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**KNJIGA SAŽETAKA
NACIONALNI KONGRES SA
MEĐUNARODNIM UČEŠĆEM**

**INFEKCIJE KOD IMUNOSUPRIMIRANIH
OSOBA – PROBLEMI PREPOZNAVANJA,
DIJAGNOSTIKE I LEČENJA**

**BOOK OF ABSTRACTS
NATIONAL CONGRESS WITH
INTERNATIONAL PARTICIPATION**

**INFECTIONS IN IMMUNOCOMPROMISED
– PROBLEMS OF RECOGNITION,
DIAGNOSIS AND THERAPY**

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EDITORIJAL



Iz dana u dan uvećavaju se naša znanja o funkcionisanju ljudskog organizma, čemu treba da zahvalimo razvoju tehnike i tehnologije. Postepeno nam se razjašnjavaju neke nedoumice, ali smo i dalje duboko svesni da malo znamo o tome kako čovek funkcioniše, svesni smo da je sadašnji moment samo jedna stepenica u znanjima koja će se tek steći.

Luj Paster je, u drugoj polovini XIX veka, svojim zapažanjima započeo jednu od danas veoma razvijenih grana medicine, imunologiju. U međuvremenu se imunologija razvila do razmera da je potrebno da se stalno, bez obzira da li smo lekari primarne, sekundarne ili tercijarne medicinske zaštite, obaveštavamo o aktualnim saznanjima, u cilju adekvatnog pristupa pacijentu.

Evolucija čoveka je evolucija koegzistencije čoveka i mikroorganizama, mikroorganizama koji su se adaptirali za suživot sa čovekom i drugih životinjskih mikroorganizama. Ovaj saživot nije miroljubiva koegzistencija, ovaj suživot je stalna borba. Ljudi su se oduvek snalazili, sa manje ili više uspeha, kako da izađu na kraj sa infekcijama, ali je pronalazak antibiotika, antimikotika i antivirusika, napravio kvalitativan i kvantitativan skok ka bržem i efikasnijem izlečenju.

Infektivne bolesti i infekcije uopšte, odlično oslikavaju vreme u kome živimo. Svetska zdravstvena organizacija je za 2019. godinu bila navela deset globalnozdravstvenih problema na našoj planeti, od kojih su šest u vezi infekcija i svih problema koji iz toga proizilaze. Svakodnevno se susrećemo sa mnogobrojnim problemima koje infektivni agensi svakodnevno donose (epidemiološki, klinički, terapijski, ekonomski, socijalni, etički, pravni itd.), u odnosu na naše mogućnosti da se tim izazovima suprotstavimo i da ih na neki način držimo pod kontrolom. Ovo je u izvesnoj meri moguće sofisticiranom dijagnostikom, nespecifičnim i specifičnim preventivnim merama, dostupnom antimikrobnom terapijom itd. Odnos između delovanja mikroorganizama i naših mogućnosti da se izborimo sa njima, zavisi od naših znanja s jedne strane i sposobnosti mikroorganizama da se prilagode novonastaloj situaciji, da prežive. Stoga je naš zadatak da, kao lekari koji smo u stalnoj borbi sa mikroorganizmima, stalno obnavljamo znanja kako o stanjima u kojima mogu biti naši pacijenti, tako i o mikroorganizmima koji narušavaju njihovo zdravlje.

U smislu razumevanja imuniteta, pojavio se pojam nedostatka adekvatnog imunskog odgovora, tj. imunodeficijencija. Razvojem raznih medicinskih procedura, na prvom mestu lečenjem maligniteta, autoimunih bolesti i transplantacijom organa, razvio se pojam jatrogenog nedostatka imuniteta. Saznanjima da je poneka virusna infekcija praćena prolaznim oslabljenim imunskim odgovorom, a i da postoji infekcija koja će tokom niza godina dovesti do potpunog gubitka imuniteta, razvio se pojam stečene imunodeficijencije. Za urođene nedostatke imuniteta znalo se, empirijski, odavno, ali se današnjim dijagnostičkim metodama saznaje da postoji veliki broj modaliteta, od kojih se neki prepoznaju u najranijem uzrastu, drugi kasnije, a neki tek ako se pred imunitet postave specifični zahtevi.

EDITORIAL



From day to day our knowledge about the functioning of the human body is increasing, for which we should thank the development of techniques and technology. Gradually some doubts have been clarified, but we are still deeply aware that we know little about how the human body functions and that today's knowledge is only one step further in the knowledge that will be acquired in the future.

Today's highly developed branch of medicine, immunology, began with Louis Pasteur's discoveries in the second half of XIX century. In the meantime, immunology has developed to the extent that it is indispensable, regardless of whether we are doctors of primary, secondary, or tertiary medical care, in order to be informed about current knowledge, and therefore adequately approach the patient.

The evolution of man is the evolution of the coexistence of man with microorganisms, microorganisms that have adapted for coexistence with man, and other animal microorganisms. This coexistence is not a peaceful coexistence, this coexistence is a constant struggle. Humans have always managed to cope, with success, with infections, but the invention of antibiotics, antivirals, and antifungal drugs, has made a qualitative and quantitative leap towards a faster patient recovery.

Infectious diseases and infections in general, perfectly reflect the time in which we live. For 2019, the World Health Organization (WHO) listed ten global public health problems on our planet, of which as many as six are related to infections, and all the problems they cause. Every day we encounter numerous problems that infectious agents bring daily (epidemiological, clinical, therapeutic, economic, social, ethical, legal, etc.), in relation to our ability to counter these challenges and somehow keep them under control. This is to some extent possible with sophisticated diagnostics, non-specific and specific preventive measures, available antimicrobial therapy, etc. The relationship between the activity of microorganisms and our ability to cope with them depends on our knowledge on the one hand and the sensibility of microorganisms to adapt to the new situation on the other. Therefore, our task, as doctors who are in constant struggle with microorganisms, is to constantly renew knowledge both about the conditions in which our patients may be, as well as about the microorganisms that harm their health.

In terms of understanding immunity, the notion of a lack of adequate immune response has emerged, i.e. immunodeficiency. With the development of various medical procedures, in the first-place treatment of malignancies of autoimmune diseases and organ transplantation, the concept of iatrogenic deficiency of immunity has developed. As the result of the discovery that some viral infections are accompanied by a brief weakened immune response, and that there is an infection that will lead to complete loss of immunodeficiency over the years, the concept of acquired immunodeficiency has developed. Innate immunity deficiencies have been known, empirically, for a long time, but today's diagnostic methods reveal that there are a large number of modalities, some of which are recognized at an early age, others later, and some only if specific demands are placed on immunity.

U pristupu pacijentu, koji ima infekciju, možemo unapred da znamo ili da ne znamo da je imunodeficijantan, ali uvek moramo imati na umu i tu mogućnost. Organizacioni i naučni odbor kongresa želeo je da proširimo i osavremenimo znanja o stanjima nedostatka imuniteta (imunodeficijencijama), mogućnostima dijagnostike, odabiru adekvatne terapije i mogućnostima prevencije infekcije.

U tom cilju angažovani su istaknuti strani i domaći predavači. Sažeci objavljeni u suplementu Srpskog medicinskog časopisa Lekarske komore, prošli su recenziju od strane Naučnog odbora kongresa.

Regionalna lekarska komora Beograd, Poseban odbor za medicinsko obrazovanje i Klinika za infektivne i tropske bolesti Univerzitetskog kliničkog centra Srbije, žele vam uspešan rad.

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In the approach to the infected patient, we can know in advance whether he has immunodeficiency, or not be aware of it at all. Anyhow, we must always keep in mind this possibility. The focus of this gathering is based on the understanding that we will expand our knowledge about immunity deficiency/immunodeficiency conditions, diagnostic possibilities, selection of adequate therapy and infection prevention options.

Foreign and domestic eminent lecturers are engaged. Abstracts published in the supplement of the Serbian Journal of the Medical Chamber, were reviewed by the Scientific Committee of the Congress.

Regional Medical Chamber of Belgrade, Special Committee for Medical Education and Clinic for Infectious and Tropical Diseases of the University Clinical Center of Serbia, wish you successful work.

With kind regards,

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SAŽETAK

Primarne imunodeficijencije (PID) predstavljaju grupu urođenih, uglavnom monogenih bolesti koje odlikuje povećana sklonost ka infekcijama od ranog uzrasta. Do danas je na molekularnom nivou dijagnostikovano oko 400 PID. Najčešće su humoralne imunodeficijencije (60% bolesnika), zatim kombinovane i ćelijske PID (20%), fagocitne (15-18%) i deficijencije komplementa (2%).

Humoralne imunodeficijencije zbog deficita B limfocita se odlikuju nemogućnošću produkcije antitela, i samim tim najčešće su infekcije respiratornog sistema inkapsularnim bakterijama (*H. influenzae*, *S. pneumoniae*). Odbrana protiv virusa je očuvana, s izuzetkom enterovirusnih infekcija.

Kombinovane PID imaju poremećaj funkcije i T i B limfocita, a česta je pojava autoimunskih manifestacija. Primeri za kombinovane PID su klasični Wiskott-Aldrich sindrom ili npr. skorije otkriveni PI3-delta sindrom.

Primer za ćelijske PID je teška kombinovana imunodeficijencija (SCID), sa više oblika koji se nasleđuju autozomno-recesivno i jednim X-vezanim oblikom. SCID odlikuje rana pojava oportunističkih, bakterijskih i virusnih infekcija.

Fagocitne PID se odlikuju sklonošću ka ponavljanim piogenim (*S. aureus*) i gljivičnim infekcijama (*Aspergillus* spp.). Deficijencije komplementa odlikuje autoimunost, a deficit terminalnih komponenti ponavljane meningokokne infekcije.

Za sprečavanje sekvela ponavljanih infekcija neophodna je rana dijagnoza. Terapija se zasniva na primeni antibiotika, intravenskih i supkutanih imunoglobulina, a kod pojedinih PID indikovana je transplantacija matičnih ćelija hematopoeze kao vid definitivnog izlečenja.

Ključne reči: ponavljane infekcije, produkcija antitela, ćelijska imunost

ABSTRACT

Primary immunodeficiency diseases (PID) represent group of inherited, mostly monogenic conditions with an increased susceptibility to infections in childhood. Until now more than 400 of PID is characterized on molecular level. Among PID, the most common are antibody deficiencies (60% of the patients), followed by combined and cellular PID (20%), phagocytic disorders (15-18%) and complement deficiencies (2%), respectively.

In antibody deficiencies production of specific antibodies is impaired leading to repeated respiratory infections caused with encapsulated bacteria (*H. influenzae*, *S. pneumoniae*). Generally, defense against viruses is preserved, with an exception of enteroviruses.

In combined PID, function of T and B lymphocytes is impaired. Also, autoimmune features could be associated. The following examples for combined PID are classical Wiskott-Aldrich syndrome or newly discovered PI3-delta syndrome

Severe combined immunodeficiency (SCID) is characterized by block in an early T-cell development. Several gene mutations lead to autosomal-recessive SCID while one form has X-linked mode of inheritance. SCID is clinically characterized by an early onset of opportunistic, bacterial or viral infections.

Phagocytic PID present with recurrent pyogenic (*S. aureus*) or deep-seated fungal infections (*Aspergillus* spp.). Complement deficiencies (C1-C5) present with autoimmune features while terminal component deficiency are characterized with repeated meningococcal infections.

An early diagnosis of PID is important in prevention of organ damage in PID. Treatment is consisted by the use of antimicrobial agents, intravenous or subcutaneous immunoglobulins. In certain forms of PID bone marrow transplantation represents an option for definite cure.

Keywords: repeated infections, antibody production, cellular immunity

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SAŽETAK

Pandemija bolesti kovid-19, naglasila je značaj interferona tipa I u ranoj odbrani od virusnih infekcija kod ljudi i ograničenju oštećenja tkiva posredovanih virusima. Urođeni defekti gena koji kodiraju proteine učesnike u sprovođenju signala interferona tip I ili efektorskih molekula tog važnog, ranog, mehanizma odbrane, i kao takvi povećavaju osetljivost na virusne infekcije, mogli su da se dokažu kod 5% pacijenata smeštenih u jedinice intenzivnog lečenja. Međutim, još veći značaj, posebno u grupi pacijenata starijih od 70 godina i kod muškaraca detektovano je prisustvo neutrališućih autoantitela protiv interferona tipa I kod do 20% pacijenata sa teškim kliničkim slikama kovid-19 i kod 20% preminulih starijih od 80 godina. Interesantno je da se pojava tih autoantitela povećava sa starošću i da se ta činjenica mora uzeti u obzir prilikom tretmana pacijenata sa teškim formama virusnih infekcija.

Ključne reči: interferon tip I, kovid-19, senijum

ABSTRACT

The pandemic of COVID-19 highlighted the importance of type I interferon system in early antiviral defense infections and in the limitation of tissue damage mediated by viruses, in humans. Congenital defects of genes that encode proteins involved in the type I interferon signaling or effector molecules of that early defense mechanism, thus increasing susceptibility to viral infections, could be proven in 5% of COVID-19 patients treated in intensive care units. Even of greater importance is the fact that in up to 20% of patients with severe clinical images of COVID-19 and in 20% of deceased over 80 years neutralizing autoantibodies against interferon type I were detected. Presence of these neutralizing autoantibodies was increases with age especially in the group of patients over 70 years of age and in men. Their appearance may modify the response to viral in general and must be taken into account when treating patients with severe forms of viral infections.

Keywords: interferon type I, Covid-19, senium

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SYNDROME OF DIMINISHED RESISTANCE TO INFECTION – WHEN TO SUSPECT IMMUNODEFICIENCY?

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SAŽETAK

Urodjene greške imunosti su retke monogeneske bolesti (prevalencija ~1/10,000) uzrokovane mutacijama (danas poznatih ~500) gena neophodnih za ključne funkcije imunskog sistema, odbranu od infekcije i imunsku toleranciju prema sebi.

1950-ih su opisane urodjene, primarne imunodeficijencije (PID), karakterisane neuobičajenom podložnosti teškim i ponavljanim infekcijama (bakterije, virusi, gljivice) koja se ispoljava od samog rođenja ili u ranom detinjstvu, a tokom života i povećanom učestalosti autoimunskih i alergijskih bolesti, i maligniteta.

1990-ih su opisane prve monogeneske autoimunske bolesti uzrokovane mutacijama gena odgovornih za održavanje periferne i centralne (u timusu) imunske tolerancije, kao i prva od autoinflamatornih bolesti, potpuno nove kategorije „naslednih poremećaja urođene imunosti, odlikovanih epizodama sistemskog zapaljenja bez poznatog infektivnog uzročnika, koje je većinom posredovano ćelijama mijeloidne loze, bez prisustva autoantitela i/ili autoreaktivnih T limfocita”, tj. različite od autoimunskih bolesti i tzv. 'konvencionalnih' PID. Za ove sistemske bolesti je karakterističan neuobičajeno rani početak tokom detinjstva, često sa 'kompleksnom' prezentacijom (kožni osipi, limfadenopatija, hepatosplenomegalija, vaskulopatija, enteropatija, artritis, endokrinopatije, citopenije) i sa progresivnim tokom bolesti, mada ovii poremećaji imunske regulacije mogu da se ispolje prvi put u odraslih.

Edukacija lekara, pre svega u podizanju pozornosti o postojanju ovih retkih bolesti, ranom prepoznavanju 'smanjene otpornosti prema infekcijama' kao i raznolikosti kliničkih fenotipova imunodisregulacije (autoimunske bolesti, alergije, malignitet, autoinflamacijske bolesti) je od izuzetnog značaja. Pravovremeno upućivanje u specijalizovane ustanove i uspostavljanje rane (genetske) dijagnoze, kao i primena adekvatne i (danas moguće) precizne terapije i genetskog saveta u znatnoj meri umanjuju komplikacije i značajno doprinose poboljšanju dugoročne prognoze i kvalitetu života.

Ključne reči: ponavljane infekcije, imunodisregulacija, autoimunost, inflamacija

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ABSTRACT

Inborn errors of immunity are rare monogenic diseases (prevalence ~1 in 10,000) caused by mutations of (as of today known ~500) genes essential for the two main functions of the immune system, defence from invading pathogens and immunological tolerance to self.

These Mendelian disorders are recognised since 1950's as primary immunodeficiency disorders (PID), with main clinical characteristics of unusual susceptibility to various infectious agents (bacteria, viruses, fungi) causing serious, recurrent infections manifesting since birth or in very early infancy, and increased incidence of autoimmunity, allergy, and malignancy during lifetime.

By the end of 1990's, first monogenic autoimmune disorders due to mutations in genes responsible for maintaining central (thymus) and/or peripheral immunological tolerance were reported, as well as the first of the autoinflammatory disorders, an entirely novel category of "inborn disorders of the innate immune system characterized by episodes of systemic inflammation that are mediated largely by myeloid cells, and absence of autoantibodies and/or autoreactive T cells", i.e. different from autoimmune diseases and 'conventional' PIDs. Onset of 'complex disease' manifestations (skin rash, lymphadenopathy, hepatosplenomegaly, vasculopathy, enteropathy, arthritis, endocrinopathy, cytopenia) is unusually early in childhood, although immunodysregulatory disease may present later in life, and the disease course is often progressive.

Education of physicians in raising the awareness of existence of these rare diseases, above all in early recognition of the 'syndrome of diminished resistance to infection' and of the heterogeneity of clinical phenotypes is of utmost importance. Timely referral to specialized centres is essential for early (genetic) diagnosis, adequate (today available) precision therapy and genetic counselling, reduction of complications and improvement of long-term prognosis, and significant improvement of life quality.

Keywords: recurrent infections, immunodysregulation, autoimmunity, inflammation

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PROBLEMS AND DOUBTS OF PRIMARY CARE DOCTORS IN THE RECOGNITION AND TREATMENT OF PATIENTS WITH IMMUNODEFICIENCY

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SAŽETAK

Uvod/Cilj: Utvrditi koliko često se lekari u službi opšte medicine susreću sa problemom imunodeficijencije kod pacijenata.

Metode: U našem istraživanju koristili smo upitnik koji je podeljen lekarima zaposlenim na primarnom nivou zdravstvene zaštite u službi opšte medicine. Elektronsku formu upitnika koji se sastojao od tri pitanja sa ponuđenim odgovorima o tome šta je imunodeficijencija, kada se ispoljava nedostatak imuniteta i koliko često su se sa njom susretali u praksi popunilo je 95 lekara.

Rezultati: Od ukupnog broja 100% (N=95) lekara smatra da imunodeficijencija zavisi od vrste nedostatka imuniteta, 95,8% (N=91) da se nedostatak imuniteta ispoljava u različitom vremenu u zavisnosti od vrste nedostatka imuniteta, 61,0% (N=58) imalo je pacijenta kod kojeg se kasnije potvrdila imunodeficijencija, 17,9% (N=16) je imalo pacijenta sa učestalim infekcijama koje nisu kasnije potvrđene kao imunodeficijencija, a 22,1% (N=21) se nije sretalo sa pacijentima koji imaju imunodeficijenciju.

Zaključak: Lekari primarne zdravstvene zaštite se retko u praksi susreću sa osobama koje imaju urođen, do tada neprepoznat nedostatak imuniteta, ali je zbog specifičnosti terapije neophodno znanje, prepoznavanje i saradnja sa specijalistima koji se bave ovom oblašću medicine.

Cljučne reči: imunodeficijencija, opšta medicina, nedostatak imuniteta

ABSTRACT

Introduction/Aim: To determine how often doctors in the service of general medicine encounter the problem of immunodeficiency in patients.

Methods: In our research, we used a questionnaire that was distributed to doctors employed at the primary level of health care in general medical practice. The electronic form of the questionnaire, which consisted of three questions with suggested answers about what immunodeficiency is, when the lack of immunity manifests itself and how often they encountered it in practice, was filled out by 95 doctors.

Results: Out of the total number, 100% (N=95) of doctors believe that immunodeficiency depends on the type of immunity deficiency, 95.8% (N=91) that immunity deficiency manifests itself at different times depending on the type of immunity deficiency, 61.0% (N=58) had a patient in whom immunodeficiency was later confirmed, 17.9% (N=16) had a patient with frequent infections that were not later confirmed as immunodeficiency, and 22.1% (N=21) did not encounter with patients who have immunodeficiency.

Conclusion: Doctors of primary health care rarely in practice meet with people who have a congenital, until then unrecognized lack of immunity, but due to the specificity of the therapy, knowledge, recognition and cooperation with specialists who deal with this field of medicine are necessary.

Keywords: immunodeficiency, general medicine, lack of immunity

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ANTIBIOTICI PRVOG IZBORA U LEČENJU PACIJENATA KOD KOJIH SE SUMNJA ILI IMAJU DOKAZANU INFEKCIJU TOKOM NEDOSTATKA IMUNITETA

ANTIBIOTICS OF FIRST CHOICE IN THE TREATMENT OF PATIENTS WITH SUSPECTED OR PROVEN INFECTION DURING IMMUNODEFICIENCY

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SAŽETAK

U uslovima savremene medicine sve veći broj pacijenata živi sa većim ili manjim nedostatkom imuniteta, bilo da njega izaziva osnovna bolest ili primenjeni terapijski protokoli. Zahvaljujući savremenim terapijskim opcijama kvalitet života ovih pacijenata je značajno bolji, njihov vek je značajno produžen u odnosu na neke ranije perioda. Ipak stalni rizik razvoja infekcija i izmenjen i neadekvatan imunološki odgovor predstavljaju veliki i realan rizik po ove pacijenta.

Osnov uspešne terapije oportunističkih infekcija kod pacijenata koji žive sa nedostatkom imuniteta predstavlja pravovremena i pravilno odabrana antimikrobna terapija. Spekter izazivača infekcija kod bolesnika sa nedostatkom imuniteta obuhvata i virusne i gljivične infekcije, ali su bakterijske još uvek naj učestalije i još uvek od najvećeg značaja.

Pravovremena terapija mora da bude efikasna prema pretpostavljenom, a zatim i dokazanom izazivaču, ali i da bude prilagođena karakteristikama samog pacijenta. U uslovima značajne rezistencije izazivača kako u bolničkoj, tako i u vanbolničkoj sredini empirijska terapija često nije adekvatna i obaveza je kliničara da stalno prati terapijski efekat i rezultate mikrobioloških analiza i prema njima prilagođava terapiju. Značaj brzih mikrobioloških tehnika u određivanju što ranije prema izazivaču vođene terapije u savremenoj medicini je sve češći i polako zauzima svoje mesto u svakodnevnom radu. Na kliničaru koji leči pacijenta je velika obaveza da integriše sve informacije koje ima o pacijentu, obezbedi adekvatne uzorke za mikrobiološku dijagnostiku i prvo empirijski, a zatim zasnovano na dokazima odabere najadekvatniji mogući antibiotik za datog bolesnika. Veliku pomoć u izboru sem vodiča predstavlja i poznavanje lokalne epidemiologije izazivača i naravno adekvatna mikrobiološka dijagnostika.

Ključne reči: antibiotici, imunodefijencija, oportunistička infekcija

ABSTRACT

In modern medical circumstances, an increasing number of patients live with varying degrees of immunodeficiency, either due to their underlying disease or the therapeutic protocols they've undergone. Thanks to modern therapeutic options, the quality of life of these patients has significantly improved, and their lifespan has been extended compared to earlier times. However, they are constantly at risk of developing infections, and their altered and inadequate immune response puts them at great risk.

The timely and appropriate selection of antimicrobial therapy is the basis of the successful treatment of opportunistic infections in immunocompromised patients. These infections include viral, fungal, and bacterial infections, which are the most common and important.

Timely therapy must be effective according to the suspected and/or confirmed causative agent, and should also be tailored to the patient's unique characteristics. In the face of significant resistance of the pathogens in both hospital and outpatient settings, empirical therapy may not be sufficient, and the clinician must continually monitor the therapeutic effect and the results of microbiological analyses to adjust the treatment accordingly.

The importance of rapid microbiological techniques in early determination of the cause, and guided therapy is increasingly common in modern medicine and is progressively finding its place in everyday practice. The clinician treating the patient has a great responsibility to integrate all available information about the patient, provide adequate samples for microbiological diagnostics, and choose the most appropriate antibiotic for the patient, initially empirically based on treatment guidelines, experiences, and available epidemiological data and then on solid evidence. Knowledge of the local epidemiology of the causative agent and adequate microbiological diagnostics are helpful in choosing an appropriate antibiotic treatment.

