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GLOBALNA GEOGRAFIJA UZROČNIKA ENDOKARDITISA: ETIOLOGIJA I REZISTENCIJA U 21. VEKU

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SAŽETAK

Uvod/cilj: Etiologija infektivnog endokarditisa je raznolika i kompleksna. Značajno se razlikuje u zavisnosti od geografskog područja, socioekonomskih uslova, dostupnosti zdravstvene zaštite i prevalencije predisponirajućih faktora. Cilj ovog rada je analiza globalne geografske raspodele uzročnika infektivnog endokarditisa u 21. veku, sa fokusom na regionalne razlike u etiologiji, dijagnostici, terapiji i problemu antimikrobne rezistencije.
Metode: Sprovedena je sekundarna analiza podataka. U obradi podataka korišćena je deskriptivna statistika radi kvantifikovanja učestalosti uzročnika, zastupljenosti rezistentnih sojeva i regionalnih etioloških razlika.
Rezultati: U razvijenim regionima (Severna Amerika i Zapadna Evropa) dominira *Staphylococcus aureus*, često povezan sa zdravstvenom negom (30–35%) i visokom stopom MRSA rezistencije (do 28%). Nasuprot tome, u zemljama u razvoju i dalje su zastupljeniji streptokoki, uz perzistenciju reumatske bolesti srca. Dostupnost transezofagealne ehokardiografije (TEE) i hirurškog lečenja značajno je veća u razvijenim zemljama, što direktno utiče na nižu stopu mortaliteta (14–15%) u odnosu na regione sa ograničenim resursima (22%).
Zaključak: Infektivni endokarditis evoluirao je u bolest povezanu sa savremenom medicinom i starenjem populacije u razvijenim zemljama, dok u ostatku sveta ostaje bolest povezana sa nepovoljnim socioekonomskim uslovima. Visok mortalitet i rastuća antimikrobna rezistencija zahtevaju globalnu standardizaciju dijagnostike i lokalno prilagođene terapijske strategije.

Ključne reči: infektivni endokarditis, uzročnici, globalna rasprostranjenost, ehokardiografija

Uvod

Infektivni endokarditis (IE) predstavlja ozbiljno, potencijalno životno ugrožavajuće oboljenje koje karakteriše inflamacija i infekcija endokarda, prvenstveno srčanih zalistaka, ali i drugih struktura endokarda ili ugrađenih intrakardijalnih uređaja (1). Bolest nastaje kao posledica kolonizacije endokarda mikroorganizmima, najčešće bakterijskim, koji dospevaju u krvotok, pri čemu se formiraju vegetacije sastavljene od fibrina, trombocita i patogena. Klinički tok infektivnog endokarditisa varira u zavisnosti od uzročnika, osnovnog stanja srca, dijagnoze i lečenja i može biti akutan, subakutan ili hroničan, sa širokim spektrom simptoma – od nespecifičnih sistemskih znakova infekcije, poput febrilnosti i malaksalosti, do teških komplikacija kao što su srčana insuficijencija, embolijski događaji i multiorganska disfunkcija (2). Uprkos savremenim dijagnostičkim i terapijskim mogućnostima, infektivni endokarditis i dalje nosi visoku stopu mortaliteta i morbiditeta (3).

Etiologija infektivnog endokarditisa je raznolika i kompleksna. Značajno se razlikuje u zavisnosti od geografskog područja, socioekonomskih uslova, dostupnosti zdravstvene zaštite i prevalencije predisponirajućih faktora. Tradicionalno, streptokoki grupe viridans su bili najčešći uzročnici endokarditisa, naročito kod pacijenata sa ranijim oštećenjem zalistaka (4). Međutim, tokom poslednjih decenija primećen je značajan porast infekcija izazvanim *Staphylococcus aureus*, koji danas predstavlja najvažnijeg i najagresivnijeg uzročnika, uključujući i metilin-rezistentne sojeve (MRSA). Ovaj trend se

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GLOBAL GEOGRAPHY OF INFECTIVE ENDOCARDITIS PATHOGENS: ETIOLOGY AND RESISTANCE IN THE 21ST CENTURY

