresiju perikardijalnog izljeva. Iako je soj bio teško uzgojiv, izvrsnom suradnjom sa infektolozima OBS, te uz veliku pomoć HVI i KIB, dokazali smo brucelozu, te je pacijentica dobila ciljanu terapiju, nakon koje je uslijedilo potpuno izlječenje.

Microbiological diagnostics of brucellosis

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The goal is to show the microbiological diagnostics of the patient with brucellosis.

Methods: Three sets of blood cultures, female patient, age 47, were received from General Hospital "Dr. Ivo Pedišić" Emergency Department (GHS). After 72 hours, all three aerobic bottles were positive. Tiny gram negative coccobacilli were noticed. The blood from blood culture bottles was cultured on sheep blood agar and chocolate agar and incubated in 5% CO₂ at 37°C. After 48 hours gentle small colonies, with positive oxidase and catalase, were noticed. Patient was febrile (up to 39°C) during the last month, and had maculopapular skin rash over belly and extremities. The rash was not itchy and turned pale on pressure. The patient also had an asymptomatic pericardial effluent. Recently she visited Cazin (BiH). Differential diagnosis showed brucellosis, therefore the culture was directed to University Hospital for Infection Diseases "Dr. Fran Mihaljević" (CID) and to Croatian Veterinary Institute (CVI).

Results: Results from CVI, using the Brucella Rose Bengal test, complement binding reaction and molecular method Bruceladder, were positive on *Brucella melitensis*. Results from CID, using molecular method of gene sequencing for 16 S RNA, were positive on *Brucella* spp. At the same time, in our laboratory, using gram negative card by Vitek 2, *Brucella melitensis* was also identified.

Conclusion: Patient was treated for 6 weeks with doxycycline and rifampicin therapy. After 14 days of hospitalization the patient was afebrile and discharged from hospital after 19 days, with complete regression of maculopapular rash. After 4 weeks the heart ultrasound test did not show any pericardial effluent. Although the cultivation was very demanding, by the help and support of our colleagues from GHS, CID and CVI the suspected diagnosis was confirmed. Patient received the appropriate therapy and was completely cured.

PO-32 Kliničke karakteristike hospitaliziranih pacijenata s gram negativnim spondilodiscitisom

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Clinical characteristics of hospitalized patients with gram-negative spondylodiscitis

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Objectives: To analyze the clinical characteristics of 25 hospitalized patients with spondylodiscitis (SD) caused by gram-negative bacteria.

Methods: We retrospectively analyzed 25 patients with SD treated at the University hospital for infectious diseases „Dr. Fran Mihaljević“ in Zagreb in the period from 01 January 2008 to 31 December 2017. SD diagnosis was based on the clinical, laboratory and radiological features. The causative organism was detected from blood culture 19 (76%) or biopsy material 6 (24%).

Results: The study included 14/25 (56%) male patients, and the majority of patients (19/25) were older than 50 years of age (median 60 years, IQR 17.5). Nearly half of the patients (12 or 48%) had attributed risk factors. The majority of patients had an acute-subacute course of the disease (median 15 days, IQR 40). All patients had back-pain while fever (tymp. >38.0 °C) was recorded in 19/25 (76%) of the patients. The neurological deficit was detected in 5/25 (20%) of the patients. Thoracic spine was most frequently affected 8 (32%), followed by lumbar 5 (20%), thoracolumbar junction Th12-L1 5 (20%), and lumbosacral junction L5-S1 4 (16%). Two (8%) patients had multiple levels of infection. A distant site infections has been identified in more than half of the patients, most commonly the genitourinary tract (40%) followed by the gastrointestinal tract (12%). The most common pathogen was Escherichia coli 11 (44%), followed by Pseudomonas aeruginosa 5 (20%) and Salmonella enteritidis 4 (16%). Elevated erythrocyte sedimentation rate (median 70 mm/1.h, IQR 45) and C-reactive protein (median 76 mg/L, IQR 140.5) were recorded in all patients, while leukocytosis had 11 (44% of the patients (median 10×10⁹/L, IQR 5). The surgical procedure was performed in 5 (20% of the patients with disease complications, and one patient (4%) died.

Conclusion: The most frequently involved vertebral level of the gram-negative SD was the thoracic and lumbar spine. E. coli was the most common cause of SD with the genitourinary tract being the usual source of infection.

PO-33 Septički artritis preponske simfize i osteomijelitis povezani s abscesom uzrokovanim *Staphylococcus aureus*

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Pubic symphysis septic arthritis and osteomyelitis associated with abscess caused by *Staphylococcus aureus*

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Objectives: Dalbavancin is a novel lipoglycopeptide with a long half-life approved for the treatment of acute bacterial skin and skin structure infections and has a sufficiently promising pharmacokinetic and pharmacodynamic profile to be considered for the treatment of osteomyelitis.

Methods: We present a patient with pubic septic arthritis and osteomyelitis with abscess caused by *Staphylococcus aureus* (MSSA)

Results: A 72-year-old female patient, with type 2 diabetes as the only comorbidity, was admitted to the University Hospital for Infectious diseases (UHID), Zagreb, Croatia with a one-month history of progressive suprapubic pain with fatigue and subfebrile temperature. Due to the isolated sensitive *Klebsiella pneumoniae* from the urine sample and suspected urinary tract infection, the peroral therapy with ciprofloxacin 500 mg BID for 9 days, followed by three days of parenteral gentamicin was applied until admission, both with unfavourable clinical response. At admission the patient had normal vital parameters, barely lifting the legs from the floor, and beside skin edema and pain in the pubic region other clinical status was normal. Erythrocyte sedimentation rate (ESR) was 80 mm/1hour, C-reactive protein (CRP) 172.4 mg/L, leukocyte (L) 10.7 x10⁹/L while other routine blood and urine laboratory tests revealed normal results. Cellulitis and osteomyelitis of the pubic region was suspected and empirical intravenous therapy with clindamycin 900 mg TID was started. *S. aureus* (MSSA) was isolated from blood culture (penicillin resistant, methicillin and clindamycin sensitive). Magnetic resonance imaging (MRI) revealed centrally necrotic abscess affecting the pubic bone bilaterally and the joint space. Soft tissue and surrounding bone oedema was also seen. Posteriorly, the process abutted/affected the retroperitoneal fat. After 11 days of slow response to clindamycin, the therapy was continued with dalbavancin. The patient received two doses of dalbavancin, each of the 1500 mg applied intravenously at 8-days interval, without significant adverse effects. A few days after the last dose of dalbavancin, 22 days after admission, the patient was discharged from UHID. At the first follow up visit three weeks later, the patient had complete resolution of symptoms, and normalization of all disturbed laboratory findings (ESR 36 mm/1.hours, CRP 3.4 mg/L, L 6.1×10⁹/L).

Conclusion: Two 1500 mg intravenous doses, applied 8 days apart, make dalbavancin a valuable option for treating MSSA osteomyelitis and soft tissue abscess.

PO-34 Kronične rane: najčešće izolirani mikroorganizmi i njihova antimikrobna osjetljivost

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CILJEVI RADA:

1. Utvrditi najčešće izolirane mikroorganizme iz kroničnih rana u Požeško – slavonskoj županiji.
2. Utvrditi antimikrobnu osjetljivost najčešće izoliranih mikroorganizama iz kroničnih rana.
3. Utvrditi najčešće antimikrobne lijekove koji se primjenjuju u liječenju infekcija kroničnih rana.

MATERIJALI I METODE: U ovom retrospektivnom opservacijskom istraživanju koje je trajalo od 1.1.2018. do 31.12.2018. godine sudjelovalo je 139 pacijenata koji su bili hospitalizirani na Odjelu opće kirurgije opće županijske bolnice Požega. Svakom pacijentu, biopsijom, je uzet jedan uzorak tkiva iz kronične rane. Nakon biopsije, komadići tkiva su dostavljeni u sterilnim Petrijevim posudicama u mikrobiološki laboratorij. Bioptate tkiva smo obradili po standardnom laboratorijskom protokolu, a broj poraslih kolonija po gramu tkiva (CFU/g) smo određivali semikvantitativnom metodom. Antimikrobnu osjetljivost smo odredili standardnom disk difuzijskom metodom prema EUCAST-u. Istovremeno, pratili smo vrstu antimikrobnih lijekova koji su se koristili u terapiji infekcija.

REZULTATI: U istraživanju je sudjelovalo 139 pacijenata. Ukupno je izolirano 150 izolata od čega su gram negativni uzročnici činili 53%, a gram pozitivni uzročnici 47% izolata. Najčešće izolirani uzročnik je bio *Staphylococcus aureus* (31%), zatim *Pseudomonas aeruginosa* (15%) i *Staphylococcus epidermidis* (15%) te *Escherichia coli* (14%). Antimikrobna osjetljivost najčešće izoliranih izolata je dobra na testirane antibiotike. Izolirali smo mali broj rezistentnih sojeva (MRSA 2%; *E.coli* ESBL 5%). Najčešće ordinirani antimikrobni lijek je bio ko-amoksiklav.

ZAKLJUČAK: U liječenju infekcija kroničnih rana koristi se veliki broj antimikrobnih lijekova širokog spektra djelovanja. I nakon gotovog antibiograma, terapija se ne eskalira na uže spektralni antibiotik. Potrebna je dodatna edukacija kliničara o djelovanju antimikrobnih lijekova.

Ključne riječi: kronične rane, infekcije, antimikrobna osjetljivost

Chronic wounds: The most common isolated microorganisms and their antimicrobial susceptibility

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OBJECTIVES:

1. Identify the most common microorganisms isolated from chronic wounds in Požega-Slavonia County.
2. To determine the antimicrobial susceptibility of the most common microorganisms isolated from chronic wounds.
3. Identify the most common antimicrobials used in the treatment of chronic wound infections.

MATERIALS AND METHODS: In this retrospective observational study participated 139 patients who were hospitalized at the Department of General Surgery. The study was conducted between January 2018 and December 2018. Each patient was biopsied to take one tissue sample from a chronic wound. After biopsy, tissue pieces were delivered in sterile Petri dishes to a microbiology laboratory. Tissue biopsies were processed according to standard laboratory protocol, and the number of colonies grown per gram of tissue (CFU / g) was determined by the semi-quantitative method. Antimicrobial susceptibility was determined using a standard disc diffusion method according to EUCAST. At the same time, we monitored the type of antimicrobial drugs used in infection therapy.

RESULTS: 150 bacterial strains were isolated from 139 samples of chronic wounds. Gram negative pathogens accounted for 53% and Gram positive pathogens for 47%. The most commonly isolated bacteria were *Staphylococcus aureus* (31%), followed by *Pseudomonas aeruginosa* (15%) and *Staphylococcus epidermidis* (15%) and *Escherichia coli* (14%). The antimicrobial susceptibility of isolated bacteria is good. A small number of resistant strains were isolated (MRSA 2%; *Escherichia coli* ESBL 5%). The most commonly administered antimicrobial drug was co-amoxiclav.

CONCLUSION: A wide range of antimicrobial drugs are used in the treatment of chronic wounds infections. Even after the finished antibiogram, the therapy does not escalate to the narrower spectrum antibiotic. Further education of clinicians on the effects of antimicrobials is required.

Keywords: chronic wounds, infections, antimicrobial susceptibility

PO-35 Mikrobiološki spektar iz kroničnih rana nogu

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Uvod i ciljevi: Kronične rane nogu koloniziraju različite bakterije koje mogu biti uzrokom infekcije čak i sustavnih komplikacija. Cilj istraživanja bio je utvrditi prevalenciju i osjetljivost izolata na antibiotike u bolesnika s kroničnom ranom nogu hospitaliziranih na Klinici za dermatovenerologiju KBC Rijeka radi lokalnih i/ili sustavnih znakova infekcije u periodu od 2016-2018.

Metode: U studiji je utvrđena učestalost i osjetljivost izoliranih uzročnika iz briseva i bioptata kroničnih rana u bolesnika hospitaliziranih zbog kliničkih i/ili laboratorijskih znakova lokalne ili sistemne infekcije. Osjetljivost izolata na antimikrobne lijekove utvrđena je disk difuzijskom metodom ili e-testom prema EUCAST standardima.

Rezultati: Ukupno je analizirano 266 uzoraka briseva/bioptata kroničnih rana nogu u 51% žena i 49% muškaraca. Najčešći uzrok kronične rane bila je kronična venska insuficijencija 72.6%, dijabetične rane 10.4%, arterijske 6.2% te ulkusi druge etiologije 10.8%. Najčešće izolirani uzročnici bili su *Pseudomonas aeruginosa* i *Staphylococcus aureus*, s tendencijom porasta gram-negativnih mikroorganizama. Rijetko su izolirani višestrukorezistentni mikroorganizmi. Rekurentne infekcije češće su u bolesnika s dugotrajnijom ranom neovisno o izoliranom uzročniku.

Zaključak: Rezultati istraživanja prikazuju mikrobiološki spektar u bolesnika s inficiranom kroničnom ranom hospitaliziranih u Klinici za dermatovenerologiju KBC Rijeka. Rezultati sugeriraju da kolonizacija i recidivne infekcije kroničnih rana nogu različitim Gram-pozitivnim i Gram-negativnim mikroorganizmima mogu doprinijeti poremećenom cijeljenju rane. Studija pokazuje pomak bakterijskog spektra prema gram-negativnim bakterijama kao značajnim uzročnicima infekcije u ovih bolesnika posljednjih godina.

Microbiological spectrum from infected chronic leg wounds

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Introduction and objective: Chronic leg wounds are colonized by different bacteria that could lead to an infection and even systemic complications. The aim of our clinical investigation was to determine the prevalence and antibiotic susceptibility patterns of bacteria isolated from chronic leg ulcers specimens in patients hospitalized at Dermatovenereology, Clinical Hospital Center Rijeka due to local and/or systemic signs of infection during the period from 2016 to 2018.

Methods: We have evaluated the frequency and antimicrobial sensitivity of strains isolated from swabs and tissue biopsies in chronic leg wound patients hospitalized due to the clinical signs and/or laboratory findings of local or systemic infection. Sensitivity of isolated strains to different antibiotics was performed by the disc diffusion, or e-test method according to EUCAST standard protocol.

Results: 266 chronic wound samples were collected from 59% women and 41% men, mostly in patients with chronic venous insufficiency 72.6%, diabetic ulcers 10.4%, followed by arterial 6.2% and ulcers of other aethyology 10.8%. Most common bacteria identified were *Pseudomonas aeruginosa* and *Staphylococcus aureus* but the presence of gram-negative bacteria species showed a tendency to increase. Multi-drug resistant organisms were rare. Recurrent infections were more common in wounds with longer duration regardless of microorganisms isolated.

Conclusions: The results of our investigation demonstrate the frequency and antimicrobial susceptibility of bacteria isolated in patients with infected chronic leg ulcers hospitalized in our Department. A shift towards gram-negative bacteria as significant cause of infection in patients with chronic wounds was noted over the years. The results suggest that the colonization and recurrent infection of chronic leg ulcers with different Gram-positive and Gram-negative organisms could contribute to impaired wound healing

PO-36 Kliničke značajke hospitaliziranih bolesnika s infekcijom mokraćnog sustava

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Cilj istraživanja: Utvrditi kliničko-epidemiološke osobitosti IMS-a, ispitati postoji li povezanost težine kliničke slike (iskazane kliničkim i laboratorijskim pokazateljima) i komplicirajućih čimbenika, te utvrditi zastupljenost bolesnika s IMS-om u ukupnom broju hospitaliziranih infektoloških bolesnika u promatranom razdoblju.

Ispitanici i metode: S obzirom na ključni kriterij (klinički i laboratorijski dokazan simptomatski IMS), istraživanje je obuhvatilo sve hospitalizirane bolesnike s IMS-om u Klinici za infektologiju KBC-a Osijek u razdoblju od lipnja do prosinca 2016. godine. Iz Povijesti bolesti hospitaliziranih bolesnika s IMS-om prikupljeni su i analizirani klinički, demografski, mikrobiološki, biokemijski i hematološki podaci.

Rezultati: IMS je utvrđen kod 188 bolesnika, pretežno starijih žena. Prisutni su bili brojni komplicirajući čimbenici za IMS. Većina bolesnika imala je vrućicu, a manji dio ostale simptome IMS-a – dizuriju, polakizuriju, suprapubičnu i lumbalnu bol. Nešto više od 12 % bolesnika imalo je pozitivnu hemokulturu, a više od 1/3 bolesnika pozitivnu urinokulturu. Najčešći izolat bio je *E. coli*. Bolesnici s višim upalnim parametrima i prisutstvom komplicirajućih čimbenika prosječno su dulje hospitalizirani, a prosječna duljina hospitalizacije bila je 7,68 dana. Ishod je liječenja uglavnom bio povoljan, a smrtnost rijetka.

Zaključak: Učestalost IMS-a u svakodnevnom kliničkom radu, značajan komorbiditet, kao i predisponirajući komplicirajući čimbenici iziskuju daljnje napore u sprječavanju tih infekcija, a ključ uspješnosti njihovo je rano prepoznavanje i primjereno antimikrobno liječenje

Ključne riječi: antimikrobna terapija, bakterije, hemokultura, infekcija mokraćnog sustava, komplicirajući čimbenici, urinokultura, uroanamneza.

Clinical characteristics of hospitalized patients with urinary tract infections

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Objectives: The aim of this study is to determine the clinical-epidemiological characteristics of UTI, and to examine whether a correlation exists between clinical entity (expressed by clinical and laboratory indicators) and complicating factors (comorbidity, sex, tumor, foreign body), and to determine share of UTI patients in the total number of hospitalized infectious patients in the observed period.

Participants and methods: Taking into account the criterion of inclusion (clinically and laboratory-proven symptomatic UTI), the study included all hospitalized patients with UTI at the Clinical Hospital Center Osijek, at the Clinic for infectology in the period from June to December 2016. Clinical, demographic, microbiological, biochemical and hematological data was collected and analyzed using the history of hospitalized patients with UTI.

Results: UTI was diagnosed in 188 patients, predominantly elderly women. There were many factors that complicated infection. Most patients had fever, fewer had other symptoms of UTI, like dysuria, pollakisuria, suprapubic or lumbar pain. More than 12% of the patients had positive blood cultures, and more than 1/3 of the patients had positive urine cultures. The most common isolate was *E. coli*. Patients with higher inflammatory parameters and the presence of complicating factors were, on average, hospitalized longer with average duration of hospitalization being 7,68 days. The outcome of the treatment was mostly positive, and lethal outcome was rare.

Conclusion: Factors that require further effort in order to prevent these infections are incidence of UTI in daily clinical work, as well as significant comorbidity, and predisposing complicating factors. The key to success is their early detection and appropriate antimicrobial treatment.

Key words: antimicrobial therapy, bacteria, blood culture, complicating factors, urinary tract infections, urine culture, uroanamnesis.

PO-37 Ima li mjesta fosfomicinu u liječenju infekcija mokraćnog sustava uzrokovanih *Pseudomonas aeruginosa*?

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Ciljevi: Fosfomicin, izvorno opisan 1969. godine, danas se zbog visoke koncentracije koju postiže u urinu te malog utjecaja na gastrointestinalnu floru sve više koristi u liječenju i profilaksi cistitisa. Interpretacija testa osjetljivosti dostupna je u EUCAST standardu za enterobakterije i stafilokoke, dok se u CLSI standardu navodi za *E. coli* i *Enterococcus faecalis*. EUCAST standard također navodi da se infekcije uzrokovane izolatima *P. aeruginosa* s minimalnom inhibicijskom koncentracijom $\leq 128 \mu\text{g/ml}$ (epidemiološka prijelomna točka) mogu uspješno liječiti kombinacijom lijekova koja sadržava fosfomicin. Cilj ovog istraživanja bio je utvrditi distribuciju MIK-ova za urinarne izolate *P. aeruginosa* te moguću ulogu fosfomicina u liječenju infekcija mokraćnog sustava uzrokovanih ovom bakterijom.

Metode: Tijekom 2019. godine ukupno je prikupljeno 52 izvanbolnička i bolnička izolata *P. aeruginosa*. Minimalna inhibicijska koncentracija fosfomicina određena je E-testom na Mueller-Hinton agaru, dok je osjetljivost na ostale antipseudomonasne antibiotike određena disk difuzijskom metodom i interpretirana po EUCAST standardu.

Rezultat: Od ukupno 52 testirana izolata, njih 26 (50%) je bilo osjetljivo na sve testirane antipseudomonasne lijekove, dok su preostali izolati pokazivali otpornost makar na jedan od antipseudomonasnih antibiotika. Većina izolata, njih 47 (90,4%), imala je MIK za fosfomicin manji ili jednak $128 \mu\text{g/ml}$, pri čemu je od ukupnog broja 38 (73%) imalo MIK manji ili jednak $32 \mu\text{g/ml}$ (prijelomna točka za osjetljivost za enterobakterije). MIK₅₀ na fosfomicin bio je $32 \mu\text{g/ml}$, a MIK₉₀ $256 \mu\text{g/ml}$.

Zaključak: Kliničko zapažanje na 52 urinarna izolata *P. aeruginosa* o distribuciji MIK-ova za fosfomicin dobivenih metodom E-testa, (a ne standardnom propisanom metodom agar dilucije) pokazalo je da se minimalne inhibicijske koncentracije za većinu izolata nalaze ispod epidemiološke prijelomne točke po čemu bi fosfomicin mogao imati mjesto u liječenju infekcija mokraćnog sustava uzrokovanih *Pseudomonas aeruginosa*. Optimalna kombinacija, put primjene i doziranje fosfomicina, kao i standardizacija i interpretacija testa osjetljivosti za *Pseudomonas aeruginosa* biti će zasigurno predmet budućih istraživanja, posebice u svjetlu rastućeg problema antibiotske rezistencije.

Potential use of fosfomycin in the treatment of urinary tract infections caused by *Pseudomonas aeruginosa*

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Goals: Fosfomycin, firstly described in 1969, is nowadays frequently used in the treatment and prophylaxis of cystitis, due to the high concentrations achieved in urine and low effect on gut flora. EUCAST standard defines interpretative criteria for antimicrobial susceptibility testing of fosfomycin only for *Enterobacterales* and staphylococci, while CLSI standard gives interpretation for *E. coli* and *Enterococcus faecalis*, respectively. There is a note in EUCAST standard regarding *Pseudomonas aeruginosa* and fosfomycin citing that strains with MIC ≤ 128 $\mu\text{g/ml}$ (epidemiological cut off) have been treated with combination of fosfomycin with other agents. The aim of this study is to get insight into MICs distribution for urinary *Pseudomonas aeruginosa* isolates and correspondingly to the potential use of fosfomycin in the treatment of urinary tract infections caused by pseudomonas.

Methods: During 2019 in total 52 *P. aeruginosa* strains were analysed, including those from outpatients and hospital patients. Minimal inhibitory concentration of fosfomycin was determined by E-test on Mueller-Hinton agar, while the susceptibility to other antibiotics was determined by disk diffusion method and interpreted by EUCAST standard.

Results: Among 52 tested isolates, 26 (50%) were susceptible to all tested antipseudomonal antibiotics while the others showed resistance to at least one of the antibiotics tested. Majority of isolates, 47 out of 52 (90.4%) showed MIC of ≤ 128 $\mu\text{g/ml}$ to fosfomycin, out of which 38 (73%) had MIC ≤ 32 $\mu\text{g/ml}$ (the cut off value for susceptible Enterobacterales). MIC₅₀ to fosfomycin was 32 $\mu\text{g/ml}$, while MIC₉₀ was 256 $\mu\text{g/ml}$.

Conclusion: Clinical observation on 52 urinary *P. aeruginosa* isolates regarding the fosfomycin MICs' distribution obtained using E-test (and not the standard method of agar dilution) has shown that the majority of urinary isolates showed MICs below the epidemiological cut off challenging the potential role of fosfomycin in the treatment of urinary tract infections caused by *Pseudomonas aeruginosa*. The optimal drug combination, the route of administrations or the proper dose of fosfomycin as well as standardization and interpretation of susceptibility testing for *Pseudomonas aeruginosa* will surely be the matter of further studies, especially in the era of arising problem of antibiotic resistance.

PO-38 Nitroksolin: učinkovitost u liječenju infekcija mokraćnog sustava uzrokovanih bakterijom *E.coli* otpornom na fluorokinolone

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Ciljevi: Infekcije mokraćnoga sustava (IMS) uzrokovane bakterijom *Escherichia coli* otpornom na fluorokinolone sve su učestalija pojava u kliničkoj praksi, kako kod bolničkih, tako i kod izvanbolničkih pacijenata. Navedene infekcije teško se liječe i izbor terapije za njihovo liječenje je ograničen. Cilj ovog istraživanja bio je odrediti osjetljivost izoliranih sojeva fluorokinolon-otporne *E. coli*, uzročnika IMS izvanbolničkih pacijenata, na stari i gotovo zaboravljeni antimikrobni lijek – nitroksolin. Za liječenje IMS nitroksolin se u nekim zemljama koristi već više od 50 godina, ali ne kao antibiotik prvog izbora.

Metode: Iz pozitivnih urinokultura izvanbolničkih bolesnika tijekom dvomjesečnog perioda u 2018.g. standardnim metodama je izolirano 146 sojeva *E. coli* koji su otporni na fluorokinolone. Copy sojevi nisu uzeti u testiranje. Kriterij uključenja u studiju bila je otpornost na fluorokinolonske antibiotike ciprofloksacin i norfloksacin. Testiranje osjetljivosti *E.coli* na ciprofloksacin i norfloksacin, kao i na nitroksolin, provedeno je metodom disk difuzije. Korišten je nitroksolinski disk sa 30 µg nitroksolina, a rezultati su interpretirani prema EUCAST standardima.

Rezultat: Po navedenim standardima, od ukupno 146 testiranih sojeva fluorokinolon-otporne *E.coli*, njih čak 142 (97,26%) su imala zonu inhibicije ≥ 15 mm, odnosno bili su osjetljivi na nitroksolin. Samo 4 testirana soja (2,74%) imala su zonu inhibicije 14 mm i manju te su proglašeni otpornima na nitroksolin.

Zaključak: Izolati *E. coli* u ovoj su studiji pokazali 97,26% in vitro osjetljivost na nitroksolin. Trend porasta stope otpornosti na fluorokinolone kod sojeva *E. coli* izoliranih iz urinokultura prisutan je, kako u Hrvatskoj, tako i širom svijeta. Ovakvi izolati često pokazuju i multiplu otpornost na antibiotike. Zbog porasta stope otpornosti, fluorokinoloni više ne mogu biti antibiotici prvog izbora za liječenje IMS. Obzirom da su fluorokinolon-otporni sojevi *E. coli* pokazali vrlo nisku stopu otpornosti na nitroksolin, trebalo bi revalorizirati njegovo mjesto u liječenju IMS.

Ključne riječi: nitroksolin, infekcije mokraćnog sustava, fluorokinolon-otporna *E. coli*

Nitroxoline: effectiveness in the treatment of urinary tract infections caused by fluoroquinolone-resistant *E. coli*

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Introduction: Urinary tract infections (UTIs) caused by fluoroquinolone-resistant *Escherichia coli* are increasingly seen in clinical practice among both inpatients and outpatients. The aim of this study was to determine susceptibility of isolated fluoroquinolone-resistant *E. coli* strains to the old and almost forgotten antimicrobial drug – nitroxoline. In some countries nitroxoline treatment has been used for over 50 years, but not as the first-choice antibiotic.

Methods: In this retrospective study over a two-month period in 2018, 146 fluoroquinolone-resistant *E. coli* strains were isolated and collected from positive urine cultures of outpatients. Copy strains were not taken for testing. Inclusion criteria was resistance to fluoroquinolone antibiotics: ciprofloxacin and norfloxacin. In vitro susceptibility to ciprofloxacin and norfloxacin, as well as nitroxoline, was tested by agar disk diffusion method. Nitroxoline disc 30 µg was used and the results were interpreted according to EUCAST standards.

Result: According to mentioned standards, 142 (97.26%) out of 146 tested strains of fluoroquinolone-resistant *E. coli* had an inhibition zone ≥ 15 mm, and were rated as susceptible to nitroxoline. Only 4 (2.74%) tested strains had a zone of inhibition 14 mm or less and were rated as resistant to nitroxoline.

Conclusion: In this study, 97.26% isolates of *E. coli* showed in vitro susceptibility to nitroxoline. An upward trend in the rate of resistance to fluoroquinolones in *E. coli* strains isolated from urine cultures is present in Croatia as well as worldwide. Such isolates often show multiple antibiotic resistance. Due to the increasing rate of resistance, fluoroquinolones can no longer be the first-choice antibiotics for the treatment of UTIs. Considering that fluoroquinolone-resistant *E. coli* strains showed a very low resistance to nitroxoline, its place in the treatment of UTIs should be revalued.

Key words: nitroxoline, urinary tract infections, fluoroquinolone-resistant *E. coli*

PO-39 Liječenje uroinfekcija uzrokovanih fluorokinolon-otpornom ESBL-producirajućom *E. coli* – “stari” antibiotici jedini izbor?

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Ciljevi: Infekcije mokraćnog sustava među najčešćim su infekcijama širom svijeta i u 70 do 80% slučajeva uzrokovane su bakterijom *Escherichia coli*. Sojevi *E. coli* koji produciraju β -laktamaze proširenog spektra (ESBL) sve se češće izoliraju i u izvanbolničkoj populaciji. Geni koji kodiraju ESBL uglavnom se nalaze na istom plazmidu s genima koji posreduju otpornost na fluorokinolone. Po ISKRA smjernicama u liječenju akutnih nekompliciranih infekcija mokraćnog sustava (NIMS) prvi izbor je nitrofurantoin, a alternativa su koamoksiklav, cefaleksin te norfloksacin. Cilj ovog istraživanja bio je utvrditi osjetljivost fluorokinolon-otpornih ESBL-producirajućih (FOESBL) izolata *E. coli* na dostupne peroralne antibiotike koji se mogu dati u liječenju NIMS.

Metode: U ovoj retrospektivnoj studiji tijekom 3 mjeseca u 2018. godini iz urinokultura izvanbolničkih pacijenata prikupljeno je 50 FOESBL sojeva *E. coli*. ESBL-produkcija utvrđena je metodom dvostrukog diska. Osjetljivost na fluorokinolone, koamoksiklav, nitroksolin, nitrofurantoin, fosfomicin i sulfametoksazol-trimetoprim testirana je metodom disk difuzije na Mueller-Hinton agaru inkubiranom aerobno pri $35\pm 1^\circ\text{C}$ tijekom 16-20 h. Zone inhibicije interpretirane su po EUCAST standardu. Rezultat: Od ukupno 50 sojeva, 38 (76%) je bilo otporno na sulfametoksazol-trimetoprim. Dvanaest sojeva, odnosno 24%, bilo je otporno na koamoksiklav, dok je devet (18%) bilo otporno na nitrofurantoin. Samo 2 soja bila su otporna na fosfomicin (4%), dok su svi sojevi bili osjetljivi na nitroksolin.

Zaključak: Ovim istraživanjem utvrđen je vrlo visok postotak izolata otpornih na sulfametoksazol-trimetoprim, kao i relativno visok postotak izolata otpornih na koamoksiklav i nitrofurantoin pa je upitna njihova uloga u peroralnoj terapiji NIMS uzrokovanih fluorokinolon-otpornim ESBL-producirajućim izolatima *E. coli*. Svi testirani izolati bili su osjetljivi na nitroksolin te većina na fosfomicin čime je naglašena moguća uloga „starih“ antibiotika u liječenju NIMS uzrokovanih ESBL-producirajućom *E. coli*, a posebice izolatima otpornim na fluorokinolonske antibiotike, koji se zbog kolateralne štete sve više izbjegavaju u liječenju izvanbolničke populacije.

Treatment of urinary tract infections caused by fluoroquinolone-resistant ESBL-producing *E. coli* – "old" antibiotics are the only option?