Ključne reči: antibiotics, immunodeficiency, opportunistic infection

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ZAŠTO JE ANTIMIKROBNA REZISTENCIJA VAŽNA ZA IMUNODEFICIJENTNE BOLESNIKE

IMPORTANCE OF ANTIMICROBIAL RESISTANCE FOR IMMUNODEFICIENT PATIENTS

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SAŽETAK

Već više od 80 godina antibiotici se uspešno koriste u lečenju bakterijskih infekcija. Međutim, kao posledica selektivnog pritiska kontinuirane primene antibiotika došlo je do selekcije i širenja rezistentnih sojeva bakterija. Pravilno izvođenje i očitavanje rezultata antibiograma utiče na tok lečenja svakog pojedinačnog pacijenta, ali i na detekciju rezistentnih i multirezistentnih bakterija, što sve zajedno je preduslov za uspešnu terapiju, prevenciju i kontrolu infekcija kako u bolničkoj tako i u vanbolničkoj sredini.

Problem antimikrobne rezistencije (AMR) je odavno uočen i već decenijama se u ekonomski razvijenim zemljama sprovode precizno dizajnirane studije nadzora nad rezistentnim patogenima. Nadzor nad AMR predstavlja sistematsko i neprestano sakupljanje, analizu i upotrebu podataka, što ima za cilj da omogući optimalnu upotrebu antibiotika i definisanje strategija za prevenciju, kontrolu i sprečavanje pojave i širenja AMR na lokalnom, regionalnom i nacionalnom nivou. Svuda u svetu, nadzorom nad AMR su najčešće obuhvaćeni sledeći bakterijski patogeni: *Staphylococcus aureus* i meticilin-rezistentni *S. aureus* (MRSA), *Enterococcus* spp. i vankomicin-rezistentni *Enterococcus* spp. (VRE), enterobakterije (*Escherichia coli*, *Klebsiella pneumoniae* i druge) i Gram-negativni nefermentujući bacili (*Pseudomonas aeruginosa*, *Acinetobacter* spp., i druge).

Bez sumnje, pacijenti sa imunosupresijom su u najvećem riziku od teških infekcija. Ali mogu li svi imunosuprimirani pacijenti da se stavljaju pod isti kišobran? Da li svi imaju iste faktore rizika? Da li svi treba da primaju isti spektar antibiotika? Smatramo da je za adekvatan odgovor na ova pitanja potrebna adekvatna klasifikacija vrsta i stepen imunosupresije, koji takođe uzima u obzir lokalnu epidemiologiju i težinu pacijenta. Umesto da koristimo crno-beli pristup, trebalo bi razmotriti sve nijanse imunosupresije.

Ključne reči: antibiotici, antimikrobna rezistencija, imunosupresija

ABSTRACT

For more than 80 years, antibiotics have been successfully used in the treatment of bacterial infections. However, as a result of the selective pressure of continuous use of antibiotics, there was a selection and spread of resistant strains of bacteria. Proper performance and reading of antibiogram results affects the course of treatment of each individual patient, but also on the detection of resistant and multi-resistant bacteria, which all together is a prerequisite for successful therapy, prevention and infection control both in hospital and outpatient environment.

The problem of antimicrobial resistance (AMR) has long been observed and for decades, precisely designed surveillance studies of resistant pathogens have been conducted in economically developed countries. AMR surveillance is the systematic and continuous collection, analysis and use of data, which aims to enable optimal use of antibiotics and define strategies for the prevention, control and prevention of the occurrence and spread of AMR at the local, regional and national levels. All over the world, the surveillance of AMR most often includes the following bacterial pathogens: *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA), *Enterococcus* spp. and vancomycin-resistant *Enterococcus* spp. (VRE), enterobacteria (*Escherichia coli*, *Klebsiella pneumoniae* and others) and Gram-negative nonfermenting bacilli (*Pseudomonas aeruginosa*, *Acinetobacter* spp., and others).

Undoubtedly, patients with immunosuppression are at the highest risk of severe infections but can all immunosuppressed patients be placed under the same umbrella? Do they all have the same risk factors? Should everyone receive the same spectrum of antibiotics? We believe that an adequate classification of types i degree of immunosuppression is required to adequately answer these questions, which also takes into account the local epidemiology and severity of the patient. Instead of using the black-and-white approach, one should consider all the nuances of immunosuppression.

Keywords: antibiotics, antimicrobial resistance, immunosuppression

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TREATMENT OF VIRAL INFECTIONS IN IMMUNOCOMPROMISED INDIVIDUALS – WHAT HAS CHANGED?

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SAŽETAK

Iako već godinama očekujemo nove antibiotike, situacija na planu antivirusnih lekova je, u tom istom periodu, bila vrlo dinamična.

Antiretrovirusna terapija je napredovala i uvedene su nove klase lekova (inhibitori fuzije) što je produžilo životni vek osoba koje žive sa HIV-om i ovu infekciju pretvorilo u hroničnu bolest, sličnu drugih hroničnim, neinfektivnim bolestima.

Uvođenje direktno delujućih pangenotipskih lekova za HCV omogućilo, izlečenje jedne hronične bolesti, prvi put u medicini. S obzirom da je stopa izlečenja preko 95%, Svetska zdravstvena organizacija je postavila ambiciozne ciljeve za eliminaciju HCV infekcije kao javno-zdravstvenog problema do 2030. godine.

COVID-19 je bio povod za pojavu više novih antivirusnih lekova koji su promenili paradigmu pandemije. U Srbiji su u terapiji obolelih od COVID-19 korišćeni molnupiravir, remdesvir i nirmatrelvir/ritonavir. Pored infektologa, antivirusne lekove za COVID-19 propisivali su i lekari drugih specijalnosti, a što je posebno važno i lekarima opšte prakse. Tako je omogućeno lečenje velikog broja bolesnika u prvim danima bolesti, tj. u periodu kada antivirusna terapija ima efekat.

U Srbiji je dostupan i baloksavir, marboksil, nova terapijska opcija za grip. Ovaj lek ima niz prednosti u odnosu na prethodno korišćene lekove. Pre svega, ima drugi mehanizam dejstva, čime se prevazilazi moguća rezistencija na inhibitore neuraminidaze. Lek se daje u jednoj dozi, što je takođe prednost u odnosu na višednevnu terapiju koja je neophodna kod inhibitora neuraminidaze.

Konačno, postoje i nove terapijske mogućnosti za CMV infekciju – letermovir i maribavir. Sve veći broj imunokompromitovanih bolesnika, znači i veće izazove na planu lečenja CMV infekcije.

Otkrića novih antivirusnih lekova tokom poslednje decenije, promenila su tok i ishod mnogih virusnih infekcija. Napredak na planu lečenja virusnih infekcijau mnogome je popravio prognozu lečenja.

Ključne reči: COVID-19 pandemija, antivirusni lekovi, HIV, HCV, CMV

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ABSTRACT

Although the anticipation of new antibiotics has been ongoing for years, the situation regarding antiviral drugs has been very dynamic during the same period.

Antiretroviral therapy has advanced, and new classes of drugs (fusion inhibitors, etc.) have been introduced. This has led to an extension of the lifespan for people living with HIV and the transformation of this infection into a chronic disease, similar to other chronic, non-infectious diseases.

The introduction of directly acting pan-genotypic drugs for HCV has allowed the cure of a chronic disease for the first time in medicine. Given the cure rate of over 95%, the World Health Organization has set ambitious goals for eliminating HCV infection as a public health issue by 2030.

COVID-19 prompted the introduction of several new antiviral drugs that changed the paradigm of the pandemic. In Serbia, molnupiravir, remdesivir, and nirmatrelvir/ritonavir were used in the treatment of COVID-19 patients. In addition to infectious disease specialists, doctors from various specialties, including general practitioners, were prescribing antiviral drugs for COVID-19. This enabled the treatment of a large number of patients in the early stages of the disease, when antiviral therapy is most effective.

Baloxavirmarboxil, a new therapeutic option for the flu, is also available in Serbia. This drug has several advantages over previously used medications. Firstly, it has a different mechanism of action, overcoming possible resistance to neuraminidase inhibitors. The drug is administered in a single dose, which is also an advantage compared to the multi-day therapy required with neuraminidase inhibitors.

Finally, there are new therapeutic options for CMV infection – letermovir and maribavir. The increasing number of immunocompromised patients underscores the growing challenges in treating CMV infection, emphasizing the necessity for diverse therapeutic options.

The discovery of new antiviral drugs over the last decade has changed the course and outcome of many viral infections. Progress in the treatment of viral infections has significantly improved the prognosis for those undergoing treatment.

Keywords: COVID-19 pandemia, antivirals, HIV, HCV, CMV

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MICROBIOLOGICAL DIAGNOSIS OF INFECTIONS IN IMMUNOSUPPRESSED PERSONS – OUR EXPERIENCE

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SAŽETAK

Napredak u lečenju malignih i imunoloških bolesti uz duže preživljavanje bolesnika sa različitim presađenim organima, povećao je broj bolesnika sa poremećajima imunološkog sistema. Ova grupa pacijenata posebno je osetljiva na bakterijske, gljivične, virusne i parazitske infekcije koje zdravi imunološki sistem obično savlada, a takođe su osetljiviji na komplikacije od uobičajenih infekcija. Takođe, broj imunokompromitovanih pacijenata sa stanjima koja zahtevaju stručnost i mogućnosti lečenja u jedinici intenzivne nege povećao se poslednjih godina.

Standardni dijagnostički testovi, često daju neadekvatne rezultate kod imunokompromitovanih pacijenata što može komplikovati diferencijalno-dijagnostičke mogućnosti i terapijsku strategiju. Služba za medicinsku mikrobiologiju Univerzitetskog kliničkog centra Srbije ima aktivnu ulogu u prevenciji i dijagnostici infekcija, praćenju efikasnosti i pojavi rezistencije na primenjenu antimikrobnu terapiju. Serološki imunoenzimski testovi (ELISA, ECLIA) i molekularna dijagnostika (real-time PCR, reverzna hibridizacija) omogućavaju kvalitativno i/ili kvantitativno određivanje prisustva različitih mikroorganizama, antigena, specifičnih antitela. Komercijalni, preporučeni, standardizovani testovi koji imaju nizak prag osetljivosti, omogućavaju brzu, efikasnu i pouzdanu mikrobiološku (etiološku) dijagnozu kod ove grupe pacijenata i izdavanje pouzdanog rezultata kliničarima.

Ključne reči: imunokompromitovani pacijenti, molekularne metode, real-time PCR, ELISA test

ABSTRACT

Advances in the therapy and management of malignancies and immunologic diseases, together with improved survival of patients with various transplanted organs, have added to the number of patients with profound derangements of the immune system. For the same reasons the number of immunocompromised patients with medical, surgical, or neurologic conditions requiring the expertise and facilities of intensive care treatment has increased within recent years. This group of patients is particularly susceptible to bacterial, fungal, viral, and parasitic infections that healthy immune systems usually overcome. They are also more susceptible to complications from common infections. Furthermore, standard diagnostic tests, often give inadequate results in such patients; this which may complicate differential diagnostic possibilities and therapeutic strategies.

The Medical Microbiology Service, University Clinical Center of Serbia, plays an active role in the prevention and diagnosis of infections, monitoring efficiency and the appearance of resistance to received antimicrobial therapy. Serological immunoassays and molecular tests (real-time PCR, reversal hybridization) allow qualitative and/or quantitative determination of the presence of different microorganisms, antigens, specific antibodies. Commercial, recommended, standardized tests that have a low threshold, allow us a quick, efficient and reliable microbiological (etiological) diagnosis in this group of patients and issuing reliable results to clinicians.

Keywords: immunocompromised patients, molecular methods, real-time PCR, ELISA test

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DA LI MIKROBIOM KANALIZACIJE MOŽE DA UKAŽE NA IMUNODEFICIJENCIJU U ODREĐENOJ ZAJEDNICI?

CAN SEWAGE MICROBIOME INDICATE IMMUNODEFICIENCY IN THE RESPECTIVE COMMUNITIES?

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SAŽETAK

Prisustvo poliovirusa moglo je da se dokaže u otpadnim vodama od 1939. godine, ali je Svetska zdravstvena organizacija tek 2003. godine prihvatila to kao zlatni standard. Analiza otpadnih voda, kada se pravilno koristi, pruža dragocene podatke o zajednici i javnim zdravstvenim službama, kao i o mnogim opasnostima po zdravlje, s obzirom da se u otpadnim vodama mogu naći gastrointestinalni, urinarni, seksualno prenosivi i respiratorni infektivni agensi kao što su virus gripe, respiratorni sincijalni virus, SARS-COV-2, enterovirus D68 itd. Sistematsko osmatranje otpadnih voda može da otkrije prisustvo farmaceutskih proizvoda, hormone, multirezistentne bakterije, kao i druge opasnosti po životnu sredinu. Rezultati ispitivanja otpadnih voda su rani pokazatelji pretnji po zdravlje naroda, stavljajući izazove javno-zdravstvenoj inteligenciji.

Analiziranje kanalizacione vode može ponuditi dragocen uvid u zdravstveni status zajednica obuhvaćene zajedničkim kanalizacijskim sistemom. Na primer, rezultatima pregleda kanalizacione vode mogu se moguće infekcije preduprediti vakcinacijom, merama socijalne zaštite ili adekvatnim lekovima. Ovakav pristup je posebno važan za visoko rizične zajednice kao što su stambene zajednice i dugotrajan boravak u domovima za negu, zdravstvenim ustanovama i zatvorima. Pored toga, praćenjem mikrobioma kanalizacije može pomoći u uvođenju mera bitnih za zdravlje ljudi, životinja, biljaka i uopšte bolju životnu sredinu. Pristup „zdravlje je jedno“ nam može pomoći da razumemo složene veze između mikrobioma, zdravlja i imunološkog statusa.

Prezentacijom će biti obuhvaćeni različiti aspekti praćenja otpadnih voda za osmatranje, otkrivanje i lečenje imunokompromitovanih pojedinaca, kao i moguće korelacije sa platformom „zdravlje za sve“.

Ključne reči: otpadne vode, virusi, testiranje otpadnih voda

ABSTRACT

Wastewater has been used for detecting poliovirus since 1939. However, the World Health Organization only recognized it as a recommended surveillance tool in 2003. When utilized correctly, it provides valuable information to communities and public health services about many bio-hazards, such as gastrointestinal and urinary, sexually transmitted, and respiratory infectious agents like influenza, respiratory syncytial virus, SARS-COV-2, and enterovirus D68. Wastewater surveillance systems can also detect pharmaceuticals, hormones, antimicrobial resistance, environmental hazards, etc. Acting as early warning systems, wastewater tests monitor known, emerging, and novel threats, putting public health intelligence at the forefront.

Sewage testing can offer valuable insights into the health status of communities covered by specific sewage systems. For example, sewage testing can protect individuals and communities through vaccinations, public health and social measures, and targeted medications. This is done by identifying vaccine-derived polioviruses, new variants of SARS-COV-2, opportunistic pathogens, and specific medications. This approach is particularly critical for high-risk communities such as residential and long-term care homes, healthcare facilities, and prisons. In addition, monitoring the sewage microbiome can help guide measures related to humans, animals, plants, and the environment. The One Health Approach can help us understand the complex connections between the microbiome, health, and immune status.

The presentation will cover the various aspects of monitoring wastewater for surveillance, targeting and treating immunocompromised individuals, and the possible correlations with the One Health platform.

Keywords: wastewater, viruses, sewage testing

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ROLE OF THE CLINICAL MICROBIOLOGIST IN THE DIAGNOSIS AND TREATMENT OF PATIENT WITH IMMUNODEFICIENCY

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SAŽETAK

Bolesnici s imunodeficijencijom izloženi su većem riziku za razvoj teških i smrtonosnih infekcija, te predstavljaju veliki izazov u dijagnostici i liječenju. Klinički mikrobiolog pomaže u postavljanju diferencijalne dijagnoze, predlaže kako, kada i koje uzorke pacijenata poslati u laboratorij i kojim metodama se služiti u otkrivanja uzročnika u cilju što ranijeg postavljanja točne dijagnoze. Rano otkrivanje patogena pridonosi uspješnosti izlječenja. 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. Sudjeluju u praćenju i prevenciji širenja zaraznih bolesti i hospitalnih infekcija. Potpuno razumijevanje rezultata mikrobioloških testova ne samo da poboljšava medicinsku skrb pacijenata već i smanjuje njene troškove. U Kliničkom bolničkom centru Zagreb klinički mikrobiolozi redovito sudjeluju u multidisciplinarnim sastancima s kolegama, drugim specijalistima, koji imaju veliki broj pacijenata sklonih infekcijama, s odjela poput pedijatrije, intenzivnih jedinica i hematologije. Cilj ovog predavanja je rasvijetliti ulogu i odgovornosti kliničkog mikrobiologa u liječenju bolesnika s imunodeficijencijom.

Ključne reči: infekcije, imunodeficijencija, dijagnostika, liječenje, mikrobiolog

ABSTRACT

Patients with immunodeficiency are exposed to a greater risk for the development of severe and fatal infections, and represent a huge challenge in diagnosis and treatment. A clinical microbiologist helps in establishing a differential diagnosis, suggests how, when and which patient samples to send to the laboratory and which methods to use in detecting the causative agent in order to establish an accurate diagnosis as early as possible. Early detection of pathogens contributes to successful treatment. In order to take full advantage of all the advantages of laboratory diagnostics, the microbiologist and the clinician should communicate directly. Clinical microbiologists interpret the obtained results, advise on the possibilities and the need for further testing of the causative agent's susceptibility and treatment with antibiotics. In cases where treatment with antimicrobial drugs is necessary, they provide advice on the choice of such drugs and the duration of treatment. They participate in the monitoring and prevention of the spread of infectious diseases and hospital-acquired infections. A complete understanding of the results of microbiological tests not only improves the medical care of patients but also reduces its costs. At the Clinical Hospital Center Zagreb, clinical microbiologists regularly participate in multidisciplinary meetings with colleagues, other specialists, who have a large number of patients prone to infections, from departments such as pediatric, intensive care units and hematology. The aim of this lecture is to shed light on the role and responsibilities of the clinical microbiologist in the treatment of patients with immunodeficiency.

Keywords: infections, immunodeficiency, diagnosis, treatment, microbiologist

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BIOCHEMICAL MARKERS OF IMMUNODEFICIENCY

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SAŽETAK

Primarne imunodeficijencije se mogu ogledati kao deficit humoralnog imunog odgovora, deficit ćelijskog imunog odgovora, ali i kao deficit drugih komponenti imunog odgovora (sistem komplementa, fagocitne ćelije itd.). Stečene imunodeficijencije postaju zastupljenije od primarnih nastaju usled primene hemoterapij (kortikosteroide, imunosupresiva,...), primene zračenja u terapiji, prisustva raznih hroničnih oboljenja (DM, hepatitis, poremećaji u metabolizmu i/ili unošenju proteina, neke hematološke bolesti, karcinomi...), kao posledica raznih infekcija (HIV i druge virusne i neke bakterijske infekcije), nekih stanja (npr. trudnoća), kao posledica prisustva raznih toksina u okruženju (živa, drugi teški metali, pesticidi, petrohemijska), kao i u zavisnosti od životnog doba (dečija populacija, stari). U skriningu radi detekcije ali i u praćenju toka bolesti i terapijskog efekta koriste se pojedini biohemijski parametri kao što su: kompletna krvna slika, apsolutni broj limfocita, apsolutni broj neutrofila, ukupni sadržaj imunoglobulina u klasama i nekim subklasama, C3c i C4 komponente komplementa, elektroforeza serumskih i urinarnih proteina i detekcija M komponente (paraproteina). Za postavljanje definitivnih dijagnoza i uspostavljanja adekvatnog terapijskog protokola koriste se molekularne tehnike kojima se definišu deficiti ili defekti u biosintezi i/ili biološkoj funkciji proteina ili peptida u okviru imunog sistema. Metode koje se koriste u rutinskom radu radi određivanja biohemijskih markera imunodeficijencija su: protočna „flow“ citometrija, impedanca, imunoturbidimetrija, nefelometrija, elektroforeza i imunofiksacija.

Ključne reči: imunodeficijencije, terapijski efekat, imunoglobulini, C3c, C4, elektroforeza

ABSTRACT

Primary immunodeficiencies can be reflected as a deficit of the humoral immune response, a deficit of the cellular immune response, but also as a deficit of other components of the immune response (complement system, phagocytic cells, etc.). Acquired immunodeficiencies become more prevalent than primary ones and arise as a result of the use of chemotherapeutics (corticosteroids, immunosuppressants,...), the use of radiation therapy, the presence of various chronic diseases (DM, hepatitis, disorders in metabolism and/or protein intake, some hematological diseases, cancers,...), as a consequence of various infections (HIV and other viral and some bacterial infections), some conditions (e.g. pregnancy), as a consequence of the presence of various toxins in the environment (mercury, other heavy metals, pesticides, petrochemical), as well as depending on the age (child population, geriatric population). In screening for the purpose of detection, but also in monitoring the course of the disease and the therapeutic effect, certain biochemical parameters are used, such as: complete blood count, absolute number of lymphocytes, absolute number of neutrophils, total content of immunoglobulins in classes and some subclasses, C3c and C4 components of complement, serum and urinary protein electrophoresis and detection of the M component (paraprotein). To achieve definitive diagnoses and establish an adequate therapeutic protocol, molecular techniques are used to define deficits or defects in the biosynthesis and/or biological function of proteins or peptides within the immune system. Methods used in routine work to determine biochemical markers of immunodeficiency are "flow" cytometry, impedance, immunoturbidimetry, nephelometry, electrophoresis and immunofixation.

Keywords: immunodeficiencies, therapeutic effect, immunoglobulins, C3c, C4, electrophoresis

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RELAPSING COVID-19 PNEUMONIA AND *HELICOBACTER CINEADI* CELLULITIS IN A PATIENT WITH X-LINKED AGAMAGLOBULINEMIA

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SAŽETAK

Uvod: Agamaglobulinemija vezana za X hromozom je primarna humoralna imunodeficijencija koja se odlikuje odsustvom zrelih B limfocita i imunoglobulina.

Prikaz slučaja: Muškarac star 39 godina kome je dijagnoza agamaglobulinemije postavljena u 13. mesecu života. Pacijent je redovno dobio supstitucionu terapiju imunoglobulinima. Lečen je od pneumonije izazvane infekcijom virusom SARS-CoV-2 po prvi put u aprilu 2020. godine uz primenu plazme rekonvalescenta i tocilizumaba. Nakon potpunog povlačenja tegoba i normalizacije rendgenološkog nalaza javlja se prvi, a nakon njega još tri relapsa pneumonije uz ponavljano negativne nalaze prisustva virusa u nazofaringealnom brisu. Primenjivan je tocilizumab u jednoj mesečnoj dozi od 800 mg uzastopno tri meseca tokom kojih je pacijent bio bez simptoma. Nakon smanjenja doze tocilizumaba na 400 mg javlja se ponovni relaps pneumonije, kada je prisustvo virusa detektovano u sputumu. Uspešno je izlečen primenom remdesivira tokom 10 dana.

U avgustu 2022. godine javljaju se promene na potkolenicama koje odgovaraju celulitisu uz porast zapaljenjskih parametara. Nakon ukidanja antibiotske terapije javljaju se mnogobrojni recidivi celulitisa. Tokom aktivne faze celulitisa iz produžene hemokulture izolovan je i masenom spektrometrijom potvrđen *Helicobacter cineadi*. Lečenje je nastavljeno kontinuiranom primenom različitih kombinacija antibiotika tokom godinu dana. Pacijent je bez simptoma bolesti unazad 6 meseci i uzima minociklin.

Zaključak: Antitela su neophodna za opsonizaciju i otklanjanje infektivnih uzročnika. U preparatima imunoglobulina iz krvi mnogobrojnih davalaca koje je naš pacijent redovno dobio verovatno nije bilo dovoljno antitela specifičnih za SARS-CoV-2 i *H. cineadi* kako bi došlo do eradikacije ovih infekcija.