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SUMMARY

Introduction/Aim: The etiology of infective endocarditis is diverse and complex. It varies significantly depending on geographical region, socioeconomic conditions, healthcare availability, and the prevalence of predisposing factors. The aim of this paper is to analyze the global geographical distribution of infective endocarditis pathogens in the 21st century, focusing on regional differences in etiology, diagnostics, therapy, and antimicrobial resistance.
Methods: A secondary data analysis was conducted. Descriptive statistics were used to quantify pathogen frequency, the prevalence of resistant strains, and regional etiological differences.
Results: In developed regions (North America and Western Europe), *Staphylococcus aureus* predominates, often associated with healthcare settings (30–35%) and high rates of MRSA resistance (up to 28%). Conversely, in developing countries, streptococci remain more prevalent, alongside the persistence of rheumatic heart disease. The availability of transesophageal echocardiography (TEE) and surgical treatment is significantly higher in developed countries, which directly contributes to a lower mortality rate (14–15%) compared to resource-limited regions (22%).
Conclusion: Infective endocarditis has evolved into a disease associated with modern medicine and aging populations in developed countries, while in the rest of the world, it remains strongly associated with low socioeconomic conditions. High mortality and increasing resistance necessitate the global standardization of diagnostics and locally adapted therapeutic strategies.

Keywords: infective endocarditis, causative agents, global distribution, echocardiography

Introduction

Infective endocarditis (IE) is a serious, potentially life-threatening disease, characterized by inflammation and infection of the endocardium, primarily heart valves, but also other structures of the endocardium or implanted intracardiac devices (1). This disease occurs as the consequence of the colonization of the endocardium by microorganisms (often bacterial) that enter the bloodstream, where vegetations composed of fibrin, platelets and pathogens are formed. The clinical course of infective endocarditis varies depending on the causative agent, underlying heart condition, diagnosis and treatment and it can be acute, subacute or chronic, with a wide range of symptoms –from non-specific signs of infection, such as fever and malaise, to severe complications (heart failure, embolic events and multiorgan dysfunction) (2). Despite modern diagnostic and therapeutic possibilities, infective endocarditis still carries high mortality and morbidity rates (3).

The etiology of infective endocarditis is diverse and complex. It varies significantly depending on the geographic region, socioeconomic conditions, availability of health care and prevalence of predisposing factors. Traditionally, viridans streptococci are the most common causes of endocarditis, especially in patients with the previous heart valve damage (4). However, in recent decades, there has been a significant increase in infections caused by *Staphylococcus aureus*, which are the most important and aggressive agents today, including the methicillin-resistant strains (MRSA), which is associated

dovodi u vezu sa porastom invazivnih medicinskih procedura, učestalijom primenom intravaskularnih kateterai intravenske upotrebe droga (5).

Globalna distribucija uzročnika endokarditisa pokazuje izražene regionalne razlike. U razvijenim zemljama Severne Amerike, Zapadne Evrope i Skandinavije dominiraju stafilokokne infekcije, često povezane sa zdravstvenom negom (engl. *healthcare-associated endocarditis*), dok su u siromašnijim i nerazvijenijim zemljama sa nižim i srednjim prihodima i dalje češći streptokoki i enterokoki, naročito zbog reumatske bolesti srca koja ostaje jedan od značajanih faktora rizika. Ove razlike odražavaju ne samo varijacije u epidemiologiji patogena, već i razlike u dostupnosti preventivne zdravstvene zaštite, stomatološke nege i ranog lečenja infekcija (6).

Lečenje infektivnog endokarditisa je kompleksno i teško. Poseban izazov u savremenom lečenju infektivnog endokarditisa predstavlja rastuća antimikrobna rezistencija. Pojava multirezistentnih bakterijskih sojeva, uključujući MRSA (meticilin-rezistentni *S. aureus*), vankomicin-rezistentne enterokoke (VRE) i gram-negativne patogene sa proširenom rezistencijom, značajno otežava terapijske procedure i utiče na ishod bolesti. Neadekvatna i prekomerna upotreba antibiotika, dodatno doprinosi ovom globalnom problemu, čineći izbor efikasne empirijske terapije sve zahtevnijim.

Dijagnoza infektivnog endokarditisa se postavlja kombinacijom kliničkih kriterijuma, mikrobioloških nalaza i vizualizacionih metoda, pri čemu modifikovani Duke kriterijumi predstavljaju standardizovani dijagnostički okvir (7).