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Introduction: Urinary tract infections (UTIs) are most frequently (70-80% of cases) caused by *Escherichia coli*. Extended-spectrum β -lactamases (ESBL)-producing strains of *E. coli* are increasingly isolated in outpatients. Genes encoding ESBL are mostly located on the same plasmid as genes that mediate resistance to fluoroquinolones. According to ISKRA guidelines, nitrofurantoin is antibiotic of the first choice, and co-amoxiclav, cephalexin and norfloxacin are alternatives for the treatment of acute uncomplicated urinary tract infections (AUUTIs). The aim of this study was to determine susceptibility of fluoroquinolone-resistant ESBL-producing (FRESBL) isolates of *E. coli* to available oral antibiotics that can be used in the treatment of AUUTIs.

Methods: In this retrospective study during a 3-month period in 2018, fifty FRESBL strains of *E. coli* were collected from urine cultures of outpatients. ESBL production was determined by double disc method. Susceptibility to fluoroquinolones, co-amoxiclav, nitroxoline, nitrofurantoin, phosphomycin and sulfamethoxazole-trimethoprim was tested by disc diffusion method on Mueller-Hinton agar incubated aerobically at 35 ± 1 ° C for 16-20 h. The inhibition zones were interpreted according to EUCAST standard.

Result: Thirty eight strains out of fifty tested (76%) were resistant to sulfamethoxazole-trimethoprim. Twelve strains (24%) were resistant to co-amoxiclav, while nine (18%) were resistant to nitrofurantoin. Only two strains were resistant to phosphomycin (4%), while all of the tested strains were susceptible to nitroxoline.

Conclusion: Very high percentage of isolates were resistant to sulfamethoxazole-trimethoprim and relatively high percentage of isolates were resistant to co-amoxiclav and nitrofurantoin, so their role in oral AUUTIs therapy caused by fluoroquinolone-resistant ESBL-producing *E. coli* is questionable. All tested isolates were susceptible to nitroxoline and majority to phosphomycin, stressing the possible role of "old" antibiotics in the treatment of AUUTIs caused by ESBL-producing fluoroquinolone resistant *E. coli*.

PO-40 Klinički značaj i antimikrobna osjetljivost bakterije *Corynebacterium glucuronolyticum* u mokraćno-spolnom sustavu muškaraca

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CILJ: Korineformne bakterije u urogenitalnom traktu se često smatraju saprofitima, no sve je više dokaza koji upućuju na patogeni potencijal vrste *Corynebacterium glucuronolyticum* (*C. glucuronolyticum*). Nekoliko istraživačkih skupina je opisalo značaj ovog rijetkog izolata u sindromu uretritisa kod muškaraca, dok su drugi ukazali na ulogu u razvoju monomikrobnog paucisimptomatskog bakterijskog prostatitisa. Cilj našeg istraživanja bilo je dodatno razjasniti ulogu ove bakterije u muškom spolnom sustavu te istražiti njenu antibiotsku osjetljivost.

METODE: U skupini pacijenata koji su provodili dijagnostičku obradu za spolno prenosive i druge infekcije tijekom 4-godišnjeg razdoblja, 35 muškaraca kod kojih je *C. glucuronolyticum* izoliran u čistoj kulturi i broju $>10^4$ CFU/mL podvrgnuti su daljnjoj dijagnostičkoj obradi. Izolati su potvrđeni korištenjem API Coryne sustava i MALDI-TOF masene spektrometrije, a provelo se i testiranje antimikrobne osjetljivosti (sukladno EUCAST-u). Također je pacijentima uzeta anamneza, opisana klinička slika te proveden urološki pregled.

REZULTATI: Pet pacijenata s dokazanom monoinfekcijom *C. glucuronolyticum* u značajnoj količini imalo je izražene simptome uretritisa i/ili prostatitisa, dok su tri mjeseca po završetku liječenja (te mikrobiološke potvrde odsutnosti bakterije) simptomi bili prisutni u još samo jednog od njih; navedeno sugerira patogeni učinak ove bakterijske vrste u muškom genitalnom traktu. Izolati *C. glucuronolyticum* pokazali su potpunu osjetljivost na rifampicin (100%) i vankomicin (100%), vrlo dobru osjetljivost na penicilin G (97,14%) i gentamicin (91,43%), umjerenu osjetljivost na ciprofloksacin (68,57%), te nisku osjetljivost na tetraciklin (45,71%) i klindamicin (40%).

ZAKLJUČAK: Ovo istraživanje uključuje dosad najveći broj izolata *C. glucuronolyticum* iz muškog urogenitalnog trakta (s brojem kolonija $>10^4$ CFU/mL i pretpostavljenom etiološkom značajnošću). Pokazalo se kako je kliničko-mikrobiološka korelacija prije i nakon liječenja dobar put za utvrđivanje patogenoga potencijala uzročnika, dok antimikrobna osjetljivost ukazuje kako tetraciklin (lijek koji se vrlo često propisuje empirijski u slučajevima uretritisa) u ovom slučaju može biti neučinkovit terapijski izbor.

Clinical significance and antimicrobial susceptibility trends of *Corynebacterium glucuronolyticum* in the male urogenital system

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AIMS: *Coryneform* bacteria in urogenital tract have been generally regarded as saprophytes, but pathogenic potential of *Corynebacterium glucuronolyticum* (*C. glucuronolyticum*) is becoming increasingly evident. Several research groups demonstrated a pathogenic role of this rare isolate in male urethritis syndrome, while others have exposed its potential for causing monomicrobial paucisymptomatic bacterial prostatitis. We aimed to further elucidate its role in the male urogenital system and to appraise its antibiotic sensitivity pattern.

METHODS: From a pool of patients that visited outpatient clinic for sexually transmitted diseases during a 4-year period, a total of 35 men with *C. glucuronolyticum* isolates showing pure-culture growth and $>10^4$ CFU/mL were subjected to further diagnostic workup. Isolates were confirmed by API Coryne and MALDI-TOF mass-spectrometry, and antimicrobial susceptibility testing was also pursued (in accordance with EUCAST). Medical history and symptom appraisal, as well as urological examination have been conducted.

RESULTS: Five patients with *C. glucuronolyticum* as a monoisolate in significant quantities presented with frank symptoms of urethritis and/or prostatitis, whereas three months after treatment (and following microbiological confirmation of bacteriological clearance) the symptoms persisted in only one of them – suggesting a purported pathogenic role of this species. Isolated strains *C. glucuronolyticum* showed excellent sensitivity to rifampicin and vancomycin (100% of strains susceptible), very good sensitivity to penicillin G and gentamicin (97.14% and 91.43% of strains susceptible, respectively), modest sensitivity to ciprofloxacin (68.57% of strains susceptible) and low susceptibility to tetracycline and clindamycin (45.71% and 40% of strains susceptible, respectively).

CONCLUSION: This research entails the largest collection of *C. glucuronolyticum* isolates from male urogenital specimens (with colony counts $>10^4$ CFU/mL and purported etiological relevance) in a single study. Pretreatment-posttreatment approach may reveal its pathogenic potential, and antibiotic sensitivity results showed how tetracycline (common empiric therapy for urethritis) may not be an effective treatment choice.

**PO-41 Evaluacija seroloških testova za sifilis u Klinici za infektivne bolesti
“Dr. Fran Mihaljević” u Zagrebu**

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Ciljevi: Dijagnoza sifilisa postavlja se treponemskim i ne-treponemskim serološkim testovima uz pravilnu interpretaciju rezultata. U reverznom algoritmu probirno testiranje započinje hemaglutinacijskim (TPHA), imunoenzimskim ili kemiluminiscentnim (CLIA) testom nakon čega se pozitivni serumi testiraju metodom RPR. Definira se titar protutijela i preporuča praćenje parnih seruma. Analizirali smo rezultate TPHA, RPR i CLIA za sifilis u osoba kod kojih je prvi puta registriran HIV.

Metode: Od 2015. do 2017. godine testirano je 5681 seruma od 3929 ispitanika metodom TPHA (Trinity Biotech, Irska ili Newmarket Biomedical, Velika Britanija). Pozitivni serumi testirani su RPR-om (BioMerieux, Francuska). Serumi s prvi puta registriranim HIV-om usporedno su testirani metodom CLIA (Architect Syphilis TP, Abbott, Njemačka). Svi testovi rađeni su prema preporukama proizvođača. Za statističku obradu korišten je računalni program MedCalc® Software, verzija 19.0.7. Rezultati: Pozitivan TPHA dijagnosticiran je u 415 (10.6%) od 3929 ispitanika. Pozitivan RPR imalo je 130 (3.3%), a titar 32 i veći 47 (1.2%) ispitanika. CLIA metodom dodatno je testirano 324 od ukupno 333 ispitanika kod kojih je prvi puta registriran HIV u Klinici. Pozitivan TPHA imalo je njih 82 (25.3%), CLIA 88 (27.2%), a RPR 32 (9.9%). U 6 TPHA/RPR negativnih HIV-ispitanika nađen je slabo pozitivan CLIA rezultat (1.52 – 8.49 S/CO). Korelacija između TPHA i CLIA je visoka ($r = 0.77$; $P < 0.0001$; 95% CI 0.72 – 0.81), za razliku od korelacije između RPR i CLIA ($r = 0.51$; $P < 0.0001$; 95% CI 0.43 – 0.59).

Zaključak: Reverzni algoritam za dijagnostiku sifilisa može započeti testom CLIA ili TPHA koji pokazuju dobru korelaciju. Oprezno treba evaluirati rezultate niskih titrova. Reaktivni serumi obavezno se testiraju metodom RPR. RPR je još uvijek ključan u dijagnostici akutnog sifilisa, ali nije metoda izbora za probir. Svaka četvrta osoba s prvi puta registriranim HIV-om imala je protutijela na sifilis.

Evaluation of serological tests for syphilis at the University Hospital for Infectious Diseases „Dr. Fran Mihaljević” in Zagreb

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Objectives: Syphilis serology diagnosis is based on treponemal and non-treponemal tests with proper interpretation of results. The reverse algorithm begins with a hemagglutination (TPHA), enzyme or chemiluminescent (CLIA) immunoassay, followed by reactive sera RPR testing. The antibody titer needs to be defined and paired sera testing are recommended. We analysed the results of TPHA, RPR and CLIA for syphilis in newly diagnosed HIV-positive persons.

Methods: From 2015 to 2017, 5681 sera out of 3929 subjects were tested with TPHA (Trinity Biotech, Ireland or Newmarket Biomedical, UK). Reactive sera were further analysed with RPR (BioMerieux, France). Sera from newly diagnosed HIV-positives were analysed by CLIA method (Architect Syphilis TP, Abbott, Germany). All assays were performed according to manufacturer's recommendations. For statistical analysis MedCalc® software version 19.0.7 was used.

Results: Positive TPHA were detected in 415 (10.6%) out of 3929 tested subjects. RPR was positive in 130 (3.3%); RPR titre 32 and higher had 47 (1.2%) subjects. Out of 333 newly diagnosed HIV-positives at the University Hospital, 324 were further tested with CLIA. Positive TPHA, CLIA and RPR in newly diagnosed HIV-positives were detected in 82 (25.3%), 88 (27.2%) and 32 (9.9%), respectively. A low positive CLIA results (1.52 – 8.49 S/CO) were detected in 6 newly diagnosed HIV-positives with negative TPHA/RPR. The correlation between TPHA and CLIA was high ($r = 0.77$; $P < 0.0001$; 95% CI 0.72 – 0.81), as opposed to the correlation between RPR and CLIA ($r = 0.51$; $P < 0.0001$; 95% CI 0.43 – 0.59).

Conclusion: The reverse algorithm for syphilis begins with CLIA or TPHA testing which show good correlation. Low titers should be carefully evaluated. Reactive sera must be further tested with RPR. RPR is still essential in the diagnosis of acute syphilis, but it is not preferred for screening. One in four newly diagnosed HIV-positive persons had syphilis antibodies.

PO-42 Dijagnostika sifilisa reverznim algoritmom testiranja u Hrvatskom zavodu za transfuzijsku medicinu: rezultati testiranja u periodu od 2011. do 2017. godine

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Uvod: Tradicionalni algoritmi testiranja na sifilis uključuju netreponemske testove, VDRL i/ili RPR, koji nisu: a) dovoljno osjetljivi ni u akutnom ni u davnom sifilisu, b) specifični za sifilis, c) automatizirani i d) dovoljno brzi. Reverzni algoritam testiranja (RAT) počinje s testovima koji detektiraju specifična IgM i IgG antitijela na *Treponema pallidum*. U HZTM-u (OKB) koristi se kombinacija dva različita testa/metode za dijagnostičko pretraživanje – ELISA i CMIA. Reaktivni uzorci krvi refleksno se testiraju potvrdnim algoritmom.

Cilj: Analizirati učestalost sifilisa u ispitivanoj populaciji pacijenata/ispitanika i usporediti s učestalošću u populaciji dobrovoljnih davatelja krvi (DDK); determinirati akutne i davne infekcije pomoću RAT-a i potvrdnim testiranjem.

Materijali i metode: U periodu od 2011. do 2017. godine testirano je 72867 uzoraka krvi na sifilis (anti-TP), od čega je bilo 65060 uzorka krvi trudnica. Testovi korišteni u pretraživanju su Abbott Architect Syphilis TP, Bio-Rad Syphilis TA EIA (do 2016.) te Dia.Pro Syphilis Ab v. ULTRA, a u potvrdnom algoritmu: Dia.Pro Syphilis IgM, Bio-Rad TPHA i RPR, Mikrogen recomLine *Treponema* IgG i Fujirebio INNO-LIA Syphilis Score.

Rezultati: Ukupno potvrđeno pozitivnih pacijenata/ispitanika na sifilis bilo je 199, od čega prvi put 172 – akutnih infekcija 76 i davnih 96. 111 davnih sifilisa bilo je RPR negativno. Ukupna učestalost po godinama, od 2011. do 2017. godine, bila je (%): 0,22, 0,19, 0,24, 0,32, 0,21, 0,33, 0,15 – prosječna 0,24%, a u trudnica (%): 0,13, 0,04, 0,02, 0,05, 0,06, 0 i 0.

Zaključak: Ukupna učestalost sifilisa u našoj populaciji ispitanika, kao i u trudnica, stabilna je kroz ispitivane godine i očekivano viša nego u DDK (cca 0,004%). RAT-om na sifilis laboratorijski smo dokazali značajno više sifilis infekcija (davnih), koje nije detektirao netreponemski test RPR. RAT s potvrdnim testiranjem je točna, pouzdana i reproducibilna dijagnostika sifilisa s mogućnošću distinkcije akutne i davne infekcije.

Diagnosis of syphilis by a reverse testing algorithm at the Croatian Institute for Transfusion Medicine: test results from 2011 to 2017

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Introduction: Traditional syphilis testing algorithms include nonreponemal tests, VDRL and/or RPR, which are not: a) sensitive enough in either acute or long-standing syphilis, b) syphilis-specific, c) automated, and d) fast enough. The Reverse Testing Algorithm (RAT) begins with tests that detect specific IgM and IgG antibodies to *Treponema pallidum*. CITM uses a combination of two different tests /methods for diagnostic screening – ELISA and CMLA. Reactive blood samples are reflexively tested by a confirmatory algorithm.

Objective: To analyze the prevalence of syphilis in the study population of patients and to compare it with the prevalence in the voluntary blood donor (VBD) population; determine acute and long-standing infections using RAT and confirmatory testing.

Materials and methods: From 2011 to 2017, 72867 blood samples were tested for syphilis (anti-TP), of which 65060 were pregnant women samples. The tests used in the screening are Abbott Architect Syphilis TP, Bio-Rad Syphilis TA EIA (until 2016) and Dia.Pro Syphilis Ab v. ULTRA, and in the confirmatory algorithm: Dia.Pro Syphilis IgM, Bio-Rad TPHA and RPR, Mikrogen recomLine *Treponema* IgG and Fujirebio INNO-LIA Syphilis Score.

Results: The total number of confirmed syphilis positive patients was 199, of which 172 for the first time – acute infection 76 and long-standing 96. 111 long-standing syphilis was negative for RPR. The overall prevalence by years was (%): 0.22, 0.19, 0.24, 0, 32, 0.21, 0.33, 0.15, respectively, – average 0.24%, and in pregnant women (%): 0.13, 0.04, 0.02, 0.05, 0.06, 0 and 0.

Conclusion: The overall prevalence of syphilis in our study population as well as in pregnant women is stable throughout the study years and expectedly higher than in VBD (approximately 0.004%). By RAT for syphilis, we have laboratory-proven more syphilis, 111 infections (long-standing), that were not detected by the RPR test. RAT followed by confirmatory testing is an accurate, reliable and reproducible diagnosis of syphilis with the ability to distinguish acute and long-standing infection.

PO-43 Suvremeni pristup liječenju kroničnog hepatitisa C u Republici Srpskoj

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UVOD: Milijuni ljudi širom svijeta boluju od hepatitisa C, što može dovesti do teške bolesti jetre, raka jetre i smrti. Procjenjivali smo djelotvornost i sigurnost interferon-free terapije Ombitasvir/ Paritaprevir/Ritonavir±Dasabuvir sa ili bez ribavirina (OBV/PTV/RTV+DSV+/-RBV) u bolesnika s kroničnim hepatitisom C.

METODE: Uključili smo pacijente s infekcijom HCV genotipom 1 i 4 koji su prethodno bili liječeni peg-interferonom i ribavirinom i imali relaps, djelomični odgovor ili izostanak virusološkog odgovora. Bolesnici su primali OBV/PTV/RTV+DSV+/-RBV tijekom 12/24 tjedana, u cilju postizanja stabilnog virološkog odgovora. Primarna krajnja točka bila je stopa stabilnog virološkog odgovora u 12 tjednu nakon završetka tretmana.

REZULTATI: Ova studija je uključila ukupno 89 bolesnika. RBV je dan svim pacijentima osim onih koji imaju HCV podgenotip 1b. DSV nije primijenjen pacijentima zaraženim HCV genotipom 4. Za većinu bolesnika trajanje liječenja bilo je 12 tjedana. Deset bolesnika s cirozom jetre koji su zaraženi HCV genotipom 1 trajanje liječenja bilo je 24 tjedna. Viremija je procjenjena u tri točke u vremenu: na početku, 12 ili 24 tjednu nakon početka liječenja (završetak liječenja - ETR) i 12 tjedan nakon završetka liječenja (stabilni virusni odgovor - SVO). Kompletan ETR nakon 12 tjedana liječenja postignuta je u 79 bolesnika, dok je u 10 pacijenata s visokim rizikom postignuto nakon 24 tjedana liječenja. Kompletan SVR zabilježen je kod 88 (98.9%) pacijenata 12 tjedana nakon završetka liječenja. Jedan pacijent je imao relaps i detektibilnu viremiju. Ova terapija se dobro podnosila i blage nuspojave zabilježene su samo u 10 bolesnika. Liječenje bolesnika s kroničnom HCV infekcijom s OBV/PTV/RTV + DSV +/- RBV rezultiralo je izvrsnom antivirusnom aktivnošću i blagim nuspojavama.

ZAKLJUČAK: Režim bez interferona OBV/PTV/RTV+DSV+/- RBV, dovodi do visokog stupnja SVR12 u bolesnika s HCV genotipom 1 koji su prethodno liječeni.

Ključne riječi: hepatitisa C virus; Ombitasvir; Paritaprevir; Ritonavir; Dasabuvir; Ribavirin

Contemporary approach to the treatment of chronic hepatitis C in Republic of Srpska

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BACKGROUND: Millions of people worldwide suffer from hepatitis C, which can lead to severe liver disease, liver cancer, and death. We evaluated the efficacy and safety of the interferon-free combination of ABT-450 with ritonavir, ombitasvir, dasabuvir and ribavirin for the treatment of chronic hepatitis C.

METHODS: We enrolled patients with HCV genotype 1 infection and no cirrhosis who had previously been treated with peginterferon-ribavirin and had a relapse, a partial response, or a null response. Patients received of dasabuvir/ombitasvir/paritaprevir/ritonavir during the 12/24-week, in achieving sustained virological response. The primary end point was the rate of sustained virologic response 12 weeks after the end of study treatment.

RESULTS: This study was included a total of 89 patients. RBV was given to all patients except to those with HCV sub-genotype 1b. DSV was not administered to patients infected with HCV genotype 4. For the majority of patient the treatment duration was 12 weeks. Ten patients with liver cirrhosis who were infected with HCV genotype 1 the duration of treatment was 24 weeks. Viremia was assessed at four points in time: at baseline, 12 or 24 weeks after the beginning of treatment (end of treatment response – ETR), and 12 weeks after the end of treatment (sustained viral response – SVR).

Complete ETR after 12 weeks of treatment was achieved in 79 patients, while in 10 high-risk patients it was achieved after 24 weeks of treatment. Full SVR was recorded in 88 (98.9%) patients 12 weeks after the end of treatment. One patient had relaps and detectable viremia. This therapy was well tolerated and mild adverse effects were recorded in only ten patients. Treatment of patients with chronic HCV infection with OBV/PTV/RTV + DSV + RBV resulted in excellent antiviral activity and mild adverse events.

CONCLUSIONS: The interferon-free regimen of ABT-450, ritonavir, ombitasvir, and dasabuvir, with or without ribavirin, produces a high rate of SVR12 in treatment-experienced patients with HCV genotype 1 infection.

Key words: Hepatitis C virus; Ombitasvir; Paritaprevir; Ritonavir; Dasabuvir; Ribavirin

PO-44 Kronični hepatitis C u djece liječene na Klinici na infektologiju Kliničkog bolničkog centra Split u dvadesetogodišnjem razdoblju (1998.-2018.)

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Ciljevi: prikazati epidemiološki osobine, kliničku sliku i liječenje bolesnika dječje dobi s kroničnim hepatitisom C. Metode: iz arhive Klinike za infektologiju prikupljeni su podaci o dobi, načinu infekcije, genotipu HCV, trajanju bolesti, stupnjevima fibroze, kretanju alanin aminotrasferaze i ishodu liječenja 34 bolesnika dječje dobi. Podaci su prikazani tabelarno. Rezultati: Većinom se radilo o infekcijama stečenim nakon 1992.godine, u 15/34 djece put infekcije bilo je dobivanje krvi i krvnih pripravaka, vertikalni prijenos je utvrđen tek u 4/34 djece, a u čak 10/34 djece jedini čimbenik rizika bio je bolničko liječenje bez primanja krvi ili krvnih derivata. Nakon višegodišnjeg praćenja (raspon 7-16 godina) većina ih je imala stupnjeve fibroze 0-1 po Metaviru. Kombinacijom PegInterferon i ribavirina liječeno je 11 bolesnika, od kojih 5 prije navršениh 18 godina života. Trajni virološki odgovor postignut je u 50% u bolesnika s genotipom 1 i svih u bolesnika s genotipom 3 HCV. Zaključak: većina kroničnih hepatitisa C u dječjoj su sporo napredujuće bolesti, terapijski odgovor na kombinaciju PegINF i ribavirina usporediv je s bolesnicima odrasle dobi.

Chronic hepatitis C in children treated in the twenty-year period (1998-2018) in Clinic for Infectology, Clinical Hospital Centre Split

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Aims: to show epidemiological characteristics, clinical feature and treatment of children with chronic hepatitis C.

Methods: from the archives of the Clinic for Infectology, data were collected on age, mode of infection, HCV genotype, duration of disease, degree of fibrosis, alanine aminotransferase values and therapeutic outcome of 34 children. The data are presented in tables.

Results: Most were infections acquired after 1992. In 15/34 children the route of infection was the use of blood and blood products, vertical transmission was found in only 4/34 children, , and in 10/34 children the only risk factor was hospitalization without receiving blood or blood products. After 7 to 16 years of follow-up most of the patients had Metavir fibrosis degree between 0-1. Eleven patients was treated with PegInterferon plus ribavirin, 5 of them before 18 years of age. Sustained virological response was achieved in 50% of patients with genotype 1 and in all patients with genotype 3 of HCV.

Conclusion: Most chronic hepatitis C in children are slowly progressing disease, and treatment response to a combination of PegINF and ribavirin is comparable to adults.

PO-45 Primjena izravno djelujućih antivirusnih lijekova (DAA) u liječenju bolesnika s kroničnim hepatitisom C u Splitsko – dalmatinskoj županiji

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Cilj: prevalencija HCV infekcije u Hrvatskoj je niska i iznosi 0.9%. Od 2014. godine za liječenje bolesnika s kroničnim hepatitisom C dostupni su izravno djelujući antivirusni lijekovi (DAA). Cilj ovog rada je prikazati učinkovitost DAA kod 170 bolesnika s kroničnim hepatitisom C koji su liječeni u Splitsko-dalmatinskoj županiji. Metode: u razdoblju od 1. kolovoza 2015. do 28. veljače 2019. godine ukupno je liječeno 170 bolesnika s kroničnim hepatitisom C u Splitsko-dalmatinskoj županiji. Od 170 bolesnika njih 83(48.88%) je prethodno liječeno, a 87 (51,12%) su bili naivni. Većina bolesnika imala je genotip 1 (60.59%), manji broj genotip 3 (35.89%), dok su genotip 2 i 4 bili rijetki (1.17% i 2.35%). U svih bolesnika stupanj fibroze utvrđen je elastografijom koristeći FibroScan (raspon od 7.1 do 70.6 kPa). Većina bolesnika (76.47%) imala je cirozu (F4), 16.47% fibrozu 3, a 6.47% njih fibrozu 2.

Rezultati: od 170 bolesnika s kroničnom HCV infekcijom, 50 (29.41%) je liječeno ombitasvirom/paritaprevirom/ritonavinom i dasabuvirom +/- ribavirinom (RBV). Jednak broj bolesnika liječen je glekaprevirom/pibrentasvirom. Slijede sofosbuvir/velpatasvir +/- RBV kojim je liječeno 29 (17.06%) bolesnika, zatim elbasvir/grazoprevir +/- RBV 19 (11.18%), sofosbuvir/ledipasvir +/- RBV 16 (9.41%) i sofosbuvir+RBV 6 (3.53%). Trajni virološki odgovor (SVR), 12 tjedana nakon završetka liječenja, ispitan je kod svih bolesnika. Samo 3 (1.76%) bolesnika nisu postigla SVR, dok je kod preostalih 167 (98,24%) postignuta eliminacija infekcije HCV-om. Svi bolesnici su dobro podnijeli liječenje i kod niti jednog bolesnika nisu zabilježene značajnije nuspojave niti je došlo do prekida terapije.

Zaključak: prikazani su prvi rezultati liječenja kronične HCV infekcije s DAA u Splitsko-dalmatinskoj županiji. Izlječenje je postiglo 98.24% liječenih, što je očekivan rezultat, usporediv s drugim objavljenim istraživanjima u Hrvatskoj. U budućnosti očekujemo povećanje broja liječenih bolesnika na godišnjoj razini kao i ranije započinjanje terapije kod bolesnika s nižim stadijima fibroze.

Direct-acting antiviral agents in the treatment of chronic hepatitis C infection in Split – Dalmatia County

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Background and Aims: Prevalence of hepatitis C virus (HCV) infection in Croatia is low (0.9%). Treatment and cure of HCV infection with direct-acting antiviral agents (DAA) began in 2014. The aim of this study is to demonstrate the efficacy of DAA therapy in 170 patients with chronic hepatitis C infection treated in Split-Dalmatia County.

Methods: In the period between August 1, 2015 and February 28, 2019, 170 HCV infected patients in Split-Dalmatia County completed therapy with DAA. Out of 170 patients, 83 (48.88%) were treatment-experienced (TE) and 87 (51.12%) were treatment-naïve (TN). Considering genotype distribution, most of the patients were genotype 1 (60.59%), followed by G3 (35.89%), G4 (2.35%) and G2 (1.17%). In all patients fibrosis was determined by FibroScan® (range 7.1-70.6 kPa). Majority of patients (76.47%) had cirrhosis (F4), 16.47% had fibrosis 3 and 6.47% had fibrosis 2.

Results: Among 170 patients with chronic HCV infection, 50 (29.41%) were treated with ombitasvir/paritaprevir/ritonavir plus dasabuvir +/- ribavirin (RBV). The same number was treated with glecaprevir/pibrentasvir. The following were: 29 (17.06%) patients were treated with sofosbuvir/velpatasvir +/- RBV, 19 (11.18%) with elbasvir/grazoprevir +/- RBV, 16 (9.41%) with ledipasvir/sofosbuvir +/- RBV and finally, 6 (3.53%) with sofosbuvir + RBV. SVR 12 weeks after completion of therapy was available for all patients. Only 3 (1.76%) patients did not achieve SVR while the remaining 167 (98.24%) achieved elimination of HCV infection. The treatment was well-tolerated in all patients. None of the patients had any significant side effects and there was no discontinuation of treatment.

Conclusions: We present the first results of treatment of chronic HCV infection with DAA in the Split-Dalmatia County. Among 170 treated patients, 98.24% achieved cure, which is an expected result, comparable to other published studies in Croatia. In the future, we expect an increase in the number of treated patients on an annual basis as well as earlier onset of treatment in patients with lower fibrosis stages.

PO-46 Dijagnostika hepatitisa C od 2014. do 2018. godine u Klinici za infektivne bolesti „Dr. Fran Mihaljević“ u Zagrebu

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Cilj: Analizirati rezultate serološke i molekularne dijagnostike hepatitisa C (HCV) u Klinici za infektivne bolesti (KZIB) u petogodišnjem razdoblju.

Metode: Od 2014. do 2018. godine testirano je 23524 seruma za HCV (HCV AgAb ili anti-HCV ELISA, BioRad), a potvrdno testiranje western blotom (WB, Fujirebio; Mikrogen) rađeno je iz 755 pozitivnih seruma. Molekularna dijagnostika rađena je iz 5946 uzoraka. Analizirali smo odrasle ispitanike s pozitivnim anti-HCV probirnim testom. HCV RNA kvantificirana je PCR-om u stvarnom vremenu (RealTime HCV RNA quantification assay). Genotipovi i subtipovi HCV-a određeni su metodom PCR-a i reverzne hibridizacije (INNO-LiPA HCV Genotyping). Prikazani su rezultati deskriptivne statistike.

Rezultati: Obradeno je 428 anti-HCV ELISA pozitivnih odraslih osoba (68.7% muškaraca, 31.3% žena, medijan dobi 43 godine, raspon 19-88 godina). Hepatitis C potvrđen je WB-om u 390, a 28 ispitanika imalo je graničan WB. Anti-HCV protutijela nisu potvrđena WB-om u 10 ispitanika. HCV RNA testirana je za 331 ispitanika. Pozitivnu viremiju imalo je 218. Medijan viremije iznosio je 456,024.5 IU/ml (raspon 78-43,041,938 IU RNA HCV/mL). HCV RNA nije detektirana u 87 ispitanika s pozitivnim, 16 s graničnim i 10 s negativnim HCV WB-om. Za 85 ispitanika s pozitivnim i 12 s graničnim HCV WB-om nema podataka o testiranju HCV RNA u KZIB. Genotipovi i/ili subtipovi HCV-a određeni su u 185 od 218 anti-HCV WB pozitivnih ispitanika kod kojih je viremija u serumu iznosila >1,000 IU/ml. Genotip 1 detektiran je u 97/185 (52,4%), dok je subtip 3a detektiran u 76/185 (41,1%) ispitanika.

Zaključak: Dijagnostika hepatitisa C temelji se na probirnom testiranju protutijela nakon čega treba odrediti viremiju (HCV RNA). Ako je HCV RNA negativna, potrebno je utvrditi značajnost anti-HCV metodom WB. Rezultati ukazuju na potrebu sistematičnijeg praćenja i određivanja viremije potencijalnih bolesnika kako bi mogli započeti liječenje, jer za 23.2% ispitanika s pozitivnim anti-HCV-om u KZIB viremija nije bila poznata.

Diagnosis of hepatitis C virus from 2014 to 2018 at the University Hospital for Infectious Diseases „Dr. Fran Mihaljević“ in Zagreb

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Objective: To analyze the results of HCV serological and molecular diagnostics at the University Hospital for Infectious Diseases (UHID) in a five-year period

Methods: From 2014 to 2018 sera from 23,524 patients were tested for HCV (HCV AgAb or anti-HCV ELISA, BioRad), and confirmatory testing was performed by Western blot (WB, Fujirebio; Microgen) in 755 positive sera. Molecular diagnostics was performed on 5946 samples. We analyzed adult patients with an anti-HCV positive screening test. HCV RNA was quantified by real-time PCR. HCV genotyping was performed by reverse hybridization (INNO-LiPA HCV Genotyping) method.