Ključne reči: Covid-19 pneumonija, *Helicobacter cineadi* celulitis, agamaglobulinemija

ABSTRACT

Introduction: X-chromosome-bound agamaglobulinemia is a primary humoral immunodeficiency characterized by the absence of mature B lymphocytes and immunoglobulins.

Case report: Patient is 39-year-old man who was diagnosed with agamaglobulinemia at 13 months of age. The patient was regularly given immunoglobulin replacement therapy. He was treated for pneumonia caused by SARS-CoV-2 infection for the first time in April 2020. with the use of plasma convalescent and tocilizumab. After complete withdrawal of problems and normalization of X-ray results, occurs the first, followed by three more relapses of pneumonia with repeated negative findings of the presence of the virus in the nasopharyngeal swab. Tocilizumab was administered at one consecutive monthly dose of 800 mg for three consecutive months during which the patient was symptom-free. After reducing the dose of tocilizumab to 400 mg, there is a relapse of pneumonia, when the presence of the virus is detected in sputum. He was successfully cured with remdesivir for 10 days.

In August 2022, there are changes in the lower legs corresponding to cellulitis with an increase in inflammatory parameters. After the abolition of antibiotic therapy, there are numerous relapses of cellulitis. During the active phase of cellulitis from prolonged hemoculture, *Helicobacter cineadi* was isolated and confirmed by mass spectrometry. Treatment continued with the continuous use of various combinations of antibiotics for a year. The patient has been without symptoms of the disease for the past 6 months and has taken minocycline.

Conclusion: Antibodies are necessary to oppose and eliminate infectious agents. In the preparations of immunoglobulins from the blood of many donors that our patient regularly received, there were probably not enough antibodies specific to SARS-CoV-2 and *H. cineadi* to eradicate these infections.

Keywords: COVID-19 pneumonia, *Helicobacter cineadi* cellulitis, X-linked agamaglobulinemia

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NEUROINFECTIONS IN IMMUNOCOMPROMISED PATIENTS

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SAŽETAK

Uvod: Uprkos odgovarajućim antimikrobnim lekovima, infekcije centralnog nervnog sistema (CNS) i dalje izazivaju značajno oboljevanje i smrtnost. Kliničke prezentacije, neuroradiološka dijagnostika i abnormalnosti cerebrospinalne tečnosti (CST) se razlikuju između imunokompromitovanih i imunokompetentnih pacijenata.

Diskusija: Imunokompromitovani pacijenti uključuju pacijente sa transplantacijom solidnih organa i matičnih ćelija hematopoeze, pacijente sa malignitetom, izmenjenim imunološkim sistemom usled lečenja inflamatornih bolesti creva, reumatoidnog artritisa, sistemskog eritematoznog lupusa, sarkoidoze, miastenije, miozitisa i multiple skleroze. Ovi pacijenti često imaju odsustvo tipičnih znakova infekcije kao što su povišena temperatura ili meningizam, zatim prisustvo više istovremenih infekcija, neuobičajenu virulentnost patogenaobično nisko rizičnih kod imunokompetentnih pacijenata, kao što su virus Zapadnog Nila, Babesia, Borrelia i Varicella-zoster virus (VZV), toksičnost novih lekova, i indeterminantne laboratorijske rezultate zbog lečenja. To mogu biti citopenije povezane sa bolestima koje mogu smanjiti ili eliminisati pleocitozu u cerebrospinalnoj tečnosti (CST), kao i razvoj autoimunih sindroma izazvanih neuroinfekcijama. Intenzivna antibiotska terapija dovela je do razvoja rezistentnih mikroorganizama. Meticilin rezistentan Staphylococcus aureus (MRSA) preuzima sve veću ulogu i može biti udružen sa neuroinfekcijama i fatalnim sistemskim komplikacijama. Oportunističke gljivice su postale sve češći smrtonosni patogeni, jer se učestalost nozokomijalnih gljivičnih infekcija značajno povećala.

Zaključak: Lekari bi trebalo da obrate pažnju na moguće prisustvo infekcija CNS-a kod imunokompromitovanih pacijenata. Dijagnostički pristup infekcijama CNS-a uključuje neuroradiološku dijagnostiku i lumbalnu punkciju. CST treba kultivisati na bakterijske i gljivične patogene, a PCR meningitis/encefalitis paneli omogućavaju dijagnozu širokog spektra mikroorganizama.

Ključne reči: infekcije centralnog nervnog sistema, cerebrospinalna tečnost, antibiotska terapija

ABSTRACT

Introduction: Despite appropriate antimicrobials central nervous system (CNS) infections continue to cause significant morbidity and mortality. Clinical presentations, neuroimaging, and cerebrospinal fluid (CSF) abnormalities differ between immunocompromised and immunocompetent patients.

Discussion: Immunocompromised patients include hematopoietic and solid organ transplant recipients, patients with malignancy, altered immune systems due to treatment for inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, patients with myasthenia, myositis and multiple sclerosis patients. These patients often have absence of typical clues to infection such as fever or meningismus, then presence of multiple concurrent infections, unusual virulence of pathogens normally of low risk in immunocompetent patients such as West Nile virus, Babesia, Borrelia, and Varicella-Zoster virus (VZV), novel drug toxicities and indeterminate laboratory results due to treatment. It can be disease-related cytopenias that may reduce or eliminate cerebrospinal fluid (CSF) pleocytosis, and as well as development of neuroinfections-triggered autoimmunity syndromes. Intensive antibiotic therapy led to the development of resistant microorganisms. Methicillin-resistant Staphylococcus aureus (MRSA) is taking on an increasing role and can be associated with neuroinfections and fatal systemic complications. Opportunistic fungi have become increasingly common lethal pathogens as the incidence of nosocomial fungal infections has increased significantly.

Conclusion: The physicians should pay attention to the possible presence of CNS infections in immunocompromised patients. The diagnostic approach to the CNS infections include neuroimaging and lumbar puncture. The CSF should be cultured for bacterial and fungal pathogens, and PCR meningitis/encephalitis panels provide a diagnosis of broad spectrum of microorganisms.

Keywords: central nervous system infections, cerebrospinal fluid, antibiotic therapy

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CHALLENGES IN PREVENTION AND TREATMENT OF HEPATITIS B IN IMMUNOCOMPROMISED

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SAŽETAK

Populacija imunosuprimiranih predstavlja poseban izazov u lečenju i prevenciji, kako *de novo* hepatitis B virusne (HBV) infekcije, tako i reaktivaciji postojeće infekcije. Pojava nukleozidnih/nukleotidnih analoga sa visokom barijerom za razvoj rezistencije dovele su do preokreta u lečenju hronične HBV infekcije. Obavezan je skrining na HBV svih bolesnika u okviru pripreme za imunosupresivnu terapiju koji podrazumeva analizu HBsAg, anti HBcore IgG i anti HBsAg, uz određivanje nivoa viremije (HBV DNK PCR) u slučaju HBsAg ili anti HBc IgG pozitivnosti. U slučaju HBV „naivnih“ pacijenata indicirana je vakcinacija pre uvođenja imunosupresivne terapije, sa ciljnim titrom antiHBsAg >100 IU/ml koji je potrebno proveravati na 2 godine. Reaktivacija HBV infekcije može nastupiti kako kod bolesnika sa hroničnom, tako i sa preležanom infekcijom i može proteći kao blagi hepatitis, ali dovesti do akutne insuficijencije jetre i smrtnog ishoda. Kod HBsAg + pacijenata savetuje se profilaksis antivirusnim lekovima visokom barijerom za rezistenciju (entecavir, tenofovir) mesec dana pre započinjanja imunosupresivne terapije, sve vreme njene primene i još najmanje 6-12 meseci, u slučajevima manje, odnosno 12-18 meseci u slučaju potentnije imunosupresivne terapije. Kod HBsAg negativnih, antiHBc pozitivnih pacijenata, zavisno od vrste imunosupresivne terapije, savetuje se ili antivirusna profilaksa ili praćenje HBsAg i HBV DNK PCR (jednom u 1-3 meseca) i preventivno davanje terapije u slučaju pozitivnosti bilo kog od ova dva parametra. Prilikom transplantacije, potrebno je uklapanje HBV statusa donora i recipijenta organa, međutim, s obzirom na vitalni značaj, korist od transplantiranja organa antiHBc ili čak HBsAg pozitivnog donora daleko prevazilazi rizik od moguće infekcije, ukoliko se primene adekvatne profilaktičke mere.

Ključne reči: hepatitis B, imunoterapija, transplantacija organa

ABSTRACT

Immunocompromised patients represent a challenge in treatment and prevention of hepatitis B virus (HBV) infection, as well as in prevention of HBV reactivation. The appearance of nucleoside/nucleotide analogues with high resistance barrier made a substantial improvement in the treatment of chronic hepatitis B. Screening for HBV is mandatory for all patients awaiting immunosuppressive therapy and should include testing for HBsAg, antiHB core IgG and anti HBs antibodies, followed by HBV DNK PCR in case of HBsAg or antiHBc IgG positivity. In case of HBV „naive“ patients vaccination against HBV is warranted, aiming for the titer of antiHBs antibodies > 100 IU/ml, which should be reassessed every two years. HBV reactivation can occur in patients with chronic, but also in those with resolved HBV infection and can present as mild hepatitis, but also cause acute liver failure and death. In HBsAg positive patients antiviral prophylaxis with nucleotide/nucleoside analogues with high resistance barrier (entecavir, tenofovir) is indicated one month before, during the course of immunosuppressive therapy, and at least 6-12 months and 12- 18 months after its completion in case of less and more potent immunosuppressive treatment, respectively. In HBsAg negative, anti HB core positive patients depending on the type of immunosuppressive drugs, patients can be given antiviral prophylaxis or they can be monitored for HBsAg and HBV DNK at least every 1-3 months, and pre-emptive therapy should be introduced in case of the positivity of any of the abovementioned. During transplantation, matching of the donor and recipient according to HBV status is suggested, but the vital significance of organ transplantation outweighs the possible risk of HBV transmission in case of HBsAg or antiHB core positive donors.

Keywords: hepatitis B, immunotherapy, organ transplantation

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LIVER CIRRHOSIS AS A CAUSE OF IMMUNE DYSFUNCTION AND IMMUNOSUPPRESSION

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SAŽETAK

Jetra je važan imunološki organ koji na različite načine utiče na efikasno funkcionisanje odbrambenih snaga organizma. Ciroza, kao relativno uniformna terminalna faza oštećenja jetre različitim uzrocima, dovodi do imunske disfunkcije. Ova disfunkcija zahvata urođene (nespecifične) i stečene (specifične) komponente imuniteta, a oštećeni su lokalni imunitet jetre, kao i specifični sistemski T i B ćelijski imunitet. Kod monocita i makrofaga redukovana je hemotaksa, fagocitoza, lizozomna aktivnost i superoksidna degeneracija, kod neutrofila prisutna je perzistentna aktivacija uz redukovanu migraciju, hemotaksu i fagocitozu, a kod limfocita defect imemorijskih ćelija, poremećaj odnosa CD4+/CD8+, perzistentna aktivacija i povećana apoptoza. Poremećeni su i sistem komplementa kao i prepoznavanje receptora. Navedeni procesi udruženo uvode organizam u stanje imunosupresije, a sa druge strane imunska disfunkcija se manifestuje i kroz stimulisanje sistemske inflamacije usled poremećaja proizvodnje proinflamatornih citokina – hepatokina. Oba mehanizma su odgovorna za akutnu ili hroničnu dekompenzaciju funkcije jetre kod osoba sa cirozom, a uzrok su 30% mortaliteta kod ovih osoba. Infekcije tokom ciroze jetre mogu biti endogenog porekla (translokacija bakterija iz gastrointestinalnog trakta, usne duplje, sa kože) ili egzogenog porekla, klasifikovane kao vanbolničke (stečene u zajednici), infekcije u vezi sa zdravstvenom zaštitom bolničke (nozokomijalne) infekcije. Kod osoba sacirozom povećana je sklonost ka bakterijemiji edotoksemiji koji prouzrokuju sistemski inflamatorni odgovor (SIRS), sepsu, multiorgansku disfunkciju (MODS) i u krajnoj instanci smrtni ishod. S obzirom da su naveden iprocesi veoma dinamičnii da za kratko vreme mogu progredirati, veoma je važno njihovo promptno prepoznavanje i lečenje u cilju preživljavanja.

Ključne reči: ciroza jetre, imunosupresija, imunomodulacija, superinfekcije

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ABSTRACT

The liver is an important immune organ that influences the efficient functioning of the body's immune defenses in various ways. Cirrhosis, as a relatively uniform terminal phase of the liver, leads to immune dysfunction. This dysfunction encompasses both the innate (non-specific) and acquired (specific) components of immunity. Both local liver immunity and specific systemic T and B cell immunity are impaired. In monocytes and macrophages, chemotaxis, phagocytosis, lysosomal activity, and superoxide generation are reduced. Neutrophils experience persistent activation with decreased migration, chemotaxis, and phagocytosis. Lymphocytes exhibit memory cell defects, a disturbance in the CD4+/CD8+ ratio, persistent activation, and increased apoptosis. Both the complement system and the receptor recognition system are disrupted. These processes collectively lead the organism into a state of immunosuppression. Conversely, immune dysfunction manifests through the stimulation of systemic inflammation, resulting from the disruption of the production of proinflammatory cytokines – hepatokines. Both of these mechanisms contribute to the acute or chronic decompensation of liver function in individuals with cirrhosis, causing 30% of mortality in these patients. Infections during cirrhosis can originate endogenously (resulting from the translocation of bacteria from the gut, oral cavity, or skin) or exogenously, classified as community-acquired, healthcare-associated, or hospital-acquired (nosocomial) infections. Patients with cirrhosis face an increased risk of bacteremia and endotoxemia, leading to systemic inflammatory response syndrome (SIRS), sepsis, multiorgan dysfunction (MODS), and ultimately death. Given that these processes are highly dynamic and can progress rapidly, prompt recognition and treatment are crucial and necessary to improve survival.

Keywords: liver cirrhosis, immunosuppression, immunomodulation, superinfections

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CHALLENGES IN THERAPY AND DIAGNOSIS OF VIRAL HEPATITIS IN IMMUNOSUPPRESSED PERSONS

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SAŽETAK

Procenjuje se da oko 22 % osoba koje su primale neku od imunosupresivnih terapija (IS) bilo zbog automimunih, malignih oboljenja nakon transplantacije solidnih organa su imale neko oštećenje jetre. S druge strane, preegzistentno prisustvo virusnih infekcija jetre često dovodi do egzacerbacije bolesti jetre kod primene IS terapije ili u stanjima imunosupresije.

Dobro je poznato da se u stanjima imunosupresije hronična HBV infekcija može reaktivirati i dovesti do razbuktavanja hepatitisa. Za razliku od monoinfekcije HBV, koinfekcija HBV/HDV je retko opisana u kontekstu reaktivacije kod imunosupresije. Međutim opisano je par slučajeva udružene HDV infekcije sa autoimunim hepatitisom i to najčešće u kontekstu terapije pegilovanim interferonom.

Saznanja o postojanju hronične HEV infekcije u stanjima imunodeficiencije naročito kod primalaca transplantiranih organa bilo bubrega ili jetre je prvi put objavio Kamar sa saradnicima 2008, uz podatak da više od 66% primalaca solidnih organa razvija hroničnu, uglavnom asimptomatsku HEV infekciju uzrokovanu genotipom 3, ređe genotipom 4 HEV virusa. Primarna prezentacija HEV infekcije često je udružena sa ekstrahepatičnim manifestacijama uključujući neurološke, nefrološke, hematološke i imunoposredovane manifestacije.

Stanje imunosupresije sa sobom nosi i dijagnostičke probleme jer pojedini dijagnostički testovi uglavnom serološki, koji su bazirani na detekciji specifičnih antitela na pojedine virusne antigene može biti odloženo ili odsutno u stanjima imunosupresije što dodatne komplikuje pravovremeno prepoznavanja i dijagnostikovanje hroničnih virusnih hepatitisa. Tako je važan dijagnostički marker akutne HEV infekcije detekcija anti HEV IgM antitela. Kada se testiraju ova antitela komercijalno dostupnim testovima senzitivnost je preko > 97% kod imunokompetentnih osoba ali ta senzitivnost pada na 80-85% kod imunosuprimiranih – zato je neophodno testiranje na prisustvo HEV RNK u ovoj populaciji. Pravovremeni i ciljani skrining na markere virusnih infekcije jetre jedan od imperativa u planiranju IC terapije i lečenju i monitoringu imunosupresivnih stanja.

Ključne reči: virusni hepatitis, imunosupresija, HEV RNK

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ABSTRACT

Liver-related injuries are estimated to affect up to 22% of patients receiving immunosuppressive therapies (IS) (either due to autoimmune, malignant diseases or solid organ transplantation). Also of concern, is the risk of exacerbating liver injury in patients infected with chronic viral hepatitis: hepatitis B virus (HBV), hepatitis D virus, hepatitis E virus), as immunotherapy can damage liver function due to the immune response against viral antigens.

It is well known that in conditions of immunosuppression, chronic HBV infection can be reactivated and lead to flare of hepatitis. Unlike HBV monoinfection, HBV/HDV co-infection has rarely been described in the context of reactivation in immunosuppression. However, a couple of cases of combined HDV infection with autoimmune hepatitis have been described, most often in the context of pegylated interferon therapy.

Knowledge about the existence of chronic HEV infection in states of immunodeficiency, especially in kidney or liver transplant recipients, was first published by Kamar et al. in 2008, that more than 66% of solid organ recipients develop chronic, mostly asymptomatic HEV infection caused by genotype 3, less often by genotype 4 HEV viruses. The primary presentation of HEV infection is often associated with extrahepatic manifestations including neurological, nephrological, hematological and immune-mediated manifestations.

The state of immunosuppression also brings with it diagnostic problems because certain diagnostic tests, mainly serological, which are based on the detection of specific antibodies to certain viral antigens, may be delayed or absent in states of immunosuppression. The detection of anti-HEV IgM antibodies is thus an important diagnostic marker of acute HEV infection. When antibodies are tested with commercially available tests, the sensitivity is over > 97% in immunocompetent persons, but this sensitivity drops to 80-85% in immunosuppressed persons – that is why testing for the presence of HEV RNA in this population is necessary. Timely and targeted screening for markers of viral liver infections is one of the imperatives in planning IC therapy and treatment and monitoring of immunosuppressive conditions.

Keywords: viral hepatitis, immunosuppression, HEV RNA

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LIVER TRANSPLANTATION IN VIRUS INDUCED ESLD

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SAŽETAK

Od momenta otkrića virusa početkom početkom '90-tih godina, kroz naredne 4 decenije, HCV infekcija je bila vodeći uzrok transplantacije jetre u svetu. Centar za transplantaciju jetre KCV započeo je sa radom na Vidovdan, 28.6.2008. godine kadaveričnom transplantacijom jetre bolesnici sa HCV cirozom jetre i HCC.

Do sada je na listi čekanja za transplantaciju jetre u KCV bilo 99 bolesnika, od kojih je 36 (36%) obolelih je imalo HCV infekciju: 18 bolesnika je transplantirano (3 bolesnika sa HCC), 13 je preminulo čekajući transplantaciju, 4 bolesnika su isključena sa liste zbog poboljšanja, a 2 bolesnika još uvek čekaju na novi organ.

Od ukupno 40 transplantiranih, transplantirano je 18 bolesnika sa HCV infekcijom (43%). Ukupno preživljavanje svih transplantiranih bolesnika iznosi 68,2%. Većina transplantacija je urađena u periodu kada terapija DAA nije bila dostupna, reinfekcija grafta je bila očekivana, a samim tim i veća smrtnost – 33,3% naspram 22,8% umrlih među transplantiranim zbog drugih indikacija. Od ukupno 14 (77,7%) bolesnika koji su preživeli prvi mesec posle transplantacije, kod dva bolesnika (14,2%) re-infekcija grafta je protekla pod kliničkom slikom fibrozirajućeg holestaznog hepatitisa, dok je rekurentni HHC je dijagnostikovao kod preostalih 11 bolesnika (61,2%). Dva bolesnika sa rekurentnim HHC lečena su PegIFN alfa-2b i ribavirinom unutar godinu dana od transplantacije jetre, postignut je SVR i oni su stabilni. Kod 3 od 11 (27,3%) bolesnika se razvija dekompenzovana ciroza jetre i umiru unutar narednih 7 godina po slikom ESLD.

U eri DAA terapije lečili smo 6 bolesnika sa rekurentnim HHC i svi su postigli SVR. Tri bolesnika su preminula, jedan zbog dekompenzovane ciroze jetre uzrokovane konkomitantnom primarnom bilijarnom cirozom (PBC), a dva zbog razvoja maligniteta.

Ključne reči: transplantacija jetre, hepatitis C, direktno dejstvujući antivirusni lekovi

ABSTRACT

Since the discovery of the virus at the beginning of the '90s, through the next 4 decades, HCV infection was the leading cause of liver transplantation in the world. The first cadaveric liver transplantation in Center for Liver Transplantation CCV was performed in patients with HCV- associated liver cirrhosis and HCC on June 28, 2008.

Until now, there were 99 patients on the waiting list for liver transplantation in CCV, of which 36 (36%) patients had HCV infection: 18 patients underwent transplantation (3 patients with HCC), 13 died while waiting for transplantation, 4 patients were excluded from the list due to improvement, and 2 patients are still waiting for a new organ.

Out of a total of 40 transplanted, 18 patients with HCV infection underwent transplantation (43%). The total survival of all transplant patients is 68.2%. Most transplants were performed in the period when DAA therapy was not available, re-infection of the graft was expected, and therefore higher mortality – 33.3% versus 22.8% of those transplanted due to other indications. Out of a total of 14 (77.7%) patients who survived the first month after transplantation, in two patients (14.2%) graft re-infection took place under the clinical picture of fibrosing cholestatic hepatitis, while recurrent HHC was diagnosed in the remaining 11 patients. (61.2%). Two patients with recurrent HHC were treated with PegIFN alfa-2b and ribavirin within one year of liver transplantation, SVR was achieved and they are stable. 3 out of 11 (27.3%) patients developed decompensated liver cirrhosis and died within the next 7 years under the clinical presentation of ESLD. In the era of DAA therapy, we treated 6 patients with recurrent HHC and all achieved SVR. Three patients died, one due to decompensated liver cirrhosis caused by concomitant primary biliary cirrhosis (PBC), and two due to the development of malignancy.

Keywords: liver transplantation, hepatitis C, direct-acting antiviral drugs

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TUBERCULOSIS (TB) IN IMMUNODEFICIENT STATES

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SAŽETAK

Aktivna TB je vodeći uzrok smrti u svetu među zaraznim bolestima, a prema podacima SZO 10,4 miliona ljudi je obolelo.

U Srbiji 2018. godine prijavljeno je 695 slučajeva obolevanja od svih oblika tuberkuloze koji podležu prijavljivanju. U Beogradu 203 novoobolelih. Najveća zastupljenost u posmatranoj godini bila je u Mačvanskom i Kolubarskom okrugu.

Pandemija SARS-CoV-2 infekcije je angažovala sve zdravstvene i druge resurse, tako da je pristup službama za dijagnostiku, lečenje i izveštavanje o podacima za tuberkulozu znatno onemogućen. Zbog čega je 2020. godine broj prijavljenih prepolovljen. Ukupno prijavljenih obolelih 259, a u Beogradu 88.

2022. godine postaje dostupniji zdravstveni sistem pacijentima, te je prijavljeno 466 obolelih u Srbiji od čega u Beogradu 147.

Strategija za eliminaciju TB počiva na brzom prepoznavanju obolelih od aktivne tuberkuloze i brzom započinjanju lečenja antituberkuloticima. Suštinska strategija SZO za eliminaciju TB zapravo počiva na prevenciji aktivne tuberkuloze kroz detekciju latentne TB i identifikaciju osoba u rizičnim populacijama.

Savetuje se testiranje za bolesnike koji započinju anti-TNF terapiju, bolesnici na dijalizi, bolesnici koji se pripremaju za transplantaciju solidnih organa ili kostne srži, bolesnici sa silikozom.