Hemokulturesu ključne za identifikaciju uzročnika i određivanje antimikrobne osetljivosti, dok ehokardiografija (zlatni standard) ima najvažniju slikovnu ulogu u detekciji vegetacija i proceni oštećenja srčanih struktura. Ipak, u pojedinim regionima sveta ograničen pristup savremenim dijagnostičkim metodama može dovesti do kašnjenja u postavljanju dijagnoze i započinjanja adekvatne terapije.

S obzirom da etiologija infektivnog endokarditisa nije univerzalna i razlikuje se od geografskog regiona, ekonomskog statusa i rastućeg problema antimikrobne rezistencije, neophodno je sagledati ovu bolest u širem epidemiološkom i geografskom kontekstu. Razumevanje regionalnih obrazaca uzročnika i njihove rezistencije predstavlja osnovu za unapređenje preventivnih strategija, racionalnu primenu antibiotika i optimizaciju terapijskih protokola.

Cilj ovog rada je da prikaže i analizira globalnu geografsku raspodelu uzročnika infektivnog endokarditisa u 21. veku, sa posebnim osvrtom na etiološke razlike između različitih regiona sveta. Akcenat je stavljen na promene u dominaciji mikroorganizama, učestalost pojedinih patogena i njihov odnos sa savremenim faktorima rizika, uključujući invazivne medicinske procedure i upotrebu intravaskularnih uređaja. Kao glavni izazov u lečenju ističe se problem antimikrobne rezistencije, njen uticaj na izbor terapije i ishode lečenja, kao i na značaj regionalno prilagođenih dijagnostičkih i terapijskih strategija u savremenoj kliničkoj praksi.

Metode

U ovom radu sprovedena je sekundarna analiza podataka o infektivnom endokarditisu sa ciljem sagledavanja globalne geografske raspodele uzročnika, etioloških obrazaca i problema antimikrobne rezistencije u 21. veku. Posebna pažnja posvećena je poređenju razvijenih i nerazvijenih regiona, kao i uticaju zdravstvenih sistema na dijagnostiku i terapiju infektivnog endokarditisa. Prva faza istraživanja obuhvatila je sistematsku pretragu naučne literature u međunarodnim bazama podataka kao što su PubMed, Scopus, Web of Science i Google Scholar. Pretraga je obuhvatila radove objavljene u periodu od 2005. do 2025. godine, sa fokusom na epidemiologiju infektivnog endokarditisa, etiološke uzročnike, antimikrobnu rezistenciju i regionalne razlike u kliničkoj praksi. Uključeni su originalni istraživački radovi, meta-analize, sistematski pregledi i relevantne kliničke studije na engleskom jeziku.

U okviru ove sekundarne analize podataka uključeni su podaci iz velikih multicentričnih i nacionalnih epidemioloških studija, pružajući uvid u incidenciju i etiologiju infektivnog endokarditisa širom sveta. Analiza je obuhvatila vremenske promene u etiološkoj strukturi, sa posebnim akcentom na porast udela stafilokoknih infekcija i zdravstveno-asociranog endokarditisa. Posebno su razmotrene razlike u pristupu lečenju koje proističu iz regionalne dostupnosti antibiotika i dijagnostičkih metoda (8). Podaci o rezistenciji uzročnika infektivnog endokarditisa prikupljeni su iz studija koje su se bavile mikrobiološkim profilima izolovanih patogena i njihovom osetljivošću na antibiotike. Poseban fokus stavljen je na meticilin-rezistentni *Staphylococcus aureus* (MRSA) globalno najvažniji rezistentni patogen, vankomicin-rezistentne enterokoke (posebno *Enterococcus faecium* - VREfm) i druge multirezistentne mikroorganizme.

with the increase in invasive medical procedures, more frequent use of intravascular catheters and intravenous drug use (5).

The global distribution of causative agents of endocarditis shows pronounced regional differences. In the developed countries of North America, Western Europe and Scandinavia, staphylococcal infections are dominant, and often associated with healthcare, while in poorer and developing countries with low and middle incomes, streptococci and enterococci are still more common, especially due to rheumatic heart disease, which remains one of significant factors. These differences reflect not only variations in the etiology of pathogens, but also differences in the availability of preventive health care, dental care and early treatment of infections (6).