Results: A total of 428 anti-HCV ELISA positive adults were analysed (68.7% males, 31.3% females, median age 43 years, range 19-88 years). Hepatitis C was confirmed by WB in 390, while 28 patients had borderline WB results. Anti-HCV was not confirmed by WB in 10 patients. HCV RNA was tested in 331 patients and viremia was detected in 218. Median viremia was 456,024.5 IU/ml (range 78-43,041,938 IU RNA HCV/mL). HCV RNA was not detected in 87 patients with positive, 16 with borderline and 10 with negative HCV WB. There was no data on HCV RNA testing in the UHID for 85 patients with positive and 12 with borderline HCV WB. HCV genotypes/subtypes were determined in 185 of 218 anti-HCV WB positive patients with >1,000 IU/ml in serum. Genotype 1 was detected in 97/185 (52.4%), while subtype 3a was detected in 76/185 (41.1%) patients.

Conclusion: Diagnosis of hepatitis C is based on antibody screening, followed by determination of viremia. If HCV RNA is negative, the significance of anti-HCV by the WB method should be established. The results indicate the need for a more systematic monitoring and determination of viremia in potential patients in order to initiate treatment, because 23.2% of patients with positive anti-HCV in UHID had unknown viremia.

PO-47 Virološki relaps nakon liječenja bolesnice inficirane HCV-om genotipa 3a i mutacijom Y93H s glecaprevirom/pibrentasvirom

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Ciljevi: Rezistencija HCV-a na direktno djelujuće antivirusne lijekove (DAA) predstavlja potencijalno ograničenje efikasnosti antivirusnog liječenja, naročito mutacija Y93H koja se povezuje s klinički značajnom rezistencijom na prvu generaciju NS5A inhibitora. Cilj ovog istraživanja bio je razjasniti prvi slučaj bolesnice u Hrvatskoj inficirane HCV-om genotipa 3a i mutacijom Y93H koja nije postigla SVR12 nakon 8 tjedana liječenja s glecaprevirom/pibrentasvirom.

Metode: Rutinskom dijagnostičkom obradom bolesnice provedenom prilikom ulaska u kliničku skrb određeni su viremija i genotip virusa. Sekvenciranjem regije NS5A virusa Sangerovom metodom te analizom sekvenci u algoritmu Geno2Pheno detektirana je prisutnost Y93H mutacije.

Rezultati: Pedesetdevetogodišnja bolesnica inficirana je 1991. putem transfuzije krvi. Unatoč dugom trajanju infekcije, tranzijentnom elastografijom detektiran je nizak stadij fibroze jetre (F1, 7.4 kPa) bez značajnih komorbiditeta. Bolesnica nije prethodno bila liječena DAA te imala početnu viremiju 7,659,530 IU/ml HCV RNA. Liječenje je provedeno tijekom 8 tjedana pri čemu je uslijedio brzi pad viremije uz nedetektibilnu HCV RNA (<12 IU/ml) nakon završetka terapije. Međutim, unutar 12 tjedana nakon prestanka primjene DAA došlo je do virološkog relapsa te bolesnica nije postigla SVR12. Viremija 12 tjedana nakon završetka liječenja iznosila je 957,289 IU/ml HCV RNA. Analizom mutacija koje uzrokuju rezistenciju na NS5A inhibitore detektirana je dobro karakterizirana, s rezistencijom povezana supstitucija Y93H. Prema preporukama EASL 2018, započeto je liječenje bolesnice sofosbuvikom/velpatasvirom/voxilaprevirom.

Zaključak: Iako pibrentasvir pokazuje značajno poboljšanu učinkovitost u liječenju hepatitisa C u usporedbi s ostalim NS5A inhibitorima, nedavne publikacije pokazuju kako bi Y93H supstitucija mogla doprinijeti povećanju faktora rezistencije do <3 puta za ovaj DAA in vitro. Stoga je moguće kako je u ove bolesnice neuspjeh odgovora na terapiju djelomično povezan s prisutnošću mutacije Y93H.

Virologic relapse after treatment of a patient with HCV genotype 3a and Y93H mutation with glecaprevir/pibrentasvir

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Objectives: Resistance of HCV to direct acting antiviral drugs (DAA) represents a potential limitation to the effectiveness of antiviral treatment, especially mutation Y93H which is associated with clinically relevant resistance to first generation NS5A inhibitors. The aim of this study was to elucidate the first case of a patient in Croatia infected with HCV genotype 3a who failed to achieve SVR12 after 8 weeks of treatment with glecaprevir/pibrentasvir and had Y93H mutation.

Methods: Diagnostic and clinical workup of the patient was performed according to the standard of care. The presence of Y93H mutation was detected by Sanger sequencing of HCV NS5A region amplified from serum of the patient followed by mutational analysis with Geno2Pheno algorithm.

Results: A 59-year old woman was infected through blood transfusion in 1991. According to values obtained from transient elastography in 2018 the patient had minimal fibrosis (F1, 7.4 kPa) despite the long period of infection and no significant comorbidities. Prior to administration of DAA the patient had HCV RNA of 7,659,530 IU/ml and was treatment naive. Antiviral therapy with glecaprevir/pibrentasvir was administered for 8 weeks and resulted in rapid decline of viral RNA. The patient showed end of treatment response (HCV RNA<12 IU/ml). However, the patient relapsed within 12 weeks after DAA discontinuation and failed to achieve SVR12. HCV RNA at week 12 post-treatment was 957,289 IU/ml. NS5A resistance testing was performed and well-characterised, resistance-associated substitution Y93H was detected. According to EASL 2018 recommendations, retreatment of the patient with sofosbuvir/velpatasvir/voxilaprevir was initiated.

Conclusion: Even though pibrentasvir demonstrates improved anti-HCV activity compared to other NS5A inhibitors, recent publications have shown that Y93H substitution could conferr up to <3-fold resistance to this DAA in vitro. Therefore, it is possible that failure to achieve treatment response in this patients is, in part, associated with the presence of Y93H.

PO-48 Promjene stadija fibroze i steatoze u bolesnika s kroničnim hepatitisom C koji su liječeni direktno djelujućim antivirusnim lijekovima i postigli trajni virološki odgovor

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Cilj: Analizirati promjenu stadija fibroze i steatoze u bolesnika s kroničnim hepatitisom C (CHC) koji su postigli trajni virološki odgovor (SVR).

Metode: Stupanj fibroze (F1-F4) i steatoze jetre (S0-S3) primjenom parametra CAP (controlled attenuation parameter) određeni su metodom elastografije (FibroScan) prije započinjanja antivirusnog liječenja te nakon postizanja SVR-a (12 ili 24 tjedna nakon završetka terapije). Analizirane su demografske, laboratorijske i kliničke karakteristike bolesnika.

Rezultati: Od 205 bolesnika s CHC-om, 57.6% bili su muškarci (medijan dobi 53.3 godina, IQ 41.4- 58.7). Svi ispitanici uključeni u istraživanje postigli su SVR 12 i/ili 24 tjedna nakon završetka liječenja direktno djelujućim antivirusnim lijekovima. Subtip 1a detektiran je u 53(26.1%), 1b u 92 (45.3%), genotip 2 u 3 (1,4%), genotip 3 u 46 (22,7%) te genotip 4 u 6 (3%) ispitanika. Prije započinjanja antivirusnog liječenja stadij fibroze F1 dokazan je u 25% ispitanika, F2 u 26%, F3 u 8%, dok je 41% ispitanika imalo stadij F4 (median 9.25,IQR 7.1-18.0 kPa). Nakon antivirusnog liječenja, u grupi bolesnika s inicijalnim stadijem fibroze F4, stadij fibroze se smanjio u F1 kod 13%, u F2 kod 22% , u F3 kod 9%, dok je u 56% ispitanika stadij fibroze ostao nepromjenjen (F4). Prije započinjanja liječenja steatoza nije detektirana (S0) u 56% ispitanika, stadij S1 je imalo 21%, S2 7% i S3 16% bolesnika (median CAP 239, IQR 210-276 db/m). Nakon završetka liječenja 22.2% ispitanika s preterapijskim stadijem S3 nisu više imali steatozu (S0), u 22.2% bolesnika steatoza je regresirala u S1, u 11.1% u S2, dok je u 44.4% ispitanika vrijednost CAP ostala identična (S3). Nakon postizanja SVR-a vrijednosti jetrenih enzima AST i ALT bile su u granicama referentnih vrijednosti u 84.7%, odnosno 91.8% ispitanika.

Zaključak: Antivirusno liječenje i postizanje SVR-a povezani su sa smanjenjem stadija fibroze i steatoze te normalizacijom vrijednosti jetrenih enzima u dijela bolesnika s CHC-om.

Changes in the stage of fibrosis and steatosis in patients with chronic hepatitis C virus treated with direct-acting antiviral drugs who achieved sustained virological response

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Objective: To analyze changes in fibrosis and steatosis stages in patients with chronic hepatitis C (CHC) who achieved sustained virological response (SVR).

Methods: The stage of fibrosis (F1-F4) and liver steatosis (S0-S3) using CAP (controlled attenuation parameter) were determined by elastography (FibroScan) before antiviral treatment and after SVR. Demographic, laboratory and clinical characteristics of the patients were analyzed.

Results: A total of 205 patients with CHC, 57.6% were men (median age 53.3 years, IQ 41.4-58.7). All patients achieved SVR 12 and/or 24 weeks after the end of antiviral treatment. Subtype 1a was detected in 53 (26.1%), 1b in 92 (45.3%), genotype 2 in 3 (1.4%), genotype 3 in 46 (22.7%) and genotype 4 in 6 (3%) patients. Prior to treatment initiation, F1 fibrosis stage was determined in 25% of patients, F2 in 26%, F3 in 8%, while 41% of patients had F4 stage (median 9.25, IQR 7.1-18.0 kPa). After treatment, in patients with initial stage F4, the stage of fibrosis decreased to F1 in 13%, F2 in 22% and F3 in 9%, while in 56% of patients fibrosis stage remained unchanged (F4). Before treatment, steatosis was not detected (S0) in 56% of patients, stage S1 had 21%, S2 7% and S3 16% of patients (median CAP 239, IQR 210-276 db/m). After treatment, 22.2% of patients who had S3 pre-therapy no longer had steatosis (S0), in 22.2% of patients steatosis regressed to S1, in 11.1% to S2, while in 44.4% of patients the CAP value remained identical (S3). After achieving SVR, levels of liver enzymes AST and ALT were within the reference values for 84.7% and 91.8% of patients, respectively.

Conclusion: The use of antiviral drugs and achieving SVR is associated with a decrease in the fibrosis and steatosis stages and normalization of liver enzymes levels in some CHC patients.

PO-49 Stopa pozitivnih rezultata na HBsAg i anti-HCV među serumima pacijenata testiranim u Nastavnom zavodu za javno zdravstvo Splitsko – dalmatinske županije u razdoblju od tri godine

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Nastavni zavod za javno zdravstvo Splitsko – dalmatinske županije

Cilj: Virus hepatitis B (HBV) i hepatitis C (HCV) su globalno značajni patogeni kod kojih zloupotreba droga i seksualni promiskuitet čine glavne faktore rizika za prijenos. Budući da raspolažemo s vrlo malo podataka o prevalenciji hepatitisa B i C za Splitsko-dalmatinsku županiju, cilj ovoga istraživanja bio je utvrditi stopu pozitivnih rezultata među serumima testiranim na hepatitis viruse u Nastavnom zavodu za javno zdravstvo Splitsko-dalmatinske županije.

Metode: Tijekom razdoblja od tri godine (od 1. siječnja 2016. do 31. prosinca 2018.) rutinski smo testirali 4402 pacijenta na HBsAg i 4345 na anti-HCV, kao markere hepatitis B i hepatitis C infekcije. Hepatitis B površinski antigen (HBsAg) za HBV i anti-HCV protutijelo za HCV u serumima analizirani su komercijalno dostupnim enzimskim imunološkim testovima HBsAg ULTRA (Dia.Pro, Italy) i HCV Ab (Dia.Pro, Italy).

Rezultati: Od ukupnog broja od 4402 testirana seruma na HBV, 45 (1,0%) ih je bilo pozitivno na HBsAg, s više pozitivnih rezultata u dobnoj skupini iznad 30 godina, 1,3% (40/3168) u odnosu na 0,4% (5/1234) u dobnoj skupini ispod 30 godina. Kod HCV-a, od ukupnog broja od 4345 testiranih seruma, 200 (4,6%) ih je bilo pozitivno na anti-HCV (200/4345) sa značajno višom stopom pozitivnih među starijima od 30 godina, 5,9% (184/3110) u odnosu na 1,3% (16/1235) među mlađima od 30 godina. Utvrđena je statistički značajna razlika u stopama pozitivnih rezultata, kako za HBV tako i za HCV, između testiranih koji su upućeni kao pacijenti i onih koji su testirani u sklopu anonimnog programa.

Zaključci: Podatci testiranja u Nastavnom zavodu za javno zdravstvo ukazuju na višu stopu pozitivnih rezultata za hepatitis C u odnosu na udio pozitivnih rezultata u testiranih na hepatitis B. Također, za oba virusa, uočena je viša stopa pozitivnih rezultata među testiranim pacijentima koji pripadaju dobnoj skupini iznad 30 godina.

Rate of positive HBsAg and anti-HCV among patient sera tested at the Public Health Institute of Split and Dalmatia County in a three-year period

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Aim: Hepatitis B virus (HBV) and hepatitis C virus (HCV) are globally significant pathogens with drug abuse and sexual promiscuity being major risk factors for transmission. Since we have a lack of data for hepatitis B and C prevalence in Split and Dalmatia County, the aim of this study was to determine rate of positive hepatitis results among sera tested at the Public Health Institute of Split and Dalmatia County.

Methods: During a three-year period (January 1, 2016 to December 31, 2018) we routinely tested 4402 patients for HBsAg and 4345 for anti-HCV, as markers of hepatitis B and C virus infection.

Hepatitis B surface antigen (HBsAg) for HBV and anti-HCV antibody for HCV in the sera were analyzed using commercially available enzyme immunoassays HBsAg ULTRA (Dia.Pro, Italy) and HCV Ab (Dia.Pro, Italy).

Results: Out of the total number of 4402 tested sera for HBV, 45 (1,0%) of them were positive to HBsAg, with higher rate in group above 30 years, 1,3 % (40/3168) compared to 0,4 % (5/1234) in younger than 30 years. For HCV, out of the total number of 4345 tested sera, 200 (4,6%) of them were positive to anti-HCV (200/4345), with significantly higher rate in group older than 30 years, 5,9 % (184/3110) compared to 1,3 % (16/1235) in younger than 30 years. Statistically significant difference was found in the rate of positive results for HBV and for HCV among those referred for testing as patients or who were tested as part of an anonymous program.

Conclusions: Data from the Public Health Institute indicates a higher rate of hepatitis C positive results than those tested for hepatitis B. Also, the data indicates a higher rate of positive results in the group of tested patients older than 30 years, for both hepatitis B and hepatitis C virus.

PO-50 Uloga programa u zajednici u postizanju eliminacije hepatitisa

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Infekcija hepatitis C virusom (HCV) je vrlo važan javnozdravstveni problem, kako u Splitsko-dalmatinskoj županiji (SDŽ), tako i u Hrvatskoj. Zbog tihog kliničkog tijeka većina bolesnika s hepatitisom C uopće ne zna da su zaraženi pa stoga ne budu na vrijeme prepoznati i liječeni, te predstavljaju izvor infekcije za druge ljude. Nacionalna strategija za kontrolu virusnih hepatitisa, uz ostalo, uključuje edukaciju liječnika primarne zdravstvene zaštite o HCV infekciji, ali isto tako potiče povećanje aktivnosti u pronalaženju novih bolesnika u tzv. „screening“ programima. Od 1993.-2015. godine u SDŽ prijavljeno je 1434 osobe s HCV infekcijom. Budući da je procjena da u SDŽ ima barem još 3000 osoba sa HCV infekcijom koje nisu prijavljene, poduzet je aktivniji pristup u pronalaženju ovih bolesnika. Sastavljen je tim koji se sastoji od različitih zdravstvenih i nezdravstvenih djelatnika radnika, te je poduzet niz aktivnosti koje su usmjerene prema skupinama s višom incidencijom HCV infekcije. Unutar terapijskih zajednica za prevenciju i liječenje bolesti ovisnosti proveden je „screening“ HCV infekcije, a fibroelastografijom su otkrivene ugroženije skupine bolesnika, koje su po ubrzanijem postupku pripremljene za liječenje. Slične aktivnosti poduzete su i u udrugama veterana domovinskog rata, u kojima su testirani branitelji koji u anamnezi imaju podatke o ranjavanju, operacijama i primanju krvi i krvnih pripravaka do 1993. godine. Kao rezultat ovih aktivnosti od 2015. godine povećan je broj novootkrivenih HCV infekcija u stanovnika SDŽ, te je mnogima skraćen put do liječenja. Već spomenuti tim je kroz zadnje četiri godine imao 36 izlazaka na teren tijekom kojih su testirane 652 osobe oralnim brzim testom na C virus i napravljena im je fibroelastografija kojim je utvrđen stupanj oštećenja jetrenog parenhima. Iste aktivnosti planiraju se provesti i u lokalnoj navijačkoj udruzi te u zatvorima u SDŽ među osobama lišenim slobode.

The role of outreach programs in achieving goals for the elimination for hepatitis

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The HCV infection is a serious public health problem, both in Split Dalmatia County (SDC), and in Croatia. Due to a rather silent course of disease, most patients with hepatitis C don't even know they have been infected. Therefore they are neither recognized nor treated on time, and are a source of infection for other people. From 1993 to 2015, there were 1,434 reported cases of HCV infection in SDC. Since it is estimated that there are at least 3,000 persons with HCV infection in the SDC who are not registered, a more active approach in indentifying these patients has been initiated. A multidisciplinary team has been established to initiate a number of activities aimed at groups with higher incidence of HCV. Screening for HCV infection was implemented within the therapeutic communities for the prevention and treatment of addiction. Using fibroelastography high-risk patient groups were identified. These patients were enrolled into an urgent treatment program. Similar activities have been taken within the war veterans associations for those that were wounded, had a surgery or received blood transfusion until 1993. As a result of these activities, the number of newly diagnosed HCV infections in the population of SDC has increased since 2015, and many have received their therapy faster. The aforementioned team has had thirty-six field trips over the last four years, during which time 652 people were tested by oral rapid C virus test and fibroelastography was performed to determine the extent of liver parenchyma damage. The same activities are planned in the local fan club associations, as well as in SDC prisons.

PO-51 Etiologija i ishod bakterijskih infekcija u bolesnika sa kroničnom jetrenom bolesti

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Ciljevi: proučiti etiologiju, kliničke manifestacije i tok bakterijskih infekcija te identificirati naznake mortaliteta kod bolesnika sa kroničnom jetrenom bolesti (KJB).

Materijali/metode: retrospektivna, kohortna studija s uzorkom od 86 bolesnika sa od ranije poznatom i/ili novootkrivenom KJB te bakterijskom infekcijom provedena u KZIB «Dr. Fran Mihaljević» tokom 2011.-2015.

Rezultati: najčešći klinički sindrom bila je primarna bakterijemija bez poznatog ishodišta. Uzročnik je izoliran u 70 bolesnika (Gram pozitivni koki u 31, Gram negativni bacili u 39 bolesnika). Child Pugh score kod primitka bio je 9, MELD-Na 18 i CLIF-C AD score 60.9. Do komplikacija je došlo u 62.2% bolesnika. 33.7% bolesnika liječeno je u JIL-u. Mortalitet tokom hospitalizacije bio je 28.5%.

Zaključak: 54.7% bolesnika, KJB je prvi put dijagnosticirana tokom liječenja bakterijske infekcije. U ovih bolesnika stopa mortaliteta je 27% viša nego u bolesnika bez KJB.

Etiology and outcome of bacterial infections in patients with chronic liver disease

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Goals: to evaluate the etiology, clinical manifestations and course of bacterial infections, to identify signs of mortality in patients with chronic liver disease (CLD).

Materials/methods: a retrospective, cohort study with a sample of 86 patients with previously known and/or newly diagnosed CLD and bacterial infection performed in UHID "Dr. Fran Mihaljević" during 2011.-2015.

Results: the most common clinical syndrome was primary bacteraemia of unknown origin. The causative agent was isolated in 70 patients (Gram positive cocci in 31, Gram negative bacilli in 39 patients). Child Pugh score at admission was 9, MELD-on 18 and CLIF-C AD score 60.9. Complications occurred in 62.2% of patients. 33.7% were treated in the ICU. Mortality during hospitalization was 28.5%.

Conclusion: 54.7% of patients, CLD was first diagnosed during treatment of bacterial infection. In these patients the rate of mortality is 27% higher than those without CLD.

PO-52 Teška pneumonija uzrokovana humanim bokavirusom u imunokompetentnog djeteta – prikaz slučaja

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UVOD: Humani bokavirus (hBoV) otkriven je 2005. godine u djece s respiratornom infekcijom, a dosad su opisana četiri genotipa. HBoV1 se najčešće izolira u uzorcima respiratornog, a hBoV2-4 u uzorcima probavnog sustava. Specifična protutijela na hBoV prisutna su u 64 do 95% odraslih što upućuje na učestale susrete s tim virusom. HBoV je opisan kao uzročnik pneumonije, bronhiolitisa, bronhitisa i infekcija gornjeg dišnog sustava.

PRIKAZ SLUČAJA: Imunokompetentna djevojčica u dobi 17 mjeseci hospitalizirana je drugog dana bolesti koja se prezentirala febrilitetom, kašljem i otežanim disanjem. Pri primitku djevojčica je bila subfebrilna, tahikardna i tahidispnoična. Na rendgenogramu srca i pluća opisani su manji peribronhalni infiltrati, nekoliko pločastih atelektaza i hiperinflacija plućnog parenhima. U laboratorijskim nalazima bila je prisutna leukocitoza ($22.1 \times 10^9/L$) s neutrofilijom (79%), a najviša vrijednost C-reaktivnog proteina iznosila je 7.1 mg/L. Zbog respiratorne insuficijencije provedena je mehanička ventilacija tijekom 7 dana. Liječena je ceftriaksonom, azitromicinom, oseltamivirom, ribavirinom te opsežnom simptomatskom terapijom – inhalacije salbutamola, ipratropij bromida, parenteralna primjena metilprednizolona, itd. Lančanom reakcijom polimeraze (PCR) na 15 respiratornih virusa u aspiratu traheje detektirana je prisutnost humanog bokavirusa. Broj kopija hBoV po mililitru u aspiratu traheje iznosio je 1.86×10^6 , a u krvi 1.47×10^2 . Opsežnom mikrobiološkom obradom nije dokazan drugi uzročnik. S obzirom na trajanje febriliteta i refrakterni bronhospazam u terapiju su tijekom dva dana uvedeni intravenski imunoglobulini (6,5 ml/kg/dan) obogaćeni IgM protutijelima (Pentaglobin®). Na provedeno liječenje došlo je do poboljšanja respiratorne funkcije te je ekstubirana uz potpuni oporavak.

ZAKLJUČAK: Infekcija dišnih putova uzrokovana hBoV-om obično je blaga i samoograničavajuća, ali može uzrokovati i tešku infekciju u imunokompetentnog, prethodno zdravog djeteta s razvojem akutne respiratorne insuficijencije. Specifično antimikrobno liječenje zasad ne postoji, a terapija intravenskim imunoglobulinima obogaćenim IgM protutijelima mogla bi imati povoljan učinak.

Severe Pneumonia Caused by Human Bocavirus in an Immunocompetent Child – a Case Report

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INTRODUCTION: Human bocavirus (hBoV) was discovered in 2005 in children with respiratory infection and four genotypes have been described so far. HBoV1 is mostly detected in respiratory samples while hBoV2-4 in stool of patients with gastroenteritis. Specific antibodies against hBoV are present in 64 to 95% of adults which indicates frequent encounters with hBoV. HBoV causes pneumonia, bronchiolitis, bronchitis and upper respiratory tract infections.

CASE REPORT: An immunocompetent 17-month-old girl was admitted to our hospital during the second day of a febrile illness with symptoms of cough, breathing difficulties and lack of appetite. On admission she was subfebrile, tachycardic and tachypneic. Chest X-ray showed minor peribronchial infiltrates, several plate-like atelectasis and hyperinflation of the pulmonary parenchyma. Laboratory results showed leukocytosis ($22.1 \times 10^9/L$) with neutrophilia (79%) and the highest level of C-reactive protein was 7.1 mg/L. Mechanical ventilation was performed during 7 days due to respiratory failure. She was treated with ceftriaxone, azithromycin, oseltamivir, ribavirin and extensive symptomatic therapy – nebulization with salbutamol, ipratropium bromide, venous methylprednisolone, etc. Multiplex PCR testing for 15 different respiratory viruses detected hBoV DNA in tracheal aspirate. HBoV viral load was 1.86×10^6 copies/ml in tracheal aspirate and 1.47×10^2 copies/ml in blood. Extensive testing for wide variety of respiratory pathogens detected no other causative agent. Considering the duration of fever and refractory bronchospasm IgM-enriched intravenous immunoglobulins (Pentaglobin®) were applied during two consecutive days (6.5 ml/kg/day). Respiratory function improved and the girl was extubated with full recovery.

CONCLUSION: HBoV respiratory infection is usually mild and self-limiting but can also lead to the acute respiratory insufficiency in a previously healthy, immunocompetent child. Specific treatment is not available, but IgM-enriched immunoglobulins could have a favourable effect.

PO-53 Bolničke infekcije uzrokovane virusom influence u dječjoj bolnici

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Uvod/ciljevi: Respiratorni virusi mogu uzrokovati bolničke infekcije na pedijatrijskim odjelima. Respiratorni sincicijski virus i virus influence najčešći su i najznačajniji uzročnici ovih infekcija u djece.

Cilj ovog rada bio je odrediti epidemiološke karakteristike bolničkih infekcija uzrokovanih virusom influence u Klinici za dječje bolesti Zagreb tijekom zimske sezone 2018/2019.

Metode: Za detekciju virusa influence u uzorcima nazofaringealnog brisa ili aspirata korišten je multianalitički point-of-care test detekcije antigena (mariPOC®, ArcDia International, Turku, Finland) ili molekularna metoda. Podaci su prikupljeni iz medicinske dokumentacije.

Rezultati: Od ukupno 157 hospitaliziranih bolesnika kod koji je detektiran virus influence, 12% (19/157) infekciju je akviriralo tijekom boravka u bolnici. Većina pacijenata (84%) u anamnezi ima neku priležću kroničnu bolest. Ni jedan bolesnik nije bio cjepljen protiv gripe. Medijan dobi bio je 4,4 godine, a gripa stečena u bolnici češće je detektirana u djece muškog spola (63%). Prosječno trajanje boravka u bolnici prije stjecanja infekcije bilo je 37,7 dana (raspon od 3 do 313 dana). U 68% (13/19) pacijenata primijenjena je specifična antivirusna terapija oseltamivirom. Jedno muško dojenče razvilo je pneumoniju kao komplikaciju gripe. Većina infekcija (63%) detektirana je u pacijenata hospitaliziranih na pedijatrijskim odjelima onkologije, neurologije i gastroenterologije. Virus influence tip A bio je uzročnik svih bolničkih gripa.

Zaključak: Djeca s priležćim kroničnim bolestima hospitalizirana na pedijatrijskim odjelima kroz dulji period pod posebnim su rizikom za razvoj bolničke infekcije virusom influence tijekom zimske sezone. To treba uzeti u obzir prilikom planiranja mjera kontrole bolničkih infekcija.

Hospital-acquired influenza infections in children's hospital

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Background/aim: Respiratory viruses often cause hospital-acquired infections in pediatric wards. Respiratory syncytial virus and influenza viruses are the most frequent and important cause of those infections in children. The aim of this study was to determine epidemiological characteristics of hospital-acquired influenza infections in Children's hospital Zagreb during 2018/19 winter season.

Methods: Influenza virus was detected from nasopharyngeal aspirates/swabs using multianalyte point-of-care antigen detection test system (mariPOC®, ArcDia International, Turku, Finland) or molecular diagnostics. Analyzed data were collected from the medical documentation.

Results: Out of 157 hospitalized patients with detected influenza virus, 12% (19/157) acquired the infection during the hospital stay. Most (84%) had an underlying chronic medical disorder. None was vaccinated against influenza. The median age was 4,41 years. The infection was detected more often in male sex (63%). The average length of hospital stay prior the infection was 37,7 days (range of 3 to 313 days). Specific antiviral therapy (oseltamivir) was used in 68% (13/19) of patients. One male infant (5%) developed pneumonia as complication. Most of infections (63%) were detected in pediatric departments of oncology, neurology and gastroenterology. Influenza A virus caused all nosocomial infections.

Conclusion: During influenza season, children with underlying medical disorders hospitalized in paediatric departments for longer period are at risk of acquiring influenza nosocomial infection. This should be considered while planning hospital infection control measures.

PO-54 Epidemije uzrokovane respiratornim sincicijskim virusom u Hrvatskoj 2016.-2018.

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Respiratorni sincicijski virus (RSV) najznačajniji je virusni uzročnik teških oblika infekcija dišnog sustava (IDS) u djece i dojenčadi te u vrhuncu sezone infekcija dišnog sustava može biti dokazan kao uzročnik u 70-80% slučajeva infekcija donjih dijelova dišnog sustava (IDDS). Ove infekcije se pojavljuju sezonski svake godine te obično traju od četiri do šest mjeseci. Prethodna epidemiološka istraživanja u Hrvatskoj utvrdila su da se ove infekcije javljaju u dvogodišnjim ciklusima. Cilj ove studije je utvrđivanje epidemioloških značajki i težine kliničkih obilježja RSV infekcija u Hrvatskoj od 2016. do 2018. godine.

Uzorci iz dišnog sustava uzeti su od djece sa simptomima akutnog IDS-a i testirani na RSV, adenovirus, viruse parainfluence i humani metapneumovirus. Za detekciju su korištena monoklonalna protutijela protiv specifičnog virusnog antigena metodom izravne imunofluorescencije.

Ukupno je analizirano 5674 uzoraka. Prevalencija RSV-a, za svaku godinu, bila je identična, 18,7%. Počeci i vrhunci RSV epidemija tijekom promatranih godina nisu bili značajno varirali, za razliku od završetaka ovih epidemija. Tako su počeci RSV epidemija bili u prosincu 2016. i 2017. (49. i 52. tjedan), vrhunci u veljači (7. i 8. tjedan), a završeci u ožujku 2016. (12. tjedan), travnju 2017. (14. tjedan) i svibnju 2018. (18. tjedan). Nije bilo značajne razlike u broju oboljelih dječaka i djevojčica ($p > 0,05$). Najveći broj oboljelih bila je dojenčad u dobi 0-5 mjeseci (32,8%, 42,7% i 49,6% godišnje). Najčešća klinička prezentacija u dojenčadi bio je bronhiolitis (50,3%, 68,5% i 58,9%). RSV je uzrokovao IDDS u 58,9%, 64,6% odnosno 58,9% slučajeva.

Budući da RSV infekcije nisu na listi zaraznih bolesti koje se obavezno prijavljuju, ovi rezultati doprinose boljem uvidu u opterećenje akutnim IDS-ovima te mogu pomoći u planiranju mjera kontrole RSV infekcija i s IDS-om povezane primjene antibiotika. Stoga se preporuča kontinuirano praćenje RSV infekcija kako bi se na vrijeme prepoznalo razdoblje visokog rizika za pojavu ovih infekcija.

Respiratory syncytial virus outbreaks in Croatia 2016-2018

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Respiratory syncytial virus (RSV) is the most important viral agent causing severe respiratory infections (RI) in infants and small children and during high season may cause 70-80% of lower respiratory tract infections. RSV infections occur seasonally every year and last from four to six months. Previous investigations of the epidemiology of RSV infections in Croatia found that RSV outbreaks occurred in biennial cycle. The aim of this study is to analyze the epidemiology and severity of RSV infections in Croatia during 2016–2018.

Respiratory tract specimens collected from children with symptoms of acute RI were tested for RSV, adenovirus, parainfluenza viruses, and human metapneumovirus. Detection was carried out using detection of viral antigen with monoclonal antibodies (direct immunofluorescence assay).