Trećina svetske populacije je nosilac latentne *M. tuberculosis* infekcije, koja se može ponovo aktivirati, posebno u različitim imunokompromitovanim stanjima.

Kod svih IMID (Immune-mediated inflammatory disease) bolesnika pre započinjanja biološke terapije, koji nemaju podatke o prethodno lečenoj aktivnoj TB, potrebno je testiranje na latentnu TB kombinovanom primenom IGRA (Interferon-gamma release assays) i PPD testova (Purified protein derivative skin test).

Kod pacijenata kod kojih se planira uvođenje biološke terapije ukoliko je dokazana latentna TB, a prethodno isključena aktivna TB potrebno je uvođenje hemioprofilakse. Upotreba hemioprofilakse kod ovih pacijenata smanjila je incidencu TB za 78%.

Bolesnici koji su dogotrajno primali imunosupresivnu terapiju oboleli od aktivne TB i lečeni šestomesečnim režimom, po izlečenju TB mogli su da nastave lečenje osnovne bolesti primenom biološke terapije.

Ključne reči: tuberkuloza, LBTI, biološka terapija, Quantiferon, hemioprofilaksa

ABSTRACT

Active TB is the leading cause of death in the world among infectious diseases, and according to data from the World Health Organization (WHO), there are 10.4 million new cases in the world every year.

In 2018, 695 cases were reported in Serbia, which is a rate of 9.95 patients per 100,000 inhabitants. Of these, 203 new patients were reported in Belgrade. The highest number of new cases in the observed year was in the Mačvan and Kolubara districts.

In Serbia in 2020 the number of reported patients was halved due to the unavailability of health care due to the Covid infection. The total number of patients reported was 259, and in Belgrade 88. In 2022, health system become more available, 466 new cases were discovered, from which 147 in Belgrade.

The strategy for the elimination of TB is based on the rapid recognition of patients, then on proving active tuberculosis and starting treatment with antituberculous drugs. But the essential strategy of the WHO for the elimination of TB actually rests on the prevention of active tuberculosis through the detection of latent TB and the identification of persons in risk populations.

A third of the world's population carries latent *M. tuberculosis* infection, which can be reactivated, especially in various immunocompromised states.

Testing for latent TB is advised for patients at increased risk; who start anti-TNF therapy, patients on dialysis, patients preparing for solid organ or bone marrow transplantation, patients with silicosis.

In all IMID (immune-mediated inflammatory disease) patients, testing for latent tuberculosis is mandatory, before biologic therapy is started, regardless if they had or not tuberculosis, by IGRA (Purified protein derivative skin test).

Patients that are planned for biologic therapy, who were proved for latent tuberculosis, and were excluded for active tuberculosis, hemioprophyllaxis is indicated. Hemioprophyllaxis in those patients lowered tuberculosis incidence in 78%.

Patients that were on immunosuppressive therapy, and got active tuberculosis, had to stop biologic therapy, to be cured by six months protocol. After being cured, they were eligible to continue immunosuppressive therapy.

Keywords: tuberculosis, LBTI, biological therapy, Quantiferon, chemoprophylaxis

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COMPLICATED NEUROTUBERCULOSIS AFTER THE USE OF BIOLOGICAL THERAPY

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SAŽETAK

Uvod: Neurotuberkuloza predstavlja značajan medicinski izazov u smislu dijagnostike i terapije, a naročito zbog mogućih trajnih neuroloških komplikacija i pored adekvatnog lečenja, uz rizik od neželjenih efekata primenjenih lekova. Navedeni problemi su od posebnog značaja kod imunokompromitovanih pacijenata. Ovdje je prikazan kompleksan klinički tok neurotuberkuloze kod imunokompromitovanog bolesnika sa preegzistentnim reumatoidnim artritisom.

Prikaz slučaja: Pacijent star 62 godine sa dugogodišnjim reumatoidnim artritisom, lečen tocilizumabom poslednja 3 meseca, krajem novembra 2022. godine je primljen u Klinički centar Crne Gore zbog povišene telesne temperature, glavobolje i konfuznosti koje su se javile sedam dana ranije. Sprovedenom dijagnostikom je tada utvrđena neurotuberkuloza i ordinirana adekvatna terapija. Nakon inicijalnog poboljšanja dolazi do relapsa koji se manifestovao mentalnim usporanjem, inkontinencijom urina i otežanim kretanjem, dok je urađeni MR pregled mozga pokazao progresiju bolesti u smislu ekstenzivnih multilokularnih nodularnih lezija sa perilezionim edemom frontoparijetalno obostrano. Zbog navedenog, ispitivanje i lečenje je nastavljeno u Klinici za infektivne i tropske bolesti Univerzitetskog Kliničkog centra Srbije. Tokom hospitalizacije, došlo je do razvoja hepatotoksičnog efekta antituberkulozne terapije koja je korigovana, i ponovo je ordinirana kortikosteroidna terapija. U daljem toku dolazi do postepenog oporavka stanja bolesnika i povlačenja svih tegoba. Kontrolni MR pregled je pokazao značajnu regresiju ranije opisanih multiplih intrakranijalnih lezija.

Zaključak: Uprkos relativno brzo postavljenoj dijagnozi i primenjenoj adekvatnoj terapiji klinički oporavak pacijenta sa neurotuberkulozom može biti neadekvatan, te je potrebno intenzivno praćenje ovakvih bolesnika, pravovremeno prepoznavanje pogoršanja i dodatna dijagnostička evaluacija radi što povoljnijeg ishoda.

Ključne reči: tuberkuloza, biološka terapija, magnetna rezonanca

ABSTRACT

Introduction: Neurotuberculosis poses a significant medical challenge in terms of diagnosis and therapy, particularly due to potential long-lasting neurological complications despite adequate treatment and risk of adverse effects of administered drugs. These issues are particularly relevant in immunocompromised patients. Here, we present a complex clinical course of neurotuberculosis in an immunocompromised patient with pre-existing rheumatoid arthritis.

Case report: A 62-year-old patient with long-standing rheumatoid arthritis, treated with tocilizumab for the last 3 months, was admitted to the Clinical Center of Montenegro in late November 2022 due to fever, headache, and confusion that had occurred 7 days earlier. Diagnostic procedures at that time revealed neurotuberculosis, and appropriate therapy was prescribed. After initial improvement, a relapse occurred, manifested by mental slowing, urinary incontinence, and difficulty in movement. Brain MRI showed disease progression with extensive multilocal nodular lesions and perilesional edema bilaterally in the frontoparietal region. Due to these findings, further investigation and treatment were continued at the Clinic for Infectious and Tropical Diseases, University Clinical Center Serbia. During hospitalization, hepatotoxic effects of antituberculous therapy occurred. The therapy was changed and corticosteroids were reintroduced. Subsequently, the patient gradually recovered, and all symptoms resolved. The follow-up MRI examination showed a significant regression of previously described multiple intracranial lesions.

Conclusion: Despite a relatively prompt diagnosis and application of appropriate therapy, the clinical recovery of a patient with neurotuberculosis may be inadequate. Intensive monitoring, timely recognition of deterioration, and additional diagnostic evaluation are necessary for a favorable outcome in such patients.

Keywords: tuberculosis, biologic therapy, MRI

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SAŽETAK

Reumatoidni artritis je hronična progresivna zapaljenska reumatska bolest, koja pogađa 0.2-1.0% populacije u razvijenim zemljama. Prevalenca bolesti je 4x veća kod žena u odnosu na muškarce. Učestalost infekcija kod bolesnika sa reumatoidnim artritisom je 70%, a učestalost sepse 50% veća, nego u opštoj populaciji. Svake godine 3-5% bolesnika sa reumatoidnim artritisom razvije ozbiljnu infekciju. Pod ozbiljnom infekcijom podrazumevamo onu koja zahteva hospitalizaciju, parenteralnu primenu antibiotika, neposredno ili posredno ugrožava život bolesnika ili je dovela do smrtnog ishoda. Razloge za povećanu učestalost infekcija treba tražiti u samoj bolesti (poremećaj imunskog odgovora, izloženost invazivnim dijagnostičkim procedurama, invaliditet), pridruženim oboljenjima (dijabetes, kardiovaskularna oboljenja) i primeni imunosupresivne terapije. Stopa infekcija u reumatoidnom artritisu, koja zahteva hospitalizaciju je 1,88. Bolesnici imaju 1,8x veći rizik da obole od upale pluća, 2,8x veći rizik za infekciju kože i mekih tkiva, 1,5x veći rizik za sepsu, 21,7x veći rizik za septički artritis i 10,6x veći rizik za osteomijelitis. Prepoznati faktori rizika povezani za ozbiljnim infekcijama kod pacijenata sa reumatoidnom artritisom su: a. starost ≥ 65 godina, b. visoka aktivnost bolesti, v. značajan stepen invaliditeta, g. komorbiditeti (npr. hronična bolest pluća ili bubrega), d. glukokortikoidi ≥ 7.5 mg/dan, đ. istorija prethodnih infekcija, e. imunosupresivna terapija (hemijska ili biološka). Primena bioloških lekova je nezavisan faktor rizika za ozbiljne infekcije. Stopa incidencije ozbiljnih infekcija kod bolesnika na TNF-inhibitorima je 6.42/100 bolesnik-godina, u poređenju sa bolesnicima koji se leče metotreksatom gde je stopa incidencije 2.64/100 bolesnik-godina (relativni rizik da osoba na biološkoj terapiji doživi ozbiljnu infekciju je 2.43 puta veći u odnosu na bolesnike koji se leče hemijskim lekovima). Rizik za razvoj ozbiljne infekcije je najveći u prvih 6-12 meseci od započinjanja biološke terapije. Bolesnik koji je „prošao” prvu godinu lečenja biološkim lekom bez ozbiljne infekcije svrstao je sebe u bolesnike sa malim rizikom za infekcije. Zbog toga je važno da se prepoznaju faktori rizika za razvoj ozbiljnih infekcija kod svih bolesnika pre započinjanja biološke terapije. Kod tih bolesnika razmatramo primenu biološkog leka sa najmanjim rizikom za nastanak infekcija. Po uvođenju biološkog leka potrebno je što pre smanjiti dozu glukokortikoida, čime će se smanjiti rizik od infekcija.

Ključne reči: reumatoidni artritis, biološka terapija, infekcije

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ABSTRACT

Rheumatoid arthritis is a chronic progressive inflammatory rheumatic disease, affecting 0.2-1.0% of the population in developed countries. The prevalence of the disease is 4x higher in women compared to men. The incidence of infections in patients with rheumatoid arthritis is 70%, and the incidence of sepsis is 50% higher than in the general population. Every year, 3-5% of patients with rheumatoid arthritis develop a serious infection. A serious infection means one that requires hospitalization, parenteral administration of antibiotics, impermanently or indirectly endangers the patient's life or has led to death. The reasons for the increased incidence of infections should be sought in the disease itself (immune response disorder, exposure to invasive diagnostic procedures, disability), associated with diseases (diabetes, cardiovascular diseases) and the use of immunosuppressive therapy. The rate of infections in rheumatoid arthritis, which requires hospitalization, is 1.88. Patients have a 1.8x higher risk of developing pneumonia, a 2.8x higher risk of infection of the skin and soft tissues, a 1.5x higher risk for sepsis, a 21.7 x higher risk for septic arthritis and a 10.6x higher risk for osteomyelitis. Identified risk factors associated with serious infections in patients with rheumatoid arthritis are: a. age ≥ 65 years, b. high disease activity, v. significant degree of disability, g. comorbidities (e.g. chronic lung or kidney disease), d. glucocorticoids ≥ 7.5 mg/day, đ. history of previous infections, e. immunosuppressive therapy (chemical or biological). The use of biologics is an independent risk factor for serious infections. The incidence rate of serious infections in patients taking methotrexate where the incidence rate is 2.64/100 patient-year (the relative risk of a person on biological therapy experiencing a serious infection is 2.43 times higher than that of patients treated with chemical drugs). The risk of developing a serious infection is highest in the first 6-12 months of starting biological therapy. A patient who "passed" the first year of treatment with a biological drug without serious infection ranked himself among the patients at low risk for infection. Therefore, it is important to recognize the risk factors for developing serious infections in all patients before starting biological therapy. In these patients, we consider the use of a biological drug with the lowest risk of infection. After the introduction of the biological drug, it is necessary to reduce the dose of glucocorticoids as soon as possible, which will reduce the risk of infections.

Keywords: rheumatoid arthritis, biological therapy, infections

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OPORTUNISTIČKE INFEKCIJE (TUBERKULOZA I HERPES ZOSTER) KOD REUMATSKIH BOLESNIKA NA BIOLOŠKOJ TERAPIJI

OPORTUNISTIC INFECTIONS (TUBERCULOSIS AND HERPES ZOSTER) IN RHEUMATOLOGIC PATIENTS ON BIOLOGICAL THERAPY

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SAŽETAK

Blaža klinička slika, izostanak ili smanjenje deformiteta, lakša svakodnevica uz poboljšanje kvaliteta i dužine života samo su neki od rezultata primene biološke terapije kod bolesnika sa reumatoidnim artritisom (RA), psorijaznim artritisom (PsA) ili ankilozirajućim spondilitisom (AS). Pored svih benefita biološke terapije, jedan od najčešćih neželjenih efekata predstavlja pojava oportunističkih infekcija i to najčešće aktivacija latentne tuberkuloze i herpes zoster. Poslednjih 16 godina biološka terapija se sa uspehom primenjuje u Institutu za reumatologiju u Beogradu. U tom periodu preko 2000 bolesnika je lečeno biološkom terapijom i to intravenskom, supkutanom i oralnom. Najčešće primenjivani su lekovi iz grupe TNF- α inhibitora ali i blokatora IL-6, IL-1, kao i JAK kinaza inhibitora. TNF- α ima ključnu ulogu u patogenezi zapaljenjskih bolesti, među kojima i RA, AS, PsA, ali pored toga TNF- α takođe ima ključnu ulogu u odbrani domaćina od intracelularnih patogena, *Mycobacterium tuberculosis*, *Histoplasma*... U svakodnevnoj praksi (decenijskog praćenja) primećena veća osetljivost bolesnika na anti-TNF terapiji na infekcije, naročito oportunističke, uglavnom zbog reaktivacije latentne tuberkuloze kao i herpes zoster infekcije. Prema brojnim studijama rizika za nastanak infekcije *M. tuberculosis* za 1,5-17 puta je veći kod bolesnika na anti-TNF- α i drugoj biološkoj terapiji. U pojedinim Evropskim zemljama (Danska) taj rizik iznosi 15 obolelih od Tbc na 6000 lečenih bolesnika u periodu od 10 godina što je za 4 puta više u odnosu na rizik u opštoj populaciji. Sa druge strane malo ima podataka i studija koji ispituju i prate reaktivaciju virusnih infekcija kod bolesnika na TNF- α inhibitorima ili drugim biološkim lekovima. U periodu od 14 godina na 2000 lečenih bolesnika zabeleženo je 5 slučajeva aktivacije infekcije *M. tuberculosis* kao i 26 slučajeva aktivacije herpes zoster infekcije. U cilju boljeg praćenja oportunističkih infekcija kod bolesnika na biološkoj terapiji neophodne su nam nove multicentrične prospektivne studije.

Ključne reči: reumatološke bolesti, oportunističke infekcije, biološka terapija

ABSTRACT

A milder clinical picture, absence or reduction of deformities, easier everyday life with improvement in the quality and length of life are just some of the results of the application of biological therapy in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or ankylosing spondylitis (AS). In addition to all the benefits of biological therapy, one of the most common side effects is the occurrence of opportunistic infections, most often the activation of latent tuberculosis and herpes zoster. For the past 16 years, over 2,000 patients were treated, at the Institute of Rheumatology, with biological therapy, i.e. intravenous, subcutaneous and oral. The drugs from the group of TNF- α inhibitors, as well as IL-6 and IL-1 blockers, as well as JAK kinase inhibitors, were most often used. TNF- α plays a key role in the pathogenesis of inflammatory diseases, including RA, AS, PsA, but in addition, TNF- α also plays a key role in the host's defense against intracellular pathogens, *Mycobacterium tuberculosis*, *Histoplasma*... In daily practice (decades of monitoring) observed greater sensitivity of patients on anti-TNF therapy to infections, especially opportunistic ones, mainly due to reactivation of latent tuberculosis as well as herpes zoster infection. According to numerous studies, the risk of *M. tuberculosis* infection is 1.5-17 times higher in patients on anti-TNF- α and other biological therapy. In some European countries (Denmark), that risk amounts to 15 TB patients per 6,000 treated patients in a period of 10 years, which is 4 times higher than the risk in the general population. On the other side little is known about the reactivation of latent viral infections during treatment with TNF- α inhibitors and other biological therapy. In a period of 14 years, out of 2000 treated patients, 5 cases of activation of *M. tuberculosis* infection were recorded and 26 cases of herpes zoster infection.

Keywords: rheumatologic diseases, opportunistic infections, biological therapy

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INFECTIONS IN DERMATOLOGIC PATIENTS ON BIOLOGIC THERAPY

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SAŽETAK

Upotreba bioloških terapija kod dermatoloških pacijenata predstavlja složenu interakciju između terapijske efikasnosti i potencijalnih infektivnih komplikacija. Pacijenti koji su podvrgnuti lečenju stanja kao što su psorijaza ili hidradenitis suppurativa imaju veoma dobar terapijski odgovor prilikom primene biološke terapije. Međutim, imunomodulatorna priroda ovih lekova izaziva zabrinutost u vezi sa povećanim rizikom od infekcija.

Istraživanja pokazuju da određeni biološki lekovi, kao što su inhibitori faktora nekroze tumora-alfa (TNF-α), inhibitori interleukina i inhibitori Janus kinaze (JAK), mogu doprineti različitim stepenima imunosupresije. Ovaj imunosupresivni efekat može ugroziti sposobnost tela da uspostavi efikasan imunski odgovor protiv patogena, što dovodi do povećane osetljivosti na infekcije.

Kod dermatoloških pacijenata, koji možda već imaju ugrožene kožne barijere zbog osnovnih stanja, važno je pažljivo razmotriti ove vidove terapije. Dermatolozi, u saradnji sa infektolozima, moraju odmeriti benefite te terapije u odnosu na potencijalne rizike od infekcija. Strategije za ublažavanje ovih rizika uključuju skrining pre tretmana za latentne infekcije, pažljivo praćenje tokom terapije i brzo saniranje infekcija kada se pojave.

Kako se ova oblast razvija, tekuća istraživanja i klinička zapažanja doprinose preciziranju smernica za bezbednu i efikasnu upotrebu bioloških terapija kod dermatoloških pacijenata. Balansiranje potrebe za optimalnim dermatološkim ishodom, sa proaktivnim pristupom prevenciji infekcije, ostaje ključno u rešavanju ovih složenih slučajeva.

Ključne reči: psorijaza, hidradenitis suppurativa, biološka terapija

ABSTRACT

The use of biologic therapies in dermatologic patients presents a complex interplay between therapeutic efficacy and potential infectious complications. Patients undergoing treatment for conditions like psoriasis or hidradenitis suppurativa often experience a significant improvement in their dermatologic symptoms with biologics. However, the immunomodulatory nature of these drugs raises concerns regarding an increased risk of infections.

Research indicates that certain biologics, such as tumor necrosis factor-alpha (TNF-α) inhibitors, interleukin inhibitors, and Janus kinase (JAK) inhibitors, may contribute to varying degrees of immunosuppression. This immunosuppressive effect can compromise the body's ability to mount an effective immune response against pathogens, leading to an elevated susceptibility to infections.

In the context of dermatologic patients, who may already have compromised skin barriers due to their underlying conditions, careful consideration is essential. Dermatologists, in collaboration with infectious disease specialists, must weigh the benefits of improved skin conditions against the potential risks of infections. Strategies for mitigating these risks include pre-treatment screening for latent infections, close monitoring during therapy, and prompt management of any emerging infections.

As the field evolves, ongoing research and clinical observations contribute to refining guidelines for the safe and effective use of biologic therapies in dermatologic patients. Balancing the need for optimal dermatologic outcomes with a proactive approach to infection prevention remains crucial in the management of these complex cases.

Keywords: psoriasis, hidradenitis suppurativa, biologic therapy

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INFECTION AS A RESULT OF IMMUNOSUPPRESSION IN ONCOLOGICAL PATIENTS

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SAŽETAK

Karcinom pluća je najčešći i najsmrtonosniji karcinom, sa incidencom 238,340 i 127,070 smrtnih slučajeva 2023. god. Histološka vrsta tumora, proširenost bolesti, prisustvo prediktivnih biomarkera određuju vid lečenja i prognozu bolesti. Stanje imunokompromitovanosti zbog karcinoma pluća dodatno usložnjavaju predisponirajući faktori za infekcije koji se identifikuju kod čak 10-15% pacijenata u trenutku smrti: centralna lokalizacija tumora, starije životno doba, lošije opšte stanje, komorbiditet (HOBP), dugotrajna primena kortikosteroida.

Hemoterapija je do početka 21. Veka bila jedini terapijski pristup, sa neselektivnim citotoksičnim delovanjem. Primenom CTLA-4, PD-1 i PDL1 inhibitora postiže se imunološka kontrola tumora. Identifikacija genskih i molekularnih abnormalnosti u tumorskom tkivu omogućila je primenu specifičnih inhibitora kod pacijenata sa aktivirajućom mutacijom-molekularnu terapiju. Personalizovanim pristupom postižu se bolji ishodi uz manjutoksičnost lečenja, ali sa rizikom od imunološki povezanih neželjenih događaja i infekcija koje komplikuju onkološko lečenje. Brojni su mehanizmi sklonosti infekcijama kod primene imunoterapije: Sposobnost T ćelija da efikasno reaguju na patogene može da se promeni inhibicijom imunoloških kontrolnih tačaka, potom preterano jaka aktivacija imunološkog sistema što vodi reaktivaciji latentnih infekcija. Burni imunološki odgovor može dovesti do upalnih oštećenja tkiva, što može oslabiti fizičke barijere protiv infekcija. Sastav i funkcija mikrobioma, posebno u crevima, može da promeni odnos između domaćina i komensalnih mikroorganizama. Imunosupresivna terapija neželjenih efekata primene imunoterapije dodatno oslabi imunološki sistem. Specifičnost molekularne terapije je indirektan uticaj na imunološku funkciju modulacijom signalnih puteva koji su važni za imunološki odgovor. Takođe, mogu narušiti integritet epitelne barijere, posebno u gastrointestinalnom traktu, i kod pacijenata sa osipom i mukozitisom, što može olakšati translokaciju bakterija.

Bakterijske infekcije – *Streptococcus pneumoniae*, *Haemophilus influenzae* i *Staphylococcus aureus*, uključujući sojeve otporne na meticilin (MRSA), najčešće su kod pacijenata sa neutropenijom izazvanom hemoterapijom, uzrokujući pneumonije (10% do 25%). Gram-pozitivne bakterije (*Staphylococcus aureus*, uz MRSA sojeve) i gram-negativne bakterije (*Escherichia coli*, *Pseudomonas aeruginosa*) mogu da prouzrokuju sepsu. Infekcije urinarnog trakta najčešće izazivaju *Escherichia coli*, *Klebsiella* spp., *Enterobacteriaceae*. Pacijenti na molekularnoj terapiji mogu biti posebno podložni bakterijskim pneumonijama. Reaktivacija *Herpes simplex* virusa tip 1 i 2, *Varicella zoster* konstatovani su u 20-40% pacijenata na imunoterapiji, te uz virus influenza, parainfluenze, respiratorni sincicijski virus (RSV) i SARS-CoV-2 (COVID-19) komplikuju klinički tok bolesti utičući na ukupno preživljavanje. *Aspergillus fumigatus*, uzrokujući aspergilozu, javlja se u 2-10% pacijenata, *Candida albicans* često uzrokuje oralnu i ezofagealnu kandidijazu, sa prevalencom do 25%. Imunoterapija je faktor rizika i za pojavu oportunističkih infekcija: reaktivacija *Mycobacterium tuberculosis*, mikobakterioza i *Pneumocystis jirovecii* pneumonija (PJP), posebno kod pacijenata na kombinovanoj imunosupresivnoj terapiji.