The treatment of infective endocarditis is complex and difficult. A special challenge in the modern treatment of infective endocarditis is the growing antimicrobial resistance. The emergence of multi-resistant bacterial strains, including MRSA (methicillin-resistant *S.aureus*), vancomycin-resistant enterococci (VRE) and extensively drug-resistant gram-negative pathogens, significantly complicates therapeutic procedures and affects the outcome of the disease. The inadequate and excessive use of antibiotics further contributes to this global problem, thus making the selection of effective empiric therapy increasingly demanding.

The diagnosis of infective endocarditis is established using the combination of clinical criteria, microbiological findings and visualization methods, where modified Duke criteria represent a standardized diagnostic framework (7).

Blood cultures are crucial for identifying the causative agent and determining antimicrobial sensitivity, while echocardiography (gold standard) has the most important imaging role in the detection of vegetations and assessment of damage to cardiac structures. However, in certain regions of the world, limited access to modern diagnostic methods can lead to delays in establishing the diagnosis and starting adequate therapy.

Given that the etiology of infective endocarditis is not universal and varies depending on the geographical region, economic status, and the growing problem of antimicrobial resistance, it is necessary to consider this disease in a broader epidemiological and geographical context. Understanding the regional patterns of pathogens and their resistance is the basis for improving preventive strategies, rational use of antibiotics and optimization of therapeutic protocols.

The aim of this study is to present and analyze the global geographical distribution of the causative agent of infective endocarditis in the 21st century, with special reference to etiological differences between different regions of the world. Emphasis is placed on changes related to the dominance of microorganisms, the frequency of certain pathogens and their relationship with modern risk factors, including invasive medical procedures and the use of intravascular devices. The main challenge in the treatment is the problem of antimicrobial resistance, whose influence on the selection of therapy and treatment outcomes is also considered. In addition, the significance of regionally adapted diagnostic and therapeutic strategies in modern clinical practice is pointed to.

Methods

In this study, the secondary analysis of data on infective endocarditis was conducted with the aim of realizing the global geographical distribution of causative agents, etiological patterns and the problem of antimicrobial resistance in the 21st century. A special attention was paid to the comparison of developed and developing regions, as well as to the influence of healthcare systems on the diagnosis and treatment of infective endocarditis. The first phase of the research included a systematic search of scientific literature in international databases such as PubMed, Scopus, Web of Science and Google Scholar. The search included studies published from 2005 to 2025, with a focus on the epidemiology of infective endocarditis, etiological agents, antimicrobial resistance and regional differences in clinical practice. Original scientific papers, meta-analyses, systematic reviews and relevant clinical studies published in English were included.

The secondary data analysis included data from large multicenter and national epidemiological studies, providing insight into the incidence and etiology of infective endocarditis worldwide. The analysis included temporal changes in the etiological structure, with special emphasis on the increase in the share of staphylococcal infections and healthcare-associated endocarditis. Differences related to the access to treatment resulting from the regional availability of antibiotics and diagnostic methods were particularly discussed (8). Data on the resistance of causative agents of endocarditis were obtained from

U obradi podataka korišćena je deskriptivna statistika kako bi se kvantifikovala učestalost uzročnika, zastupljenost rezistentnih sojeva i regionalne etiološke razlike.

Pošto se rad temelji isključivo na analizi sekundarnih (već objavljenih) podataka, nije bilo potrebe za etičkim odobrenjem ili uključivanjem ispitanika. Tokom istraživanja strogo su poštovani naučno-etički principi (9).