A total of 5674 specimens were analyzed and RSV prevalence rates for each studied year were identical 18.7%. Onset and peak did not vary from year to year, while the offsets of the epidemics were slightly different. RSV epidemics started in December 2016 and 2017 (week 49 and 52, respectively), peaked in February (week 8, 7 and 8, respectively) and ended in March 2016 (week 12), April 2017 (week 14) and May 2018 (week 18), respectively. The ratio of males to females did not varied significantly ($p>0.05$). RSV infections were the most prevalent among infants up to 5 months of age (32.8%, 46.7%, and 49.6% respectively). The most common clinical presentation in infants was bronchiolitis (50.3%, 68.5% and 65.0%, respectively). RSV caused lower respiratory tract infections in 58.9%, 64.6% and 58.9%, respectively.

Since RSV is not notifiable disease, our results contribute to better insight into burden of ARI and may help planning the measures to control RSV infections and antibiotics use. Therefore, RSV activity has to be monitored every year to detect high risk period of the infection.

PO-55 Molekularna detekcija respiratornih virusa u djece hospitalizirane zbog akutnog bronhiolitisa

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Uvod: Akutni bronhiolitis je klinički sindrom izazvan virusnom infekcijom donjih dišnih puteva u male djece, a karakterizira ga kašalj, tahipneja, produženi ekspirij praćen karakterističnim zvižducima (eng. wheezing) i hiperinflacijom plućnog parenhima.

Metode: U sklopu projekta HRZZ „Novi i zapostavljeni virusni uzročnici infekcija dišnog sustava u vulnerabilnim skupinama bolesnika“ u razdoblju od svibnja 2017. do svibnja 2019. obrađeno je 460 djece hospitalizirane u Klinici za dječje bolesti Zagreb zbog akutne respiratorne infekcije sa sumnjom na virusnu etiologiju. Klinički uzorci (obrisi nazofarinksa i ždrijela) testirani su metodom multipleks-PCR na prisutnost 15 respiratornih virusa te su prikupljeni klinički podaci.

Rezultati: Od 460 testiranih bolesnika, u njih 39 je bila utvrđena dijagnoza akutnog bronhiolitisa (21 dječak, 18 djevojčica). Svi oboljeli od bronhiolitisa su bili u dobi mlađoj od jedne godine (medijan 2,5 mjeseci). Virusna etiologija potvrđena je u 37 slučajeva (94,9%). Najčešće detektirani virus je bio respiratorni sincicijski virus (RSV), koji je detektiran u 22 u bolesnika (56,4%), dok je drugi po učestalosti bio humani rinovirus (HRV), dokazan u 16 bolesnika, od čega u 50% slučajeva u monoinfekciji. U jednom slučaju je dokazan virus parainfluence tip 3 kao jedini uzročnik, dok su adenovirus, humani metapneumovirus, koronavirusi i virus influence detektirani u koinfekciji s drugim virusima. Najveći broj oboljelih od RSV bronhiolitisa u 2018. godini je bio u veljači, a u 2019. u siječnju. Bronhiolitisi uzrokovani rinovirusima javljali su se tijekom cijele godine, a ne samo u sezoni tipičnoj za respiratorne virusne infekcije.

Zaključak: Rezultati ovog istraživanja pokazuju da su, osim RSV-a, značajni uzročnici bronhiolitisa i rinovirusi, što treba uzeti u obzir prilikom odabira viroloških testova, osobito u slučaju pojave bronhiolitisa izvan sezone RSV-a.

Molecular detection of respiratory viruses in children hospitalized with acute bronchiolitis

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Introduction: Acute bronchiolitis is clinical syndrome caused by viral infection of lower respiratory tract in small children, characterized by cough, tachypnea, prolonged expiration with wheezing and hyperinflation of lungs.

Methods: From May 2017 to May 2019 nasopharyngeal and pharyngeal swabs from a total of 460 children with ARI of suspected viral etiology from Children's Hospital Zagreb were obtained and tested by multiplex-PCR for the presence of 15 respiratory viruses and clinical data were collected. This work was supported by Croatian Science Foundation under the project titled “New and neglected respiratory viruses in vulnerable groups of patients”.

Results: From 460 tested patients, in 39 acute bronchiolitis was diagnosed (21 boy, 18 girls). All were younger than one year old (median 2,5 months). Viral etiology was proven in 37 cases (94,9 %). Most detected virus was respiratory syncytial virus (RSV), which was detected in 22 patients (56,4 %), second most detected was human rhinovirus (HRV), proved at 16 patients, 50% in monodetection. In one case parainfluenza 3 virus was proven as the only virus, while adenovirus, human metapneumovirus, coronaviruses and influenza were detected in combination with other viruses.

Peak of RSV bronchiolitis in 2018 was in February and in 2019 in January. Cases caused by rhinoviruses appeared all year round, not only during usual season of respiratory infections.

Conclusion: Results of this study show that, beside RSV, rhinoviruses are common cause of bronchiolitis, what is important data when thinking of viral diagnostic test, especially in case of bronchiolitis outside RSV season.

PO-56 Obilježja cijelog genoma reasortanta genotipa G3P[8] rotavirusa A sličnih konjskim sojevima u hospitalizirane djece u Hrvatskoj

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Infekcije rotavirusima su vodeći uzrok akutnog gastroenteritisa u ljudi i životinja. Rotavirusi se dijele u devet vrsta (rod Rotavirus, porodica Reoviridae), a vrsta rotavirus A (RVA) ima najveći utjecaj na ljudsko zdravlje, posebno kod djece do pet godina starosti. Klasifikacija RVA je temeljena na određivanju genotipa barem dva genomski segmenta (VP7 i VP4) ili genotipske konstelacije cijelog genoma. S obzirom na segmentiranost RVA genoma i nerijetku pojavu koinfekcija s različitim RVA sojevima, novi emergentni sojevi, a među njima i humano-animalni reasortanti, mogu se pojaviti uslijed genomskog preslagivanja. U okviru istraživanja molekularne epidemiologije i zoonotskog potencijala RVA u ekosustavu Republike Hrvatske, pretražili smo 188 uzoraka stolice hospitaliziranih pacijenata (većinom djece do pet godina starosti) inficiranih rotavirusom A podrijetlom iz bolničkih centara u Zagrebu, Splitu i Osijeku u svrhu određivanja genetičkih obilježja cirkulirajućih sojeva. Korištenjem "semi-nested" multipleks PCR protokola u kombinaciji sa Sanger sekvenciranjem i filogenetičkom analizom, RVA genotipska kombinacija G3P[8] je utvrđena kao prevladavajuća u pedijatrijskoj populaciji. U oko 50% uzoraka u kojih je dokazana prisutnost genotipa G3, rezultati ukazuju na infekciju reasortantom G3 soja sličnim konjskim sojevima RVA. Primjenom sekvenciranja nove generacije (NGS) utvrdili smo cijeli genom ovog atipičnog soja (N= 3) dokazanog u Hrvatskoj po prvi puta. Rezultati otkrivaju VP7 genomski segment podrijetlom od konjskih RVA sojeva u kombinaciji s tipičnom humanom DS-1-like genotipskom konstelacijom genoma i visoku sličnost sa sojevima istog genotipa dokazanim u Europi. Nadzor i genetska karakterizacija sojeva RVA koji cirkuliraju u populaciji pedijatrijskih pacijenata će se nastaviti i u narednim godinama kako bi se utvrdila geografska i sezonska dinamika ovih emergentnih i moguće pandemijskih, konjskim sojevima sličnih, reasortanata genotipa G3.

Whole genome characterization of an equine-like Rotavirus A reassortant G3P[8] strain in hospitalized children in Croatia

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Rotavirus infections are a leading cause of acute gastroenteritis in humans and animals. Rotaviruses are divided into nine species (genus Rotavirus, family Reoviridae) among which Rotavirus A (RVA) has the greatest impact on human health, targeting mostly children under the age of five years. RVA classification is based on genotype determination of at least two genome segments (VP7 and VP4) or a genotype constellation of the whole genome. Since the genome of RVA is segmented and coinfections with different RVA strains are not rare, new strains can emerge through the genome reassortment; human-animal reassortants as well. As a part of a research on molecular epidemiology and zoonotic potential of RVA in Croatian ecosystem, herein we screened 188 stool specimens of hospitalised patients (mostly children under the age of five years) infected with RVA from Zagreb, Split and Osijek hospitals in order to genetically characterise the strains circulating in Croatia. Using semi-nested multiplex PCR in combination with Sanger sequencing and phylogenetic analysis, genotype combination G3P[8] was identified as the most common one circulating among paediatric population. Around 50% of the present G3 positive samples were intergenogroup reassortants with equine-like G3 genotype. The whole genome of this atypical strain (N= 3), detected in Croatia for the first time, was obtained by the next generation sequencing revealing VP7 genome segment of equine origin in combination with a typical human DS1-like genome constellation and high genetic resemblance with strains of the same genotype detected in Europe. Monitoring and genetic characterization of RVAs circulating in paediatric patients in Croatia will be continued in the following years in order to determine geographic and seasonal dynamics of this emerging and potentially pandemic equine-like G3 reassortant strain.

PO-57 Ortohantavirusna infekcija potiče diferencijaciju i polarizaciju primarnih ljudskih monocita u makrofage

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Uvod i cilj: Ortohantavirusi (HTV) su RNA virusi s ovojnicom, koji pripadaju rodu *Orthohantavirus*, obitelji *Hantaviridae*. Puumala ortohantavirus (PUUV) je patogeni virus uzrokujući blage do umjerene oblike hemoragijske groznice s bubrežnim sindromom (HVBS) u Euroaziji, akutne virusne bolesti. Tula ortohantavirus (TULV) se smatra apatogenim zbog ograničenih dokaza patogeneze kod ljudi. U Hrvatskoj je HVBS endemska bolest od velikog značaja za javno zdravlje. Epidemije se javljaju svakih nekoliko godina u kontinentalnom dijelu zemlje. Monociti, makrofagi i dendritičke stanice (DC), kao urođene stanice imunološkog sustava, su ciljne stanice za HTV koje potencijalno doprinose širenju virusa u tijelu i razvoju bolesti. Smatra se da citokini igraju ulogu u imunopatogenezi HBVS-a i mogu različito djelovati na kliničku sliku. Mehanizmi koji dovode do razvoja HVBS-a još uvijek su slabo razumljivi i malo se zna o imunološkom odgovoru domaćina na infekciju ortohantavirusom. Cilj ove *in vitro* studije bio je analizirati dinamiku ekspresije odabranih površinskih staničnih molekula na monocitima zaraženim s PUUV ili TULV, kao i sekreciju odabranih citokina i kemokina, kako bi se istražilo pokreće li HTV infekcija diferencijaciju i polarizaciju monocita.

Metode: Primarni ljudski monociti bili su *in vitro* inficirani s PUUV ili TULV te kultivirani sedam dana nakon infekcije. Imunofenotipizacija je napravljena u tri vremenske točke pomoću kreiranog polikromatskog panela antitijela specifičnih za površinske molekule na monocitima, makrofagima i DC. Razina ekspresije 21 citokina/kemokina u supernatantima određena je multiplex imunotestom s magnetskim kuglicama u šest vremenskih točaka.

Rezultati: Utvrđene su razlike između inficiranih i neinficiranih stanica u razinama ekspresije površinskih molekula te koncentraciji nekih citokina i kemokina u supernatantima (TNF-a, IL-1RA, IL-6, CCL2, CCL22, CD206). Ustanovljene su i razlike između infekcija s patogenim i apatogenim HTV-om (CXCL10, CD206).

Zaključak: Naši rezultati pokazuju kako HTV infekcija potiče ranu proupalnu aktivaciju primarnih ljudskih monocita, a produljena infekcija potiče diferencijaciju primarnih ljudskih monocita prema makrofagima.

Orthohantavirus infection triggers differentiation and subsequent polarization of human blood monocytes into macrophages

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Introduction and objective: Orthohantaviruses (HTV) are enveloped RNA viruses, belonging to genus *Orthohantavirus*. Puumala orthohantavirus (PUUV) is pathogenic causing mild to moderate forms of hemorrhagic fever with renal syndrome (HFRS), an acute viral disease. Tula orthohantavirus (TULV) is considered apathogenic due to limited evidence of pathogenesis in humans. In Croatia, HFRS is endemic rodent-borne disease with outbreaks occurring every few years. Monocytes, macrophages and dendritic cells (DC), as innate immune system cells, are target cells for HTV potentially contributing to virus dissemination and disease development. Cytokines are considered to play role in HFRS immunopathogenesis and possibly may drive different influence on clinical picture. The mechanisms which lead to HFRS development are still very poorly understood and little is known about the host immune response to the HTV infection. The aim of this *in vitro* study was to analyze the expression dynamics of selected cell surface molecules on monocytes infected with PUUV or TULV, as well as the secretion patterns of selected cytokines and chemokines, in order to investigate whether HTV infection triggers differentiation and polarization of monocytes.

Methods: Primary human monocytes were infected *in vitro* with PUUV or TULV and cultured for seven days post infection. Immunophenotyping was done in three time points using in-house created polychromatic panel with antibodies specific for cell surface molecules on monocytes, macrophages and DC. Expression levels of 21 cytokines/chemokines in supernatants in six time points were determined by magnetic beads multiplex immunoassays.

Results: Differences have been identified between infected and uninfected cells in cell surface molecules expression levels and concentrations of some cytokines and chemokines (TNF- α , IL-1RA, IL-6, CCL2, CCL22, CD206). Differences were also found between infections with pathogenic and apathogenic HTV (CXCL10, CD206).

Conclusion: Our findings indicate that HTV infection triggers early pro-inflammatory response of primary human monocytes. Prolonged infection further induces differentiation of primary human monocytes into macrophages.

PO-58 Osvrt na epidemiju hemoragijske groznice s bubrežnim sindromom u OB Karlovac u 2019. godini

Lorena Đapo, Luka Jerković

Opća bolnica Karlovac, Karlovac, Hrvatska

Ciljevi: Cilj našeg postera je analiza epidemije hemoragijske groznice s bubrežnim sindromom (HGBS) u 2019. godini i detaljni prikaz ambulantno i hospitalno liječenih bolesnika u Općoj bolnici Karlovac.

Metode: Prikupljani su podaci iz bolničkog informatičkog sustava (BIS) o hospitaliziranim i ambulantno liječenim bolesnicima s dijagnozom HGBS u Općoj bolnici Karlovac od 01.01.2019. do 31.07.2019. godine.

Rezultat: Većina naših bolesnika bila je iz područja endemskih žarišta bolesti. Bolest se u 75% slučajeva javljala u muškaraca, sa rasponom dobi od 19 do 62 godine. Epidemija HGBS je započela u siječnju, a vrhunac joj je bio u svibnju. Najčešći klinički simptomi bili su vrućica, mialgije, lumbalni bolovi, zimica, glavobolja, tresavica i gubitak apetita. U kliničkom statusu uočena je hepatomegalija, injekcija konjunktiva, hipotenzija, tahikardija, splenomegalija, crvenilo lica i vrata te vrlo rijetko petehijalni osip ili enantem sluznice usne šupljine. Od laboratorijskih nalaza kod dolaska je bila prisutna trombocitopenija i povišene vrijednosti CRP-a kod skoro svih bolesnika. Azotemija se tijekom boravka razvila kod 59,18% bolesnika. Oliguriju je tijekom hospitalizacije imalo samo 17,14% bolesnika, a poliuriju 89,19% bolesnika. Svi bolesnici liječeni su simptomatskom i suportivnom terapijom, a 81,3% i antibiotskom terapijom (većinom doksiciklin). Trajanje hospitalizacije bilo je od 4 do 16 dana. Svi su bolesnici ozdravili bez trajnih posljedica po zdravlje. Serološki je bolest potvrđena metodom ELISA-e kod 70,83% bolesnika (Puumala virus u 68,75% slučajeva, a Dobrava u 2,08% slučajeva). Prema indeksu težine bolesti 89,58% naših bolesnika imalo je blagi oblik bolesti, a 10,42% srednje težak oblik bolesti.

Zaključak: Ove godine, u Karlovačkoj i Ličko-Senjskoj županiji pojavila se epidemija HGBS sa 11 ambulantno liječenih i 38 hospitaliziranih bolesnika u OB Karlovac. Epidemija se prezentirala blažim oblicima bolesti sa povoljnim ishodom što je u skladu s infekcijom Puumala virusom.

Examination of the 2019 haemorrhagic fever with renal syndrome epidemic in Karlovac General Hospital

Lorena Đapo, Luka Jerković

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Aims: The aim of our poster is to analyze a 2019 hemorrhagic fever with renal syndrome (HFRS) epidemic and to present details on patients who received treatment in Karlovac General Hospital (KGH).

Methods: The data on patients diagnosed with HFRS who received ambulatory and hospital treatment in KGH between January 1 and July 31 2019 were collected from the Hospital Information System.

Results: Most of our patients were from areas of endemic foci of the disease. In 75% of cases, the afflicted patients were males between 19 to 62. The HFRS epidemic started in January, with the high point reached in May. The most common clinical symptoms were fever, myalgia, lower back pain, chills, headache, tremors, and loss of appetite. Clinical examination detected hepatomegaly, conjunctival injection, hypotension, tachycardia, splenomegaly, redness of face and neck, and very rarely petechial rash or enanthem. Laboratory tests conducted upon arrival indicated thrombocytopenia and high CRP levels in almost all patients. 59.18% of patients developed azotemia during their stay. Oliguria was present in only 17.14% of patients during hospitalization, and polyuria in 89.19%. All patients received symptomatic and supportive treatment and 81.3% also received antibiotic treatment (mostly doxycycline). The duration of hospitalization was between 4 to 16 days. All patients recovered without any long-term health effects. The disease was serologically confirmed by the ELISA method in 70.83% of the patients (Puumala virus in 68.75% and Dobrava virus in 2.08% of cases). According to the disease severity index, 89.58% of our patients had the mild form of the disease, and 10.42% the moderate form.

Conclusion: This year, an epidemic of HFRS broke out, resulting in 49 infected patients who received treatment in the KGH. The epidemic appeared as milder forms of the disease with positive treatment outcomes, which is consistent with the diagnosis Puumala virus infection.

PO-59 Prevalencija hantavirusnih infekcija i leptospiroze dokazanih na području kontinentalne Hrvatske tijekom epidemije 2017. godine

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Hantavirusne infekcije i leptospiroza pripadaju skupini zoonoza koje prenose glodavci sa sličnim epidemiološkim značajkama i kliničkim simptomima. Ljudi se inficiraju izravnim ili neizravnim kontaktom s urinom zaraženih životinja. Na području Hrvatske dokazani su hantavirusi Puumala (PUUV) i Dobrava (DOBV). Najčešći uzročnici leptospiroze pripadaju seroskupinama Sejroe, Australis i Icterohemorrhagiae.

Cilj ovog rada je analizirati prevalenciju hantavirusnih infekcija i leptospiroze detektiranih tijekom epidemije u Hrvatskoj 2017. godine.

Tijekom jednogodišnjeg razdoblja (siječanj-prosinac 2017. godine), analiziran je ukupno 301 bolesnik u dobi od 15 do 87 godine s kliničkim simptomima koji su upućivali na hantavirusnu infekciju/leptospirozu.

Serološko testiranje učinjeno je pomoću komercijalnog testa indirektno imunofluorescencije za detekciju najčešćih hantavirusa: PUUV, DOBV, Hantaan (HTNV), Seoul (SEOV) i Saaremaa (SAAV) (Hantavirus mosaic; Euroimmun, Lübeck, Germany) te testa mikroskopske aglutinacije (MAT) za 15 serovara leptospira: Grippotyphosa, Sejroe, Australis, Pomona, Canicola, Icterohaemorrhagiae, Tarassovi, Saxkøbing, Ballum, Bataviae, Poi, Hardjo, Autumnalis, Mitis and Patoc.

IgM i IgG protutijela na hantaviruse dokazana su u 127 (42,2%) bolesnika. Stotinu i šesnaest bolesnika (91,3%) bilo je inficirano hantavirusom PUUV, a 11 (8,7%) DOBV. U 10 (7,9%) bolesnika dokazana su samo IgG protutijela što je ukazivalo na raniju hantavirusnu infekciju. Infekcije su se javljale tijekom cijele godine s najvećom učestalošću tijekom ljetnih mjeseci (80/62,9%). Leptospiroza je dokazana u 18 (5,9%) ispitanika. Nađeno je 9 serovara, od kojih najčešći serovar Patoc (6/33,3%) i Australis (3/16,6%). Prvi je slučaj dokazan u travnju, a posljednji u studenom. Većina je oboljelih zabilježena tijekom ljetnih mjeseci (11/61,1%).

Prikazani rezultati ukazuju da je kontinentalna Hrvatska i dalje endemsko područje za hantaviruse i leptospirozu sa sezonskim pojavljivanjem bolesti (ljetno i jesen).

Prevalence of hantavirus infections and leptospirosis detected in continental Croatian regions during 2017 outbreak

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Hantavirus infections and leptospirosis are rodent-borne zoonoses with similar epidemiological features and clinical symptoms. Humans become infected through direct or indirect contact with the urine of infected animals. In Croatia, Puumala (PUUV) and Dobrava (DOBV) hantaviruses were detected. Majority of leptospira infections are caused by serogroups Sejroe, Australis and Icterohaemorrhagiae. The aim of this study was to analyze the prevalence of hantavirus infections and leptospirosis detected in 2017 Croatian outbreak.

During a one-year period (January-December 2017), a total of 301 patients aged 15 to 87 years from continental Croatian regions with clinical symptoms compatible with hantavirus infection and leptospirosis were analyzed. Serological tests were performed using an indirect immunofluorescence assay for detection of the most common hantaviruses: PUUV, DOBV, Hantaan (HTNV), Seoul (SEOV) and Saaremaa (SAAV) (Hantavirus mosaic; Euroimmun, Lübeck, Germany) and microscopic agglutination assay (MAT) for 15 leptospira serovars: Grippotyphosa, Sejro, Australis, Pomona, Canicola, Icterohaemorrhagiae, Tarassovi, Saxköbing, Ballum, Bataviae, Poi, Hardjo, Autumnalis, Mitis and Patoc.

IgM and IgG antibodies to hantaviruses were detected in 127 (42.2%) patients. A hundred and sixteen (91.3%) participants were infected with PUUV, whereas 11 (8.7%) patients were infected with DOBV. In 10 (7.9%) patients only IgG antibodies were detected indicating previous hantavirus infection. Infections occurred all year round with peak during summer months (80/62.9%). Leptospirosis was confirmed in 18 (5.9%) participants. Nine serovars were detected with serovars Patoc (6/33.3%) and Australis (3/16.6%) the most common. First case was detected in April and the last one in November. Majority of cases were detected during summer (11/61.1%).

The presented results suggest that continental Croatian regions are still endemic regions for both hantaviruses and leptospirosis with seasonal distribution of cases (summer and autumn).

PO-60 Hemorrhagic fever with renal failure syndrome in children hospitalized at Department of Infectious Diseases, University Medical Centre Ljubljana in a 5-year period

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Abstract: Background: Hemorrhagic fever with renal failure syndrome (HFRS) is a well described zoonosis, endemic in parts of Europe, including Slovenia. The clinical features consist of a triad of fever, hemorrhages and renal insufficiency. Typical clinical course has 5 stages: febrile, hypotensive, oliguric, diuretic, and convalescent. In children <15 years of age the disease is mild and often subclinical. Objectives: This is a review of children with HFRS hospitalized at our department in a 5-year period.

Methods: Using the computer database and patients discharge documents we analysed the data of children diagnosed with HFRS between August 2014 and August 2019.

Results: In the 5-year period 4 children were diagnosed with HFRS. Median age upon admission was 15.5 years. $\frac{3}{4}$ of patients presented with high fever and gastrointestinal symptoms, headache was present in $\frac{1}{2}$. Median duration of fever upon admission was 4 days and mean laboratory values were 32 mg/L for CRP, 6.0 10⁹/L for WBC, 136 g/L for Hb and 78 10⁹/L for PLT. $\frac{1}{2}$ had positive serology and PCR testing for Hantaan hantavirus, $\frac{1}{4}$ for Puumala and $\frac{1}{4}$ had a positive rapid serology test without further identification of subtype. 75% of patients had significant thrombocytopenia, with mean PLT value of 44.3 10⁹/L. Mean duration of febrile phase was 6 days and only one patient had a documented hypotensive phase with collapse. All patients presented with oliguric phase after mean time of 6 days, with mean value of urea 17.75 mmol/L and creatinine 352 μ mol/L. Hepatic involvement was present in $\frac{3}{4}$ of cases. None of the patients needed hemodialysis and all recovered without sequelae.

Conclusion: The incidence of HFRS in children is very low, probably due to high percentage of subclinical infections. HFRS should be considered in children, especially adolescents, presenting with fever, thrombocytopenia and renal involvement, particularly in endemic areas.

PO-61 Grand mal epileptički napadaj kao rijetka klinička manifestacija HVBS infekcije (Puumala virus)

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Hemoragijska vrućica s bubrežnim sindromom je akutna infektivna bolest (zoonoza) uzrokovana hantavirusima - u Hrvatskoj Puumala (lakši oblik) i Dobrava virusom (teži oblik bolesti). U 1 % oboljelih od HVBS infekcije susrećemo neurološke manifestacije.

CILJ: prikaz grand mal epileptičkih napadaja kao rijetke kliničke manifestacije HVBS infekcije (Puumala virus)

METODA: u svibnju 2019. godine u Klinici za infektologiju hospitaliziran je sporadično bolestan, prethodno zdrav, 32-godišnji bolesnik u 4.danu bolesti manifestirane hiperpireksijom, povraćanjem, vodenastim stolicama, glavoboljom, bolovima u leđima i zamućenim vidom. U laboratorijskim nalazima pri prijemu verificiran je normalan broj leukocita uz trombocitopeniju, povišene vrijednosti aminotransferaza i albuminuriju, a od 5. dana bolesti prati se i porast dušičnih metabolita u krvi. Tijekom boravka učinjena je radiološka obrada, a serološkom obradom u 10. danu bolesti dokazan je Puumala virus.

REZULTAT: Temeljito suspektan na HVBS i zbog pozitivne epidemiološke anamneze (šumski radnik), kod bolesnika je klinički nakon febrilne faze uslijedila kratka oligurična i duga poliurična faza obilježena porastom dušičnih metabolita i arterijskom hipertenzijom. Inicijalno je antimikrobno liječen beta-laktamskim antibioticima do prispjeća serološke obrade, kada je nastavljeno simptomatsko liječenje. U početku 2. faze došlo je do razvoja pleuropneumonije te niza epileptičkih grand mal napadaja, koji su se djelomično kupirali uz benzodiazepinsku parenteralnu terapiju, zbog čega je kratkotrajno liječen u Jedinici intenzivnog liječenja. Oporavak bolesnika je bio dugotrajan, inicijalno perzistentne polimorfne tegobe postupno jenjavaju uz preporučenu simptomatsku kao i peroralnu antikonvulzivnu terapiju.

ZAKLJUČAK: Kod bolesnika se radilo o serološki dokazanoj srednje teškoj kliničkoj slici hemoragijske vrućice s bubrežnim sindromom uzrokovane Puumala virusom s razvojem epileptičkih napadaja u afebrilnoj fazi bolesti.

Grand mal epileptic seizure – a rare clinical manifestation of HFRS infection (Puumala virus)

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Haemorrhagic fever with renal syndrome is an acute infectious disease, zoonosis, caused by hantaviruses – in Croatia Puumala (mild form) and Dobrava virus (severe form of the disease). 1% patients with HFRS infection have neurological manifestations.

GOAL: study of grand mal epileptic seizures as a rare clinical manifestation of HFRS infection (Puumala virus)

METHOD: Clinic for Infective Diseases admitted a sporadically ill patient (otherwise healthy) in May 2019. The patient was 32 and was ill for 4 days; symptoms were hyperpyrexia, vomiting, liquid stool, headache, backpain and blurred vision.

Laboratory results, made upon admittance, verified normal leukocyte count with thrombocytopenia, high aminotransferase count and albuminuria. Five days into the illness there was an increase of nitric metabolites. Radiological tests were conducted and ten days into the illness Puumala virus was serologically confirmed.

RESULT: Patient was admitted with a high suspicion of HFRS and a positive epidemiological case history (forestry worker). He had a febrile phase followed by short oliguric and long polyuric phase. In this phase there was an increase of nitric metabolites and arterial hypertension. Initially the patient was treated with beta-lactam antibiotics until serological testing arrived; furthermore he was treated symptomatically. Early in stage 2 of the disease the patient had a series of epileptic grand mal seizures partially controlled by parenteral treatment. The patient was briefly treated in the Intensive Care Unit. The patient had a long recovery. Initially, persistent polymorphic difficulties were present however, in due course they have subsided with the help of the recommended symptomatic and peroral anticonvulsant therapy.

CONCLUSION: The patient had a case of serological proven medium severe clinical case of haemorrhagic fever with renal syndrome caused by Puumala virus developing into epileptic seizures in the afebrile stage of the disease.

PO-62 Epidemija tuberkuloze uzrokovana istim genotipom *M.tuberculosis* otkrivena obradom kontakata na radnom mjestu

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Cilj: Prikazati epidemiju tuberkuloze otkrivenu aktivnim traženjem među radnim kolegama bolesnika s mikroskopski pozitivnim iskašljajem na ARB.

Metode: Obrada kontakata izvršena je po principu koncentričnih kružnica. Obuhvaćala je edukaciju radnika, anketiranje, PPD-test, radiografsku snimku pluća te dodatne pretrage po potrebi.

Rezultati: Nadzorom je ukupno obuhvaćeno 227 osoba. Inicijalno tuberkulinsko testiranje napravljeno je u 210 osoba od kojih se 22 nije pojavilo na otčitavanju. Zabilježeno je 86 (46%) negativnih rezultata, više od 14 mm u 11 testiranih (5,8%) te više od 20 mm u dvojice testiranih. Rtg pluća nije napravilo/dostavilo 55 kontakata. Zatražena je konzultacija pulmologa za 29 testiranih radnika. Otkrivena su tri nova bolesnika koji su imali rezultate PPD-a 17 mm, 8 mm i negativan (dijabetičar na inzulinu), svi s patološkim RTG nalazom. Kod dva sekundarna bolesnika je tuberkuloza bakteriološki potvrđena. Izolirani sojevi genotipizirali su se metodom MIRU-VNTR uz korištenje 24 lokusa te je utvrđen isti soj kao i kod indeksnog bolesnika; MLVA Mtbc 15-9 tip 2601-15. Obrada kontakata je ponovljena nakon završetka prozor-razdoblja na koju se odazvalo svega 5 radnika, među kojima je zabilježena jedna tuberkulinska konverzija te još 12 radnika koji su testiranjem obuhvaćeni po prvi put. Nisu otkriveni novi bolesnici.

Zaključak: Premda dva bolesnika nisu pripadala prioritarnim bliskim kontaktima, otkriveni su širenjem obrade. Dokazani slučajevi tuberkuloze kod negativnog i slabo pozitivnog rezultata PPD-a potvrđuju nedostatnu osjetljivost testa, premda je praktičan za obradu kontakata izvan zdravstvene ustanove. Odluku o traženju konzultacije pulmologa treba donijeti pažljivom evaluacijom anamneze, rezultata PPD-a i RTG testa. Izolirani genotip nije čest u Hrvatskoj te je zabilježen samo u Splitsko-dalmatinskoj županiji u klasteru od 15 bolesnika. To upućuje na transmisiju uzročnika kao posljedicu kasnog otkrivanja bolesti, bilo da se radi o kasnom javljanju liječniku i/ili kasnom prepoznavanju bolesti, što, uz odbijanje preporučenog testiranja među anketiranim radnicima, ukazuje na nisku razinu zdravstvene prosvijećenosti.

Tuberculosis outbreak caused by the same genotype of *M. tuberculosis* detected by contact investigation at workplace

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Objective: To present an outbreak of tuberculosis detected by contact tracing at work place among colleagues of smear-positive index patient.

Methods: Contact tracing was performed mostly in concentric circles. It involved TB education, interviewing, TST, chest X-ray and additional tests as needed.