Sveobuhvatan pristup prevenciji, brzog dijagnostici i efikasnom lečenju infekcija je ključan za poboljšanje prognoze i kvaliteta života pacijenata omogućavajući da se onkološko lečenje neometano sprovedi, uključujući skrining i testiranje latentnih infekcija, vakcinaciju, profilaktičku antimikrobnu terapiju. Informisati pacijenta i porodicu o značaju sprovođenja mera održavanja čiste i bezbedne sredine, izbegavanje kontakata, dugotajan boravak u zatvorenim prostorijama sa ciljem minimiziranja rizika od infekcija.

Ključne reči: karcinom pluća, terapija, infekcije, imunosupresija, ishodi lečenja

ABSTRACT

Lung cancer is the most common and deadliest cancer, with an incidence of 238,340 and 127,070 deaths in 2023. The histological type of the tumor, the extent of the disease, and the presence of predictive biomarkers determine the treatment approach and disease prognosis. The immunocompromised condition of the patient due to lung cancer is further complicated by predisposing factors for infections, identified in 10-15% of patients at the moment of death: central tumor localization, older age, poor general condition, comorbidity (COPD), and prolonged use of corticosteroids. Since the beginning of the 21. century, chemotherapy was the only therapeutic approach, with non-selective cytotoxic action. An immunological control of the tumor is achieved by applying the CTLA-4, PD-1 and PDL1 inhibitors. The identification of genetic and molecular abnormalities in tumor tissue has enabled the use of specific inhibitors in patients with activating mutations – molecular therapy. A personalized approach achieves better outcomes with less treatment toxicity but with the risk of immune-related adverse events and infections complicating oncological treatment. There are numerous mechanisms of susceptibility to infections due to use of immunotherapy: The ability of T cells to effectively respond to pathogens can be altered by inhibiting immune checkpoints, then excessive activation of the immune system leading to reactivation of latent infections. A vigorous immune response can lead to inflammatory tissue damage, which can weaken physical barriers against infections. The composition and function of the microbiome, especially in the intestines, can change the relationship between the host and commensal microorganisms. Immunosuppressive therapy for the adverse effects of immunotherapy further weakens the immune system. The specificity of molecular therapy is the indirect impact on immune function by modulating signaling pathways important for the immune response. They can also compromise the integrity of the epithelial barrier, especially in the gastrointestinal tract, and in patients with rash and mucositis, which can facilitate bacterial translocation.

Bacterial infections – *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus*, including methicillin-resistant strains (MRSA), are most common in patients with chemotherapy-induced neutropenia, causing pneumonia (10% to 25%). Gram-positive bacteria (*Staphylococcus aureus*, including MRSA strains) and gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) can cause sepsis. Urinary tract infections are most commonly caused by *Escherichia coli*, *Klebsiella* spp., *Enterobacteriaceae*. Patients on molecular therapy may be particularly susceptible to bacterial pneumonias. Reactivation of *Herpes simplex* virus types 1 and 2, *Varicella zoster* have been noted in 20-40% of patients on immunotherapy, and along with the influenza virus, parainfluenza, respiratory syncytial virus (RSV), and SARS-CoV-2 (COVID-19) complicate the clinical course of the disease affecting overall survival. *Aspergillus fumigatus*, causing aspergillosis, occurs in 2-10% of patients, *Candida albicans* often causes oral and esophageal candidiasis, with a prevalence of up to 25%. Immunotherapy is a risk factor for the occurrence of opportunistic infections: reactivation of *Mycobacterium tuberculosis*, mycobacteriosis, and *Pneumocystis jirovecii* pneumonia (PJP), especially in patients on combined immunosuppressive therapy.

All-encompassing approach to the prevention, fast diagnostics and the efficient treatment of infections are essential for improving prognosis and the quality of life of patients, enabling uninterrupted oncological treatment, including screening and testing for latent infections, vaccination, prophylactic antimicrobial therapy. It is necessary to inform the patient and their family about the importance of implementing measures such as maintaining a clean and safe environment, avoiding contacts, prolonged stays in closed rooms, etc., with the aim of minimizing the risk of infections.

Keywords: lung cancer, therapy, infections, immunosuppression, treatment outcomes

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POST LIVER TRANSPLANT RECURRENT AND *DE NOVO* VIRAL INFECTIONS: FROM THEORY TO CLINICAL PRACTICE

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SAŽETAK

Virusne infekcije su značajan uzrok morbiditeta i mortaliteta bolesnika sa transplantiranom jetrom, sa mnogobrojnim epizodama u prvim mesecima nakon operacije. Brojni su rizikofaktori u preoperativnom, operativnom i postoperativnom periodu za stečenu infekciju. Najčešći uzročnici su grupa herpes virusa i primarno hepatotropni virusi. Virusne infekcije se mogu klinički prezentovati kao oportunističke infekcije, reinfekcije grafta ili posttransfuzione infekcije.

Oko 2/3 bolesnika sa transplanirano jetrom imaće laboratorijske dokaze CMV infekcije (viremija ili virurija) u postoperativnom periodu. CMV je najvažniji patogen u periodu u periodu od dva do šest meseci posle transplantacije. Klinički se prezentuje kao mononukleoza sindrom, pneumonitis, miokarditis, hepatitis ili kao diseminovana CMV infekcija sa zahvatanjem mnogih organa.

HSV infekciju ima oko 50% bolesnika unutar tri meseca od transplantacije. Oralne i mukokutane lezije su česte, a ređe se viđa ezofagitis, kolitis, hepatitis i diseminovana bolest sa afekcijom i CNS-a. VZV infekcije je najčešća prvih šest meseci nakon transplantacije. Diseminovana forma sa zahvatanjem viscerálnih organa je, po pravilu, fatalna za bolesnika.

EBV infekcija kod transplantiranih bolesnika, najčešće, protiče bez specifičnih simptoma. Međutim, limfoproliferativni poremećaji ili sindromi uzrokovani EBV mogu se videti, pogotovo ako se primoinfekcija desi u posttransplantacionom periodu. EBV može uzrokovati i hroničnu disfunkciju grafta.

Reinfekcija grafta HBV infekcijom može dovesti do njegove disfunkcije i loše prognoze bolesti. Ukoliko se ne primeni profilaktička terapija (antivirusni lekovi), petogodišnje preživljavanje je moguće kod samo 50 odsto bolesnika.

Dekompenzovana ciroza jetre, uzrokovana hroničnom HCV infekcijom, najčešći je uzrok ortotopičke transplantacije jetre. Međutim, gotovo svi bolesnici (90-95 odsto) posle transplantacije jetre razvijaju perzistentnu HCV infekciju.

Pre transplantacije jetre, u cilju prevencije posttransplantacionih infekcija, obavezan je skrining krvi na specifična antitela IgG klase i virusne antigene, kako kod davaoca, tako i kod primaoca organa.

Ključne reči: transplantacija jetre, virusne infekcije, prevencija, lečenje

ABSTRACT

Viral infections are a significant cause of morbidity and mortality in patients with transplanted liver, with numerous episodes in the first months after surgery. There are numerous risk factors in the preoperative, operative, and postoperative period for acquired infection. The most common causative agents are the group of herpes viruses and primarily hepatotropic viruses. Viral infections can present clinically as opportunistic infections, graft reinfections, or post-transfusion infections.

About 2/3 of liver transplant patients will have laboratory evidence of CMV infections (viremia or viruria) in the postoperative period. CMV is the most important pathogen in the period from two to six months after transplantation. Clinically presents itself as mononucleosis syndrome, pneumonitis, myocarditis, hepatitis, or as a disseminated CMV infection involving many organs.

About 50% of patients develop HSV infection within three months of transplantation. Oral and mucocutaneous lesions are common, and esophagitis, colitis, hepatitis, and disseminated disease with CNS involvement are less common. VZV infection is most common in the first six months after transplantation. Disseminating the form with the involvement of multiple organs is, as a rule, fatal for the patient.

EBV infection in transplanted patients usually occurs without specific symptoms. However, lymphoproliferative disorders or syndromes caused by EBV can be seen, especially if the primary infection occurs in the post-transplantation period. EBV can also cause chronic graft dysfunction.

Reinfection of the graft with HBV infection can lead to its dysfunction and a poor prognosis of the disease. If prophylactic therapy (antiviral drugs) is not applied, five-year survival is possible in only 50 percent of patients.

Decompensated cirrhosis of the liver, caused by chronic HCV infection, is the most common cause of orthotopic liver transplantation. However, almost all patients (90-95 percent) develop persistent HCV infection after liver transplantation.

Before liver transplantation, it is mandatory to screen the donor and recipient blood for specific IgG antibodies and viral antigens to prevent post-transplantation infections.

Keywords: liver transplantation, viral infections, prevention, therapy

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COMPLICATIONS FOLLOWING LIVER TRANSPLANTATION

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SAŽETAK

U diferencijaciji komplikacija veoma je važno u kom vremenskom periodu nakon transplantacije nastaju. U prvoj post-transplantacionoj nedelji može doći do: pre-zervacijskog oštećenja, tromboze hepatične arterije, humoralnog odbacivanja i primarne disfunkcije grafta. Do trećeg meseca, za očekivati je: akutnu celularnu reakciju, bilijarne striktуре i/ili oportunističke infekcije. Nakon toga postoji rizik za: hronično odbacivanje, ishemijski holangitis, rekurens osnovne bolesti i virusne infekcije. Usled imunosupresivne terapije, prevashodno primene kalcineurinskih inhibitora (tacrolimusa ili ciklosporina) vremenom raste predispozicija za metaboličke, kardiovaskularne poremećaje i malignitete, najčešće melanom i limfoproliferativne bolesti.

Zbog mogućnosti citomegalovirsne (CMV) infekcije, ukoliko su i donor i recipient CMV IgG pozitivni, primenjuje se tromesečna profilaksa, valganciklovirom u dozi od 450 mg/d. Međutim, ako je donor CMV IgG pozitivan a recipient CMV IgG negativan rizik od reaktivacije virusa je >50%. Stoga se preporučuje šestomesečna profilaksa, valganciklovirom u dozi od 900 mg/d. U slučaju reaktivacije virusa, razvije se febrilni neutropenijski sindrom i odbacivanje alografta. Osim toga, u sklopu post-transplantacione re-evaluacije koje se sprovodi dva puta godišnje, obavezno se radi PCR CMV DNA i kada je nalaz pozitivan primenjuje se tronedeljna terapija valganciklovirom u dozi 2x900 mg/d. Tokom terapije, neophodno je kontrolisati krvnu sliku i bubrežnu funkciju jer su najčešće neželjene reakcije valganciklovira mijelotoksičnost i tubulointersticijski nefritis. U novije vreme, ako dođe do nuspojava valganciklovira, profilaksa/terapija, se nastavlja mebeverinom.

Zaključak: adekvatno praćenje transplantiranih pacijenata i sprovođenje profilakse, sprečava reaktivaciju CMV a samim tim i odbacivanje alografta.

Ključne reči: transplantacija jetre, citomegalovirus, profilaksa, valganciklovir

ABSTRACT

In the differentiation of post-transplant complications, the time of their occurrence during the post-surgery period is crucial. The complications which may arise in the first post-transplant week are preservation damage, thrombosis of artery hepatica, humoral rejection and primary graft dysfunction. Subsequently, up to the third month, one can anticipate acute cellular reactions, biliary strictures, and/or opportunistic infections. Beyond this period, there exists a risk of chronic rejection, ischemic cholangitis, recurrence of the primary disease, and viral infections. Due to immunosuppressive therapy, particularly with calcineurin inhibitors (tacrolimus or ciclosporin), the predisposition to metabolic and cardiovascular disorders and malignancies - chiefly melanoma and lymphoproliferative diseases - increases over time.

Because of the possible cytomegaloviral (CMV) infection, when both donor and recipient are CMV IgG positive, a three-month prophylaxis with valganciclovir at doses of 450 mg/d is recommended. However, if the donor is CMV IgG positive and the recipient CMV IgG negative, the risk of virus reactivation is >50%. Therefore, a six-month prophylaxis with valganciclovir, dosed at 900 mg/d is advisable. The virus reactivation leads to the febrile neutropenia syndrome and allograft rejection. Additionally, the post-transplant re-evaluation which is conducted twice a year, necessitates conducting PCR CMV DNA and the positive result requires three-weeks therapy with valganciclovir at 2x900 mg/d. Throughout the treatment, monitoring blood count and kidney function is imperative due to common side effects like myelotoxicity and tubulointerstitial nephritis. In case of valganciclovir side effects, recent practice involves continuing prophylaxis/therapy with mebeverine.

Conclusion: adequate monitoring of transplant patients and application of prophylaxis prevent the reactivation of CMV and rejection of allografts.

Keywords: liver transplant, cytomegalovirus, prophylaxis, valganciclovir

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SPECIFICS IN DIAGNOSIS AND TREATMENT OF INFECTIONS AFTER KIDNEY TRANSPLANTATION

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SAŽETAK

Danas se procenjuje da će čak 70% bolesnika sa transplantiranim (Tx) bubregom imati epizodu infekcije u prve 3 godine nakon transplantacije, a statistički podaci dalje pokazuju da su infekcije drugi vodeći uzrok smrti recipijenta sa funkcionalnim alograftom, odmah posle kardiovaskularnih bolesti.

Odnos imunosupresivne (IS) terapije primaoca alografta i epidemiološka izloženost određenim mikroorganizmima, određuju rizik od infekcije u datom trenutku i daje mogućnost predviđanja obrazaca javljanja određenih infekcija nakon Tx bubrega. Tako se u toku prvog meseca javljaju infekcije zbog hirurških komplikacija kao i bolničke infekcije, ali i infekcije vezane za davaoca bubrega. Infekcije urinarnog sistema su najčešće u prvih 6 meseci kao i oportunističke infekcije zbog visokih doza IS lekova. U ovom periodu može doći i do reaktivacije latentnih patogena kao što su polioima virus BK, virus hepatitisa C i mikobakterija tuberkuloze. Profilaksa za *Pneumocystis jiroveci*, viruse herpesa uključujući CMV i virus hepatitisa B čini ove infekcije manje uobičajenim tokom ranog posttransplantacionog perioda.

Nakon 6 meseci, od Tx bubrega, doze IS lekova se smanjuju kod većine pacijenata ali ostaje rizik od infekcija stečenih u zajednici, izloženost okolini, rekurentnih infekcija i kasnih virusnih infekcije, posebno CMV, kada se profilaksa prekine.

Skринing pre transplantacije, imunizacija i optimalna antibakterijska i antiviralna profilaksa mogu pomoći da se smanji uticaj infekcije. Svest o pristupu infekciji kod primaoca transplantata uključujući dijagnostičke i strategije upravljanja su od suštinskog značaja za optimizaciju rezultata.

Ključne reči: transplantacija bubrega, imunosupresivna terapija, nozokomijalne infekcije, oportunističke infekcije

ABSTRACT

It has been estimated that as many as 70% of patients with a transplanted (Tx) kidney will have an episode of infection within the first 3 years after transplantation, and statistical data further show that infections are the second leading cause of death in recipients with a functional allograft, right after cardiovascular diseases.

The ratio of immunosuppressive (IS) therapy of the allograft recipient and epidemiological exposure to certain microorganisms determines the risk of infection at a given time and provides the possibility of predicting the patterns of occurrence of certain infections after kidney Tx. Thus, during the first month, infections occur due to surgical complications as well as hospital infections, but also infections related to the kidney donor. Urinary tract infections are the most common in the first 6 months, as well as opportunistic infections due to high doses of IS drugs. During this period, reactivation of latent pathogens such as polyoma virus BK, hepatitis C virus and *Mycobacterium tuberculosis* can occur. Prophylaxis for *Pneumocystis jiroveci*, herpes viruses including CMV, and hepatitis B virus makes these infections less common during the early posttransplant period.

After 6 months from kidney Tx, the doses of IS drugs are reduced in most patients but the risk of community-acquired infections, environmental exposure, recurrent infections and late viral infections, especially CMV, remains when prophylaxis is stopped.

Pre-transplant screening, immunization, and optimal antibacterial and antiviral prophylaxis can help reduce the impact of infection. Awareness of the approach to infection in the transplant recipient including diagnostic and management strategies is essential to optimize outcomes.

Keywords: kidney transplantation, immunosuppressive therapy, nosocomial infections, opportunistic infections

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PROFILAKSA I TERAPIJA VIRUSNIH INFEKCIJA KOD 355 BOLESNIKA KOJIMA SU TRANSPLANTIRANE MATIČNE ČELIJE HEMATOPOEZE, LEČENIH NA VOJNOMEDICINSKOJ AKADEMIJI

PROPHYLAXIS AND TREATMENT FOR VIRAL INFECTIONS IN 355 PATIENTS WITH HEMATOPOIETIC STEM CELL TRANSPLANTS TREATED AT THE MILITARY MEDICAL ACADEMY

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SAŽETAK

Uvod: Virusne infekcije su značajan uzrok morbiditeta i mortaliteta kod bolesnika sa alogenom transplantacijom matičnih ćelija hematopoeze (TMHČ). Osnovna bolest, kondicioni režimi, izvor matičnih ćelija i imunosupresivna terapija posle alogene TMHČ određuju različite infekcije u periodu nakon transplantacije. Cilj ovog rada je da se prikaže učestalost i tip virusnih infekcija kod pacijenata sa alogenom TMHČ na VMA i modaliteti njihovog lečenja.

Bolesnici i metode: Analizirano je 355 bolesnika (prosečne starosti 29 godina, 144 žena, 211 muškaraca) posle alogene TMHČ u Centru za TMHČ Klinike za hematologiju VMA u periodu od 1995.-2017. godine. Alogena-TMHČ je urađena kod 130 pacijenata sa akutnom mijeloidnom leukemijom, 102 sa akutnom limfoblastnom leukemijom, 22 sa MDS/MPO (mijelodisplastični sindrom/mijeloperoxidaza) i 101 pacijentom sa drugim malignim hemopatijama. Analizirani su tip donora, izvor hematopoetskih matičnih ćelija, tip kondicionog režima i profilaksa odbacivanja.

Rezultati: Kod 21 (6%) bolesnika smo registrovali reaktivaciju Varicella zoster virus; hemoragijski cistitis povezan sa BK polyoma virusom u ranoj fazi smo dijagnostikovali kod 21 (6%) i kasnoj kod 15 (4,2%) bolesnika; influenzu kod 2 (0,5%); reaktivaciju citomegalovirusa u kasnoj fazi kod 63 (17,3%) bolesnika, hepatitis B virusnu infekciju kod 6 (1,7%) i C hepatitis kod 2 (0,5%) bolesnika. Primenjeni su antivirusni lekovi kao profilaksa, pre-emptivna i ciljana terapija.

Zaključak: Virusne infekcije su značajan uzrok morbiditeta i mortaliteta bolesnika posle alogene TMHČ, što zahteva monitoring i primenu profilaktičke, pre-emptivne ili direktne terapije.

Ključne reči: virusne infekcije, alogena TMHČ, mijelodisplastični sindrom

ABSTRACT

Introduction/Objective: Viral infections are a significant cause of morbidity and mortality in patients with allogeneic hematopoietic stem cell transplantation (allo-HSCT). Underlying disease, conditioning regimens, source of stem cells, and immunosuppressive therapy after allo-HSCT determine various infections in the posttransplant period. The aim of this work is to present the frequency and type of viral infections in patients with allo-HSCT at the Military Medical Academy and the modalities of their treatment.

Methods: This study included 355 patients (the mean age was 29 years, 144 women, 211 men) who underwent allo-HSCT at the HSCT Center of the Hematology Clinic of the Military Medical Academy from 1995 to 2017. Allo-HSCT was performed in 130 patients with acute myeloid leukemia, 102 with acute lymphoblastic leukemia, 22 with MDS/MPO (myelodysplastic syndrome/myeloperoxidase) and 101 patients with other malignant hemopathies. The type of donor, source of hematopoietic stem cells, type of conditioning regimen and GvHD (graft versus host) prophylaxis were analyzed.

Results: The reactivation of VZV infection was registered in 21 (6.0%) patients, hemorrhagic cystitis associated with BK polyoma virus (BKPyV) in the early phase in 21 (6.0%), in the late phase in 15 (4.2%), influenza in 2 (0.5%) patients, CMV reactivation in the late phase in 63 (17.7%) patients, reactivation of HBV infection in 6 (1.69%) and HCV infection in 2 (0.56%) patients. Antiviral drugs were used as prophylaxis, pre-emptive and targeted therapy.

Conclusion: Viral infections are a significant cause of morbidity and mortality in patients after allo-HSCT, which requires monitoring and application of prophylactic, pre-emptive or direct therapy.

Keywords: viral infections, allo-HSCT, myelodysplastic syndrome

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SAŽETAK

Od 5 miliona gljivičnih vrsta mali broj inficira ljude sa zdravim imunskim sistemom. Gljivice su komensalni organizmi i žive u simbiozi kao uspešni paraziti osim kad postoji oštećenje imunskog sistema.

Našim višegodišnjim istraživanjima smo definisali imunske defekte kod bolesnika sa hroničnom mukokutanom kandidijazom (Chronic Mucocutaneous Candidiasis – CMC) i to bolesnika sa autoimunom poliendokrinopijom tipa 1 (APS1/APECED) ili sa autozomno dominantnom CMC (AD-CMC).

Pokazali smo da bolesnici sa APS1-CMC imaju normalnu produkciju IL-17 i proliferaciju Th-17 limfocita koji su ključni za odbranu od CMC. Međutim, izlaganje autologoj plazmi je neutralisalo efekte IL-17 zbog postojanja antitela koja neutrališu IL-17. Ovi bolesnici imaju antitela i na interferone tipa 1 što je dovelo do teških oblika Covid-19 infekcija. Bolesnici sa AD-CMC imaju pak defect u spontanoj produkciji interleukina -17 (IL-17) i proliferaciji Th-17 limfocita nakon stimulacije kandidom. Genetskim ispitivanjima u 14 bolesnika iz 5 nesrodnih porodica iz UK i Holandije i >500 zdravih kontrola prvi smo dokazali postojanje autosomno dominantne genske mutacije koja pojačava funkciju transkriptora STAT1 pojačanjem fosforilizacije i konsekvantnom inhibicijom STAT3. Potom je 76 mutacija na STAT1 nađeno u grupi od 274 pacijenta, a do danas je nađeno 105 mutacija u grupi od 400 pacijenata.

Ova saznanja se danas koriste u kliničkoj praksi gde autoantitela na IL-17/IL-22/IFN tipa 1 potvrđuju dijagnozu APS1/APECED-CMC, a GOF mutacija na STAT1 dijagnozu AD-CMC. Kao nova terapije za AD-CMC danas se uspešno koriste JAK1/2 inhibitori aktivacije STAT1.

Ključne reči: hronična mukokutana kandidijaza, ektodermalna displazija, interleukin-17 autoantitela

ABSTRACT

Of the 5 million existing fungal species, only a small number infect humans with a normal immune system.

Our research over many years defined immune defects underlying chronic mucocutaneous candidiasis infections in the two largest cohorts of patients suffering with autoimmune polyendocrinopathy type 1 (APS1/APECED) or autosomal dominant CMC (AD-CMC).

We demonstrated that patients with APS1-CMC have normal production of interleukin (IL)-17 and proliferation of Th-17 lymphocytes that are key players in CMC immune defenses. However, exposure to autologous plasma neutralized the effects of IL-17 due to existing anti-IL17 autoantibodies (Aabs). These patients also produce Aabs to interferons type1 which lead to severe cases of Covid-19 infections. In contrast, patients with AD-CMC have a defect in IL-17 production and Th-17 lymphocyte proliferation to Candida. Our genetic studies in 14 patients from 5 unrelated families in UK and Holland and >500 healthy controls demonstrated for the first time the existence of AD gain-of-function (GOF) genetic mutations that increase phosphorylation and enhance STAT1 function with follow-on inhibition of STAT3. Subsequently, 76 genetic mutations of STAT1 were confirmed in 274 patients; to date 105 mutations were confirmed in 400 patients.

This knowledge is now incorporated into clinical practice where Aabs to IL-17 and IFN type1 confirm the diagnosis of APS1/APECED-CMC, while GOF mutations of STAT1 confirm AD-CMC. New treatments for AD-CMC successfully utilize JAK1/2 inhibitors of STAT1 activation.