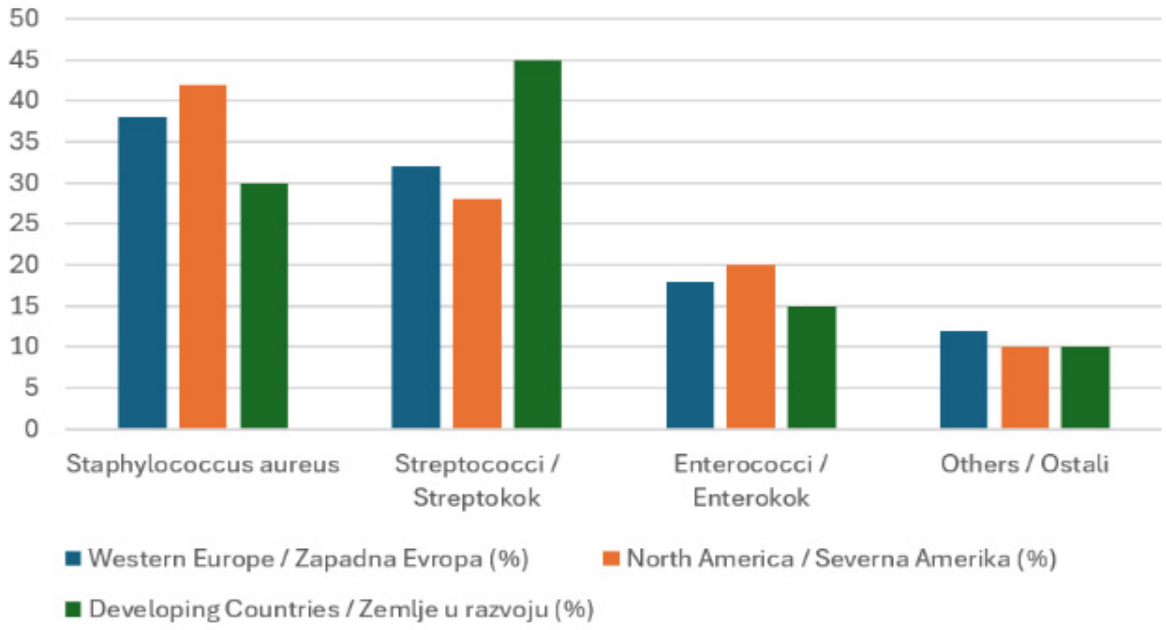
Rezultati

Analiza literaturnih podataka pokazuje da postoji evidentna regionalna razlika u dominantnim uzročnicima infektivnog endokarditisa. U razvijenim zemljama Severne Amerike i Zapadne Evrope, *Staphylococcus aureus* predstavlja najčešći uzrok infektivnog endokarditisa, dok su u zemljama sa nižim socioekonomskim statusom i dalje zastupljeniji streptokoki viridans grupe (grafikon 1).

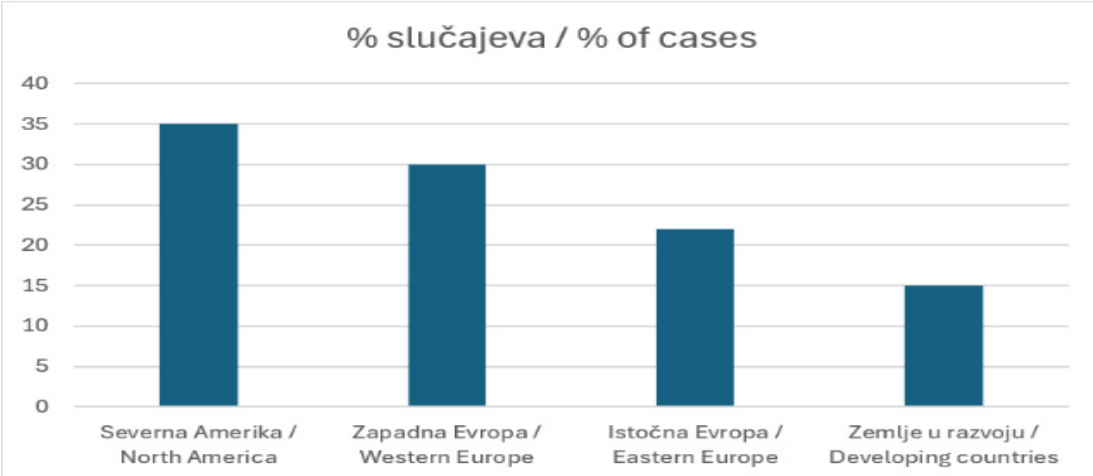
Najveća učestalost zdravstveno-asociranog infektivnog endokarditisa je zabeležena u Severnoj Americi (35% svih slučajeva infektivnog endokarditisa), zatim u Zapadnoj Evropi (30%), Istočnoj Evropi (22%) i u zemljama u razvoju (15%) (grafikon 2). Zdravstveno-asocirani infektivni endokarditis češće se javlja kod starije populacije, kao i kod lica sa većim brojem komorbiditeta i češćom hospitalizacijom.