RESULTS: Contact investigation at work place included 227 persons. Initially TST was done in 210 people, 22 of them not returned for the reading; 86 (46%) had negative result, more of 14 mm was recorded in 11 tested (5.8%) and more than 20 mm in two tested contacts. CXR was refused or CXR results were not delivered in 55 workers. Consultation of pulmonologist was requested for 29 tested workers. Three new TB patients were identified; with TST results 17 mm, 8 mm and negative (the patient with diabetes on insulin therapy), all with CXR suggestive of TB. In two of them TB was bacteriologically confirmed. Isolated strains were genotyped by a method MIRU-VNTR using 24 locuses and all three bacteriologically confirmed cases had same code; MLVA Mtb 15-9 type 2601-15. The follow-up was done after the window period, but the compliance was poor (only five contacts re-tested, one with tuberculin conversion and 12 contacts who were not present during the baseline contact investigation). There were no detected new cases.

Conclusion: Two new TB patients, who were not close contacts, were rapidly detected by spreading the contact investigation. Confirmed TB in TST negative and poorly TST positive contacts confirm insufficient TST sensitivity, though it is convenient tool for contact tracing outside health institution. The decision to seek consultation with a pulmonologist needs careful evaluation of the history, TST and CXR. Isolated genotype is not common in Croatia and is only recorded in Split-Dalmatia County in a cluster of 15 patients. That points to TB transmission as a result of late detection of the disease, due to the patients and/or health system delay. In addition, non-compliance with recommended screening points out a worrying health behaviour.

PO-63 Case report – problems in diagnostic of CNS tuberculosis

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INTRODUCTION: Tuberculous meningitis is a very severe bacterial disease of the brain membranes which occurs secondary during tuberculosis. It is caused by *Mycobacterium tuberculosis*. The major clinical symptoms are gradual start, high temperature, severe general condition, meningeal, meningoencephalitis and basilar symptoms and characteristic changes in CST. CST at TBM is mostly clear. Total Le is 100-500, with predominance of lymphocytes, hyperproteinaemia 1-5 g/l, hypoglycaemic.

METHOD: Disease history of patient at the Clinic for Infectious Diseases in 2015 was used.

RESULTS: 56-year-old male was administered at Clinic for Infectious Diseases due to paresis of left hand, right leg, ptosis of left eyelid and peripheral right facials. LP on reception (liquor clear, colourless, number of elements 296, ly-97%, glycorahia 1.3, proteinrahia 2.82), glycaemia 7.9. Meningeal signs were negative, afebrile. The patient was treated for 2 years of NHL combined with immunologic polychemotherapy. Control LP (Liquor slightly blurred, colourless, number of elements 420, ly 99%, glycorahia 0.4, proteinrahia 2.65), glycemia-9.2. DMP negative, PCR of HSV 1 and 2 – negative, PCR of Enteroviruses – negative. PH of liquor – amorphous eosinophilic material. HbsAg, HCV, HIV – negative, VDRL – negative. CT of endocranium – normal results. MR of endocranium -changes suspected to amyotrophic lateral sclerosis. Due to neurological deficits and liquor results, the Consilium made decision to include ex juvantibus tuberculostatics therapy. According to decision of Consilium of neurologists, haematologists and specialists of infectious diseases, patient was moved to the Centre for Haematology for further treatment. Tuberculostatics were excluded from the therapy after results of control MR of endocranium – lesion in brain, possible progressive leukoencephalopathy in immunosuppression (probably as a consequence of adverse reaction of immune polychemotherapy by Mabtherom) and negative results of PCR test on M. Tuberculosis (done at the Institute for Microbiology in Belgrade).

CONCLUSION: Introduction of modern diagnostic analysis (BACTEC, QUANTIFERON test, PCR of liquor) would facilitate diagnostics and adequate therapy.

PO-64 Drug Resistance profile of *Mycobacterium tuberculosis* isolates from patients referred to TB Reference Laboratory in Kosovo

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Background: Drug-resistant tuberculosis (TB) continues to threaten TB control and remains a major global public health concern. The poor patient adherence in tuberculosis (TB) treatment is the cornerstone of emerging of the Multidrug Resistance-TB (MDR-TB). The aim of this study was to evaluate the resistance of *Mycobacterium tuberculosis* to first-line TB drugs among isolates from clinical specimens.

Methods: A laboratory-based study was conducted in the Department of Microbiology, within the National Institute of Public Health of Kosovo, from January 2017 to September 2018. Sputum and other clinical specimens were obtained from patients with pulmonary and extrapulmonary TB. The specimens were stained with Ziehl–Neelsen, inoculated on Löwenstein–Jensen media for 6–8 weeks, and tested for sensitivity against first-line TB drugs [isoniazid (INH), rifampicin (RIF), ethambutol (EMB), and streptomycin (SM)].

Results: Of the 316 *M. tuberculosis* isolates collected, 31.6% showed resistance to first-line TB drugs. Among these resistant isolates, 31% showed resistance to at least one of the first-line TB drugs and 0.3% showed multidrug resistance (MDR). Resistance to EMB, INH, RIF, and SM was seen in 17%, 8%, 3%, and 72% of isolates, respectively. Polyresistance was seen in 3% of the isolates.

Conclusion: Our study confirm that resistance to Streptomycin was the most common phenomenon. The resistance pattern identified in this study could assist clinicians in providing appropriate treatment regimen to TB patients and improve their clinical outcome.

Keywords: First-line TB drugs, Resistance, Tuberculosis, Kosovo

PO-65 Tuberkuloza i gljivične infekcije, Klinički bolnički centar Zagreb, u posljednje dvije godine

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Cilj: Plućna tuberkuloza je jedna od najvažnijih zdravstvenih problema. Plućne gljivične infekcije imaju kliničke i radiološke karakteristike slične tuberkulozi i lako se mogu pogrešno dijagnosticirati kao tuberkuloza. Cilj ovog rada bio je procijeniti *Mycobacterium tuberculosis* (MTB) i drugih ne-tuberkuloznih mikobakterija (NTM) s gljivičnim infekcijama kod pacijenata, tijekom zadnje 2 godine.

Metode: Analizirana su mikrobiološka i klinička izvješća o 149 pacijenata s potvrđenim mikobakterijama. Detekcija i identifikacija mikobakterija su provedene postupkom standardne kulture pomoću BACTEC 960 MGIT sustava (BD) i Lowenstein-Jensen medija. Identifikacija pozitivnog kompleksa *Mycobacterium tuberculosis* (MTBC) se temeljila nalazom mikroskopskim razmazom acid-fast bakterija (Ziehl-Neelsen i fluorokroma), pozitivnom akumulacijom niacina, MALDI-TOF i PCR mikobakterija. TB izolati su također testirani na osjetljivost prema prvoj liniji antituberkulotika. Gljive su izolirane kultivacijom na Sabouraud dekstroza 2%, kromogenom i kukuruznom agaru. Identifikacija gljiva je bila mikroskopska morfologija (nativno i calcofluor white) i MALDI-TOF, te ispitivanje in vitro antifungalne osjetljivosti.

Rezultati: U razdoblju od travnja 2017. do travnja 2019., u 149 bolesnika nađene su mikobakterijske infekcije (MTB 64%, NMT 36%). Mikološki testovi nisu traženi u 36 24% bolesnika, a traženi su u 113 76%.

Kod većine bolesnika izolirano je više vrsta gljiva, 160 epizoda. U 113 bolesnika su izolirani kvasci, oportunističke i saprofitne plijesni (54%, 16%, 28%).

Najčešće su bile izolirane *C.albicans*, *C.dubliniensis*, *C.parapsilosis* i *C.glabrata*. Najviše je bilo izoliranih *A.niger*, *A.fumigatus*, *A.flavus*, a kod malog broja bolesnika su izolirani *Fusarium*, *Rhizopus* i *Pseudallescheria boydii*. Saprofitne plijesni su dokazane kod 28% bolesnika.

Zaključak: Naši rezultati su pokazali da treba misliti u bolesnika s tuberkulozom na koinfekcija gljivama. Moraju se analizirati klinički podaci da bi se mogla razlikovati infekcija, kolonizacija ili normalna flora.

Tuberculosis and Fungal Co-infection, University Hospital Center Zagreb, Croatia, During Past Two Years

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Objective: Pulmonary tuberculosis is one of the most important health concerns. Pulmonary fungal infections have clinical and radiological characteristics similar to tuberculosis which may be easily misdiagnosed as tuberculosis. This study aimed to evaluate *Mycobacterium tuberculosis* (MTB) and other non-tuberculous mycobacteria (NTM) with coinfection of fungal infections in patients, during last 2 years.

Methods: Microbiological and clinical reports of 149 patients with confirmed mycobacteria have been analyzed. Detection and identification of mycobacteria were performed by the standard culture method using the BACTEC MGIT 960 system (BD) and Lowenstein-Jensen medium. Identification of positive *Mycobacterium tuberculosis* complex (MTBC) was based on positive acid-fast bacilli microscopic smear (Ziehl-Neelsen and fluorochrome), positive niacin accumulation, MALDI-TOF and. Mycobacteria PCR. TB isolates were also tested for their sensitivity toward first-line anti-TB drugs.

The culture of fungi was performed on Sabouraud Dextrose agar, chrome and cornmeal agar. Identification of positive fungi was based on positive microscopic smear (native and calcofluor white), microscopic morphology, MALDI-TOF and in vitro susceptibility tests.

Results: Between April 2017 and April 2019, at 149 patients were detected Mycobacterial infections (MTB 64%, NMT 36%). Mycological tests are not required in 36 24% patients. Mycological tests are required in 113 76% patients. The majority of patients had isolated several types of fungi, 160 episodes. The patients 113 were isolated yeasts, opportunistic and saprophytic molds (54%, 16%, 28%). Frequent *Candida* were *C. albicans*, *C. dubliniensis*, *C. parapsilosis* and *C. glabrata* respectively. Frequent *Aspergillus* were *A. niger*, *A. fumigatus* and *A. flavus* respectively. In addition to *Aspergillus*, small number of patient had *Fusarium*, *Rhizopus* and *Pseudallescheria boydii*. Saprophytic molds were confirmed in 28% of patients.

Conclusion: Our findings showed the coinfection of fungi agents in patients with tuberculosis that should be considered. Clinical data must be analyzed to be able to distinguish infections, colonization, or part of normal flora.

PO-66 Istraživanje granično pozitivnih rezultata IGRA testa u Istočnoj Hrvatskoj

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Uvod: Procjenjuje se da je trećina svjetskog stanovništva inficirana uzročnikom tuberkuloze, u većini slučajeva kao latentna tuberkulozna infekcija (LTBI). Vjerojatnost razvoja aktivne tuberkulozne infekcije tijekom života kod osoba sa LTBI je 10%, te one predstavljaju rezervoar budućih infekcija. U dijagnostici LTBI koriste se testovi oslobađanja interferona gama (IGRA), kojima se, nakon in vitro stimulacije limfocita T peptidnim antigenima koji simuliraju antigene specifične za *M.tuberculosis* kompleks, potiče oslobađanje interferona gama (INF- γ). Cilj istraživanja: Odrediti udio graničnih rezultata Quantiferon-TB Gold-Plus testa kod osoba upućenih na obradu radi sumnje na LTBI. Provedena istraživanja ukazuju na značajan udio konverzije i reverzije rezultata testa čije su vrijednosti oko postavljene granične vrijednosti testa (0.35 IU/mL-1). Prema europskim studijama, određene su granične vrijednosti testa u rasponu od 0.2 do 0.7 IU/mL-1.

Metode: Istraživanje je provedeno u toku jednogodišnjeg razdoblja, od početka lipnja 2018.god do kraja svibnja 2019.god. Za određivanje INF- γ korišten je imunoenzimni test (QTB-Plus) prema uputama proizvođača.

Rezultati: Istraživanje je u navedenom razdoblju obuhvatilo 1427 ispitanika. Granična vrijednost testa u rasponu od 0.2 do 0.7 IU/mL-1 nađena je kod 82 ispitanika (5.7%). Pritom su granične vrijednosti < 0.35 IU/mL-1 nađene su kod 22 ispitanika (1.5%), odnosno granične vrijednosti > 0.35 IU/mL-1 kod 60 ispitanika (4.2%). Pozitivni rezultat testa (> 0.7 IU/mL-1) nađen je kod 199 ispitanika (13.9%). Negativan rezultat testa (< 0.2 IU/mL-1) nađen je kod 1112 ispitanika (77.9%). Dodatno, kod 34 ispitanika (2.4%) rezultat testa radi neadekvatnog imunog odgovora je bio nedeterminiran. Granične vrijednosti testa i nedeterminiranih rezultata nađeni su kod 138 ispitanika (9.6%).

Zaključak: Udio graničnih rezultata testa kao i značajna prisutnost konverzije i reverzije kod ponovljenih testiranja ukazuju na potrebu razgraničenja ovih rezultata u odnosu na stabilno pozitivne i negativne rezultate.

Investigation of borderline positive results given by IGRA in Eastern Croatia

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Introduction: It is estimated that one third of the world's population has been infected with tuberculosis infection, mostly with latent tuberculosis infection (LTBI). Development probability of active tuberculosis complex infection in individuals with LTBI is about 10%, which is a reservoir of future TB infection. Tests that are used in LTBI diagnosis rely on the host T-Cell response to *Mycobacterium tuberculosis* (*M.tuberculosis*) antigens. In vitro gamma interferon (IFN- γ) release assays (IGRAs) are based on measuring cell-mediated immune responses to peptide antigens that simulate mycobacterial proteins

Aim: Detection of borderline positive results of Quantiferon-TB Gold-Plus in tube assay (QFT-Plus) in individuals routinely screened for LTBI. Manufacturer recommended cut point for positive result is the 0.35 IU/mL-1. Research has shown the high proportion of conversions and reversions around 0.35 IU/mL-1. Borderline positive TB response was defined as IFN- γ concentration between 0.2 IU/ml and 0.7 IU/ml, according to European studies.

Methods: The study period was between June 1 2018 and May 31 2019. Detection and quantification of IFN- γ were done by enzyme-linked immunosorbent assay (QFT-Plus) according to manufacturer's instructions.

Results: During the study period total of 1427 subjects were screened for LTBI using QFT Gold-Plus test. Borderline value in the range of 0.2 do 0.7 IU/mL-1 was found in 82 subjects (5.7%), while borderline results < 0.35 IU/mL-1 in 22 subjects (1.5%) and borderline results > 0.35 IU/mL mL-1 in 60 subjects (4.2%). 1112 (77.9%) were negative (<0.2 IU/mL-1), 199 (13.9%) were positive (>0.7 IU/mL-1) and 34 (2,4%) were indeterminate.

Conclusion: The share of the borderline test result aswell as the significant presence of conversion and reversion in repeated testing point to the need for dividing these results considering stabile positive and negative results.

Keywords: Latent tuberculosis infection ; gamma interferon (IFN- γ) release assays; borderline zone

PO-67 Cerebralna toksokarijaza – prikaz slučaja

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CILJ: Istaknuti značaj neurotoksokarijaze kao oblika eozinofilnog meningitisa i rijetke kliničke manifestacije humane toksokarijaze. Premda seroprevalencija *Toxocara* spp. diljem svijeta iznosi od 1 do čak 93%, dokumentirani slučajevi cerebralne toksokarijaze su rijetki.

METODE: Prikaz slučaja 55-godišnjeg bolesnika liječenog u Klinici za infektivne bolesti KBC Rijeka zbog cerebralne toksokarijaze.

REZULTATI: bolesnik koji se prezentirao kliničkom slikom vrućice uz glavobolju u trajanju od pet dana hospitaliziran je s radnom dijagnozom aseptičnog meningitisa. Desetog dana bolesti u likvoru je dokazna eozinofilna predominacija u diferencijalnoj citološkoj analizi (689 x10⁶/L stanica uz 50% eozinofila). Serološkom analizom seruma na tkivne parazite (EIA) dokazana su protutijela na *Toxocara* spp., kao i pozitivan potvrdni test. Identičan je nalaz dobiven i serološkom analizom likvora. U višekratno ponavljanim uzorcima periferne krvi nije zabilježena eozinofilija. MR mozga je bio urednog morfološkog nalaza. Epidemiološki podaci nisu bili indikativni u pogledu akviriranja infekcije helmintom. Osim psorijaze, bolesnik je bio bez značajnijih komorbiditeta. Proširena laboratorijska i aparaturna obrada, kao i oftalmološki pregled su bili bez patoloških odstupanja. Provedena je terapija albendazolom uz prednizon per os kroz pet dana na što se postiže se brza regresija simptoma, bez zabilježenih komplikacija bolesti. U ponovljenom nalazu likvora nakon provedene terapije se prati niska mononuklearna pleocitoza uz potpuni nestanak eozinofila. U kontrolnom uzorku seruma i likvora serološki je također potvrđena akutna infekcija toksokarom (pozitivni EIA i WB).

ZAKLJUČAK: Invazija mozga larvama *Toxocara* spp. rijetko rezultira manifestnom neurološkom simptomatologijom, no treba je uzeti u obzir u diferencijalnoj dijagnozi sindroma eozinofilnog meningitisa. Primjenom adekvatne serološke i neuroradiološke dijagnostike te pravovremenim liječenjem može se postići potpun oporavak što je značajno u kontekstu prevencije nekih neuroloških poremećaja (epilepsija, demencija) koji se danas etiološki povezuju sa prisutnošću *Toxocara* spp. u moždanom tkivu i predmet su znanstvenih istraživanja.

Cerebral toxocariasis – a case report

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OBJECTIVE: To emphasize the significance of neurotoxocariasis as a form of eosinophilic meningitis and a rare clinical manifestation of human toxocariasis. Although seroprevalence of *Toxocara* spp. ranges from 1 to 93% worldwide, documented cases of cerebral toxocariasis are rare.

METHODS: A case report of a 55-year-old patient treated at the Clinic for Infectious Diseases of the Clinical Hospital Center Rijeka.

RESULTS: A patient with a history of five days fever and headache was admitted in hospital under the presumptive diagnosis of aseptic meningitis. The 10th day of the disease in differential cytological analysis of the cerebrospinal liquor eosinophilic predominance was noticed ($689 \times 10^6 / L$ cells with 50% eosinophils). Serologic analysis of serum on tissue parasites (EIA) showed antibodies to *Toxocara* spp. with a positive confirmation test. An identical finding was obtained by the serologic analysis of the cerebrospinal liquor. No eosinophilia was observed in repetitive peripheral blood samples. The MR of the brain showed no morphological pathologies. Epidemiological data were not indicative in terms of parasitic infection. Apart from psoriasis, the patient was without significant comorbidities. Expanded laboratory and device diagnostics as well as ophthalmic examination were without pathological findings. Albendazole therapy was performed with prednisone per os for five days thanks to which rapid regression of symptoms was achieved, without reported complications of the disease. In the repeated samples of cerebrospinal liquor after the performed therapy, low mononuclear pleocytosis was detected with the complete disappearance of eosinophils. In control serum and liquor samples serologically was also confirmed acute *Toxocara* infection (positive EIA and WB).

CONCLUSION: The brain invasion of the larvae of *Toxocara* spp. rarely results in manifest neurological symptomatology but should be considered in the differential diagnosis of eosinophilic meningitis syndrome. Using adequate serological and neuroradiological diagnostics and timely treatment, complete recovery can be achieved, which is significant in the context of prevention of some neurological disorders (epilepsy, dementia) that nowadays are etiologically linked to the presence of *Toxocara* spp. in the brain tissue and are the subject of scientific research.

PO-68 Prikaz dirofilarioze na Odjelu infektologije Opće bolnice Pula

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Humana dirofilarioza je zoonoza, prvenstveno bolest pasa i rjeđe mačaka uzrokovana srčanim parazitom (*Dirofilaria repens*, *Dirofilaria immitis*). Komarci su najčešći vektori, ali muhe, krpelji i uši mogu također prenijeti bolest na čovjeka.

Prikazali smo slučaj bolesnika u dobi od 64 godine iz ruralne sredine. Bolesnik je doživio ubod komarca u predjelu desnog ramena dva mjeseca prije pojave supkutanog čvorića u predjelu lijeve podlaktice. U laboratorijskim nalazima prati se eozinofilija. U sklopu obrade iste postavi se sumnja na dirofilariozu. Lančanom reakcijom polimeraze (PCR) potvrđena je *Dirofilaria repens*, a materijal je i histološki obrađen po kirurškoj eksciziji, čime je ujedno postignuto izliječenje.

Zadnjih desetljeća povećana je učestalost slučajeva humane dirofilarioze što se objašnjava klimatskim promjenama (globalno zatopljenje), te češćoj izloženosti ljudi vektorima (promjene u načinu života, češća putovanja). Prema anamnezi, kliničkoj slici, epidemiološkim karakteristikama radilo se o autohtonoj dirofilariozi.

Human dirofilariosis at the Department of Infectology General Hospital Pula – a case report

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Human dirofilariosis is a zoonotic disease, predominantly a dog disease and rarely found in cats, caused by a cardiac parasite (*Dirofilaria repens*, *Dirofilaria immitis*). Mosquitoes are the most common vectors, but flies, ticks and louses can also convey disease to humans.

We have shown the case of a male patient, 64 years, living in a rural environment. The patient experienced a sting of mosquito in the area of his right shoulder two months before the subcutaneous node appeared in the left forearm. Laboratory examination showed eosinophilia. Dirofilariosis was suspected and later *Dirofilaria repens* was confirmed by polymerase chain reaction test (PCR). The sample was also histologically proven after surgical excision, thereby achieving cure.

For the last decades, the frequency of cases of human dirofilariosis has increased. It is explained by the climate change (global warming) and frequent exposure of people to vectors (lifestyle changes, frequent travel).

According to anamnesis, clinical picture and epidemiological characteristics our case was an autochthonous human dirofilariosis.

PO-69 Pregledom sedimenta urina do dijagnoze enterobijaze među članovima obitelji – prikaz slučaja

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Cilj: Cilj rada je prikazati slučajni nalaz enterobijaze u više članova obitelji zahvaljujući jednostavnom mikroskopskom pregledu sedimenta urina pacijentice s nespecifičim simptomima urinarne infekcije (peckanje, pruritus, nelagoda u području urogenitalne regije). Pacijentica je posumnjala na uroinfekt jer je njenoj trogodišnjoj kćeri zbog istih simptoma dijagnosticirana uroinfekcija tjedan dana ranije. Dijete je neuspješno liječeno antibiotikom i zatim antifungikom.

Metode: Uzorak urina prikupljen je u skladu s uputama za uzimanje urina za urinokulturu. Uzorak urina centrifugiran je na 3000 okretaja 10 minuta, supernatant je odbačen, a sediment urina mikroskopiran na svjetlosnom mikroskopu, na povećanju 10x i 40x. Perianalni otisci uzeti su prema uputama za uzimanje perianalnog otiska.

Rezultati: Mikroskopijom sedimenta urina pri povećanju 10x identificirana je masa epitelnih stanica i CaCO_3 kristala, rijetki polimorfonuklearni leukociti, nešto bakterija i puno okruglih formacija nalik na jaje. Pregledom preparata na povećanju 40x uočene su žive larve unutar jaja koja su morfološki odgovarala maloj dječjoj glisti *Enterobius vermicularis*. Pregledom perianalnih otisaka svih članova obitelji dokazana je infestacija kod majke, kćeri i mlađeg sina. Uzorci perianalnih otisaka oca obitelji i starijeg sina bili su negativni. Kontrolni perianalni otisci svih članova obitelji nakon provedene terapiji bili su negativni.

Zaključak: Iako se radi o jednostavnom i jeftinom postupku mikroskopija sedimenta urina često je zanemarena u rutinskoj mikrobiološkoj analizi urina. Prikazani, slučajni nalaz jaja *E. vermicularis* u sedimentu urina pomogao je u dijagnozi i izlječenju obiteljske infestacije malom dječjom glistom, a spriječio moguću daljnju nepotrebnu antimikrobnu i antifungalnu terapiju.

Examination of urine sediment until diagnosis of enterobiasis among family members – a case report

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Goal: The aim of this study is to present a random finding of enterobiasis in several family members by a simple microscopic examination of the urine sediment of a patient with nonspecific symptoms of urinary tract infection (burning, pruritus, discomfort in the urogenital region). The patient suspected uroinfection because her 3-year-old daughter had been diagnosed with a urinary tract infection a week earlier due to the same symptoms. The child was unsuccessfully treated with antibiotic and antifungal therapy.

Methods: A urine sample was collected according to urine collection guidelines for urine culture. The sample was centrifuged at 3000 rpm for 10 minutes, the supernatant discarded, and urine sediment microscopied on a light microscope at 10x and 40x magnification. Scotch tape specimens were taken according to scotch tape specimen collection instructions.

Results: Microscopy of the patient's urine sediment at 10x magnification identified lots of epithelial cells and CaCO₃ crystals, rare polymorphonuclear leukocytes, some bacteria, and lots of round, egg-like formations. Examination at 40x magnification confirmed eggs of *Enterobius vermicularis*. Larva were visible inside, outside and hatching from the thin eggshell. *E. vermicularis* infection was confirmed in the mother, daughter and younger son, using scotch tape. Scotch tape specimens from the dad and older son were negative. Control specimens of all family members, following therapy, were negative.

Conclusion: Although it is a simple and inexpensive procedure, urine sediment microscopy is often overlooked in routine microbiological urine analysis. The incidental findings of *E. vermicularis* eggs in urine sediment has helped diagnose and treat a family *E. vermicularis* infestation and prevent possible unnecessary antimicrobial and antifungal therapy.

PO-70 Malaria – testiranje dobrovoljnih davatelja krvi u RH, od 2015. do 2017. godine

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Uvod: Malaria je teška i po život opasna bolest koju izazivaju paraziti roda *Plasmodium*, a koje na čovjeka prenose ugrizom zaražene ženke komaraca vrste *Anopheles*. Infektivna doza je oko 10 parazita u krvnom pripravku. Antigenski test je nedovoljne osjetljivosti za nisku parazitemiju kakva je moguća kod kronične infekcije, kao i mikroskopski nalaz parazita u gustoj kapi te PCR test na plazmodijsku DNA. Zbog svega navedenog, test na antitijela se pokazao najprikladnijim i najučinkovitijim u otkrivanju davatelja krvi u ranoj primarnoj i okultnoj infekciji uzročnikom malarije. Europske zemlje slijede Preporuke EDQM (European Directorate for the Quality of Medicines & HealthCare). Testiranje uzoraka krvi dobrovoljnih davatelja (DDK) na malariju u RH započelo je 15.09.2015. godine za one DDK koji su bili u riziku od malarije odnosno boravili u endemskim područjima za malariju.

Cilj: Analizirati rezultate testiranja DDK RH na anti-*Plasmodium* spp. i odrediti seroprevalenciju.

Metode: U periodu od 15.09.2015. do 31.12.2017. ispitano je ELISA testovima 2094 uzorka krvi (serum) od DDK. Korišteni testovi su: Dia.Pro Malaria Ab, Trinity Captia Malaria EIA i Bio-Rad Malaria EIA. Svi inicijalno reaktivni uzorci krvi retestirani su u duplikatu u istom testu te testirani s još jednim ili dva druga testa. Reaktivnim se smatra onaj DDK koji u 2/3 ili 3/3 testa ima reaktivan rezultat.

Rezultati: Od 2094 ispitanih DDK na anti-*Plasmodium* spp., 1 je bio reaktivan (trajno je odbijen prilikom liječničkog pregleda zbog navoda o preboljenoj malariji prije 26 godina u Sierra Leone). Među ispitanim DDK je oko 15% novih davatelja i to školaraca s naturalnih putovanja. Najčešći razlog za testiranje na malariju su turistička putovanja u endemske zemlje/područja za malariju, ako izuzmemo Afganistan (mirovne misije), slijede Thailand, Indija, Brazil, Vijetnam i Kina.

Zaključak: Dosadašnja testiranja DDK RH upućuju na vrlo nisku seroprevalenciju Anti-*Plasmodium* spp., 1/2094, oko 0,048%.

Malaria – Testing of voluntary blood donors in the Republic of Croatia, from 2015 to 2017

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Introduction: Malaria is a serious and life-threatening disease caused by parasites of the genus *Plasmodium*, which is transmitted to humans by the bite of an infected *Anopheles* mosquito. The infectious dose is about 10 parasites in the blood product. The antigen test is not sufficiently sensitive for the low parasitemia that is possible in chronic infection, as well as the microscopic finding of the parasite in the thick drop and the PCR test for plasmodium DNA. Because of all of the above, the antibody test has proven to be the most appropriate and effective in detecting blood donors in early primary and occult malaria infections. European countries follow the EDQM (European Directorate for Quality of Medicines & HealthCare) Recommendations. Testing of voluntary blood donors (VBDs) blood samples for malaria in the Republic of Croatia started on 15.09.2015 for those VBDs who were at risk for malaria, or resided in endemic malaria areas.

Objective: To analyze the results of VBDs testing on anti-*Plasmodium* spp. and to determine seroprevalence.

Methods: From 15.09.2015 do 31.12.2017 2.094 blood samples (serum) from VBDs were tested by ELISA tests. The tests used are: Dia.Pro Malaria Ab, Trinity Captia Malaria EIA and Bio-Rad Malaria EIA. All initially reactive blood samples were retested in duplicate in the same assay and tested with one or two other assays. Reactive is considered to be the VBD that has a reactive result in 2/3 or 3/3 tests.

Results: Of the 2.094 VBDs tested for anti-*Plasmodium* spp., 1 was reactive (permanently rejected on medical examination because of malaria 26 years ago in Sierra Leone). Among the VBDs surveyed, about 15% were the new VBDs, school leavers. The most common reason for malaria testing are traveling to endemic malaria countries / areas, with the exception of Afghanistan (peacekeeping missions), followed by Thailand, India, Brazil, Vietnam and China.

Conclusion: Testing of VBDs of the Republic of Croatia for malaria indicates a very low seroprevalence of Anti-*Plasmodium* spp., 1/2.094, about 0.048%.

PO-71 Dijagnostika i liječenje kožne lišmanijaze – prikaz slučaja i pregled literature

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Kožna lišmanijaza je često zanemarena, emergentna vektorska parazitska infekcija koju prenose ženke nevida. Infekcija je endemična u više of 98 zemalja na 5 kontinenta. Globalna prevalencija kožne lišmanijaze je u porastu, između ostalog i zbog klimatskih promjena, urbanizacije, masivnih migracija, pustolovnog turizma i sve većeg broja imunokompromitiranih domaćina. Na Klinici za infektologiju KBC-a Split liječe se 1-2 slučaja kožne lišmenioze godišnje. Dijagnoza se postavlja mikroskopskim nalazom uzročnika u bioptičkim uzorcima, a sve češće i primjenom razvijenih molekularnih tehnika. Intralezionalna primjena natrijevog stiboglukonata dokazano je učinkovita lokalna terapija. Ovdje prikazujemo slučaj dijagnostike i liječenja kožne lišmanijaze u djevojčice s teškoćama iz spektra autizma u koje nije bilo moguće učiniti biopsiju lezije niti provesti liječenje intralezionalom primjenom antiparazitarnih lijekova. Kroz prikaz slučaja i pregled literature prikazat će se aktualne mogućnosti u dijagnostici i liječenju kožne lišmanijaze.

Diagnosis and management of cutaneous leishmaniasis – case presentation and literature review

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Cutaneous Leishmaniasis (CL) is a often neglected emerging vector-borne parasitic infection transmitted by the bite of an infected female sand fly. Infection is endemic in more than 98 countries on five continents. The global prevalence of CL is increasing because of many factors, including climate changes, urbanization, mass population migration, adventure travel and increasing numbers of immunosuppressed hosts. In the Clinic for infectious diseases at University Hospital Split there are 1-2 new CL cases every year. CL is diagnosed by microscopic demonstration of the parasite in a clinical specimen but actual molecular techniques are now being used more often. Intralesional injections of sodium stibogluconate proved to be very effective local therapy. Here we present a case of CL diagnosis and treatment in a girl with autism spectrum disorder for whom neither lesion biopsy nor intralesional antiparasitic treatment could be performed. Throughout a case presentation and literature review the emphasis of our work will be on the current CL diagnostic and management options.