Keywords: chronic mucocutaneous candidiasis, ectodermal dysplasia, interleukin-17 autoantibodies

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SAŽETAK

Mukormicete, grupa gljivica koje izazivaju mukormikozu, prisutne su u okolini, posebno u zemljištu, tamo gde dolazi raspadanja organskih materija, kao što su lišće, gomile komposta i životinjska balega. Češće su u zemljištu nego u vazduhu, a leti i u jesen, nego zimi ili u proleće. Većina ljudi svakodnevno dolazi u kontakt sa mikroskopskim sporama gljivica, tako da je verovatno nemoguće u potpunosti izbeći kontakt sa mukormicetima. Ove gljivice nisu štetne za većinu ljudi. Međutim, kod ljudi koji imaju oslabljen imuni sistem, kao što su pacijenti sa dijabetesom i ketoacidozom i upotrebom kortikosteroida za lečenje COVID-19, udahnute spore gljivica, sa ponovljenim gutanjem kontaminiranih proizvoda, mogu izazvati bolest. Gljivične hife prodiru u krvne sudove, izazivajući upalu i nekrozu vaskularnog zida, što rezultira trombozom, infarktom ili krvarenjem.

Rino-orbitalno-cerebralna mukormikoza, čini 90% slučajeva u svetu.

Stopa mortaliteta može biti i do 50-80%.

Paltauf je prijavio prvi slučaj mukormikoze kod ljudi 1885. godine.

Rana dijagnoza mukormikoze je ključ za preživljavanje.

Dijagnoza mukormikoze se obično postavlja analizom patohistoloških uzoraka tkiva iz biopsije i tako se potvrđuje prisustvo hifa u uzorku.

Histopatološka dijagnoza mukormikoze nije teška, sa znanjem o nekim zamkama. Mukormikoza se uglavnom može dijagnostikovati na HE preparatima. Prva zamka je kako uzeti uzorak za patohistologiju. Osnovna istina u hirurškoj patologiji je da se za analizu mora uzeti vijabilno tkivo, jer iz nekrotičnog tkiva ne možemo da izvučemo mnogo informacija. Ovo se ne odnosi na dijagnozu mukormikoze, jer se gljivice nalaze, sa retkim izuzecima, samo u nekrotičnom tkivu. Kada ih ima mnogo, dovoljni su samo HE preparati i nije potrebno posebno bojenje za dijagnozu. Gljive se na uzdužnom preseku vide kao debele, ne-septirane, trakaste gljivične hife sa grananjem pod pravim uglom, a na poprečnom preseku se vide kao krugovi. U ovim slučajevima, gljivica nije prisutna u vijabilnom tkivu. Kada su gljivice retke, onda je potrebno izvršiti histohemijsko bojenje, i kombinacija Grocott-a i PAS-a je najbolja za identifikaciju gljivica. U retkim slučajevima, gljivica se nalazi u vijabilnom tkivu u granulomima, kod pacijenata sa boljim imunitetom.

Ključne reči : mukormikoza, kovid-19, histohemijsko bojenje

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ABSTRACT

Mucormycetes, the group of fungi that cause mucormycosis, are present throughout the environment, particularly in soil and in association with decaying organic matter, such as leaves, compost piles, and animal dung. They are more common in soil than in air, and in summer and fall than in winter or spring. Most people come in contact with microscopic fungal spores every day, so it's probably impossible to completely avoid coming in contact with mucormycetes. These fungi aren't harmful to most people. However, for people who have weakened immune systems, inhalation of fungal spores followed by repeated ingestion of contaminated products in immunocompromised patients, such as patients with diabetes and ketoacidosis, and corticosteroid use for the treatment of COVID-19 mucormycosis may develop. Fungal hyphae invade blood vessels, causing inflammation and necrosis of the vascular wall, which results in thrombosis, infarction or hemorrhage.

Rhino-orbital-cerebral mucormycosis, constitutes 90% of cases in the world.

Mortality rates can be as high as 50-80%.

Paltauf reported the first case of human rhino-cerebral mucormycosis in 1885.

Early diagnosis of mucormycosis is the key for survival.

The diagnosis for mucormycosis is typically made by analyzing the histology of the tissue samples from biopsy samples and confirmed by the presence of hyphae in the sample.

Histopathological diagnosis of mucormycosis is not difficult with some pitfalls. Mucormycosis can mostly be diagnosed on HE slides. The first pitfall is how to take sample for histopathology. The basic truth in surgical pathology is that viable tissue have to be taken for analysis, because we cannot glean a lot of information from necrotic tissue. This does not apply to the diagnosis of mucormycosis, because fungi are found, with rare exceptions, only in necrotic tissue. When there are a lot of them, only the HE slides are sufficient and no special staining is required for diagnosis. Fungi are seen in longitudinal section as thick, non-septated, ribbon-like fungal hyphae with right angle branching and in cross section they are seen as circles. In these cases, the fungus is not present in the viable tissue. When fungi are rare, then it is necessary to perform histochemical staining, combination of Grocott and PAS is best for fungi identification. In rare cases, the fungus is found in viable tissue in granulomas, in patients with better immunity.

Keywords: mucormycosis, Covid -19, histochemical staining

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FUNGAL INFECTIONS IN HIV POSITIVE AND HIV NEGATIVE PATIENTS – IS THERE A DIFFERENCE?

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SAŽETAK

Gljivične infekcije su među najčešćim oportunističkim infekcijama kod imunokompromitovanih pacijenata, sa visokom stopom mortaliteta od preko 50% uprkos dostupnosti antigljivičnih lekova. Pacijenti koji su zaraženi virusom humane imunodeficijencije (HIV) predstavljaju populaciju koja je u visokom riziku za razvoj gljivičnih infekcija, a najčešće invazivnih gljivičnih infekcija (IGI). Procenjuje se da godišnje u svetu od IGI oboli oko 1 milion pacijenata sa HIV infekcijom, od čega se kod oko 500.000 završi smrtnim ishodom. Zahvaljujući dostupnim savremenim mikrobiološkim i radiološkim dijagnostičkim metodama infekcije patogenim gljivama danas sve češće na vreme dijagnostikuju, te stopa mortaliteta od IGI u ovoj populaciji opada u poslednjih 10 godina. Najčešći uzročnici IGI su gljive iz roda *Aspergillus* i *Mucorales*, dok su od kvasnica najčešći uzročnici *Candida* i *Cryptococcus*. Podaci iz literature ukazuju da se epidemiološka situacija menja, te je danas kod pacijenata sa HIV infekcijom najčešći uzročnik IGI *Aspergillus*, dok su kod imunokompromitovanih pacijenata bez HIV infekcije najčešći uzročnici IGI *Candida* i gljive iz roda *Mucorales*. Mukormikoza se u praksi viđa kod pacijenata sa uznapredovalim sindromom stečene imunodeficijencije (AIDS), sa prijavljenom stopom mortaliteta od 52,2%. IGI kod imunokompromitovanih pacijenata zaraženih HIV-om ima podmukao početak, brzo napreduje i ima lošu prognozu. Nazofarinks i orofarinks su najčešća ulazna vrata za gljive kroz respiratorni trakt, dok su prisustvo urinarnog i centralnog venskog katetera najčešći putevi ulaska širokog spektra gljiva iz vazduha, sa kože pacijenata i medicinskog osoblja koji dovode do IGI. Rani skrining, dijagnoza i lečenje IGI su ključni za smanjenje mortaliteta kod HIV pozitivnih i HIV negativnih pacijenata.

Ključne reči: HIV, imunokompromitovani pacijenti, gljive, plesni, kvasnice

ABSTRACT

Despite the availability of antifungal medications, fungal infections remain one of the most common opportunistic infections in immunocompromised patients, with a high mortality rate of over 50%. Individuals who are HIV-positive constitute a population that is at high risk to develop fungal infections, with invasive fungal infections (IGI) being the most common type. An estimated one million HIV-positive individuals worldwide are thought to develop IGI each year, of which half a million die. Because of the availability of novel radiological and microbiological diagnostic techniques, infections with pathogenic fungus are more frequently identified early on, and throughout the past ten years, the mortality rate from IGI in this population has been declining. The most common causative agents of IGI are fungi from the genera *Aspergillus* and *Mucorales*, while the most common causative agents of yeasts are *Candida* and *Cryptococcus*. Data from the literature indicate that the epidemiological situation is changing, and today in patients with HIV infection, the most common cause of IGI is *Aspergillus*, while in immunocompromised patients without HIV infection, the most common causes of IGI are *Candida* and fungi from the genus *Mucorales*. Mucormycosis is commonly seen in patients with advanced acquired immunodeficiency syndrome (AIDS), with a reported mortality rate of 52.2%. IGI in immunocompromised HIV-infected patients has an insidious onset, progresses rapidly, and carries a poor prognosis. The nasopharynx and oropharynx are the most common portals of entry for fungi through the respiratory tract, while the presence of urinary and central venous catheters are the most common routes of entry for a wide range of fungi from the air, from the skin of patients and medical personnel leading to IGI. Early screening, diagnosis, and treatment of IGI are key to reducing mortality in both HIV-positive and HIV-negative patients.

Keywords: HIV, immunocompromised patients, fungi, molds, yeasts

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ACUTE RETROVIRAL DISEASE – HOW TO RECOGNIZE IT?

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SAŽETAK

Uvod/Cilj: Akutna retrovirusna bolest (ARB) je po definiciji vremenski period koji počinje neposredno posle infekcije HIV-om u kome je osoba u viremiji ima detektabilan p-24 antigen ili ima prisutnu HIV RNK u odsustvu utvrđenih HIV antitela. Klinički spektar ARB varira od neprepoznatljivih, neupadljivih i nespecifičnih elemenata opšteg infektivnog sindroma do klasične prezentacije mononukleoznog, gripoznog ili virusnog sindroma druge vrste. Iz tog razloga je cilj ovog rada ukazati na kliničke i laboratorijske parametre koji će uputiti na lakše dijagnostikovanje ARB.

Metode: U pisanju ovog preglednog rada korišćene su činjenice iz radova objavljenih u vodećim svetskim časopisima iz oblasti HIV medicine, ne starijih od tri godine kao i najaktuelnijih saznanja prezentovanih na 19-oj Evropskoj AIDS konferenciji održanoj u Varšavi, Poljska, 18-21. oktobra 2023.

Rezultati: Visok indeks sumnje i neodložno testiranje na HIV treba da budu realizovani kod osoba koje prijavljuju visoko-rizično ponašanje i/ili prezentuju znake ili simptome influenza, mononukleoze, raznih virusnih bolesti ili čak nejasnog febrilnog stanja. Ključna je pravilna interpretacija kvantitativnog HIV RNA kao i serološkog testa.

Zaključak: S obzirom da je HIV visoko transmisibilan tokom akutne infekcije, prepoznavanje ARB smanjuje transmisiju. Time se postiže dobrobit na nivou javnog zdravlja ali i na ličnom nivou zaražene osobe, s obzirom da se uspostavlja rana virusna supresija, sprečava narušavanje imunske funkcije i inhibiše u najvećoj meri započet proces hronične inflamacije.

Ključne reči: akutna retrovirusna bolest, prepoznavanje, dijagnostika

ABSTRACT

Introduction/Aim: Acute retroviral disease (ARD) is by definition a period beginning immediately after HIV infection in which a person is viremic with detectable p-24 antigen or present HIV RNA without detectable HIV antibodies. The clinical spectrum of ARD varies from unrecognizable, inconspicuous and non-specific elements of a general infectious syndrome to the classic presentation of mononucleosis, influenza or viral syndrome of another type. For this reason, the aim of this work is to indicate the clinical and laboratory parameters that will guide the easier diagnosis of ARD.

Methods: Cognition facts from papers published in the world's leading journals in the field of HIV medicine, no older than three years, as well as the most current findings presented at the 19th European AIDS Conference, Warsaw, Poland, 18-21 October 2023, were basis of this research.

Results: A high index of suspicion and immediate HIV testing should be implemented in persons who report high-risk behavior and/or present with signs or symptoms of influenza, mononucleosis, various viral diseases, or even an unclear febrile condition. Correct interpretation of the quantitative HIV RNA as well as the serological test is crucial.

Conclusion: Given that HIV is highly transmissible during acute infection, recognition of ARD reduces transmission. This provides well-being at the public health level, and the personal level of the infected person, since early viral suppression is achieved, immune dysfunction is prevented and the process of chronic inflammation is inhibited to the greatest extent.

Keywords: acute retroviral disease, recognition, diagnostics

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CONTEMPORARY PRINCIPLES OF ANTIRETROVIRAL THERAPY IN SERBIA

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SAŽETAK

Antiretrovirusna terapija (ART) doprinela je značajnom smanjenju morbiditeta i mortaliteta kod osoba sa HIV infekcijom („Person with HIV”, PWH). Takođe, dovela je i do produženja i poboljšanja kvaliteta života PWH. Predstavlja istovremenu upotrebu najčešće tri antiretrovirusna leka. Karakteristike savremene ART koje čine ovu strategiju idealnom strategijom u tretmanu osoba koje žive sa HIV infekcijom, u ovom trenutku, su: visoka antivirusna potencija, dobra genetska barijera, odnosno, dobar profil rezistencije, bezbednost, odnosno, odsustvo neželjenih efekata i komforst.

Pored virusološkog, imunološkog i kliničkog efekta, ART ima i epidemiološki značaj, obzirom da su osobe sa HIV infekcijom uz ART nezarazne, što dovodi do smanjenja broja novozaraženih osoba, čime se u krajnjem smislu obavlja uspešna kontrola i zaustavljanje HIV pandemije. Prethodno navedeno, predstavlja osnovni princip Svetske zdravstvene organizacije, odnosno UNAIDS, koja za cilj ima da do 2030. godine 95% svih osoba sa HIV infekcijom dijagnostikuje, da 95% dijagnostikovanih leči ART i da od svih lečenih 95% budu uspešno lečeni, odnosno da imaju nedetektibilnu viremiju. Prema tome, rana ART, uz prethodnu rano dijagnostikovanje HIV infekcije, postaje osnovni uslov za uspešnu kontrolu HIV pandemije.

Smatra se da u Srbiji ima oko 4500 PWH. Dijagnostikovano je 3045 (68%), od kojih je 2500 (82%) na ART, a od kojih je 2325 (93%) nedetektibilno, odnosno na uspešnoj je ART. Potrebno je narednih godina unaprediti dijagnostikovanje PWH, njihovo vezivanje za zdravstveni sistem i njihov tretman ART, kako bi se zaustavila HIV epidemija u Srbiji.

Ključne reči: HIV infekcija, ART, virusološki uspeh ART

ABSTRACT

Antiretroviral therapy (ART) has contributed to a significant reduction in morbidity and mortality in persons with HIV infection (“Person with HIV”, PWH). It also led to the extension and improvement of the quality of life of PWH. It represents the simultaneous use of the most common three antiretroviral drugs. The characteristics of modern ART that make this strategy an ideal strategy in the treatment of people living with HIV infection, at the moment, are: high antiviral potency, good genetic barrier, that is, a good resistance profile, safety, that is, the absence of side effects and comfort.

In addition to the virological, immunological and clinical effect, ART also has an epidemiological significance, considering that people with HIV infection are non-infectious with ART, which leads to a reduction in the number of newly infected people, which ultimately leads to successful control and stopping of the HIV pandemic. The above is the basic principle of the World Health Organization, that is, UNAIDS, which aims to have 95% of all persons with HIV infection diagnosed by 2030, 95% of those diagnosed to be treated with ART, and 95% of all those treated to be successfully treated, that is, to have undetectable viremia. Therefore, early ART, with previous early diagnosis of HIV infection, becomes a basic condition for successful control of the HIV pandemic.

It is believed that there are about 4500 PWH in Serbia. 3045 (68%) were diagnosed, of which 2500 (82%) were on ART, and 2325 (93%) were undetectable, i.e. on successful ART. In the coming years, it is necessary to improve the diagnosis of PWH, their connection to the health system and their ART treatment, in order to stop the HIV epidemic in Serbia.

Keywords: HIV infection, ART, virological success of ART

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SPECTRUM OF OPHTHALMOLOGICAL MANIFESTATIONS IN PATIENTS WITH HIV INFECTION

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SAŽETAK

Uvod/Cilj: Virus humane imunodeficijencije (HIV) je retrovirus koji se prenosi telesnim tečnostima i krvlju. Cilj rada bio je analizirati oftalmološke manifestacije kod HIV pozitivnih pacijenata pregledanih na Klinici za očne bolesti Univerzitetskog kliničkog centra Srbije (UKCS) u periodu 2022-2023. godine. Analizirani su specifični uzroci gubitka vida, očne komplikacije, vidna oštšina i intraokularni pritisak (IOP) na početku i na kraju lečenja.

Metode: Retrospektivna analiza ambulantno pregledanih konsekutivnih HIV+ pacijenata sa oftalmološkim simptomima, bez obzira na prethodnu dužinu trajanja bolesti. Svi pacijenti su lečeni na Klinici za infektivne i tropske bolesti UKCS. Za statističku obradu podataka korišćene su deskriptivne i analitičke metode. Statistički značajnim smatran je $p < 0,05$.

Rezultati: Ukupno 24 pacijenata (83% muškog pola), prosečne starosti 44.6 ± 11.1 godina (raspon: 22–77 godina) uključeno je u studiju, 54% sa bilateralnim manifestacijama. Posteriorni uveitis je bio najčešća dijagnoza (59%). Većina pacijenata (63%) je imala koinfekciju (sifilis 34%, CMV retinitis 25%). Iako je vidna oštšina na kraju lečenja bila bolja nego na početku, razlika nije dostigla statističku značajnost. Najčešće komplikacije bili su hiororetinalni ožiljci (46%), komplikovana katarakta (33%), a 13% pacijenata je imalo sekundarni glaukom koji je kompenzovan medikamentnom terapijom. Na žalost, na kraju lečenja 5 pacijenata (21%) su zbog komplikacija bila monokularno legalno slepa (ožiljci retine kod sifilisa 8% i ablacija retine kod CMV retinitisa 13%).

Zaključak: Očni simptomi HIV pozitivnih osoba ozbiljan su problem koji zahteva temeljnu procenu i urgentno multidisciplinarno lečenje. Pacijenti su često smanjene kompliance, što praćenje i lečenje dodatno otežava. U slučaju zakasnele dijagnoze ishod može biti slepilo.

Ključne reči: HIV, imunodeficijencija, uveitis, CMV retinitis, sifilis oka

ABSTRACT

Introduction/Aim: Human immunodeficiency virus (HIV) is a retrovirus transmitted by body fluids and blood. The aim of the work was to analyze ophthalmological manifestations in HIV-positive patients examined at the Clinic for Eye Diseases, University Clinical Center of Serbia (UCCS) in the period 2022-2023. years. Specific causes of vision loss, eye complications, visual acuity, and intraocular pressure at the beginning and end of treatment were analyzed.

Methods: Retrospective analysis of consecutive outpatient HIV+ patients with ophthalmological symptoms, regardless of the previous duration of the disease. All patients were treated at the UCCS Clinic for Infectious and Tropical Diseases. Descriptive and analytical methods were used for statistical data processing. $P < 0.05$ was considered statistically significant.

Results: A total of 24 patients (83% male), average age 44.6 ± 11.1 years (range: 22 - 77 years) were included in the study, 54% with bilateral manifestations. Posterior uveitis was the most common diagnosis (59%). Most patients (63%) had co-infection (syphilis 34%, CMV retinitis 25%). Although visual acuity at the end of treatment was better than at the beginning, the difference did not reach statistical significance. The most common complications were chorioretinal scars (46%), complicated cataracts (33%), and 13% of patients had secondary glaucoma that was compensated by medical therapy. Unfortunately, at the end of treatment, 5 patients (21%) had monocular legal blindness due to complications (retinal scarring in syphilis 8% and retinal detachment in CMV retinitis 13%).

Conclusion: Ocular symptoms of HIV-positive persons are a serious problem that requires thorough evaluation and urgent multidisciplinary treatment. Patients often have reduced compliance, which makes monitoring and treatment even more difficult. In case of late diagnosis, the outcome can be blindness.

Keywords: HIV, immunodeficiency, uveitis, CMV retinitis, eye syphilis

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CRYPTOCOCCAL MENINGOENCEPHALITIS IN NON-HIV IMMUNODEFICIENCY

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SAŽETAK

Uvod: Gljivica *Cryptococcus neoformans*, koja se nalazi u spoljašnjoj sredini (zemlja, biljke, izmet ptica), izaziva infekcije kod ljudi i životinja. Infekcije kod ljudi se javljaju u stanjima imunodeficijencije i najčešće zahvataju centralni nervni sistem i respiratorni trakt. Najčešća manifestacija kriptokokoze je meningoencefalitis.

Cilj: Prikaz bolesnika s kriptokoknim meningoencefalitisom obolelog od karcinoma prostate.

Prikaz slučaja: R. Z. 68 g lečen od 05.01.2017. – 24.02.2017. u Klinici za infektivne i tropske bolesti u Beogradu u Odeljenju za neuroinfekcije, zbog glavobolje, bezvoljnosti, visoke temperature, gubitka svesti. Tri meseca pre pojave tegoba je lečen u Klinici za plućne bolesti zbog infiltracije u plućima, zbog čega je između ostalog dobio i kortikosteroidnu terapiju u trajanju od tri meseca. U ličnoj anamnezi karcinom prostate (zakazana operacija), hronična kardiomiopatija, tri infarkta miokarda, ulkus želudca. Na prijemu febrilan, dezorjentisan, bleđ, tahipnoičan, tahikardičan. Nad plućima obostrano čujni pukoti. Meningealni znaci pozitivni. U cerebrospinalnoj tečnosti 122 elementa (90% segmentiranih leukocita), hipoglikorahija, hiperproteinorahija. Likvorokulturom dokazan *Cryptococcus neoformans*. Lečen amfotericinom i flukonazolom, nakon čega dolazi do povlačenja tegoba, normalizacije kliničkog nalaza, povlačenja promena na plućima i normalizacije citobiohemijskog i mikrobiološkog nalaza u cerebrospinalnoj tečnosti. Maja 2017 godine urađena radikalna prostatektomija (adenokarcinom). Kontrolisan u Klinici za infektivne i tropske bolesti tokom 2017 i 2018 godine (uređan klinički nalaz). Pacijent je 2020 godine preminuo zbog karcinoma prostate.

Zaključak: Kod svih imunodeficientnih stanja treba misliti na kriptokoknu infekciju, naročito kod onih koje imaju spor tok.

Ključne reči: *Cryptococcus neoformans*, meningoencefalitis, imunodeficijencija

ABSTRACT

Introduction: The fungus *Cryptococcus neoformans*, which is found in the external environment (soil, plants, bird droppings), causes infections in humans and animals. Infections in humans occur in states of immunodeficiency and most often affect the central nervous system and respiratory tract. The most common manifestation of cryptococcosis is meningoencephalitis.

Objective: Presentation of a patient with cryptococcal meningoencephalitis suffering from carcinoma prostate.

Case report: R. Z. 68 years old, treated from 05.01.2017 – 24.02.2017. in the Clinic for Infectious and Tropical Diseases in Belgrade in the Department of Neuroinfections, due to headache, lethargy, high temperature, loss of consciousness. Three months before the onset of symptoms, he was treated at the Pulmonary Disease Clinic for infiltration in the lungs, for which, among other things, he received corticosteroid therapy for three months. Personal history of prostate cancer (scheduled surgery), chronic cardiomyopathy, three myocardial infarctions, stomach ulcer. On admission, febrile, disoriented, pale, tachypneic, tachycardic. Bilateral audible crackles over the lungs. Meningeal signs positive. In the cerebrospinal fluid, 122 elements (90% of segmented leukocytes), hypoglycorachia, hyperproteinorachia. *Cryptococcus neoformans* confirmed by liquid culture. He was treated with amphotericin and fluconazole, after which the complaints subsided, the clinical findings normalized, the changes in the lungs subsided, and the cytobiochemical and microbiological findings in the cerebrospinal fluid normalized. Radical prostatectomy (adenocarcinoma) was performed in May 2017. Controlled in the Clinic for Infectious and Tropical Diseases during 2017 and 2018 (correct clinical findings). The patient died in 2020 due to prostate cancer.