Analiza rezistencije pokazuje značajne regionalne razlike u prisustvu multirezistentnih sojeva,

Grafikon 1. Procentualno učešće najčešćih uzročnika infektivnog endokarditisa po regionima



Grafikon 2. Prevalencija zdravstveno-asociranog infektivnog endokarditisa u ukupnoj strukturi obolevanja prema geografskim regionima



studies that dealt with the microbiological profiles of isolated pathogens and their sensitivity to antibiotics. Special focus was placed on methicillin-resistant *Staphylococcus areus* (MRSA), which is the most important resistant pathogen globally, vancomycin-resistant enterococci (especially *Enterococcus faecium* – VREfm) and other multiresistant microorganisms.

Descriptive statistics was used for the analysis of data in order to quantify the frequency of causative agents, the presence of resistant strains and regional etiological differences.

Since this study is based solely on the analysis of secondary (already published) data, there was no need for ethical approval or the inclusion of subjects. Scientific-ethical principles were strictly adhered to during research (9).

Results

The analysis of literature data shows that there is an evident regional difference in the dominant causative agents of infective endocarditis. In the developed countries of North America and Western Europe, *Staphylococcus aureus* is the most common cause of infective endocarditis, while in countries with a lower socioeconomic status, viridans streptococci are still more prevalent (Figure 1).

The highest frequency of healthcare-associated infective endocarditis is registered in North America (35% of all cases of infective endocarditis), followed

Figure 1. Percentage distribution of the most common causes of infectious endocarditis by regions

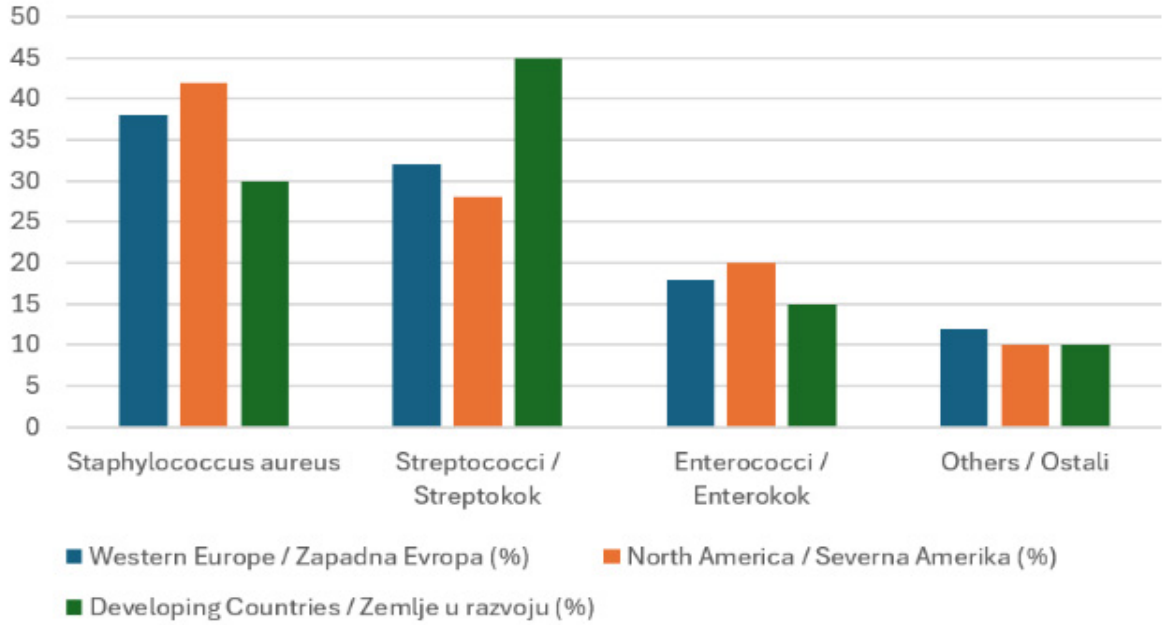
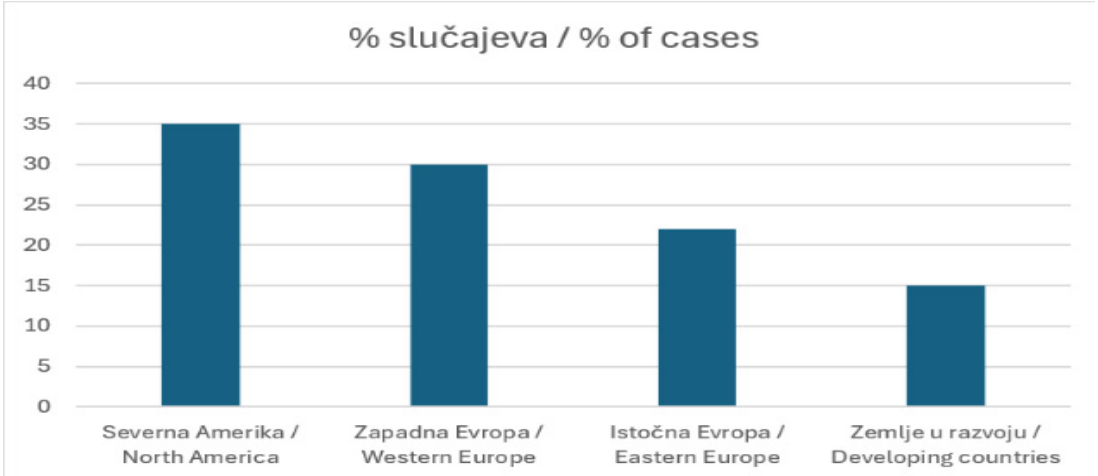