PO-72 Prisutnost *Cryptococcus neoformans* u okolišnim uzorcima u Hrvatskoj

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Cilj: Kvasac *Cryptococcus neoformans* uzrokuje po život opasne infekcije prvenstveno kod imunokompromitiranih bolesnika. Izvor ovog kvasca u okolini su prvenstveno ptičji ekskreti i propadajuće drvo. Do sada prisutnost ovog kvasca nije dokazana u okolini u Hrvatskoj. Cilj istraživanja bio je istražiti prisutnost kvasca *C. neoformans* u okolišnim uzorcima u Hrvatskoj te odrediti molekularne karakteristike ovih izolata.

Metode: U razdoblju od 2013. do 2016. godine, uzeto je ukupno 509 okolišnih uzoraka uključujući sasušene ptičje ekskrete i obriske duplji stabala na različitim geografskim područjima u Hrvatskoj. Uzeti uzorci su prikupljeni i obrađeni kao što je to opisano u ranije provedenim istraživanjima od Cafarchia i sur. (2005) te Randhawa i sur. (2006). Molekularna analiza izolata napravljena je multipleks PCR metodom.

Rezultati: Uzorci su uključivali 472 (92.73%) obriska duplji stabala i 37 (7.27%) uzoraka ptičjih ekskreta. U uzetim uzorcima dokazana su četiri izolata *C. neoformans* (4/509, 0.8%). Svi izolati dobiveni su kultivacijom iz uzoraka dobivenih iz duplji stabala u priobalnom području, dok niti jedan izolat nije dobiven iz uzoraka ptičjih ekskreta niti iz uzorak aprikupljenih iz kontinentalnog područja Hrvatske. Među dobivenim izolatima dokazani su molekularni tipovi VNI (3/4) and VNIV (1/4).

Zaključak: Ovo je prvo istraživanje u kojem je dokazana prisutnost *C. neoformans* u okolišnim uzorcima u Hrvatskoj koja pokazuje mogući ekspozicijski rizik stanovnika ovome kvascu.

Presence of *Cryptococcus neoformans* in the environmental samples in Croatia

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Aim: The encapsulated basidiomyceteous yeasts of *Cryptococcus neoformans* causes a life-threatening infection affecting primarily immunocompromised hosts. The environmental source of this yeast are mainly bird excreta and decaying wood. So far, the presence of this yeast was not found in the environment in Croatia. The aim of this study was to investigate the presence of *C. neoformans* in the environmental samples in Croatia and to determine molecular characteristics of present isolates.

Methods: In the period from 2013 to 2016, a total of 509 environmental samples including desiccated bird's excreta and swabs from the hollows of the trees were collected from different geographic locations in Croatia. Samples were collected and processed as described in previous studies by Cafarchia *et al.*, (2006) and Randhawa *et al.*, (2005). Molecular analysis of isolates was performed by multiplex PCR.

Results: Samples included 472 (92.73%) swab samples from tree hollows and 37 (7.27%) samples from bird excreta. Four *C. neoformans* species complex isolates were identified during this study (4/509, 0.8%). All four isolates were recovered from cultures of tree hollow swabs collected in the Mediterranean area, while there were no isolates recovered from bird excreta or from samples collected in the continental area. Two different molecular types VNI (3/4) and VNIV (1/4) were identified.

Conclusion: This is the first study demonstrating the presence of *C. neoformans* in the environment in Croatia and thus the potential exposure risk of the inhabitants to these yeast.

PO-73 Učestalost *Microsporium canis* vrste izolirane u Nastavnom zavodu za javno zdravstvo Splitsko – dalmatinske županije od 2009. do 2018. godine

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Cilj istraživanja: Zoofilni dermatofit *Microsporium canis* jedan je od vodećih uzročnika dermatomikoza u zemljama srednje i južne Europe. Cilj ovog istraživanja je utvrditi učestalost mikrosporoze potvrđene izolacijom u laboratoriju za dijagnostiku gljivičnih infekcija Službe za kliničku mikrobiologiju Nastavnog zavoda za javno zdravstvo Splitsko-dalmatinske županije (NZJZ SDŽ) te analizirati spolnu i dobnu strukturu oboljelih.

Materijali i metode: Retrospektivnim istraživanjem prikupljeni su podaci o rezultatima mikološke obrade bolesnika sa suspektom dermatomikozom upućenim u NZJZ SDŽ od početka 2009. do kraja 2018. godine. Analizirana je doba i spolna struktura bolesnika kod kojih je laboratorijski potvrđena mikrosporoza.

Rezultati: U promatranom periodu ukupno su obrađena 9.764 dermatomikološka uzorka (4.314 strugotina kože, 950 uzoraka vlasišta i 4.500 uzoraka noktiju). Kulturom su potvrđene dermatofitoze u 12% uzoraka (n=1.181), a najčešće izolirane vrste dermatofita su: *Microsporium canis* (n=556; 47%), *Trichophyton rubrum* (n=280; 24%) i *Trichophyton mentagrophytes/interdigitale* (n=157; 13%). *Microsporium canis* je vodeći uzročnik infekcija vlasišta (n=281; 95%) i kože (n=266; 40%), a među oboljelima od mikrosporoze prevladavaju djeca u dobi do 14 godina (n=368; 79%). U dječjoj populaciji (≤ 14 godina) podjednaka je distribucija među spolovima (48% dječaci : 52% djevojčice). U bolesnika starih 15 ili više godina *Microsporium canis* znatno je češće dokazan u žena (84%) nego muškaraca (16%).

Zaključak: U promatranom desetogodišnjem razdoblju u mikološkom laboratoriju NZJZ SDŽ, u skladu s dosadašnjim opažanjima i trendovima u susjednim zemljama, iz uzoraka vlasišta i kože najčešće izolirana vrsta dermatofita je *Microsporium canis*. Mikrosporoza se najčešće dijagnosticira u djece do 14 godina, podjednako u oba spola. Opažena je razlika učestalosti mikrosporoze u odraslih muškaraca i žena.

***Microsporium Canis* Isolated from Outpatients in the Public Health Institute of Split and Dalmatia County, 2009-2018**

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Objective: *Microsporium canis*, a zoophile dermatophyte fungus, is one of the leading etiologic agents of superficial fungal infections in Central and Southern Europe. The aim of this study was to determine frequency of *Microsporium canis* isolation in the Mycological Laboratory of the Public Health Institute of Split-Dalmatia County and to analyse the sex and age structure of the patients affected.

Methods: A retrospective study collected data on the results of mycological examination of patients with suspected dermatomycosis referred to the Public Health Institute laboratory from the beginning of 2009 to the end of 2018. The age and gender data of patients with laboratory confirmed microsporosis cases were analyzed.

Results: In the study period a total of 9,764 samples (4,314 skin, 950 hair and 4,500 nail specimens) were processed. Dermatophytes were isolated from 12% of the clinical samples (n=1,181). *Microsporium canis* was the most frequently isolated fungus (n=556; 47%), followed by *Trichophyton rubrum* (n=280; 24%) and *Trichophyton mentagrophytes/interdigitale* (n=157; 13%). *Microsporium canis* was the leading cause of tinea of the scalp (n=281; 95%) and the glabrous skin (n=266; 40%). Children under age 14 were predominantly affected with microsporosis (n=368; 79%). There was no sex difference in children (48% boys versus 52% girls). In patients aged 15 years or older, *Microsporium canis* was more frequently isolated from specimens of female (84%) patients.

Conclusion: In accordance with the previous observations and trends in neighbouring countries the most commonly isolated dermatophyte in our mycological laboratory is *Microsporium canis*. Microsporosis is most commonly diagnosed in children up to 14 years of age, equally in both sexes. A difference in the incidence of microsporosis in adult males and females was observed.

PO-74 Epidemiologija gljiva kod hematoloških bolesnika i bolesnika u jedinicama intenzivnog liječenja (JIL), Klinički bolnički centar Zagreb 2018.

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Cilj: Invazivne gljivične infekcije (IFI) se nalaze kod bolesnika s teškim bolestima. Brzo dijagnoza je komplicirana za razlikovanje infekcije od normalne flore. Liječenje je dugotrajno, smrtnost visoka. Cilj rada je praktična primjena smjernica za dijagnozu

Metode: Analizirane su elektronske baze podataka: mikrobiološke, kliničke i trajanja hospitalizacije. Gljive su kultivirane i identificirane na standardnim mikološkim podlogama, mikroskopskim pretragama (nativno, fluorescentno) i MALDI-TOF. In vitro je testirana osjetljivost na antifungike, minimalna inhibitorna koncentracija i e-testovi, CLSI.

Rezultati: Izolirane su gljive kod 1407 bolesnika. Bolesnici su liječeni 2018. na hematologiji (COI, TKS, ZZH), dječjoj hematologiji (ZHO) i jedinicama intenzivnog liječenja JIL (kirurškog AIK, AKA, internističkog ISH, pedijatrijskog JID, JIR). Gljive su izolirane u 5767 uzoraka. Mikološkim pretragama izolirano je 90% gljiva, a 10% bakteriološkim. Gljive su dokazane u 50% uzoraka iz hematologije. Ukupno je izolirano je 7817 kvasaca, oportunističkih i saprofitnih plijesni (85%, 6%, 8%). Gljive su izolirane iz sterilnih uzoraka (krv, CVK, rane, urini) 10%, gornjeg i donjeg dišnog sustava (42%, 21%), te stolica (26%). Među kvascima najčešće su *C.albicans*, *C.glabrata*, *C.parapsilosis* (45%, 17%, 7%). Među oportunističkim plijesnima najčešći su *Aspergillus*, *Fusarium*, *Mucorales* (87%, 7%, 6%). Najčešći *Aspergillus* su *A.niger*, *A.fumigatus* i *A.flavus* (32%, 30%, 8%). Samo na temelju mikoloških nalaza moguća je kandidijaza (IC), invazija oportunističkim plijesnima (IA) i kolonizacija (4%, 21%, 75%). Moguća je IC, IA kod hematoloških bolesnika (8%, 29%) prema JIL bolesnicima (4%, 16%).

Zaključak: Dijagnoza (sigurna, vjerojatna, moguća) i terapija IFI donosi se na temelju kombinacije svih kliničkih i mikoloških pretraga.

Epidemiology of Fungi in Haematological Patients and Patients in Intensive Care Units (ICU), University Hospital Centre Zagreb 2018

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Objective: Invasive fungal infections (IFI) are found in patients with severe disease. Quick diagnosis is complicated to distinguish infection from normal flora. Treatment is long-term with high mortality. The aim of study are the practical application of the guidelines for diagnosis

Methods: We analyzed electronic databases: microbiological, clinical and duration of hospitalization. Fungi are cultured and identified on mycological media, microscopical (native, fluorescent) and MALDI-TOF. Was tested in vitro sensitivity to antifungal agents, with the minimal inhibitory concentration and E-test, CLSI.

Results: Patients 1407 had isolated fungi. The patients were treated in 2018 on hematology (COI, TKS, ZZH), pediatric hematology (ZHO), and intensive care units ICU (surgical AIK, AKA, medical ISH, pediatric JID, JIR). Fungi were isolated in 5767 samples. Mycological examinations isolated 90% of the fungi and 10% of the bacteriological ones. A total of 7817 yeasts, opportunistic and saprophytic molds were isolated (85%, 6%, 8%). Fungi were isolated from sterile samples 10% (blood, CVC, wounds, urine), upper and lower respiratory tract (42%, 21%), and stools (26%). Among the yeasts the most common are *C.albicans*, *C.glabrata*, *C.parapsilosis* (45%, 17%, 7%). Among the opportunistic molds, the most common are *Aspergillus*, *Fusarium*, *Mucorales* (87%, 7%, 6%). The most common *Aspergillus* are *A.niger*, *A.fumigatus* and *A.flavus* (32%, 30%, 8%). Based on mycological findings, candidiasis (IC), invasion by opportunistic molds (IA) and colonization (4%, 21%, 75%) were possible. Possible IC, IA in haematological patients (8%, 29%) versus ICU patients (4%, 16%).

Conclusion: The diagnosis (safe, probable, possible) and IFI therapy are made based on a combination of all clinical and mycological examinations.

PO-75 Fungal co-infection in severe influenza – who is at risk?

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Incidence of fungal superinfection during severe influenza is being increasingly reported in literature over last decade, especially in patients treated with VV ECMO. Invasive pulmonary aspergilosis (IPA) is usually seen in immunocompromised patients, however over past years numbers patients with flu and IPA as superinfection is increasing, while data on candida superinfection and its significance is scarce. During 2018/2019 seasonal flu epidemics fungal superinfection during was demonstrated in 27% of patient, *Aspergillus fumigatus* and *Candida albicans* being predominant species. Fungal superfection with *Aspergillus* and *Candida* was associated with increased mortality in influenza patients. Use of systemic corticosteroids was shown to be associated with increased fungal infection rate. Patients on regular therapy with inhaled inhalation corticosteroids was don't seem to have increased incidence of fungal superinfection. Further investigation is warranted in order to better understand fungal superinfection in influenza patients.

PO-76 Program upravljanja antibioticima: planiranje i primjena u bolničkom okruženju

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Rezistencija bakterija je globalni problem koji nije samo javno zdravstveni problem već predstavlja gospodarstvenu pa i sigurnosnu prijetnju. Može nastati zbog nepravilne upotrebe antibiotika što obuhvaća prekomjernu ili pogrešnu upotrebu, subdoziranje ili zloupotrebu ovih lijekova. Program upravljanja antibioticima (PUA) je jedan od načina ukazivanja na nepravilnosti primjene antibiotika. PUA bi se mogla opisati kao neprekidni i sistematski rad na optimizaciji upotrebe antibiotika unutar bilo kojeg zdravstvenog sustava. Ključni cilj ovog programa jest redukcija nepravilne upotrebe antibiotika što će povoljno utjecati na ishod liječenja bolesnika, a ujedno će utjecati i na smanjenje učestalosti neželjenih nuspojava prilikom upotrebe antibiotika.

U idealnoj situaciji PUA se sastoji od tri osnovna dijela: 1) sistemske pretpostavke (smjernice, tim koji provodi program, odgovarajući dijagnostički, informatički i ljudski potencijali); 2) problemi koje tim za provođenje programa želi otkloniti; 3) radna strategija koju će tim provoditi.

Uobičajeno je da PUA predvodi kliničar, mikrobiolog ili farmaceut premda u određenim situacijama ovu ulogu može preuzeti medicinska sestra ili za takvu ulogu obučen drugi zdravstveni djelatnik. Ne postoji univerzalno rješenje za svaku situaciju! Nedostatak laboratorijske infrastrukture ne predstavlja valjani razlog za odlaganje primjene PUA-e. Premda je laboratorijska podrška iznimno značajna pri optimiziranju odabira antibiotika, većina početnih povoljnih učinaka primjene PUA-e proizlazi iz zaustavljanja neopravdane upotrebe antibiotika. Samom pojačanom kontrolom kliničkih indikacija za primjenu antibiotika se može značajno smanjiti količina ordiniranih antibiotika.

Zvanični početak primjene PUA-a u Kraljevskoj bolnici u Muskatu je bio listopad 2016. godine kad je na internetskoj stranici bolnice objavljena Odluka o uvođenju PUA. Rezultati PUA-e koji se provode u Kraljevskoj bolnici potvrđuju dosadašnja saznanja da je PUA iznimno važan čimbenik nacionalnog plana smanjivanja rezistencije bakterija.

Antibiotic stewardship program: planning and implementation in the hospital settings

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Antimicrobial resistance (AMR) is a global problem threatening not only public health but also economic development and security. It can stem from inappropriate antibiotic use which can include overuse, misuse, underuse or abuse of antibiotics. Antimicrobial stewardship program (ASP) is one way to address inappropriate antimicrobial use. ASP can be defined as an ongoing and systematic effort to optimize the use of antimicrobial medicines within a hospital. The key objectives of this program includes reducing of inappropriate antimicrobial use, improving patient care outcomes and mitigating adverse consequences of antimicrobial use.

Ideally, ASP has three components: 1) system prerequisites (guidelines, AMS team, adequate diagnostic, human and information technology resources); 2) issues that AMS team aims to optimize; 3) AMS team working strategy.

ASPs are usually led or co-led by prescribing doctors, microbiologists, or pharmacists, but a nurse or community health worker may occasionally take the lead. There is no 'one size fits all' model! Poor laboratory infrastructure or support to an ASP is not in itself a reason to delay initiating a program. Although laboratory support is instrumental in optimizing antibiotic choice, much of the early gains from starting stewardship activities come from reducing the use of unnecessary antibiotics. This means that many antibiotic prescriptions can be stopped purely on the basis of lack of clinical indication.

The Royal Hospital ASP was officially introduced in 2016 when the ASP statement was manifested on the Royal Portal. The results of the Royal Hospital AMS activities support the previously proven conclusion that ASPs are important part of the national plan for the AMR reduction.

PO-77 Izloženost antibioticima i razvoj antimikrobne otpornosti kod školske djece

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Ciljevi: Istraživali smo sustavnu primjenu antibiotika u školske djece i poveznicu primjene antibiotika s razvojem antimikrobne otpornosti u respiratornim patogenima. Također smo ispitali ulogu školske djece u nastajanju i širenju rezistentnih bakterija.

Metode: Ispitanici su bili 450 školske djece, starosti od 6-15 godina (225 zdrave djece, 225 djece s infekcijom gornjih dišnih putova) iz Rijeke, Hrvatska, s brisevima grla i nazofarinksa. Klinički podatci izvađeni su iz upitnika.

Rezultati: Ukupno je 17% školske djece uzimalo antibiotik u prethodnih šest mjeseci (7% zdrave djece, 27% akutno bolesnih pacijenata). Penicilini su bili najčešće upotrebljavani antibiotici. Upotreba penicilina uskog spektra bila je manje uobičajena od upotrebe amoksicilina i amoksicilina s klavulanskom kiselinom. Izloženost antibioticima kod školske djece u prethodnih šest mjeseci bila je povezana s češćom pojavom bakterija otpornih na antibiotike.

Zaključak: Prema našoj studiji, upotreba antibiotika povezana je s većom stopom otpornosti na patogene dišnih putova. Školska djeca predstavljaju važan rezervoar bakterija otpornih na antibiotike u zajednici, a ovu dobnu skupinu također treba smatrati ishodištem intenzivnog obrazovanja zdravstvenih djelatnika i pacijenata o racionalnom korištenju antibiotika s ciljem sprječavanja nastanka i širenja rezistentnih bakterija.

Antibiotic exposure and development of antimicrobial resistance in school children

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Aims: We investigated the systemic antibiotic use in school children and the association of antibiotic use with the development of antimicrobial resistance in respiratory pathogens. Also, we examined the role of school children in the emergence and spread of resistant bacteria.

Methods: Subjects were 450 school children, 6-15 years of age (225 healthy children, 225 children presented with upper respiratory tract infection) from Rijeka, Croatia, with throat and nasopharyngeal swabs. Clinical data were extracted from a questionnaire.

Results: In total, 17% of the school children had used an antibiotic in the previous six months (7% of healthy children, 27% of the acutely ill patients). Penicillins were the most frequently used antibiotics. The use of narrow-spectrum penicillins was less common than the use of amoxicillin and amoxicillin with clavulanic acid. Antibiotic exposure in school children in the previous six months was associated with the carriage of antibiotic-resistant bacteria.

Conclusion: According to our study, antibiotic use is linked with higher resistance rates of respiratory tract pathogens. School children represent an important reservoir of antibiotic-resistant bacteria in the community, and this age group should also be considered a target for medical professionals' and patients' intensive education about rational use of antibiotics with the goal to prevent the emergence and spread of resistant bacteria.

PO-78 Znanje i stavovi o upotrebi antibiotika i otpornosti bakterija na antibiotike kod roditelja

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Ciljevi: Ciljevi našeg istraživanja bili su ispitati razinu znanja, stavova i prakse u roditelja pri uzimanju antibiotika i svjesnosti o antimikrobnoj otpornosti, te razlučiti razlike između urbane i ruralne sredine kao i procijeniti utjecaj zdravstvenih djelatnika na edukaciju svojih pacijenata o ovoj važnoj temi.

Metode: Istraživanje na osnovu upitnika za uzorak od 1000 roditelja djece koja pohađaju 11 osnovnih škola Primorsko-goranske županije u Hrvatskoj.

Rezultati: Ukupan postotak odgovora bio je 65,1% (50,6% u urbanom 79,6% u ruralnom). Sveukupno znanje o antibioticima bilo je veće u roditelja gradske sredine, dok su roditelji u urbanoj i ruralnoj sredini uglavnom imali slična znanja i stavove o upotrebi antibiotika kada su podijeljeni na pojedinačne izjave. U prethodnoj godini 28,2% djece i 28,9% roditelja koristilo je antibiotik. Roditelji su imali visoko povjerenje u liječničku odluku o propisivanju antibiotika (96,3% izjavilo je da vjeruje odluci liječnika da ne prepisuju antibiotike i 93,5% da propisuju antibiotike) i visoku svjesnost o antimikrobnoj otpornosti (94,8%). Mediji masovnog priopćavanja (televizija, internet, novine) bili su više uključeni u informiranje roditelja o antimikrobnoj otpornosti nego zdravstveni djelatnici, svega 30,9%.

Zaključci: Unatoč većem znanju o antibioticima u roditelja gradske sredine, to se nije odrazilo na razinu upotrebe antibiotika. Ovo istraživanje istaknulo je potrebu za aktivnijim sudjelovanjem zdravstvenih djelatnika u komunikaciji o problemima upotrebe antibiotika i antimikrobnoj otpornosti prema njihovim pacijentima. Edukacija roditelja i povjerenje u odluku liječnika o propisivanju antibiotika moraju doprinijeti smanjenju nepotrebnog propisivanja antibiotika.

Knowledge and attitudes about antibiotic use and resistance in parents

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Aims: The goals of our study were to examine the level of parental knowledge, attitudes and practice of antibiotic use and awareness of antimicrobial resistance, and to assess differences between urban and rural area, and also to evaluate the impact of medical professionals in education of their patients about this important topic.

Methods: A questionnaire based, cross-sectional study was distributed to 1000 parents of children attending 11 elementary schools of Primorsko-Goranska County, Croatia.

Results: The overall response rate was 65.1% (50.6% urban, 79.6% rural). The overall knowledge of antibiotics was higher in urban parents, while urban and rural parents held mostly similar knowledge and attitudes related to antibiotic consumption when split into individual statements. In the previous year 28.2% of children and 28.9% of parents used an antibiotic. Parents had a high level of trust in doctors' antibiotic prescribing practice (96.3% reported trusting the doctors' decision not to prescribe antibiotics and 93.5% to prescribe antibiotics) and high awareness of antimicrobial resistance (94.8%). The mass media (television, internet, newspapers) were more involved in informing parents about antimicrobial resistance than medical professionals, only 30.9%.

Conclusions: Despite a higher knowledge about antibiotics in urban parents it was not reflected on the level of antibiotic use. The present study highlighted the need for more active participation of medical professionals in communicating the problems of antibiotic use and resistance to their patients. Parents' education and trust in doctors' decision about prescribing antibiotics must be an additional benefit in reducing futile antibiotic prescribing.

PO-79 Pilot projekt – Prevencija širenja multirezistentnih bakterija u Općoj bolnici Pula i domovima za starije osobe na području Istarske županije
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U Općoj bolnici Pula često se hospitaliziraju pacijenti koji su korisnici usluga Domova za starije osobe (Domovi). Najčešće se radi o kroničnim bolesnicima sa brojnim hospitalizacijama u Klinikama i Bolnicama, a često su inficirani ili kolonizirani multirezistentnim (MDR) bakterijama.

Tijekom 2018 godine u Općoj bolnici Pula kod 35% bolesnika primljenih iz Domova u nadzornim uzorcima izolirane su MDR bakterije.

Cilj: Praćenje trenda kretanja MDR bakterija u bolničkih pacijenata i korisnika Domova kroz niz aktivnosti sa zajedničkim ciljem smanjenja širenja MDR bakterija u Istarskoj Županiji.

Metode:

1. Prijava projekta Odjelu za zdravstvo Istarske županije, uz osiguranje financijske podrške.
2. Dogovorena je suradnja sa Domovima za starije osobe, Opće bolnice Pula, Zavoda za Javno zdravstvo Istarske Županije (epidemiolozi).
3. Trajna edukacija osoblja u Domovima na temu prevencije širenja MDR bakterija jednom mjesečno.
4. Posjet i obilazak Domova prema planu, te svakodnevna telefonska podrška.

Rezultati: 1.-6. mj. 2019.

1. Tijekom prvih 6 mj 2019 godine postotak pozitivnih nadzornih kultura pri prijemu pacijenata iz Domova smanjio se na 21%.
2. U projekt se aktivno uključilo 35 županijskih i obiteljskih Domova.
3. Savjeti i podrška putem telefonskog poziva pruženi su 56 puta.
4. Održano je 6 edukacija i 2 interaktivne radionice na temu prevencija širenja MDR bakterija, kojim je prisutvovalo ukupno 163 zaposlenika.
5. Komunikacija između zaposlenika Bolnice i Domova je poboljšana, a proces otpusta pacijenta iz Bolnice i ponovni prijem u Domove je olakšan.

Zaključak: Provedene aktivnosti Tima za kontrolu bolničkih infekcija dovele su do pozitivnih rezultata. Tim ima bolji pregled nad trendom širenja MDR bakterija u populaciji koja često gravitira u Bolnicu. Osoblje Domova primilo je stručno podršku i pomoć u njezi i skrbi korisnika sa izoliranom MDR bakterijom.

**Pilot project – Prevention of the spread of multiresistant bacteria in
General Hospital Pula and long-term care facilities in Istrian Region**

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The General Hospital Pula frequently hospitalizes patients, residents from long-term care facilities (LTCF). Most often, these are chronic patients with a history of hospitalization in clinics and hospitals, and often infected or colonized by multidrug resistant bacteria (MDR).

During 2018. in the General Hospital Pula, MDR bacteria were detected by screening samples in 35% of patients admitted from LTCF. This number of patients colonized or infected by MDR bacteria represented a big load for the hospital.

AIM OF PROJECT: Monitoring the trend of MDR bacteria in hospital patients and LCTF residents through different activities with the aim to decrease the spreading of MDR bacteria in the Istrian Region.

METHODS:

1. Applying for the Regional Fund for a grant (Health Department of Istria Region)
2. Arrange cooperation between General Hospital Pula, Public Health Institute of the Istrian Region and LTCF in the Region of Istria
3. Continuous education (monthly) of LTCF staff in the field of prevention of spreading of multidrug-resistant microorganisms
4. Visiting LTCF according to a plan and daily supporting by phone.

RESULTS FOR THE FIRST SIX MONTHS 2019.

1. During the first 6 months of 2019, the percentage of positive surveillance cultures at LTCF admissions decreased to 21%.
2. A total number of 35 LTCF were actively included in the project.
3. Advice and support by phone call have been provided 56 times.
4. There were 6 trainings and 2 interactive workshops on the prevention of the spread of MDR, attended by a total of 163 employees
5. The communication between the staff of the hospital and LTCF-s was improved so the process of the patient discharge became easier.

CONCLUSION: The activities implemented by the hospital Team for the prevention of hospital infections in this project resulted in a positive outcome. The Team has a better overview on the trend of MDR bacteria in the population that often gravitates to General Hospital Pula. LTCF staff received expert support and assistance in the care of a patient with MDR bacteria.

PO-80 Epidemija *Klebsiella pneumoniae* OXA-48 i ESBL pozitivne i rezistentne na kolistin u Općoj bolnici Karlovac

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CILJEVI: Tijekom 2018.godine a posebno u prvoj polovini 2019.godine zapažen je porast rezistencije na kolistin unutar reda *Enterobacterales* (posebno *K.pneumoniae*). Uočena je epidemija u Općoj bolnici Karlovac na odjelu neurologije sa sporadičnim slučajevima i na drugim odjelima. Cilj je komparirati rezultate screening kromogenih ploča (chromID OXA-48, bioMerieux i CHROMID Colistin R, bioMerieux) s molekularnom potvrdom mehanizama rezistencije i epidemiološki prikaz pacijenata i uzoraka kod navedenih izolata.

MATERIJALI I METODE : Tijekom rutinske obrade uzoraka, korištene su i kromogene ploče za detekciju OXA-48, ESBL, rezistencije na ertapenem (chromID CARBA) i kolisitinske rezistencije, proizvođača bioMerieux. Rezistentni sojevi su obrađeni tzv.double-disk sinergijskim testom s klavulanskom kiselinom za detekciju ESBL. Svim je sojevima rađena mikrodiluciona metoda provjere osjetljivosti na nekoliko klasa antibiotika. Inhibicija s EDTA je rađena za screen na MBL. Inhibicija s kloksacilinom je rađena za detekciju AmpC. Svi sojevi rezistentni na ertapenem i kolistin su poslani na retestiranje u KBC Zagreb i u KIB "Dr. Fran Mihaljević". Oksacilinaza je potvrđena PCR metodom (blaOXA-48) a kromosomska rezistencija na kolistin je potvrđena neuspješnom konjugacijom na recipijentni soj *E.coli* A15R.

REZULTATI : Svih 14 izolata su pozitivni screening metodama na kromogenim pločama i svi su ESBL. Uniformno su rezistentni na amoksicilin s/bez klavulanske kiseline, piperacilin/tazobaktam, cefazolin, cefuroksim, cefalosporine proširenog spektra, ciprofloksacin, gentamicin (jedan soj je osjetljiv), ceftolozan/tazobaktam, ertapenem i kolistin a svi su osjetljivi na ceftazidim/avibaktam i amikacin (3 soja su intermedijarno osjetljiva), sulfametoksazol trimetoprim (tri su rezistentna i jedan je intermedijaran). Sedam od četrnaest je rezistentno na meropenem a šest je rezistentno na imipenem. Svi su pozitivni na bla-SHV gene a svi osim dva su pozitivni i na blaOXA-48 gene. L plazmid je pozitivan u svih osim u dva izolata.

ZAKLJUČAK: Epidemija OXA-48 pozitivne, kolistin rezistentne klepsijele u općoj bolnici Karlovac prenošene L plazmidom pokazala je potencijalnu opasnost u kombinaciji s rezistencijom na kolistin ne ostavljajući puno izbora u antibiotskoj terapiji. Zasad su se ceftazidim u kombinaciji s avibaktamom i amikacin pokazali kao djelotvorni antibiotici. Svi su izolati MDR a četiri soja su i XDR (Extensive Drug Resistant). Sojevi su se zasad prezentirali uglavnom kao kolonizatori detektirani ciljanim screening pretragama na MDR, ali i iz urina kod kateteriziranih pacijenata a jedan je izoliran i iz sputuma. Predstavljaju opasnost eventualnim jačanjem virulencije, snažnim epidemijskim potencijalom i oskudnim izborom liječenja.

Outbreak of OXA-48 positive, ESBL positive, colistin-resistant *Klebsiella pneumoniae* in General Hospital Karlovac

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INTRODUCTION AND PURPOSE: During 2018., but especially in the First half of 2019. emergence of colistin resistant was observed among the order of *Enterobacteriales* in General Hospital Karlovac, mostly in *Klebsiella pneumoniae*. Outbreak was observed in the Department of Neurology with a few exceptions. Aim of this presentation is to compare results observed on screening plates (chromID OXA-48, bioMerieux,; chromID colistin R, bioMerieux ; chromID CARB and chromID ESBL) with carbapenem-resistance mechanisms as well to characterize the carbapenem-mechanisms and molecular epidemiology of colistin.

MATERIAL AND METHODS: During routine laboratory work, screening plates were used for detection of OXA-48, ESBL, ertapenem resistance and for colistin resistance. The antimicrobial susceptibility was determined mostly by broth microdilution method and double disk synergy test was performed for detection of ESBL. Inhibitor based test with EDTA was used to screen for production of metallo-beta-lactamases (MBLs), The transferability of colistin resistance was determined by conjugation (broth mating method) employing *E. coli* A15R- strain resistant to sodium azide. Carbapenem hydrolyzing oxacillinases (blaOXA-48) was determined by PCR.