Conclusion: Cryptococcal infection should be considered in all immunodeficiency conditions, especially in those with a slow course.

Keywords: *Cryptococcus neoformans*, meningoencephalitis, immunodeficiency

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SAŽETAK

Uvod/Cilj: Infekcija virusom majmunskih boginja (mpoks) je dovela do globalnog širenja od maja 2022. godine, zbog čega ju je Svetska zdravstvena organizacija proglasila javnozdravstvenom krizom od međunarodnog značaja u julu 2022. Cilj naše studije je da opiše karakteristike i ishode ove infekcije u poređenju sa HIV statusom.

Metode: Analizirali smo podatke potvrđenih slučajeva mpoksa na Klinici za infektivne i tropske bolesti UKCS. Mpoks je dijagnostikovao RT-PCR metodom iz briseva orofarinksa i lezija kože. Rezultati: Prikazujemo 30 slučajeva infekcije potvrđenih od maja do oktobra 2022.godine. Sveukupno, 73.4% su činili gej muškarci, a 36.7% su bile osobe koje žive sa virusom humane imunodeficijencije (HIV), prosečne starosti 35 godina. Novootkriveni HIV smo dijagnostikovali kod 3 pacijenta. Prosečni broj CD4 limfocita/ml je bio 648, a 78.5% je imalo nedetektabilnu viremiju. Najčešće vid transmisije je bio putem rizične seksualne aktivnosti- 60%, uz veću učestalost kod osoba sa HIV-om ($p=0.033$). Nakon prosečne inkubacije od 10 dana, 66.7% se prezentovalo osipom, a 83.3% je imalo anogenitalne lezije. Osipu su prethodile febrilnost (73.4%), limfadenopatija (43.3%) i opšta slabost (43.3%). Antivirusna terapija nije primenjivana, a 10% je zahtevalo hospitalizaciju najčešće usled bakterijskih superinfekcija kože. Svi su imali povoljan ishod.

Zaključak: U našoj studiji, mpoks se manifestovao nizom dermatoloških i sistemskih manifestacija koje nisu zahtevale primenu antivirusne terapije. Veća učestalost ove infekcije među rizičnim grupama naglašava potrebu za brзом dijagnostikom i lečenjem kako bi se zaustavilo dalje širenje u zajednici.

Ključne reči: majmunске boginje, HIV, CD4 limfociti

ABSTRACT

Background: Monkeypox (mpox) virus began spreading worldwide in May 2022, forcing the World Health Organization to declare it a public health emergency of international concern in July 2022. The aim of our study is to describe the characteristics and outcomes of mpox compared to HIV status.

Methods: We analysed data of confirmed mpox by RT-PCR from oropharyngeal swabs and skin lesions, at the Clinic for Infectious and Tropical Diseases UCCS in Belgrade. Results: We report 30 infections diagnosed between May and October, 2022. Overall, 73.4% were men who have sex with men (MSM), 36.7% had human immunodeficiency virus infection; the median age was 35. HIV was newly diagnosed in 3 patients. The median CD4 cell count/mL was 648 with undetectable viral load in 78.5%. Transmission was suspected to have occurred through sexual activity in 60%, and it was more frequent among PLWH ($p=0.033$). After average incubation period of 10 days, 66.7% presented with a rash, while 83.3% had anogenital lesions. Common systemic features preceding rash included fever (73.4%), lymphadenopathy (43.3%) and malaise (43.3%). None of the patients received antiviral treatment, while 10% required hospitalization mostly due to skin bacterial superinfection. All patients had a favourable outcome.

Conclusions: In our study, mpox was characterised by a variety of dermatological and systemic symptoms that did not necessitate the use of antivirals. The higher prevalence of this infection among risk groups emphasises the importance of rapid diagnosis and treatment to prevent further spread in the community.

Keywords: monkeypox, HIV, CD4 lymphocytes

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MALARIA – THE MECHANISM OF IMMUNOSUPPRESSION AND ITS CONSEQUENCES

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SAŽETAK

Malaria je infektivna bolest koju izazivaju paraziti roda *Plasmodium*, a prenosi se na ljude ubodom inficirane ženke komarca roda *Anopheles*. U imunološkom odgovoru na infekciju učestvuju mehanizmi stečene i urođene imunosti.

Tokom infekcije, paraziti pre eritrocitne i eitrocitne faze infekcije bivaju prepoznati od ćelija urođene imunosti koje pokreću prezentaciju antigena T ćelijama i razvoj antigen specifičnog stečenog imunog odgovora. Plasmodiumi su razvili sposobnost izbegavanja prepoznavanja od strane ćelija imunog sistema modifikovanjem površinskih proteina ili produkcijom molekula koji suprimiraju imuni odgovor. U nekim slučajevima, imuni sistem razvija toleranciju na prisustvo malaričnih parazita, što dovodi do slabijeg imunog odgovora. To je najverovatnije posledica ponavljanog izlaganja parazitima i sposobnosti organizma da ograniči preteranu inflamaciju.

Iako malaria nije direktni uzrok imunosupresije kao druge bolesti ili terapije, njen uticaj na imuni sistem može dovesti do povećane osetljivosti na druge infekcije kao i da naruši imuni odgovor, posebno kod teških ili hroničnih bolesti

Uticaj na imuni sistem može uključivati direktan efekat na ćelije imunog sistema, disregulaciju citokina, gubitka imunološke memorije, interakcije sa koinfekcijama i komorbiditetima, kao i efekat na hematopoezu. Ovi imunološki efekti doprinose povećanoj osetljivosti za druge infekcije i može uzrokovati egzacerbaciju same malarije, posebno kod teških ili hroničnih formi.

Posledice imunosupresije uzrokovane malarijom su povećana osetljivost na sekundarne bakterijske, virusne i parazitarne infekcije, oslabljen odgovor na vakcine, uticaj na težinu bolesti, organsku disfunkciju i komplikacije, hronične infekcije.

Ključne reči: malaria, imunosupresija, kliničke komplikacije

ABSTRACT

Malaria is an infectious disease caused by parasites of the *Plasmodium* spp, and is transmitted to humans by the bite of an infected female *Anopheles* mosquito. Mechanisms of acquired and innate immunity participate in the immune response to infection.

During infection, parasites before the erythrocyte and erythrocyte stages of infection are recognized by cells of innate immunity that trigger antigen presentation to T cells and the development of an antigen-specific acquired immune response. Plasmodium's have evolved the ability to evade recognition by immune system cells by modifying surface proteins or producing molecules that suppress the immune response. In some cases, the immune system develops a tolerance to the presence of malaria parasites, leading to a weaker immune response. This is most likely a consequence of repeated exposure to parasites and the body's ability to limit excessive inflammation.

Although malaria is not a direct cause of immunosuppression like other diseases or therapies, its effect on the immune system can lead to increased susceptibility to other infections as well as impair the immune response, especially in severe or chronic diseases.

The effect on the immune system may include a direct effect on cells of the immune system, dysregulation of cytokines, loss of immune memory, interactions with coinfections and comorbidities, as well as an effect on hematopoiesis. These immune effects contribute to increased susceptibility to other infections and may predict exacerbation of malaria itself, especially in severe or chronic forms.

The consequences of immunosuppression caused by malaria are increased sensitivity to secondary bacterial, viral and parasitic infections, weakened response to vaccines, impact on disease severity, organ dysfunction and complications, chronic infections.

Keywords: malaria, immunosuppression, clinical complications

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IMMUNITY DURING AND AFTER VARICELLA

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SAŽETAK

Varicella zoster virus (VZV) je član porodice *Herpesviridae* i jedan je od osam virusa ove porodice koji su značajni za humanu patologiju. Virus je sveprisutan u većini populacija širom sveta. VZV izaziva varičelu (ovčije boginje, vodene kozice, pljuškvu) tokom primarne infekcije, uspostavlja latenciju u ganglijama dorzalnog korena i može se ponovo aktivirati godinama kasnije, što se klinički ispljava kao herpes zoster (HZ). U svom životnom ciklusu VZV mora da izbegne antivirusni imunitet tokom tri važne faze virusne patogeneze, uključujući viremiju povezanu sa ćelijama karakterističnu za primarnu infekciju, perzistiranje u ganglijama dorzalnih korenova kičmene moždine tokom latencije kao i početni period reaktivacije VZV.

Primarna infekcija varičela-zoster virusom indukuje VZV-specifična antitela i VZV-specifični T ćelijski posredovani imunitet. Imunitet posredovan T ćelijama, koji se razvija u roku od 1-2 nedelje nakon pojave ospeje neophodan je za oporavak od varičele, a čine ga CD4 i CD8 efektorski limfociti i memorijske T ćelije. Primena vakcine protiv varičele takođe stvara VZV-specifične humoralne i ćelijske imune odgovore. Aktiviranje memorijskih ćelija koje se razvijaju tokom varičele ili posle vakcinacije doprinosi zaštiti nakon narednog egzogenog (ponovnog izlaganja virusu iz okruženja) ili endogenog izlaganja (tiha reaktivacija latentnog virusa). Imunitet posredovan T ćelijama specifičan za VZV takođe je neophodan za održavanje latentnog VZV u subkliničkom stanju u senzornim ganglijama. Kada ovi odgovori opadaju, kao što se dešava sa starenjem ili jatrogenom supresijom imuniteta, reaktivacija VZV dovodi do pojave erupcije herpes zoster.

Ključne reči: varičela zoster virus, imunitet, T limociti

ABSTRACT

Varicella zoster virus (VZV) is a member of the *Herpesviridae* family and is one of eight viruses of this family that are important for human pathology. The virus is ubiquitous in most populations worldwide. VZV causes varicella (chicken pox) during primary infection, establishes latency in the dorsal root ganglia, and can reactivate years later, manifesting clinically as herpes zoster (HZ). In its life cycle, VZV must evade antiviral immunity during three important phases of viral pathogenesis, including cell-associated viremia characteristic of primary infection, persistence in spinal cord dorsal root ganglia during latency, and the initial period of VZV reactivation.

Primary varicella-zoster virus infection induces VZV-specific antibodies and VZV-specific T cell-mediated immunity. T cell-mediated immunity, which develops within 1-2 weeks after the onset of smallpox, is necessary for recovery from varicella, and consists of CD4 and CD8 effector lymphocytes and memory T cells. Administration of varicella vaccine also generates VZV-specific humoral and cellular immune responses. Activation of memory cells that develop during varicella or after vaccination contributes to protection after subsequent exogenous (re-exposure to virus from the environment) or endogenous exposure (silent reactivation of latent virus). VZV-specific T cell-mediated immunity is also required to maintain latent VZV in a subclinical state in the sensory ganglia. When these responses decline, as occurs with aging or iatrogenic immune suppression, reactivation of VZV leads to herpes zoster eruptions.

Keywords: varicella zoster virus, immunity, T lymphocytes

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IMMUNODEFICIENCY DURING AND AFTER MEASLES

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SAŽETAK

Morbili su kosmopolitna bolest na koju su bili, pre uvođenja vakcinacije, osetljivi svi ljudi, bez obzira na uzrast i rasu. Bolest karakteriše izražena aktivacija imunog odgovora, uz izražene kliničke pokazatelje imunosupresije, ispoljava čestim bakterijskim superinfekcijama tokom akutne bolesti i dugotrajnom negativnošću kožnih proba (na kandidu i tuberkulozu) do dva meseca u toku rekonvalescencije, kada se vide reaktivacije hroničnih bolesti (tuberkuloze itd). Otpornost posle preležane bolesti je doživotna. Najteži oblici bolesti vide se kod dece do dve godine i starijih od 20 godina, trudnica i imunokompromitovanih osoba (deca obolela od agamaglobulinemije imaju uobičajenu težinu bolesti, a koja imaju deficit celularnog imuniteta umiru od gigantocelularne pneumonije). Lečenje je simptomatsko uz upotrebu specifičnih antibiotika u slučaju bakterijske superinfekcije. Vakcinacija jedina adekvatna mera prevencije.

Infekcija se prenosi respiratornim putem. Virus se primarno razmnožava u epitelnim ćelijama gornjeg respiratornog trakta, odakle ulazi u regionalno limfno tkivo, inficirajući produktivno B i T limfocite i monocite. Monociti ostaju dugo funkcionalno nesposobni, što utiče na funkciju T limfocita. Po ulasku u cirkulaciju inficira endotelne ćelije malih krvnih sudova, što je osnov za ispoljavanje enanrema i egzantema, kao i svih virusnih komplikacija bolesti (proliv, pneumonija, hepatitis, encefalitis). Izražena aktivacija ćelijskog imuniteta završava bolest, ali se u tome i iscrpljuje i veoma sporo se oporavlja.

S obzirom na nizak obuhvat vakcinacijom, prete nam manje ili veće epidemije malih boginja i o navedenom mora da se vodi računa.

Ključne reči: male boginje, humoralni imunitet, ćelijski imunitet, superinfekcije

ABSTRACT

Measles is a cosmopolitan disease to which, before the introduction of vaccination, all people, regardless of age and race, were susceptible. The disease is characterized by pronounced activation of the immune response, with clear clinical indicators of immunosuppression, manifested by frequent bacterial superinfections during acute illness and long-term negativity of skin tests (on candida and tuberculosis) up to two months during convalescence, when reactivation of chronic diseases (tuberculosis, etc.) are seen. Immunity, after a disease, is lifelong. The most severe forms of the disease are seen in children up to two years of age and older than 20 years, pregnant women and immunocompromised persons. Children suffering from agamaglobulinemia have the usual severity of the disease, and those who have a deficiency of cellular immunity die from gigantocellular pneumonia). Treatment is symptomatic with the use of specific antibiotics in case of bacterial superinfection. Vaccination is the only adequate measure of prevention.

It is respiratory transmitted disease. The virus reproduces primarily in the epithelial cells of the upper respiratory tract, from where it enters the regional lymphatic tissue, infecting productively B and T lymphocytes and monocytes. Upon entering the circulation, it infects the endothelial cells of small blood vessels, which is the basis for the manifestation of enanthermas and exanthermas, as well as all viral complications of the disease (diarrhea, pneumonia, hepatitis, encephalitis). Pronounced activation of cellular immunity ends the disease, but in this it also depletes and recovers very slowly. Monocytes remain functionally incapacitated for a long time, which affects the function of T lymphocytes.

Given the low coverage of vaccination, we are threatened with smaller or larger measles epidemics and consecutive complications.

Keywords: measles, humoral immunity, cellular immunity, over imposed infections

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PROGNOSTIČKI ZNAČAJ BROJA CD4+T LIMFOCITA U PERIFERNOJ KRVI KOD PACIJENATA SA TEŠKOM KLINIČKOM SLIKOM COVID-19

PROGNOSTIC SIGNIFICANCE OF CD4+T LYMPHOCYTE VALUES IN PATIENTS WITH A SEVERE CLINICAL PICTURE OF COVID-19

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SAŽETAK

Uvod/Cilj: Jedna od karakteristika COVID-19 jeste da se odlikuje padom u broju T limfocita u perifernoj krvi. S obzirom da T limfociti imaju ulogu u celularnoj imunosti, ispitivali smo da li broj CD4+T, CD8+T i odnos CD4+/CD8+ limfocita imaju prediktivni značaj kod obolelih od COVID-19.

Metode: U istraživanju je učestvovao 101 pacijent sa dokazanim COVID-19. Pacijenti su podeljeni na osnovu potrebe za kiseoničnom terapijom na grupu pacijenata sa lakom (n=38) i grupu pacijenata sa teškom kliničkom slikom (n=63). U obe grupe merene su vrednosti CD4+T, CD8+T i odnos CD4+/CD8+. Izvršene su i osnovne biohemijske analize periferne krvi, a radiografski parametri pluća su izraženi kao CXR score.

Rezultati: Broj CD4+T kao i CD8+T limfocita je bio značano manji kod pacijenata sa teškom formom bolesti, kod pacijenata sa letalnim ishodom, kao i kod pacijenata lečenih kiseoničnom terapijom. Istovremeno, broj CD4+T i CD8+T u perifernoj krvi je statistički značajno negativno korelirao sa radiografskim parametrima pluća (CXR score). Odnos CD4+/CD8+ ćelija periferne krvi se nije statistički značajno razlikovao između ispitivanih grupa pacijenata.

Zaključak: Određivanje broja CD4+T i CD8+T u perifernoj krvi ima značaja u proceni rizika od razvoja teške kliničke slike, kao i u samom ishodu bolesti kod COVID-19 pacijenata.

Ključne reči: SARS-CoV-2, COVID-19, CD4+T, CD8+T, odnos CD4+/CD8+

ABSTRACT

Introduction/Objective: One of the characteristics of COVID-19 is that it is characterized by a decrease in the number of T lymphocytes in the peripheral blood. Given that T lymphocytes play a role in cellular immunity, we investigated whether CD4+T, CD8+T and the CD4+/CD8+ ratio have predictive significance in patients with COVID-19.

Methods: 101 patients with proven COVID-19 participated in the research. Patients were divided based on the need for oxygen therapy into a group of patients with a mild (n=38) and a group of patients with a severe clinical picture (n=63). CD4+T, CD8+T and CD4+/CD8+ ratio were measured in both groups. Basic biochemical analyzes of peripheral blood were also performed, and radiographic lung parameters were expressed as CXR score.

Results: The number of CD4+T as well as CD8+T lymphocytes was significantly lower in patients with a severe form of the disease, in patients with a fatal outcome, as well as in patients treated with oxygen therapy. At the same time, the number of CD4+T and CD8+T in the peripheral blood significantly negatively correlated with the radiographic parameters of the lungs (CXR score). The ratio of peripheral blood CD4+/CD8+ cells was not significantly different between the studied patient groups.

Conclusion: The determination of the number of CD4+T and CD8+T in peripheral blood is important in assessing the risk of developing a severe clinical picture, as well as in the outcome of the disease in COVID-19 patients.

Keywords: SARS-CoV-2, COVID-19, CD4+T, CD8+T, CD4+/CD8+ ratio

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DIABETES MELLITUS AS A PREDISPOSING FACTOR FOR INFECTIONS

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SAŽETAK

Dijabetes melitus (DM) je hronični metabolički poremećaj koji karakteriše uporna hiperglikemija usled insulinske rezistencije ili neuspeha proizvodnje insulina. Pacijenti sa DM razvijaju mikrovaskularne komplikacije uključujući neuropatiju, nefropatiju, retinopatiju i makrovaskularne komplikacije, koje se uglavnom sastoje od ubrzane i teže ateroskleroze u poređenju sa subjektima opšte populacije. Infarkt miokarda i moždani udar su češći u poređenju sa opštom populacijom. DM se obično povezuje sa upalom niskog stepena koja je poznati faktor u njegovom razvoju i njegovim komplikacijama. Sada je dobro utvrđeno da zapaljenje i imune ćelije igraju glavnu ulogu kako u nastanku i progresiji ateroskleroze, tako i u nastanku kardio-vaskularnih događaja. Upalni odgovor se javlja kao rezultat imunog odgovora na visoke nivoe glukoze, kao i prisustva inflamatornih medijatora koje proizvode adipociti i makrofagi u masnom tkivu. Hiperglikemija izaziva disfunkcioni imunološki odgovor, koji ne uspeva da kontroliše širenje invazivnih patogena kod diabetičkih subjekata. Zbog toga su podložniji infekcijama. Povećana prevalencija DM će povećati učestalost infektivnih bolesti i povezanih komorbiditeta. Poseban problem predstavlja dijabetesno stopalo, gde se na mestima pritiska formira trofična promena koja kasnije ulcerise i može da dovede do osteomijelitisa i septicemije.

Razumevanje imunološke disfunkcije koja se javlja tokom hiperglikemije može dovesti do novih tretmana i prevencije zaraznih bolesti i komorbiditeta DM, čime se poboljšava ishod lečenja infektivnih bolesti kod pacijenata sa dijabetesom.

Ključne reči: dijabetes, infektivne bolesti, komorbiditeti, ateroskleroza

ABSTRACT

Diabetes mellitus (DM) as chronic metabolic disorder characterized by persistent hyperglycemia due to insulin resistance or failure to produce insulin. Patients with DM develop microvascular complications including, neuropathy, nephropathy, retinopathy and macrovascular complications that mainly consist in an accelerated and more severe atherosclerosis compared to the general populations. Myocardial infarction and stroke is more common comparing with general population. DM is commonly associated with low grade inflammation that is a known cause factor in its development and its complications. Now it is well established that inflammation and immune cells play a major role in both atherosclerosis genesis and progression as well as in CV event occurrence. An inflammatory response occurs as result of immune response to high glucose levels as well as presence of inflammatory mediators produced by adipocytes and macrophages in fat tissue. Hyperglycemia is cause of dysfunctional immune response which fails to control the spread of invading pathogens in diabetic subjects. That is why they are more susceptible to infections. The increased prevalence of DM will increase the incidence of infectious diseases and related comorbidities.

Understanding of immune dysfunction which occurs during hyperglycemia can lead to novel treatments and prevention for infection diseases and DM comorbidities, thus improving the outcome of infection disease treatment in diabetic patients.

Keywords: diabetes mellitus, infectious diseases, atherosclerosis

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SAŽETAK

Osobe starije životne dobi imaju fiziološki, starenjem oslabljen, imunitet, zatim smanjene fiziološke rezerve, prisustvo brojnih komorbidnih stanja, usporen metabolizam lekova. Sve su ovo činioci koji dovode do porasta učestalosti ali i smrtnosti starih osoba od infekcija različite etiologije i lokalizacije.

Klasični simptomi i znaci infekcija kod starih su slabije ispoljeni ili čak odsutni, te je stoga dijagnostika često otežana. Poremećaj kognitivnih funkcija, čest je a nekad i jedini znak infekcije u ovoj populaciji. Najčešće su infekcije respiratornog, urinarnog, gastrointestinalnog trakta, kože i potkožnog tkiva.

Lečenje infekcija kod starih je otežano, kako zbog izmenjene farmakokinetike antibiotika, mogućih interakcija lekova, pridruženih oboljenja. Zbog svega navedenog, a i činjenice da demografski spadamo u staro stanovništvo, dijagnostika i lečenje infekcija u gerijatrijskoj populaciji predstavlja veliki izazov za lekara kliničara.

Ključne reči: infekcija, starenje, pridružena oboljenja

ABSTRACT

The elderly people have physiological immunity, weakened by ageing, diminished physiological reserves, many comorbidities, as well as reduced metabolism of medications. All these factors contribute to an increase not only in frequency but also in mortality of the elderly from infections of various aetiology and localisation.

The classical symptoms and signs of infection in the elderly are less prominent or even missing, thus making diagnosing more difficult. Impairment of cognitive functions is a frequent and sometimes the sole sign of infection in this population. The most common are infections of the urinary or gastrointestinal tract, skin and subcutaneous tissue.

The treatment of infections in the elderly is difficult because of the altered pharmacokinetics of antibiotics, as well as possible drug interactions and comorbidities. Taking into account all this, along with the fact that we demographically fall into the elderly population, diagnosing and treating infections of the geriatric population presents a huge challenge for clinical physicians.

Keywords: infection, ageing, comorbidities

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INFECTIONS CAUSED BY IMMUNOSUPPRESSION IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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SAŽETAK

Pacijenti oboleli od hronične limfocitne leukemije (HLL) su u povećanom riziku za pojavu oportunističkih infekcija i reaktivacijulatenantih infekcija. Ne postoje standardne preporuke za profilaksu bakterijskih infekcija ali se smatra da lekari koji leče pacijente sa HLL treba da budu edukovani za zbrinjavanje infekcija respiratornog i urinarnog trakta koje su najčešće. Što se tiče virusnih infekcija, terapija primenom direktnih antiviralnih lekova preporučuje se kod svih pacijenata sa hroničnom HCV infekcijom uz praćenje potencijalnih interakcija između lekova. Kod pacijenata sa hroničnom HBV infekcijom neophodna je antiviralna profilaksa tokom primene monoklonskih anti CD 20 antitela. Antituberkulozna profilaksa se preporučuje kada je pozitivan Quantiferon test imajući u vidu da prolongiran životni vek pacijenata sa HLL omogućava veću šansu za reaktivaciju tuberkuloze. Incidenca invazivnih gljivičnih infekcija je oko 0.5% i ne posoje jasni podaci koji pacijenti će imati benefit od profilakse. Smatra se da bi kandidati bili osobe starije od 75 godina, sa relaps 'refraktarnom HLL i' ili prolongiranom neutropenijom kao i osobe na prolongiranoj kortikosteroidnoj terapiji. U eri COVID 19 infekcije neophodno je primenjivati preventivne mere koje podrazumevaju vakcinaciju i preekspozicijsku profilaksu primenom monoklonskih neutrališućih antitela.