RESULTS: All 14 isolates were uniformly positive on screening plates (OXA-48, ESBL, colistin R) and resistant to amoxicillin alone and combined with clavulanic acid, piperacillin/tazobactam, cefazoline, cefuroxime, expanded spectrum cephalosporines, ciprofloxacin, ceftolozane-tazobactam, ertapenem, colistin and all but one to gentamicin. Isolates were sensitive to ceftazidime- avibactam, amikacin (three isolates were susceptible, increased exposure – I category), trimetoprim-sulfamethoxazole (three resistant , one I category); Seven isolates resistant to meropenem, six to imipenem. PCR was positive for blaSHV genes whereas all except two tested positive for blaOXA-48 genes. L plasmid revealed by PBRT in all but two isolates.

CONCLUSIONS: The study demonstrated emergence and spread of colistin resistant *K. pneumoniae* associated with severe infections which could pose a serious therapeutic problem. L plasmid is responsible for the fast dissemination of blaOXA-48 genes. All isolates were MDR with four XDRs (Extensive Drug Resistant). So far isolates were sensitive to ceftazidime -avibactam and amikacin. Isolates are mostly detected in the routine MDR screen and several were detected from urine in patients with urine catheter and one from sputum.

PO-81 Utjecaj promjene pH vrijednosti kromogene podloge na porast *K.pneumoniae*

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Ciljevi: Infekcije donjeg urinarnog trakta najčešće uzrokuju *Enterobacteriaceae*, čiji je optimalni rast pri pH=7,00. U ovom istraživanju praćen je porast *K. pneumoniae* u ovisnosti o promjenama pH vrijednosti, koje su se pak mijenjale ovisno o različitim koncentracijama NaCl-a dodanim u kromogenu podlogu za izolaciju patogena iz urinarnog trakta.

Metode: Analizom urinokultura izvanbolničkih pacijenata kroz mjesec dana u 2019. godini, prikupljeno je i testirano 30 različitih sojeva *K. pneumoniae*. Za izolaciju patogena korištena je kromogena podloga HiCrome UTI Agar Modified, koja u svom sastavu ne sadržava NaCl. Za identifikaciju su korištene standardne biokemijske metode. U medij su prije autoklaviranja (121 °C/15 min) dodane različite koncentracije NaCl-a: od 5,0% do 7,0% (w/v). Podlogama su, nakon kalibracije uređaja odgovarajućim puferima, pH metrom s pripadajućom elektrodom izmjerene pH vrijednosti. Nacijepljene podloge inkubirane su u aerobnim uvjetima pri $37 \pm 1^\circ\text{C}$, a porast je očitao nakon 18–24 h.

Rezultat: Od ukupno 30 testiranih sojeva *K. pneumoniae* laboratorijskim ispitivanjem dokazan je porast njih 26, što predstavlja 86% svih analiziranih sojeva. Dok su četiri soja, odnosno 13% od svih testiranih bila inhibirana, te nije bilo porasta pri koncentraciji NaCl-a manjoj od 5%. Najveći porast sojeva *K. pneumoniae* (N=10) zabilježen je pri pH medija 6,95 sa dodanom koncentracijom NaCl-a od 6%, a potom slijedi porast (N=9) sojeva u mediju sa 7% NaCl pri pH=6,84. Najslabiji porast izoliranih sojeva zabilježen je pri pH=7,00, odnosno pri dodanoj koncentraciji NaCl-a od 5%.

Zaključak: Promjena pH vrijednosti tj. promjena koncentracije NaCl-a u kromogenoj podlozi za izolaciju patogena iz urinarnog trakta ima utjecaj na porast mikrobiološke vrste. U kromogenoj podlozi uz dodatak 6% NaCl-a dokazan je najbolji porast *K. pneumoniae* pri pH vrijednosti 6,95. Ovo istraživanje ukazuje na alkalnu pH homeostazu navedene bakterije, s akcentom na smanjeni broj ili nemogućnost porasta određenih sojeva kod prijelaza ka alkalnijem pH području mikrobiološke podloge.

Influence of changes in pH of the chromogenic media to growth of *K. pneumoniae*

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Aims: Infections of the lower urinary tract are most commonly caused by *Enterobacteriaceae*, whose optimum growth at pH = 7.00. In this study, the growth of *Klebsiella pneumoniae* was monitored depending on pH variations, which varied depending on the different NaCl concentrations added to the Chromogenic media for the isolation of the pathogen from the urinary tract.

Methods: By analyzing the urinary culture of outpatient patients during a one month-period in 2019, 30 different strains of *K. pneumoniae* were collected and tested. The Chromogenic HiCrome UTI Agar Modified was used for the isolation of the pathogen, which does not contain NaCl. Standard biochemical methods were used for identification. In the medium, prior to autoclaving (121 °C/15 min), various NaCl concentrations were added: from 5.0% to 7.0% (w/v). Chromogenic mediums were, after calibration of the device with suitable buffers, pH meter with the associated electrode measured pH value. Cultures were incubated under aerobic conditions at 37 ± 1 °C during 18-24 h.

Results: Out of a total of 30 tested strains of *K. pneumoniae*, growth showed 26, representing 86% of all analyzed strains. While four strains, or 13% of all tested, were inhibited and there was no growth in medium with NaCl concentration of less than 5%. The highest growth rate of *K. pneumoniae* strains (N=10) was recorded at pH 6.95 with 6% NaCl added, followed by growth (N=9) strains in medium with 7% NaCl at pH = 6.84. The lowest growth of isolated strains was recorded at pH = 7.00 at 5% NaCl concentration.

Conclusion: Changing the pH value or changing the concentration of NaCl in the Chromogenic medium for the isolation and direct identification of pathogens from the urinary tract has an influence on the growth of the microbiological species. In the Chromogenic medium with the addition of 6% NaCl, the best growth of *K. pneumoniae* was demonstrated at pH of 6.95. This study points to the alkaline pH of homeostasis of *Klebsiella pneumoniae*, with an accent on the reduced number or the inability to increase certain strains when passing to the alkaline pH range of the microbial medium.

PO-82 Utjecaj različitih koncentracija NaCl u kromogenoj podlozi na porast uropatogene *E.coli*

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Uvod: *Enterobacteriaceae* su najčešći uzročnici urinarnih infekcija, te pri rastu i aktivnom razmnožavanju uglavnom ne toleriraju visoke koncentracije soli (NaCl), no neke, kao npr. *E.coli*, ipak pokazuju osobine osmotolerancije. Cilj ovog istraživanja bio je utvrditi sposobnost preživljavanja *E.coli* pri različitim koncentracijama NaCl dodanih u kromogenu podlogu.

Materijali i metode: Tijekom mjesec dana u 2019. godini prikupljeno je i testirano ukupno 40 kliničkih izolata *E.coli* iz rutinskih urinokultura izvanbolničkih pacijenata. Za izolaciju i direktnu identifikaciju koristila se kromogena podloga HiCrome UTI Agar, HiMedia, koja u svom sastavu ne sadržava NaCl. U medij korišten za invitro uzgoj bakterija prije autoklaviranja, pri radnim uvjetima 121°C / 15 min, dodavane su različite koncentracije NaCl (7%-18%). Čiste kulture *E.coli* su potom nasijane na kromogenu podlogu s dodatkom NaCl, te su inkubirane na 37 ± 1°C te je nakon 18-24 h očitavan porast.

Rezultati: Od ukupno 40 testiranih sojeva *E.coli*, 22 soja (55%) su bila inhibirana koncentracijama NaCl-a od 7% i nižima, dok ih je 18 (45%) bilo inhibirano pri koncentracijama NaCl-a od 8% do 16%. Analiza pozitivnih rezultata pokazala je inhibiciju 4 soja pri koncentraciji 8% NaCl te 14 sojeva pri koncentracijama 11%-16% NaCl. Dvanaest sojeva je inhibirano pri koncentraciji od čak 16% NaCl, što predstavlja 30% od svih testiranih sojeva.

Zaključak: Rezultati provedenog istraživanja ukazuju da je najveći porast *E.coli* u prisutnosti 15% NaCl-a u kromogenoj podlozi, dok pri većim koncentracijama (16%-18%) nije zabilježen porast. To bi značilo da pri visokim koncentracijama NaCl djeluje antimikrobno, stoga studija ima i klinički značaj. S obzirom da je urin hipertonični medij, važno je pratiti hoće li bakterije preživjeti ovakva antimikrobna svojstva urina. Ovim istraživanjem dokazano je da većina sojeva *E.coli*, ima dobru osmotolerantnost, te kao takvi imaju veću sposobnost preživljavanja u hipertoničnom urinu, što pak može objasniti zašto je upravo ta bakterija vodeći uzročnik urinarnih infekcija.

The Influence of Different Concentrations of NaCl in the Chromogenic Medium on the Growth of the Uropathogenic *E. coli*

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Aim: Infections of the lower urinary tract are most commonly caused by *Enterobacteriaceae* which mostly do not tolerate high salt concentration (NaCl), but some still show the osmotolerance ability (like *E. coli*). The aim of this study was to determine ability of *E. coli* to survive at different NaCl concentrations added to chromogenic agar.

Methods: During a one-month-period in 2019, 40 clinical isolates of *E. coli* were collected from routine urine cultures of outpatients. The medium used for in vitro cultivation and identification was chromogenic agar CHROMagar™ Orientation, HiMedia, which does not contain NaCl. Before autoclaving at 121°C/15 min various NaCl concentrations were added (7%-18%). Cultures were incubated under aerobic conditions at 37 °C ± 1 during 18-24 h.

Results: Out of a total of 40 tested strains of *E. coli*, 22 isolates (55%) were inhibited by concentrations of NaCl-a of 7% and less, while 18 (45%) of them were inhibited by NaCl concentrations from 8 to 16%. From them, 4 isolates were inhibited by 8% NaCl and 14 isolates were inhibited by NaCl concentrations from 11% to 16%. Twelve isolates (30% of all tested isolates) were inhibited by concentration of as much as 16% NaCl.

Conclusion: Results of this study show that most *E. coli* strains can survive 15% NaCl in chromatogenic media and there was no survival in higher concentrations (16%-18%). It means that high concentration of NaCl acts antimicrobial which is of clinical importance. Since urine is a hypertonic medium, it is important to monitor whether bacteria survive these antimicrobial properties of urine. Tested strains of *E. coli*, have shown good osmotolerance and as such have a greater ability to survive in urine, which perhaps explains why these bacteria are the most common cause of urinary infections.

PO-83 Primjena brzih dijagnostičkih testova u rutinsku praksu mikrobiološkog laboratorija u Općoj bolnici Pula

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Uvod: Europska unija definira brzi test kao kvalitativni i polukvalitativni in vitro dijagnostički medicinski test, koji se koristi pojedinačno ili u maloj seriji, a koji uključuje neautomatske postupke, a dizajnirani su tako da daju brze rezultate. U našem mikrobiološkom laboratoriju, koji je dio Odjela infektologije, od samog osnutka provodile su se isključivo parazitološke pretrage. U ožujku 2018. u rutinsku praksu uvedeni su brzi dijagnostički testovi za brzo otkrivanje antigena *Legionella* spp u urinu, adenovirusa, Respiratornog sincicijskog virusa (RSV) i virusa gripe u respiratornim uzorcima kao i testovi za otkrivanje antigena toksina *Clostridioides difficile*, *H. pylori*, adenovirusa, rotavirusa i norovirusa u uzorku stolice.

Cilj: Cilj nam je pokazati kliničke prednosti provođenja brzih testova u našoj bolnici, kao i rezultate.

Metode: Podaci su dobiveni iz bolničkog informatičkog sistema.

Rezultati: Tijekom jednogodišnjeg razdoblja (1.4.2018.-31.03.2019) u našem je laboratoriju učinjeno ukupno 639 brzih testova. Većina ih je korištena za detekciju adenovirusa i rotavirusa (193) te *Cl. difficile* toxin (161) u uzorcima stolice. Respiratorni uzorci su najviše testirani na virus gripe (124). RSV testovi pokazali su najbolju korelaciju sa kliničkom dijagnozom sa 46,5 % pozitivnih rezultata. Kliničari Opće bolnice Pula prepoznali su brze testove kao vrijednu pomoć u postavljanju dijagnoze radi brzog rezultata vidljivog u bolničkoj bazi podataka u roku od 2 sata. Brzi testovi za otkrivanje antigena *Legionella* spp u urinu te virusa gripe i adenovirusa u respiratornim uzorcima su po prvi put uvedeni u dijagnostiku te su stoga dobro prihvaćeni od strane kliničara.

Incorporating rapid diagnostic tests into routine practice in a small microbiology laboratory – General hospital Pula, Croatia

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Introduction: The European Union defines that a rapid test means qualitative or semi-quantitative in vitro-diagnostic medical device, used singly or in a small series, which involve non-automated procedures and have been designed to give a fast result. Our microbiology laboratory, which is part of the Department of infectology, used to perform only parasitological analysis. In March, 2018. rapid diagnostic tests were introduced into routine practice for rapid antigen detection of *Legionella* spp, adenovirus, Respiratory Syncytial Virus (RSV) and influenza virus in respiratory samples. Rapid tests for antigen detection of *Cl. difficile* toxin, *H. pylori* , adenovirus, rotavirus and norovirus were introduced for rapid detection of gastrointestinal infections.

Objective: Our objective was to show the clinical benefits of performing rapid tests in our hospital as well as the results.

Method: We used the hospital database for our research.

Results: During one year period (1.4.2018.-31.03.2019) a total number of 639 rapid tests were performed in our lab. Most of them were used for detection of both adenovirus and rotavirus (193) and *Cl. difficile* toxin (161) in stool samples and influenza virus (124) in respiratory samples. RSV tests showed the best correlation with the clinical diagnose, 46,5% of all performed tests were positive. The clinical benefit was recognized by all the clinicians working in the General hospital Pula because of the quick result visible in hospital database within 2 hours. Some rapid tests like antigen detection of *Legionella* spp in urine, influenza virus and adenovirus in respiratory samples were not available before, so they were well accepted by the clinicians.

PO-84 Usporedba tri metode za određivanje minimalne inhibitorne koncentracije

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CILJ: U posljednjih deset godina zapažen je dramatičan porast karbapenem-rezistentnih Gram-negativnih bakterija. Kolistin i tigeciklin su često zadnja terapijska opcija za liječenje infekcija uzrokovanih karbapenem-rezistentnim Gram-negativnim bakterijama. Testiranje osjetljivosti na kolistin i tigeciklin predstavlja tehnički problem jer disk-difuzijski test koji je rutinska metoda u većini laboratorija ne daje pouzdane rezultate zbog slabe penetracije antibiotika u agar. Utvrđeno je da E-test i VITEK 2 daju često vrlo veliku pogrešku (lažnu osjetljivost).

MATERIJAL I METODE: Ukupno je testirano 36 sojeva. Pet sojeva enterobakterija uzeti su iz vanjske kontrole UK NEQAS, a preostalih 31 su klinički izolati s definiranim mehanizmima rezistencije. Osjetljivost na meropenem, kolistin i tigeciklin je testirana pomoću tri metode i određivana je stopa rezistencije dobivena različitim metodama testiranja. Kategorička podudarnost je definirana kao postotak izolata svrstani u istu kategoriju osjetljivosti pomoću Erbascan metode i druga dva testa (E-test, VITEK 2). Kategorička nepodudarnost je definirana kao: (i) vrlo velika pogreška (VME) u slučaju da ERBASCAN daje rezistenciju, a komparativni testovi osjetljivost; (ii) veliku grešku (ME) ako je izolat proglašen osjetljivim pomoću Erbascan a rezistentan s komparativnim metodama; (iii) i mala greška (mE) ako je razlika u jednoj interpretacijskoj kategoriji između Erbascan i ostalih metoda. Esencijalna podudarnost je definirana kao postotak sojeva koji imaju MIK unutar jednog razrijeđenja u odnosu na Erbascan.

REZULTATI: Testiranje osjetljivosti na kolistin je utvrdilo VME (lažnu osjetljivost) s VITEK 2 i E-testom u *A. baumannii* (3/2017). *K. pneumoniae* ESBL (4/2013) je imala VME samo s E-testom. Testiranje osjetljivost na meropenem je pokazalo VME kod VIM pozitivnog izolata *K. pneumoniae* i NDM pozitivnog izolata *E. aerogenes*. ME (lažna rezistencija) je zapažena kod dva OXA-48 pozitivna izolata *K. pneumoniae*. Samo jedan izolat je pokazivao VME pri testiranju osjetljivosti na tigeciklin (*K. pneumoniae* 7/2016 ESBL) dok je ME zapažena kod dva izolata *A. baumannii* isolate (3/2017) i *E. aerogenes* (10/2018) kod VITEK 2 automatizirane metode. Esencijalna nepodudarnost (razlika u više od jednog razrijeđenja) je zapažena u sedam izolata testiranih na kolistin i šest testiranih na tigeciklin s E-testom. VITEK 2 je pokazao esencijalnu nepodudarnost u četiri soja testirana na meropenem. I E-test i VITEK 2 su imali stopu od 5% (2/36) VME. S druge strane, VITEK 2 je imao 14% (5/36) ME. MIK-ovi kolistina za *A. baumannii* su bili niži s VITEK-om i E-testom u usporedbi s ERBASCAN-om. S druge strane VITEK 2 je iskazivao više MIK-ove tigeciklina u usporedbi s ERABASCAN metodom iako su sojevi vanjske kontrole bili u osjetljivom

rasponu sa sve tri metode. U karbapenem osjetljivih izolata su MIK-ovi meropenema bili podjednaki sa sve tri metode, ali u OXA-48 pozitivnih izolata su vrijednosti MIK-a meropenema bili niži s E-testom i VITEK 2 automatiziranom metodom u odnosu na ERBASCAN. MIK-ovi kolistina dobiveni E-testom su bili niži nego oni dobiveni ERBASCAN-om u kolistin osjetljivih sojeva dok kod u kolistin rezistentnih sojeva nije bilo razlike između tri metode. Kontradiktorni rezultati su opisani i kod meropenema. Osjetljivi sojevi su pokazivali podudarnost sve tri metode dok su kod ertapenem-rezistentnih izolata MIK-ovi meropenema bili niži E-testom u odnosu na ERBASCAN.

ZAKLJUČCI: Kliničari i laboratorijsko osoblje bi trebali biti svjesni razlika u rezultatima testiranja osjetljivosti između E-testa, VITEK 2 automatizirane metode i standardnog testiranja dilucijom u bujonu (ERBASCAN). Te razlike su posebno značajne kod teško bolesnih osoba. Prema našim rezultatima ERBASCAN bi se mogao preporučiti za testiranje osjetljivosti na meropenem, tigeciklin i kolistin u multirezistentnih ili ekstenzivno rezistentnih Gram-negativnih bakterija.

Comparison of three methods for determining the minimum inhibitor concentration

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AIM: There is dramatic increase of carbapenemase producing Gram-negative bacteria all over the world. Colistin and tigecycline are often the last resort antibiotic for the treatment of infections associated with carbapenemase producing Gram-negative bacteria. Recently, colistin resistant isolates have been reported. However, there are technical problems with colistin and tigecycline susceptibility testing. Disk diffusion test does not provide reliable results due to the low penetration of antibiotic in agar. Broth microdilution method is the recommended standard technique. E-test and Vitek2 are known to yield false lower MICs resulting in very major errors (false susceptibility).

MATERIAL AND METHODS: In total 36 UK NEQAS strains and clinical isolates with defined resistance mechanism were tested. The susceptibility to meropenem, colistin and tigecycline was tested by three different method and the rate of resistant strains were calculated and compared between the different testing methods. Categorical agreement (CA) was defined as the percentage of isolates classified in the same susceptibility category by ERBASCAN compared to VITEK 2 and E-test. Category discrepancies were classified as follows: (i) very major errors (VME), cases where ERBASCAN indicated resistance and the comparative method indicated susceptibility; (ii) major errors (ME), an isolate categorized as susceptible by ERBASCAN and resistant by the comparative method; (iii) minor errors (mE), one interpretation category difference between ERBASCAN and the comparative methods. Essential agreement (EA) was considered as the percentage of MICs within 1 doubling dilution of the MIC determined by ERBASCAN.

RESULTS: Colistin susceptibility revealed VME (false susceptibility) with both VITEK 2 and E test in *A. Baumannii* (3/2017). *K. pneumoniae* ESBL (4/2013) col R exhibited VME with E-test. Meropenem susceptibility testing demonstrated VME With E-.test for the VIM-positive strain of *K. pneumoniae*. Essential disagreement (difference in more than one dilution) was observed in seven strains tested for colistin and in six strains tested for tigecycline. with E-test. VITEK 2 showed essential disagreement in four strains tested for meropenem. In total both E-test and VITEK 2 yielded 5% (2/36) VME. On the other hand, VITEK 2 yielded 14% (5/36) ME. The study demonstrated significant rate of categorical disagreement between ERBASCAN and other two methods. The MIC values of colistin for *A. baumannii* strains were lower with VITEK 2 and E-test compared to ERBASCAN. On the other hand, VITEK 2 demonstrated higher MIC values of tigecycline compared to ERBASCAN although UK NEQAS strains showed susceptibility with all testing methods. Carbapenem-

susceptible strains of *K. pneumoniae* meropenem MICs were in concordance with all three testing methods. *K. pneumoniae* OXA-48 showed disagreement between the testing methods. Colistin MICs obtained by E-test and VITEK 2 were slightly lower than those obtained by ERBASCAN in colistin susceptible strains in contrast to colistin resistant strains which showed concordance between the three testing methods. The contradictory results were observed from meropenem. Susceptible strains showed concordance between testing methods whereas ertapenem resistance strains displayed lower MIC values with E-test compared to ERBASCAN.

CONCLUSIONS: Clinicians and laboratory staff alike should be aware of the discordances between E-test and VITEK 2 and standard methods based on broth dilution, particularly in critically ill patients. According to our results, ERBASCAN should be recommended for colistin, meropenem and susceptibility testing of multidrug-resistant Gram-negative bacteria.

PO-85 Beta laktamaze proširenog spektra i plazmidna raznolikost u urinarnim izolatima *Escherichia coli* u Hrvatskoj: nacionalna, multicentrična, retrospektivna studija

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U posljednjih nekoliko godina primijećeno je dramatično povećanje prevalencije sojeva *Escherichia coli* (*E. coli*) koji proizvode β -laktamaze proširenog spektra (ESBL) – i u zajednici i u zdravstvenim ustanovama. Cilj ove nacionalne, multicentrične studije je karakterizirati *E. coli* ESBL sojeve koji uzrokuju bolničke infekcije, dugotrajno liječenje i infekcije mokraćnih putova širom Hrvatske, te usporediti njihove obrasce osjetljivosti na antibiotike, molekularne i epidemiološke specifičnosti i plazmide vrste. Provedeni su fenotipski testovi za otkrivanje ESBL-a i plazmidom posredovanih AmpC β -laktamaza (uključujući novu verziju modificiranog CIM testa nazvana metodom inaktivacije cefalosporina), nakon čega su provedeni testovi konjugacije, molekularno otkrivanje gena rezistencije, ekstrakcija plazmida pomoću PCR-a tipizacija replikona, serotipizacija, genotipizacija gel elektroforezom u pulzirajućem polju (PFGE) i sekvenciranje cijelog genoma (WGS). Ova studija pokazala je širenje *E. coli* CTX-M (grupa1) u različitim geografskim regijama Hrvatske i različitim komponentama zdravstvenog sustava, ali je također potvrdila prelazak sa SHV-2 i SHV-5 ESBL na CTX-M β laktamazu sa apsolutnom dominacijom u cijeloj državi. Rezultati PFGE pokazali su visoku genetsku varijabilnost izolata nakupljenih u osam klonova. Regionalne razlike bile su povezane s različitim vrstama plazmida koji nose blaCTX-M gene. Izolati iz Brodsko-posavske županije posjedovali su plazmide koji pretežno pripadaju IncB / O skupini i IncW grupi; obrnuto, u Zagrebu su najzastupljeniji tipovi plazmida bili FII i FIA, dok je FIA bila dominantni tip plazmida u Dubrovačko neretvanskoj županiji. Pored gena blaTEM i blaCTX-M, WGS je pokazao da svi reprezentativni izolati nose aac (6 ') Ib-cr koji kodira otpornost na aminoglikozide i fluorokinolone, sa značajnim kliničkim implikacijama. Zaključno, naša je studija pokazala širenje *E. coli* pozitivne CTX-M u različite geografske regije Hrvatske. Međutim, regionalne razlike su bile povezane s različitim vrstama plazmida koji nose bla CTX-M gene. Buduća istraživanja trebali bi razjasniti specifična metabolička i virulentna svojstva ovog uspješnog klona, odgovoran za širenje širom svijeta.

Extended-spectrum beta-lactamases and plasmid diversity in urinary isolates of *Escherichia coli* in Croatia: a nation-wide, multicentric, retrospective study

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In recent years, a dramatic increase in the prevalence of *Escherichia coli* (*E. coli*) strains producing extended-spectrum β -lactamases (ESBLs) has been observed – both in the community and in healthcare settings. This nation-wide, multicentric study aimed to characterize ESBLs produced by *E. coli* isolates causing hospital-onset, long-term care facility and community urinary tract infections throughout Croatia, and to compare their antimicrobial sensitivity patterns, molecular and epidemiological specificities, and plasmid types. Phenotypic tests for the detection of ESBLs and plasmid-mediated AmpC β -lactamases were initially pursued (including a novel version of modified CIM test named cephalosporin inactivation method), followed by conjugation experiments, molecular detection of resistance genes, plasmid extraction with PCR-based replicon typing, serotyping, genotyping with pulsed-field gel electrophoresis (PFGE), and whole genome sequencing (WGS). This study demonstrated a dissemination of group 1 CTXM-positive *E. coli* in different geographic regions of Croatia and different components of the health care system, but also confirmed the switch from SHV-2 and SHV-5 ESBLs to the absolute nation-wide predominance of group 1 CTX-M β -lactamases. PFGE results revealed high genetic variability of isolates clustered into eight clones. Regional differences were associated with different plasmid types carrying blaCTX-M genes. The isolates from Brod-Posavina County possessed plasmids predominantly belonging to IncB/O group and IncW group; conversely, the most prevalent plasmid types in Zagreb were FII₁ and FIA, while FIA was the dominant plasmid type in DubrovnikNeretva County. In addition to blaTEM and blaCTX-M genes, WGS showed that all representative isolates harboured aac(6')Ib-cr encoding aminoglycoside and fluoroquinolone resistance, with significant clinical implications. In conclusion, our study demonstrated dissemination of group 1 CTX-M positive *E. coli* in different geographic regions of Croatia. However, regional differences were associated with different plasmid types carrying blaCTX-M genes. Future research undertakings should clarify the specific virulent properties of this successful clone, responsible for a worldwide spread.

PO-86 Učestalost i tip karbapenemaza-producirajućih enterobakterija u kliničkom bolničkom centru

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Cilj: Cilj naše studije bio je utvrditi učestalost i vrstu karbapenemaza-producirajućih enterobakterija (KPE), kao i njihovu distribuciju prema odjelima u Kliničkom bolničkom centru (KBC) Rijeka.

Materijali i metode: Ova retrospektivna studija provedena je na Kliničkom zavodu za kliničku mikrobiologiju, KBC Rijeka. Izolirani su KPE sojevi iz različitih kliničkih uzoraka poslanih u laboratorij na mikrobiološku analizu. Identifikacija vrsta provedena je korištenjem Vitek 2 sustava (BioMérieux, Francuska). Izolati su testirani na imipenem, meropenem i ertapenem disk-difuzijskom metodom i e-testom. Za sojeve koji pokazuju smanjenu osjetljivost na bilo koji karbapenem, izvedeni su potvrdni testovi primjenom diskova Combi Carba Plus (Mast Group, Velika Britanija) i Xpert Carba-R testom (Cepheid, Kalifornija) prema uputama proizvođača.

Rezultati: Od siječnja 2013. do kraja lipnja 2019. otkriven je 131 soj KPE. Većina (81%) izolirana je iz nadzornih kultura (bris rektuma, urin, endotrahealni aspirat) upućujući na kolonizaciju i identificirajući kliconoše koji predstavljaju rezervoari za kontinuirani horizontalni prijenos. Najčešće zahvaćeni odjeli bili su jedinica intenzivnog liječenja, neurologija i neurokirurgija, gdje se teški pacijenti uglavnom liječe kroz duže vrijeme. Treba napomenuti da se učestalost KPE posljednjih godina značajno povećala. Od početka 2018. godine izolirano je 113 KPE što je 86% od ukupnog broja sojeva otkrivenih tijekom obuhvaćenog razdoblja. Najčešće KPE bile su *Klebsiella pneumoniae* OXA-48 (55%) te *Enterobacter cloacae* NDM (20%).

Zaključak: Pouzdano otkrivanje KPE bitan je prvi korak u borbi s tim problemom. Određivanje tipova karbapenemaza koristi, ne samo zbog epidemiološkog praćenja, nego i planiranja antimikrobne terapije. Rano otkrivanje KPE i primjena strogih mjera suzbijanja bolničkih infekcija ključne su za kontrolu širenja tih višestruko-rezistentnih mikroorganizama.

Incidence and type of Carbapenemase-Producing Enterobacteria in a tertiary care hospital

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Aim: The aim of our study was to determine incidence and type of carbapenemase producing enterobacteria (CPE) as well as its distribution by wards in Clinical Hospital Centre (CHC) Rijeka.

Materials and Methods: This retrospective study was carried out in the Department of Clinical Microbiology, CHC Rijeka. CPE strains were isolated in different clinical samples sent to the laboratory for microbiological testing. Species identification was performed using the Vitek 2 system (BioMérieux, France). The isolates were tested against imipenem, meropenem, and ertapenem by disk diffusion and MIC assays. For strains showing reducing susceptibility to any carbapenem, a carbapenemase confirmation test was conducted using discs Combi Carba Plus (Mast Group, Great Britain), and the Xpert Carba-R assay (Cepheid, California) according to the manufacturer's instructions.

Results: From January 2013 to the end of June 2019, 131 CPE were detected. The majority (81%) of the strains were isolated from surveillance cultures (rectal swab, urine, endotracheal aspirate) referring to colonization thus identifying potential carriers who may serve as reservoirs for sustained horizontal transmission. The most commonly affected wards were intensive care, neurology and neurosurgery, where severe patients are generally treated for a prolonged time. It should be noted that CPE have significantly increased in recent years. From the beginning of 2018, 113 CPE were isolated which is 86% of the total number of CPE strains detected during the period covered. The most common CPE were *Klebsiella pneumoniae* OXA-48-like (55%) following by *Enterobacter cloacae* NDM (20%).

Conclusion: Reliable detection of carbapenemase production is an essential first step in combating this problem. Differentiation between the various carbapenemase families may also be useful, not only to inform epidemiology but also to guide patient treatment. Early detection of CPE and implementation of strict infection control measures are essential to control the spread of these multidrug-resistant organisms.

PO-87 Usporedba nove Alifax-ove platforme za probir multirezistentnih organizama (MDRO) s klasičnom metodom kultivacije na selektivnim podlogama – iskustvo iz Kliničkog bolničkog centra Split

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Cilj: Cilj istraživanja je bio usporediti novu poluautomatiziranu metodu za otkrivanje MDRO-a s kultivacijom na selektivnim medijima.

Metode: Proveden je nadzor nad svim pacijentima u Jedinicama intenzivne njege u Kliničkom bolničkom centru Split, tijekom dva nasumice odabrana dana. Traženi su meticilin rezistentni *Staphylococcus aureus* (MRSA) i enterobakterije koje stvaraju β-laktamaze proširenog spektra (ESBL). Ukupno je uzorkovano 20 briseva vestibuluma nosa, 21 bris pazuha i 19 rektalnih briseva. Svaki bris je uzet u dublikatu, jedan za brzu dijagnostiku i drugi za klasičnu kultivaciju. Klasična metoda provedena je kultivacijom na krutim i tekućim selektivnim podlogama (MRSA ploča i ESBL selektivni medij) koji su inkubirani 24 sata na 37° C. Drugog dana, tekuće podloge su subkultivirane na krute podloge koje su inkubirane idućih 24 sata. Svi izolirani sojevi identificirani su sustavom Vitek 2 (BioMerieux) unutar dodatnih 24 sata. Ukupno vrijeme izolacije i identifikacije je bilo 3 dana. Metoda brzog probira zasnovana je na tehnologiji raspršivanja laserskog svjetla na tekuće kulture (HB&L Uroquattro, Alifax), a izvedena je prema uputama proizvođača. U tu svrhu su korišteni posebni HB&L MRSA i HB&L ESBL / AmpC reagensi. Tijekom rada, sustav prikazuje bakterijske krivulje rasta u realnom vremenu, a porast MDRO otkriva se unutar 6,5 sati.