Ključne reči: hronična limfocitna leukemija, infekcija, antivirusna terapija, profilaksa

ABSTRACT

Patients with chronic lymphocytic leukemia (HLL) are at increased risk for the occurrence of opportunistic infections and reactivation of latent infections. There are no standard recommendations for the prophylaxis of bacterial infections, but it is thought that doctors who treat patients with HLL should be educated to manage the respiratory and urinary tract infections that are most common. As for viral infections, therapy with direct antiviral drugs is recommended in all patients with chronic HCV infection, taking care about possible interaction. During the therapy with monoclonal anti CD20 antibodies, antiviral prophylaxis is necessary in patients with chronic HBV infection. Antituberculous prophylaxis is recommended when quantiferon test is positive, considering that prolonged life of patients with HLL could be basis of reactivation of latent tuberculosis. The incidence of invasive fungal infections is about 0.5% and there is no clear data on which patients will benefit from prophylaxis. It is believed that candidates would be people over the age of 75, with relapsing/refractory HLLs and/or prolonged neutropenia as well as people on prolonged corticosteroid therapy. In the era of COVID-19 infection, it is necessary to apply preventive measures that include vaccination and pre-exposure prophylaxis using monoclonal neutralizing antibodies.

Keywords: chronic lymphocytic leukemia, infection, antiviral therapy, prophylaxis

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GASTROINTESTINAL INFECTIONS IN IMMUNOCOMPROMISED

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SAŽETAK

Crevne infekcije imaju značajan udeo u oboljevanju i smrtnosti ljudske populacije. Ovo se naročito odnosi na decu uzrasta do pet (5) godina, osobe starije od 65 godina, imunokompromitovane, kao i na one kojima nisu dostupni osnovni higijenski uslovi.

Iako su crevne infekcije smatrane bolešću siromašnih sa najvećom stopom javljanja i rasprostranjenosti u nerazvijenim krajevima Afrike i Azije, razvoj medicine, produženje životnog veka čoveka i hvatanje u koštac sa bolestima modernog doba je dovelo do izvesnog pomeranja ovakvog shvatanja čemu je u najvećoj meri doprinelo povećanje broja imunokompromitovanih osoba na globalnom nivou. Imunokompromitovani pacijenti, uključujući pacijente sa AIDS-om, transplantiranom koštanom srži, transplantiranim solidnim organom, pacijente obolele od limfoma i leukemije, pacijente na imunosupresivnoj terapiji, kao i one sa naslednim imunodeficijntnim stanjima, su u povišenom riziku od razvoja infekcija. Kod imunokompromitovanih osoba treba obratiti posebnu pažnju na razvoj oportunističkih infekcija koje mogu zahvatiti bilo koji sistem organa, uključujući ceo gastrointestinalni trakt, ili njegove pojedine delove i ispoljiti svoj patogeni efekatna bilo kom njegovom delu. Posebnu pažnju treba obratiti na razvoj oportunističkih infekcija kod imunokompromitovanih osoba zbog često neprimetnog početka, neubičajenih i sniženih simptoma i neretko mnogo teže kliničke slike praćene nepovoljnim ishodom nego kod imunokompentnog domaćina. Gastrointestinalni trakt je potencijalno ishodište infekcije za mnoge patogene, uključujući viruse, bakterije, gljivice i protozoe. Neki od najčešćih uzročnika u stanjima imunodeficijencije su enterične bakterije roda *Salmonella*, *Šigela*, *Kampilobakter*, *Klostridioides* i *Jersinija*, zatim *Citomegalovirus*, *Kandida* i protozoe poput *Cryptosporidijuma*, *Izospore* i *Đardije*. Raznovrsnost prouzrokovaca infekcije, „nema” simptomatologija zbog smanjenog imunološkog odgovora na infekciju, kao i težina ovih infekcija iziskuju potpunu pažnju prilikom bavljenja gastrointestinalnim infekcijama imunokompromitovanih osoba.

Ključne reči: crevne infekcije, oportunističke infekcije, imunosupresija

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ABSTRACT

Gastrointestinal infections comprise a significant portion of morbidity and mortality in human population. This in particular concerns young children of up to five (5) years of age, elderly, those older than 65, immunocompromised, and people without access to basic hygienic conditions.

Gastrointestinal infections are generally considered to be a disease of the poor, with greatest incidence and prevalence rates among underprivileged in underdeveloped areas of Africa and Asia. However, with advances made in medical science, the extension of human life expectancy, and the development of treatment options of modern era diseases and conditions, there has recently been a certain shift in such an understanding triggered by the observation of ever-increasing number of immunocompromised patients across meridians. Immunocompromised patients, including patients with AIDS, bone-marrow and solid organ transplants, lymphomas and leukemias, as well as those on immunosuppressive therapy for various conditions are at increased risk of infections which can affect any organ system, including the entire gastrointestinal system, or any part of it. Special attention should be paid to the development of opportunistic infections in such patients for they can often present with slow onset and scarce, diminished symptoms, but can cause more severe disease than in an immunocompetent host (2). Gastrointestinal tract is a potential site of infection with various pathogens, including viruses, bacteria, fungi, and protozoa. Certain enteric bacteria such as *Salmonella*, *Shigella*, *Campylobacter*, *Clostridioides* and *Yersinia*, as well as *Cytomegalovirus*, *Candida*, and protozoa like *Cryptosporidium*, *Isospora* and *Giardia* should evoke immediate attention in immunodeficient patients. Diversity of infectious agents, often diminished symptoms due to decreased immune response to infection, as well as severity of these infections, prompt undivided vigilance when dealing with gastrointestinal infections in immunocompromised.

Keywords: gastrointestinal infections, opportunistic infections, immunosuppression

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SEPSIS – A CONSEQUENCE OR CAUSE OF IMMUNODEFICIENCY?

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SAŽETAK

Sepsa se definiše kao disfunkcija organa opasna po život koja je prouzrokovana neregulisanim odgovorom domaćina na infekciju. To je takođe jedan od značajnih uzroka smrti i povećanja troškova zdravstvene zaštite u jedinicama intenzivne nege. Iako je patofiziologija sepse i dalje nerazjašnjena, imunosupresija je od skoro prepoznata kao jedan od glavnih uzroka smrti nastale usled sepse. Imunosupresija je prema jednim autorima uzrok poremećaja imunološke homeostaze nastale u toku sepse. Karakteriše je oslobađanje antiinflamatornih citokina, programirana smrt imunih efektorskih ćelija, hiperproliferacija imunosupresorskih ćelija. Brojne prekliničke studije su imunosupresiju kao terapijsku metu, pokazale kao glavnu tačku za preokret disfunkcije imunocita i uspostavljanje otpornosti prema patogenu. Povećana ekspresija proinflamatornih citokina koje oslobađaju inflamatorne ćelije i aktivacija sistema komplementa i koagulacije, rezultiraju prekomernom inflamacijom, što dalje dovodi do citokinske oluje i MODS-a. Istovremeno ili naknadno, povećano oslobađanje antiinflamatornih citokina i kohibitornih molekula, smanjena ekspresija HLA-DR, smrt imunocita i ekspanzija regulatornih ćelija dovode do imunosupresije, povećavajući podložnost sekundarnim infekcijama, što je glavni uzrok progresije bolesti kao i mortaliteta usled sepse. Najnovije terapijske mogućnosti u prekliničkim studijama jesu upravo imunološki lekovi ali je u kliničkoj praksi i dalje izazov primena bilo kakvih oblika imunomodulatornih lekova u lečenju teških sistemskih infekcija, te je neophodno dalje istraživanje u ovoj oblasti kako bi se unapredila prevencija septičnog šoka i ostalih posledica sepse.

Cljučne reči: sepsa, imunosupresija, HLA-DR

ABSTRACT

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. It is also a significant cause of death and increased health care costs in intensive care units. Although the pathophysiology of sepsis remains unclear, immunosuppression has recently been recognized as one of the main causes of death due to sepsis. According to some authors, immunosuppression is the cause of immune homeostasis disorders that occur during sepsis. It is characterized by the release of anti-inflammatory cytokines, programmed death of immune effector cells, hyperproliferation of immunosuppressive cells. Numerous preclinical studies have shown immunosuppression as a therapeutic target, as the main point for reversing immune cell dysfunction and establishing resistance to the pathogen. Increased expression of proinflammatory cytokines released by inflammatory cells and activation of the complement and coagulation systems result in excessive inflammation, further leading to cytokine storms and MODS. Simultaneously or subsequently, increased release of anti-inflammatory cytokines and inhibitory molecules, reduced expression of HLA-DR, death of immune cells and expansion of regulatory cells lead to immunosuppression, increasing susceptibility to secondary infections, which is the main cause of disease progression and mortality due to sepsis. The latest therapeutic options in preclinical studies are immune drugs, but in clinical practice, the application of any form of immunomodulatory drugs in the treatment of severe systemic infections is still a challenge, and further research in this area is necessary in order to improve the prevention of septic shock and other consequences of sepsis.

Keywords: sepsis, immunodeficiency, HLA-DR

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VACCINATION AGAINST INFLUENZA IN PATIENTS WITH AUTOIMMUNE RHEUMATIC DISEASES

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SAŽETAK

Uvod: Pacijenti koji boluju od autoimunih reumatskih bolesti imaju značajno veći rizik od razvoja raznih infekcija u odnosu na zdravu populaciju, pogotovo stariji pacijenti.

Materijal i metode: Naša studija je obuhvatila pacijente koji boluju od sistemskog eritematoznog lupusa (n = 30), reumatoidnog artritisa (n = 37) ili Sjogrenovog sindroma (n = 32), sa stabilnim statusom osnovne bolesti. U novembru 2010. godine, 47 pacijenata, uključujući 35 ispitanika vakcinisanih godišnje tokom 2006-2010, vakcinisano je protiv gripa trovalentnom inaktiviranom split vakcinom, dok 52 pacijenta nisu prihvatili predloženu vakcinaciju u tom periodu. Potom je praćeno prisustvo virusnih (pre svega gripa) i bakterijskih infekcija, parametara aktivnosti bolesti (od dana vakcinacije do aprila 2011. godine), kao i titra antitela protiv virusa gripa A H1N1 kod vakcinisanih i nevakcinisanih pacijenata (korišćena je metoda – reakcija inhibicije hemaglutinacije).

Rezultati: Utvrdili smo značaj predisponirajućih faktora za nastanak gripa (tj. prethodne respiratorne infekcije i vakcinacije u poslednjih pet godina, starost, pol, vrsta i trajanje bolesti, lekovi, pušenje) kod ovih grupa pacijenata. Incidenca gripa ili bakterijskih komplikacija (bronhitis) među vakcinisanim pacijentima bila je značajno manja u odnosu na nevakcinisanu grupu. Važno je da nije bilo slučajeva pogoršanja osnovne bolesti. Poslednja vakcinacija 2010. smanjila je rizik od gripa za 87%, ali su prethodne bakterijske infekcije (bronhitis i pneumonija) značajno povećale rizik od gripa (12 puta).

Zaključak: U ovoj studiji smo pokazali efikasnost, dovoljnu imunogenost i bezbednost primene savremene vakcine protiv gripa kod pacijenata koji boluju od sistemskog eritematoznog lupusa, reumatoidnog artritisa ili Sjogrenovog sindroma.

Ključne reči: reumatoidni artritis, lupus eritematosus, Sjogrenov sindrom, vakcinacija protiv gripa

ABSTRACT

Introduction: Patients suffering from autoimmune rheumatic diseases have a significantly higher risk of developing various infections compared to the healthy population, especially older patients.

Material and methods: Our study included patients with systemic lupus erythematosus (n = 30), rheumatoid arthritis (n = 37) or Sjogren's syndrome (n = 32), with stable underlying disease status. In November 2010, 47 patients, including 35 subjects vaccinated annually during 2006-2010, were vaccinated against influenza with the trivalent inactivated split vaccine, while 52 patients did not accept the proposed vaccination during that period. Then the presence of viral (mainly influenza) and bacterial infections, disease activity parameters (from the day of vaccination until April 2011), as well as the antibody titer against the influenza A H1N1 virus in vaccinated and unvaccinated patients were monitored (the method used was the hemagglutination inhibition reaction).

Results: We determined the importance of predisposing factors for the onset of influenza (ie, previous respiratory infections and vaccinations in the last five years, age, sex, type and duration of illness, medications, smoking) in these groups of patients. The incidence of influenza or bacterial complications (bronchitis) among vaccinated patients was significantly lower compared to the unvaccinated group. It is important that there were no cases of exacerbation of the underlying disease. The last vaccination in 2010 reduced the risk of influenza by 87%, but previous bacterial infections (bronchitis and pneumonia) significantly increased the risk of influenza (12-fold).

Conclusion: In this study, we demonstrated the efficacy, sufficient immunogenicity and safety of the modern influenza vaccine in patients suffering from systemic lupus erythematosus, rheumatoid arthritis or Sjogren's syndrome.

Keywords: rheumatoid arthritis, lupus erythematosus, Sjogren's syndrome, vaccination against flu

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SAŽETAK

Vakcina protiv velikih boginja je bila najagresivnija vakcina koja je, mimo mnogobrojnih komplikacija koje je izazivala, dovela do eradikacije bolesti koja je imala smrtnost 30%.

Sve kasnije vakcine su imale mnogo manje komplikacija i neželjenih reakcija. O neželjenim reakcijama i komplikacijama svake pojedine vakcine treba biti detaljno obavešten i pacijentu predložiti česte neželjene reakcije (otok ili bol na mestu inokulacije).

Iako pretpostavljamo da niko neće doći da se vakciniše kad je bolestan, moramo imati na umu da se u današnje vreme zna da postoje razne vrste nedostatka imuniteta, koji ne moraju biti klinički prepoznati. Moramo znati koje vakcine su neophodne i bezbedne, kod kojih vakcina ne očekujemo komplikacije i koje možemo da damo bez velikog razmišljanja da li je osoba imunokompetentna ili ne. S druge strane moramo da znamo koje vakcine mogu da daju komplikacije i da se, pre davanja tih vakcina obavestimo kakvo je stanje imuniteta te osobe, da procenimo da li je u datoj situaciji bolje da bude ili da ne bude vakcinisana, da joj se vakcinacijom ne nanese šteta. Tj. pre vakcinacije potrebno je da se uzme detaljna anamneza i da se osoba pregleda.

Najjasniji primer, na kome treba da naučimo da je imunitet promenljiv i kada je i koja vakcinacija moguća, je infekcija virusom humane imunodeficiencije. Potrebno je znati kakav je prirodni tok infekcije, kakav je rezultat terapije infekcije, u kojoj se fazi terapije pacijent nalazi i koje je vakcine primio i kako je reagovao, u kojoj fazi infekcije je tada bio, da bi procenili koje je vakcine moguće dati, a da se ne poremeti imunološka ravnoteža i time ugrozi stanje zdravlja.

U cilju pravovremene vakcinacije pomaže nam pravilnik o vakcinaciji, u kome su navedene privremene i stalne kontraindikacije za vakcinaciju, kao i vodiči za vakcinaciju SZO koji se menjaju u skladu sa novim saznanjima.

Ključne reči: HIV infekcija, vakcinacija, kontraindikacije

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ABSTRACT

The smallpox vaccine was the most aggressive vaccine that, beyond many complications it caused, led to the eradication of the disease, which had a mortality rate of 30%.

All subsequent vaccines had far fewer complications and adverse reactions. Doctor should be informed in detail about adverse reactions and complications of each vaccine, and the patient should be informed about frequent adverse reactions (swelling or pain at the inoculation site).

Although we assume that no one will come to be vaccinated when they are sick, we must bear in mind that nowadays it is known that there are various types of immunity deficiencies, which do not have to be clinically recognized. We need to know which vaccines are necessary and safe, in which vaccines we do not expect complications, and which one we can give without much thinking whether the person is immunocompetent or not. On the other hand, we need to know which vaccines can give complications and, before giving these vaccines, to inform ourselves what the state of immunity of that person is, to assess whether it is better for him to be or not to be vaccinated, in order not to make him any harm. I.e. before vaccination, it is necessary to take a detailed medical history and have the person examined.

The clearest example, on which we need to learn that immunity is variable and when and what vaccination is possible, is infection with the human immunodeficiency virus. It is necessary to know what is the natural course of infection, what is actual state of the therapy, in what stage of the disease the patient is, what vaccines he received and how he reacted, at what stage of infection he was then, in order to assess which vaccines can be given, without disturbing the immune balance and thus worsen his state of health.

For the purpose of timely vaccination, we are assisted by the vaccination regulations, which outline temporary and permanent contraindications to vaccination, as well as WHO provide us with vaccination guidelines, that are changing in accordance with new knowledge.

Keywords: HIV infection, vaccination, contraindications

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PROBLEMS PERTAINING TO ACTIVE IMMUNIZATION IN PERSONS WITH PRIMARY AND SECONDARY IMMUNE DEFICIENCIES

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SAŽETAK

Aktivna imunizacija (vakcinacija) je jedan od osnovnih načina prevencije zaraznih bolesti. S obzirom da aktivna imunizacija deluje kontrolisanim pokretanjem imunskog odgovora na uzročnike bolesti i sledstvenim stvaranjem imunskog pamćenja, odgovarajuća funkcija imunskog sistema je preduslov za njen optimalan učinak. Sa druge strane, osobe koje pate od oboljenja ili stanja što se odlikuju nepotpunošću, oslabljenošću ili neadekvatnom regulacijom imunskih odgovora (primarne i sekundarne imunodefijencije) izložene su značajno većim rizicima u slučaju infekcija, te je kod njih potreba za vakcinacijom – a i dobrobit od nje – još veća nego u opštoj populaciji. Mogućnosti vakcinacije osoba sa imunodefijencijom se suštinski razlikuju između živih i neživih vakcina: dok su prve apsolutno kontraindikovane kod svih ozbiljnih imunodefijencija, druge se kod praktično svih takvih osoba mogu bezbedno primeniti, premda će njihov učinak potencijalno biti umanjen. Pa ipak, kod velike većine stanja imunodefijencije ili imunokompromitovanosti, izuzev onih najtežih, vakcinacija je i dalje visokoprotektivna, te se davanje svih vakcina koje nisu kontraindikovane snažno preporučuje. Osim toga, pojedina stanja, kao što je asplenija, iziskuju i primenu dodatnih vakcina kako bi se sprečile određene infekcije prema kojima su osobe pogođene takvim stanjima posebno osetljive. Usled svega navedenog utoliko više zabrinjavaju objavljeni podaci koji svedoče da značajan deo osoba sa primarnim i sekundarnim imunodefijencijama ostaje nevakcinisan, uključujući i vakcine za koje ne postoji nikakva kontraindikacija. Otud postoje razlozi da se bolje razumevanje specifičnosti aktivne imunizacije kod osoba sa različitim oboljenima ili stanjima koja se odražavaju na imunski system uvrsti među narodnozdravstvene prioritete.

Ključne reči: oslabljen imunitet, imunodefijencija, aktivna imunizacija

ABSTRACT

Active immunization (vaccination) is one of the principal methods of prevention of infectious disease. Since active immunization works by controlled eliciting of an immune response to causal agents and consequent creation of immune memory, adequate immune function is a prerequisite for its optimal effect. On the other hand, persons affected by disorders or conditions characterized by incomplete, weakened or poorly regulated immune responses (primary and secondary immune deficiencies) are at a significantly higher risk in the event of infections, and therefore need vaccination – and benefit from it – even more than the general population. The possibilities of vaccination of immunodeficient persons fundamentally differ between live and non-live vaccines: while the former are absolutely contraindicated in all substantial immune deficiencies, the latter can be applied safely in most patients, although their effect may be diminished. Nevertheless, in all but the most severe immunodeficient or immunocompromised states vaccination is still highly protective and administration of all permissible vaccines is strongly recommended. Moreover, certain conditions, such as asplenia, require additional vaccines in order to prevent infections where to affected people are particularly predisposed. In view of the above, published data signalling that a significant portion of persons with primary and secondary immune deficiencies does not get vaccinated even in the absence of contraindications is all the more cause for concern. There is, thus, a clear rationale to include a better understanding of specific problems of active immunization in various conditions affecting the immune system among public health priorities.

Keywords: weak immunity, immunodeficiency, active immunization

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COMORBIDITIES AMONG PEOPLE LIVING WITH HIV IN SERBIA

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SAŽETAK

HIV infekcija i AIDS se i dalje nalaze među najvećim problemima javnog zdravlja širom sveta, uprkos efikasnoj antiretrovirusnoj terapiji. Povoljni efekti antiretrovirusne terapije na sada praktično normalan životni vek ljudi koji žive sa HIV infekcijom primećuju se tokom poslednje dve decenije, tokom kojih je drastično smanjena incidencija AIDS definišućih stanja kao što su oportunističke infekcije i maligniteti, dok je incidenca neinfektivnih komorbiditeta u porastu. Ovi komorbiditeti uključuju kardiovaskularne bolesti, metaboličke poremećaje, hronične bolesti jetre i bubrega, poremećaje nervnog sistema, osteoporoze i maligne bolesti. Većina HIV pozitivnih osoba na antiretrovirusnim lekovima ima patološki nivo pokazatelja imunološke aktivacije, hroničnu inflamaciju i hiperkoagulabilno stanje, što je takođe karakteristično za HIV negativne osobe starije životne dobi i imunosenescentnog fenotipa. Iako je tačna etiologija ovih pojava nepoznata, postoji više mogućih patofizioloških mehanizama koji ih mogu objasniti, uključujući sindrom rezidualne imunološke disregulacije i uzgrednih dejstva antiretrovirusnih lekova. Ljudi u Srbiji koji žive sa HIV infekcijom nisu izuzetak kada su komorbiditeti u pitanju, jer vidimo sve veći broj starijih, imuno suprimiranih osoba sa oboljenjima koja nisu bila karakteristična za AIDS. Ovi trendovi zahtevaju da se zdravstvena služba donekle reorganizuje kako bi se zadovoljile nove šire potrebe ovih pacijenata koji više nemaju akutnu fatalnu infekciju, već hronično oboljenje. Cilj predavanja je da približi lekarima problematiku komorbiditeta kod ljudi koji žive sa HIV infekcijom, globalno i u Srbiji, kroz literaturne podatke i prikaze slučajeva iz kliničke prakse.

Ključne reči: HIV, Non-AIDS definišuće bolesti, antiretrovirusni lekovi

ABSTRACT

HIV and AIDS continue to be one of the major public health problems worldwide, despite potent antiretroviral therapy. Beneficial effects of antiretroviral therapy on the now practically normal life expectancy of people living with HIV are seen during the past two decades, during which the incidence AIDS defining illnesses such as opportunistic infections and malignancies have been dramatically reduced, whereas the non-infectious comorbidities have emerged. These comorbidities include cardiovascular diseases, metabolic disorders, chronic liver and renal diseases, nervous system disorders, osteoporosis, and malignancies. Most HIV positive individuals on antiretrovirals present with an abnormal level of immune activation, chronic inflammation, and hypercoagulable condition which is also characteristic of HIV negative individuals of older age and immunosenescent phenotype. Although the exact mechanism for these phenomena is unclear, there are multiple factors which may apply pathophysiologically, including the residual immune dysregulation syndrome and antiretrovirals alone. Serbian people living with HIV are no exception when it comes to comorbidities, as we are seeing increased number of older immunologically suppressed individuals with non-AIDS defining illnesses. These trends require that the health service must be somewhat reorganized to meet the new broader need of these patients who no longer have acute fatal infection but are living with a chronic condition.

The aim of this lecture is to bring doctors closer to the issue of comorbidities in people living with HIV globally and in Serbia, through literature data and presentation of cases from clinical practice.

Keywords: HIV, Non-AIDS illness, antiretrovirals

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