Rezultati: Konvencionalnom metodom dokazano je 10 ESBL-producirajućih bakterija iz 10 različitih rektalnih uzoraka. Upravo isti uzorci bili su ESBL pozitivni brzom Alifax metodom. Na selektivnoj MRSA podlozi, porasla su 4 izolata koagulaza negativnih *Staphylococcus* sp rezistentnih na meticilin, 5 izolata MDR-Acinetobacter baumannii i 2 izolata MRSA, dok je u HB&L MRSA mediju detektirano 11 pozitivnih uzoraka.

Zaključak: Rezultati dobiveni klasičnom i brzom metodom pokazuju visoki stupanj podudarnosti. Nova metoda je brza i pouzdana i može se preporučiti za rutinski probir MDRO. Njenom primjenom bi se značajno skratilo vrijeme otkrivanja koloniziranih pacijenata i primjene adekvatnih epidemioloških mjera.

Comparison of a novel Alifax platform for a rapid screening of multi drug resistant organisms (MDRO) with classical phenotypic method in the University Hospital of Split, Croatia

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Aim: Aim of the study was to compare the performance of a new rapid method for the detection of MDRO with cultivation on selective media.

Material/methods: On two selected days, Intensive Care Unit's patients in University Hospital of Split, Croatia, were screened for the presence of methicillin-resistant *Staphylococcus aureus* (MRSA) and Extended Spectrum β -Lactamase (ESBL)-producing Enterobacteriaceae. Twenty one axillary's swabs, twenty nose swabs and 19 rectal swabs were collected. Specimens were taken in duplicate, one for rapid and the other one for a classical screening. Classic method was performed by cultivation on solid and liquid selective media and incubated at 37°C for 24 h. On the second day, all liquid media were subcultivated and incubated for another 24 h. All isolated strains were identified with Vitek 2 system (additional 24 h). Rapid screening method, based on laser light scattering technology, (HB&L Uroquattro, Alifax) was performed according to the manufacturer's instructions. For that purpose, HB&L MRSA and HB&L ESBL/AmpC kits were used. The growth phases of bacteria were monitored, providing real time growth curves. The presence of MDRO was detected in 6.5 hours.

Results: With conventional method, 10 positive ESBL stains from 10 different rectal specimens were isolated on ESBL media. Exactly the same specimens were positive for ESBL grow by rapid Alifax method. On selective MRSA media, 4 strains of Coagulase negative methicillin resistant *Staphylococcus* sp, 5 strains of MDR *Acinetobacter baumannii* and 2 MRSA strains were cultured. Rapid method detected 11 positive specimens.

Conclusions: High concordance of results obtained with classical and rapid method is encouraging. A novel method is fast and reliable and it can be recommended for a routine screening. Colonized patients could be isolated at the same day while patients transferred from another hospitals with negative screening result, could be safely admitted to the hospital wards.

PO-88 Evaluacija imunokromatografskog testa za određivanje galaktomanana u uzorcima seruma i bronhoalveolarnih lavata – preliminarni rezultati

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CILJEVI: Kod pacijenata sa sumnjom na invazivnu aspergilozu (IA) galaktomanan (GM) se odnedavno osim imunoenzimskom (ELISA) metodom u uzorcima seruma i bronhoalveolarnog lavata (BAL) može odrediti i imunokromatografskim testom. Cilj ovog istraživanja bio je evaluirati rezultate imunokromatografskog testa na kliničkim uzorcima s pozitivnim rezultatom ELISA metode.

METODE: Ispitivanje je provedeno na uzorcima seruma i BAL-a uzetih od pacijenata sa sumnjom na IA u razdoblju od veljače do rujna 2019. godine koji su ELISA metodom (Platelia Aspergillus Ag, Biorad, Hercules, USA) pokazali pozitivan rezultat. Pozitivnima su smatrani uzorci s vrijednostima optičke gustoće (OD) $\geq 0,5$ prema uputi proizvođača. Uzorci s pozitivnim rezultatom su potom testirani imunokromatografskim testom Aspergillus Galactomannan LFA (IMMY Inc, Hannover, Njemačka) (LFA). Prisutnost dvije linije (kontrola i test), bez obzira na njihov intenzitet, interpretirana je kao pozitivan rezultat. Intenzitet testne linije očitao je pomoću kartice za očitavanje priložene u kitu i rangiran na ljestvici intenziteta od 1+ do 4+.

REZULTATI: U razdoblju ispitivanja GM je ELISA metodom bio pozitivan u ukupno 22 uzorka od čega 12 (54.6%) BAL-ova i 10 (45.4%) seruma. LFA imunokromatografski test pokazao je pozitivan rezultat u ukupno 15 (68.1%) uzoraka. Navedeni test bio je pozitivan u 7 (70.0%) uzoraka seruma i 8 (66.7%) uzoraka BAL-a. Kod 10 (67.7%) uzoraka pozitivnih LFA imunokromatografskim testom testna linija bila je intenziteta 1+. Svih pet (33.3%) rezultata s intenzitetom testne linije većim od 1+ dobiveni su na uzorcima BAL-a s visokim OD vrijednostima (>5).

ZAKLJUČAK: Preliminarni rezultati LFA imunokromatografskog testa u našem ispitivanju u skladu su s podacima iz literature te govore u prilog manje osjetljivosti u usporedbi s ELISA metodom. Prednosti testa su brzina i jednostavnost te mogućnost testiranja pojedinačnih uzoraka. U odnosu na ELISA metodu određivanje GM tako postaje pristupačno i laboratorijima s manjim brojem uzoraka jer nije potrebno čekati dok se prikupi njihov dovoljan broj.

Evaluation of immunochromatographic test for detection of galactomannan in serum and bronchoalveolar lavage samples – preliminary results

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AIM: Beside immunoenzymatic (ELISA) method, immunochromatographic test is recently available for detection of galactomannan (GM) in serum and bronchoalveolar lavage (BAL) samples in patients with suspected invasive aspergillosis (IA). The aim of this study was to evaluate the results of immunochromatographic test on clinical samples with positive ELISA results.

METHODS: The study was conducted on serum and BAL samples obtained from patients with suspected IA from February to September 2019 with positive ELISA result (Platelia Aspergillus Ag, Biorad, Hercules, USA). Samples with optical density (OD) value $\geq 0,5$ were considered positive according to manufacturer's instructions. Positive samples were then tested with immunochromatographic test Aspergillus Galactomannan LFA (IMMY Inc, Hannover, Njemačka) (LFA). Presence of two lines (control and test), regardless of intensity, was interpreted as positive result. The intensity of the test line was read using a reading card included in the kit and ranked on an intensity scale from 1+ to 4+.

RESULTS: In this study GM tested with ELISA was positive in total of 22 samples including 12 (54.6%) BAL and 10 (45.4%) serum samples. LFA demonstrated positive result in total of 15 (68.1%) samples. It was positive in 7 (70.0%) serum and 8 (66.7%) BAL samples. In 10 (67.7%) samples positive with LFA, the test line had intensity level 1+. All five (33.3%) samples with line intensity stronger than 1+ were BAL samples with high OD values (>5).

CONCLUSION: Preliminary LFA results in our study were in concordance with the literature data and are confirming its lower sensitivity in comparison to ELISA method. However, this test is fast, easy to perform and allows testing of single specimen making GM detection available to laboratories with lower number of samples because it is not necessary to collect enough samples to perform the test.

PO-89 Razlike u detekciji enteropatogena u djece s dijarejom kod upotrebe molekularnih i konvencionalnih metoda

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Uvod: Klasične kultivacijske metode usmjerene na izolaciju patogena sve više postaju postupak koji se rabi u drugom aktu, samo kod obrade pozitivnih uzoraka nakon molekularnog testiranja. Takav postupak optimizira mogućnost detekcije patogena iz stolice i dramatično skraćuje vrijeme dijagnostike. Multiplex PCR paneli koji detektiraju enteropatogene nisu još u rutinskoj upotrebi u Hrvatskoj. Cilj istraživanja bio je usporediti razlike u detekciji enteropatogena kod upotrebe molekularnih i konvencionalnih metoda u djece s gastroenteritisom na području Grada Zagreba.

Materijal i metode: Uzastupno zaprimljeni uzorci stolice tijekom dva mjeseca prikupljeni od 34 djece od jednog mjeseca do osam godina starosti s dijagnozom gastroenteritisa i dijarejom testirani su pomoću FilmArray GI panela (BioFire Diagnostics, Salt Lake City, UT, USA) i konvencionalnim metodama. Metode klasične kultivacije za bakterijske uzročnike, mikroskopska identifikacija parazita i brzi imunokromatografski testovi za antigene virusa i parazita korišteni su pri testiranju konvencionalnim metodama.

Rezultati: Od 34 uzorka, njih pet je bilo negativno, u 13 je detektiran samo jedan mikroorganizam, a u 16 više mikroorganizama. U 15 pacijenata enteropatogeni su detektirani samo pomoću FilmArray-a. FilmArray GI Panel detektirao je najmanje jednog uzročnika u 64,7% (22/34) uzoraka, dok je u 12 od 22 pozitivna uzorka detektirao više od jednog uzročnika. Od 22 ciljanih patogena u ovom panelu, 10 je detektirano najmanje jednom. Rotavirusi, EPEC i sapovirusi bili su najčešće detektirani patogeni. Usporedbom molekularnih i brzih testova koji detektiraju antigene virusa u uzorku tvrđeno je šest lažno negativnih i čak 16 lažno pozitivnih rezultata brzih imunokromatografskih testova za virusne enteropatogene.

Zaključci: Višestruki PCR testovi mogu značajno poboljšati rutinsku dijagnostiku detekcije uzročnika dijareje u pacijenata s gastroenteritisom, posebice u djece. FilmArray GI panel je jednako uspješan u detekciji bakterijskih patogena kao metode klasične kultivacije, dok je pokazao zabrinjavajuće visoku učestalost lažnih rezultata kada se brzi imunokromatografski testovi upotrebljavaju za detekciju virusnih enteropatogena u djece s gastroenteritisom.

Differences in enteropathogens detection in children with diarrhea by using molecular and conventional techniques

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Background: Classic culture methods directed at the isolation of specific pathogens are increasingly becoming second-line tools, being deployed when rapid molecular tests give positive results. This optimizes the yield from stool examinations and dramatically improves the timeliness of diagnosis. Multiplex PCR panels for detection of enteropathogens are not yet in routine use in Croatia. The aim of this study was to compare differences in enteropathogens detection by using molecular and conventional techniques in children with gastroenteritis in Zagreb region.

Material and methods: Stool samples from 34 consecutive patients with diarrhea aged from one month to 8 years old were tested with the FilmArray GI Panel (BioFire Diagnostics, Salt Lake City, UT, USA), and with conventional techniques. Classic culture methods for bacterial pathogens, microscopic identification of parasites and rapid immunochromatographic tests for viral and parasite antigens were used when testing was performed with conventional techniques.

Results: Out of the 34 samples, five tested negative, 13 yielded only one organism, and 16 yielded multiple organisms. In 15 patients enteropathogens were detected only by FilmArray. Overall, the FilmArray GI Panel detected at least one organism in 64.7% (22/34) of the samples, and 12 of 22 positive samples yielded multiple organisms. Out of 22 targeted pathogens by FilmArray, 10 pathogens were detected at least once. Rotavirus, EPEC and sapoviruses were the most commonly detected pathogens. Comparing the results of molecular and antigen-detection tests, six fouts negative and 16 fouts positive rapid immunochromatographic tests for viral enteropathogens were detected.

Conclusions: Multiplex PCR tests can significantly improve routine stool diagnostics in community-acquired diarrhea, particularly in children. FilmArray GI Panel was equally successful in detection of bacterial pathogens as classic culture method, and detected a high frequency of fouts results when rapid antigen detection test were used for detection of viral enteropathogens in children with acute gastroenteritis.

PO-90 Genotyping of *Pseudomonas aeruginosa* in clinical isolates at University Clinical Centre of Kosovo

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Objectives: *Pseudomonas aeruginosa* is one of the important causes of nosocomial infections that easily gains resistance to many antibiotics. There are different methods available for the genotyping of *P. aeruginosa* today, however, pulsed-field gel electrophoresis (PFGE) is still considered the "gold standard". Information on molecular investigation of *Pseudomonas* in Kosovo is lacking. The aim of the present study was to investigate the clonal relationships of *P. aeruginosa* among the clinical isolates in the University Clinical Centre of Kosovo (UCCK) using Pulse field gel electrophoresis.

Methods: All collected samples were identified by conventional methods and Vitek-2 Compact system. Antimicrobial susceptibility testing was done by the disk diffusion method according to the EUCAST guidelines and E-test methods. Genotyping was performed by CHEF Mapper XA Pulsed Field Electrophoresis System (BIO-RAD) after macro-restriction with *SpeI* restriction enzyme.

Results: 40 clinical isolates of *P. aeruginosa* were collected from hospitalized patients in different units of the UCCK. The most common diagnosis were polytrauma, sepsis and coma cerebri. Bacterial isolates were most frequently recovered from tracheostomy tube (mechanically ventilated patients) 24 (60%) and originated from ICU. Genotype analysis of *P. aeruginosa* isolates identified seven distinct PFGE patterns. The largest group (PFGE-A) comprised 16 out of 40 isolates (40%). All of these strains were indistinguishable (based on >90% similarity criterion). There were 2 more groups comprising 5 and 3 isolates, respectively. 12 (30%) strains of *P. aeruginosa* were resistant to carbapenems. The highest sensitivity was shown to colistin 96.1%

Conclusion: The results demonstrated a high incidence of *P. aeruginosa* in ICU. The distribution of strains shows a correlation with the location of hospital units where the isolates were collected. The results emphasize the need for strict infection control measures in order to prevent nosocomial transmission of *P. aeruginosa*.

Keyword: Genotyping, *P. aeruginosa*, nosocomial infection, ICU

PO-91 Karakterizacija OXA-48 producirajućih sojeva bakterije *Klebsiella pneumoniae* izoliranih iz mokraće izvanbolničkih pacijenata u Zagrebu

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Uvod: Tijekom 2016. zabilježeno je epidemijsko širenje OXA-48 pozitivnih enterobakterija sa sjeverozapada u druge dijelove Hrvatske. U ranoj fazi diseminacije samo su bolnice bile zahvaćene, ali u posljednje tri godine zapaženo je širenje u domove za starije osobe. Cilj ovog istraživanja bio je analizirati ukupno 98 sojeva OXA-48 producirajućih sojeva bakterije *Klebsiella pneumoniae* izoliranih iz mokraće izvanbolničkih pacijenata od 2016-2018 u Zagrebu.

Metode: Antimikrobna osjetljivost i produkcija karbapenemaza fenotipski je određena. Prijenos cefotaksimske rezistencije testirana je konjugacijom upotrebom *E. coli* J53 rezistentnom na natrijev azid. PCR je upotrijebljen za detekciju gena koji kodiraju β -laktamaze proširenog spektra (ESBL), plasmidski-posredovane AmpC β -laktamaze, karbapenemaze klase A, B i D, te qnr fluorokinolonsku rezistenciju.

Rezultati: Izolati su bili uniformno rezistentni na amoksicilin i amoksicilin-klavulanat, piperacilin-tazobaktam, cefazolin i cefuroksim. Rezistencija na kolistin utvrđena je u samo dva soja. Pedeset i pet izolata (56%) fenotipski su bili pozitivni na ESBL. ESBL-pozitivni izolati bili su rezistentni na cefalosporine proširenog spektra, cefepim, gentamicin i ciprofloksacin. Četrnaest od 32 testirana ESBL-pozitivna soja imala su CTX-M-15 β -laktamazu, a njih 12 TEM-1. PCR je utvrdio OXA-48 karbapenemazu klase D kao jedini mehanizam karbapenemske rezistencije. L plasmid je nađen u svih testiranih izolata. Od 98 testiranih sojeva njih 54 (55%) izolirano je u bolesnika iz domova za starije osobe u Zagrebu. Ti izolati su pokazivali značajno nižu stopu dodatnog ESBL pozitiviteta nego sojevi izolirani u izvanbolničkih pacijenata koji nisu bili u domu ($p < 0.01$). Nadalje, pokazivali su vrlo niske MIK-ove imipenema i meropenema koje su za većinu izolata bile u osjetljivom rasponu vrijednosti ($MIC < 2 \text{ mg/L}$).

Zaključci: CTX-M-15 je bio dominantno utvrđeni tip ESBL kojeg su OXA-48 pozitivni sojevi koproducirali. OXA-48 bila je jedina karbapenemaza utvrđena u gerijatrijskih izvanbolničkih pacijenata u Zagrebu. Poznato je da L plasmid nađen u testiranih sojeva nosi blaOXA-48 gene i odgovoran je za njihovu brzu diseminaciju.

Characterization of OXA-48 producing *Klebsiella pneumoniae* strains isolated from urine of non-hospitalized patients in Zagreb

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Background: During 2016 epidemic spread of OXA-48 positive *Enterobacteriaceae* from northwest to other regions of Croatia was noticed. In the early stage of dissemination only hospitals were affected, but during the last three years spread to the long-term care facilities was observed. The aim of this research was to analyse 98 *Klebsiella pneumoniae* strains positive for OXA-48 carbapenemases isolated from urine of non-hospitalized patients from 2016-2018 in Zagreb.

Methods: Antimicrobial susceptibility profiles and production of carbapenemases were assessed phenotypically. Transferability of cefotaxime resistance was tested by conjugation using *E. coli* J53 resistant to sodium azide. PCR was used to detect genes encoding extended-spectrum β -lactamases (ESBLs), plasmid-mediated AmpC β -lactamases, carbapenemases of class A, B and D, and *qnr* encoding fluoroquinolone resistance.

Results: The isolates were uniformly resistant to amoxicillin alone and combined with clavulanic acid, piperacillin/tazobactam, ceftazidime and cefturoxime. Colistin resistance was observed in only two strains. Fifty five isolates (56%) were phenotypically positive for ESBLs. ESBL-positive isolates exhibited resistance to expanded-spectrum cephalosporins, ceftazidime, gentamicin and ciprofloxacin. Fourteen out of 32 ESBL-positive organisms tested harboured CTX-M-15 β -lactamase, and 12 TEM-1. PCR revealed OXA-48 class D carbapenemase as the sole carbapenem-resistance mechanism. L plasmid was found in all tested isolates. Out of 98 strains tested 54 (55%) were isolated from long long-term care facilities patients. Those isolates exhibited significantly lower rates of additional ESBL positivity than isolates collected from 44 outpatients ($p < 0.01$). Moreover, they showed very low MICs of both imipenem and meropenem with the majority of isolates being in the susceptible range (MIC < 2mg/L).

Conclusions: CTX-M-15 was the dominant type of ESBL coproduced by OXA-48 positive strains. OXA-48 was the sole carbapenemase detected in isolates from geriatric non-hospitalized population in Zagreb. L plasmid found in tested strains is known to carry blaOXA-48 genes and is responsible for its fast dissemination.

PO-92 In vitro antimikrobna osjetljivost *Ureaplasma urealyticum*

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Cilj: Određivanje i usporedba prevalencije i in vitro antimikrobne osjetljivosti *U.urealyticum* nađenih u urogenitalnim uzorcima žena reproduktivne dobi.

Materijali i metode: U razdoblju 2005/2006. godine evaluirana je in vitro antimikrobna osjetljivosti *U. urealyticum* urogenitalnih uzoraka 72 bolesnice s uretralnim sindrom te su rezultati komparirani s podacima 181 izolata *U.urealyticum* dobivenih iz genitourinarnog trakta bolesnica s ginekološkom problematikom iz 2015. godine. Za identifikaciju *U.urealyticum* korišten je Mycoplasma IST 2 kit. In vitro antimikrobna osjetljivost izolata visoke koncentracije $\geq 10^4$ CCU/ml određivana je metodom dilucije u bujonu na 7 antibiotika: doksiciklin, tetraciklin, azitromicin, eritromicin, klaritromicin, ciprofloksacin, ofloksacin.

Rezultati: U razdoblju 2005/2006. godine prevalencija *U.urealyticum* u urogenitalnim uzorcima žena reproduktivne dobi iznosila je 28%, a 2015. godine 22.7%. Rezultati in vitro antimikrobne osjetljivosti u razdoblju od lipnja 2005. do lipnja 2006. godine i za 2015. godinu bili su sljedeći: osjetljivost na doksiciklin 100% i 98.7%, tetraciklin 100% i 98.7%, klaritromicin 93.7% i 89.5%, eritromicin 90.3% i 85.6%, azitromicin 87% i 81.2%, ofloksacin 62% i 59.7%, ciprofloksacin 40.3% i 28.9%. Bilježi se mala stopa rezistencije na doksiciklin i tetraciklin (2.2%) i na makrolide (klaritromicin 6.3% i 10.5%; eritromicin 9.7% i 14.4%; azitromicin 13% i 18.8%) te viša na kinolone (ofloksacin 38% i 40.3%; ciprofloksacin 59% i 71.1%), a razlike u rezistencijama nisu bile statistički značajne.

Zaključak : Unatoč visokoj osjetljivosti *U urealyticum* na tetracikline i makrolide kao prvoj liniji terapije, s obzirom na trend porasta rezistencije potrebno je kontinuirano praćenje antimikrobne osjetljivosti in vitro na lokalnoj razini radi adekvatnog izbora antimikrobika.

Ključne riječi: *Ureaplasma urealyticum*, antimikrobna osjetljivost in vitro

In vitro antimicrobial susceptibility of *Ureaplasma urealyticum*

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Objective: To determine and compare the prevalence and in vitro antimicrobial susceptibility of *U.urealyticum* in urogenital samples of women of reproductive age.

Materials and methods: In 2005/2006, in vitro antimicrobial susceptibility of *U.urealyticum* from urogenital samples of 72 female patients with urethral syndrome were evaluated and the results were compared with 181 isolates of *U.Urealyticum* from the genitourinary tract of patients with gynecological issues in year 2015. Mycoplasma IST 2 kit was used for identification the *U.urealyticum*. In vitro antimicrobial susceptibility of the isolates high concentrations $\geq 10^4$ CCU / ml was determined by the dilution method in broth to 7 antibiotics: doxycycline, tetracycline, azithromycin, erythromycin, clarithromycin, ciprofloxacin, ofloxacin.

Results: In 2005/2006, the prevalence of *U.urealyticum* in women of reproductive age was 28% and 22.7% in 2015. The results in vitro antimicrobial susceptibility in the period from June 2005 to June 2006 and in 2015 were the following: sensitivity to doxycycline 100% and 97.8%, tetracycline 100% and 97.8%, clarithromycin 93.7 % and 89.5%, erythromycin 90.3% and 85.6%, azithromycin 87% and 81.2%, ofloxacin 62 % and 59.7%, ciprofloxacin 40.3% and 28.9%. Low rate of resistance to doxycycline and tetracyclines (2.2%) and the macrolides (clarithromycin 6.3% and 10.5%; erythromycin 9.7% and 14.4%; azithromycin 13% and 18.8%) and high to quinolones (ofloxacin 38% and 40.3%; ciprofloxacin 59% and 71.1%) was registered, and there were not statistically significant differences in resistance.

Conclusion: Despite the high sensitivity of *U.urealyticum* to tetracyclines and macrolides as a first-line treatment, due to the trend of increasing resistance, it is necessary to continuously monitor in vitro antimicrobial susceptibility in the local region for the purpose of an adequate choice of antibiotics.

Keywords: *Ureaplasma urealyticum*, antimicrobial susceptibility in vitro

PO-93 Osjetljivost kliničkih izolata multirezistentnih Gram-negativnih bakterija na 5-nitro-8-hydroxyquinolin

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Cilj: Cilj ovoga istraživanja bio je ispitati osjetljivost Gram-negativnih multirezistentnih bakterija izoliranih iz urina: *Escherichia coli* ESBL soj, *Klebsiella pneumoniae* ESBL soj i karbapenem rezistentnih *Pseudomonas aeruginosa* na 5-nitro-8-hydroxyquinolin (nitroxolin, NTX).

Metode: Istraživanje je izvedeno na ukupno 50 Gram-negativnih multirezistentnih izolata urinarnih patogena (23 izolata *E. coli* ESBL, 12 izolata *K. pneumoniae* ESBL i 15 izolata *P. aeruginosa*) tijekom 2018. godine izolirani iz kliničkih uzoraka urina tijekom rutinskog rada. Testiranje osjetljivosti je izvedeno sukladno standardima EUCAST-a disk-difuzijskom metodom primjenom 30 µg diska NTX. Za sve izolate je primijenjen interpretacijski kriterij osjetljivosti kao za Enterobacterales (izmjerena zone inhibicije ≥15 mm=osjetljivost, <15 mm=rezistentncija).

Rezultati: Medijan izmjerenih vrijednost zone inhibicije za *E. coli* je iznosio 20 mm (interkvartilni raspon: 18–23 mm; min-max: 14-26 mm), za *K. pneumoniae* je iznosio 17 mm (interkvartilnih raspon 10,5–18,75; min-max: 6–22 mm) te za *P. aeruginosa* je 7 mm (interkvartilni raspon 6–8; min-max 6–17 mm) te je utvrđena statistički značajna razlika (Kruskal Wallis test, p<0,001). Sukladno dosadašnjim spoznajama postoji statistički značajna razlika u osjetljivosti na NTX između vrsta što je očekivano s obzirom na izostanak učinka antibiotika na *P. aeruginosa* (Hikvadrat test, P<0,001). Ukupno je 29 (58%) osjetljivih izolata te je značajno je više bilo osjetljivih izolata *E. coli* (87%) i *K. pneumoniae* (66,77%), dok je samo jedan izolat *P. aeruginosa* (7%) imao zonu inhibicije veću od prijelomne. Zbirno, vrste koje pripadaju *Enterobacterales* su u 80% slučajeva osjetljive na NTX te između *E.coli* i *K. pneumoniae* ne postoji statistički značajna razlika u osjetljivosti na NTX (Fisher egzaktni test, p= 0.199).

Zaključak: Rezultati ovoga istraživanja potvrđuju poznate spoznaje o osjetljivosti ispitivanih bakterijskih vrsta na NTX, apostrofirajući mogućnost primjene ovog antibiotika u liječenju nekomplikiranih urinarnih infekcija i kad su izazvane rezistentnim bakterijama te mogu doprinijeti boljem razumijevanju djelovanja i mogućnosti korištenja antibiotika u svrhe liječenja ovih infekcija s ciljem racionalizacije upotrebe rezervnih antibiotika.

Susceptibility of multi-resistant Gram-negative bacteria isolated from clinical specimens to 5-nitro-8-hydroxyquinoline

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Objectives: The aim of this research is to examine the sensitivity of multi-resistant bacteria: *Escherichia coli* ESBL strain, *Klebsiella pneumoniae* ESBL strain and carbapenem-resistant *Pseudomonas aeruginosa* to the 5-nitro-8-hydroxyquinoline (nitroxoline, NTX) isolated from urine.

Methods: In this study, 50 multi-resistant Gram-negative isolates (23 *E. coli* ESBL, 12 *K. pneumoniae* ESBL and 15 *P. aeruginosa*) isolated from urine samples during 2018. were used. Susceptibility testing was performed by disc-diffusion method with 30 µg of NTX discs accordingly to EUCAST standards. The interpretation criterion was applied for all of isolates as *Enterobacterales* (inhibition zone measured ≥15 mm=sensitive, <15 mm=resistant).

Results: The median of the inhibition zones for *E. coli* was 20 mm (interquartile range: 18-23 mm; min-max: 14-26 mm), for *K. pneumoniae* was 17 mm (interquartile range 10.5-18.75; min-max: 6-22 mm) and for *P. aeruginosa* 7 mm (interquartile range 6-8; min-max 6-17 mm) which was statistically significant difference (Kruskal Wallis test, $p < 0.001$). In total, there was a statistically significant difference in susceptibility to NTX between species, which is expected given the lack of inhibitory effect on *P. aeruginosa* (chi-square test, $P < 0.001$). 29 (58%) sensitive isolates in total was found (87% of *E. coli* and 66.77% *K. pneumoniae* tested), whereas only one isolate (7%) of *P. aeruginosa* had an inhibition zone greater than the breaking point. In total, species belonging to *Enterobacterales* are susceptible to NTX in 80% of cases, and there is no statistically significant difference in susceptibility to NTX between *E.coli* and *K. pneumoniae* tested (Fisher exact test, $p = 0.199$).

Conclusion: The results of this study confirm already known insights into the susceptibility of the tested bacterial species to NTX, emphasizing the use of this antibiotic in the treatment of uncomplicated urinary infections, including those caused by resistant bacteria, as well. This may contribute to a better understanding of the antibiotic therapy for urinary tract infections in the light of the last resort antibiotics rationale usage.

PO-94 Mijaza

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Mijaza je bolest izazvana ličinkama različitih vrsta dvokrilaca, najčešće muha, koje kao nametnici napadaju životinje i čovjeka. Ženke polažu jajašca na zdravu ili oštećenu kožu, osobito u rane, iz kojih se razvijaju ličinke izazivajući vrlo bolne upale, a prodorom u tjelesne šupljine i unutarnje organe, uzrokuju raspadanje tkiva. Mijaza je peta najčešća dermatološka bolest na koju otpada oko 7,3-11% od svih kožnih promjena. Anatomska klasifikacija mijaza uključuje kožnu mijazu, furunkularnu i migrirajuću, potom mijaza rana te mijaza šupljina i otvora. Dijagnoza kutane mijaze se uglavnom postavlja u okviru kliničkih simptoma i znakova bolesti, posebno tamo gdje je bolest endemska.

Liječenje se porovodi aplikacijom toksične supstance na larve i jajašca uz mehaničko ili kirurško odstarnjenje crvi. Antimikrobna terapija provodi se u slučaju prateće bakterijske infekcije od kojih su najčešće infekcije sa gram negativnim štapićima iz roda *Ignatzschineria* i *Wohlfahrtiimonas*. U dijagnostici pratećih bakterijskih infekcija primjenu imaju mikrobiološki uzorci: hemokulture, uz molekularnu dijagnostiku primjenom genskog sekvencioniranja: PCR 16sRNA. U terapijskom postupku uz navedene tehnike mehaničkog uklanjanja larvi i primjenu antiseptika koristi se antimikrobna terapija iz kategorije beta-laktama, linkozamida i kinolona.

U prikazu slučaja bolesnika liječenog u Klinici za infektivne bolesti „Dr. Fran Mihaljević“ dati ćemo osvrt na klinički tijek bolesti i primjenu terapijskih postupaka i mikrobiološke dijagnostike.

Myiasis

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Myiasis is a disease caused by larvae of different species of bivalves, most commonly flies, which attack animals and humans as pests. Females lay eggs on healthy or damaged skin, especially in wounds, from which the larvae develop, causing very painful inflammation, and by penetrating the body cavities and internal organs, they cause tissue to break down. Myiasis is the fifth most common dermatological disease, accounting for about 7.3-11% of all skin changes. Anatomical classification of myiasis includes cutaneous myiasis, furuncular and migratory, then myiasis wounds and myasas of cavities and openings. The diagnosis of cutaneous myiasis is generally made within the clinical symptoms and signs of the disease, especially where the disease is endemic.

Treatment is given by the application of a toxic substance to larvae and eggs with mechanical or surgical removal of the worms. Antimicrobial therapy is carried out in the case of accompanying bacterial infections, of which the most common are infections with gram negative rods of the genus *Ignatzschineria* and *Wohlfahrtiimonas*. In the diagnosis of accompanying bacterial infections, microbiological samples are used: chemocultures, along with molecular diagnostics using gene sequencing: PCR 16sRNA. Antimicrobial therapy in the beta-lactam, lincosamide and quinolone categories is used in the therapeutic procedure in addition to the above mentioned techniques of mechanical larval removal and the use of antiseptics.

In a case report of a patient treated at the Infectious Diseases Clinic “Dr. Fran Mihaljević” we will give an overview of the clinical course of the disease and the application of therapeutic procedures and microbiological diagnostics.

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