Figure 2. Prevalence of healthcare-associated infective endocarditis in the total disease structure by geographical region

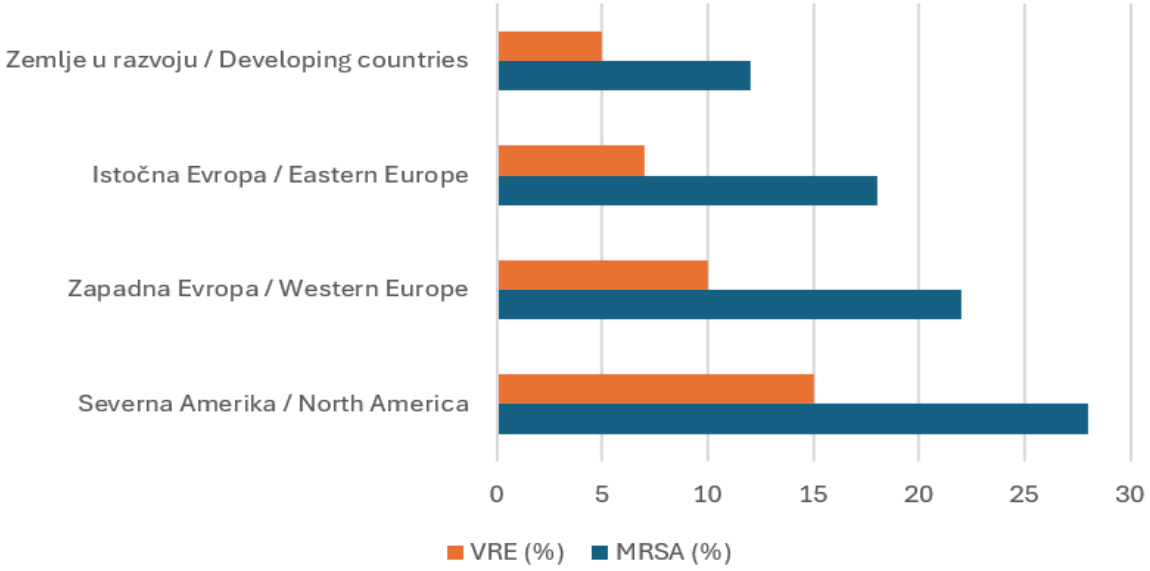


posebno kod stafilokoknih i enterokoknih infekcija. Učestalost MRSA među *Staphylococcus aureus* izolatima je najveća u Severnoj Americi (28%), zatim u Zapadnoj Evropi (22%), Istočnoj Evropi (18%) i u zemljama u razvoju (12%) (grafikon 3). Vankomicin-rezistentni enterokoki (VRE) dominiraju u Severnoj Americi (15%), dok su ređi u Zapadnoj Evropi (10%), Istočnoj Evropa (7%) i u zemljama u razvoju (5%).

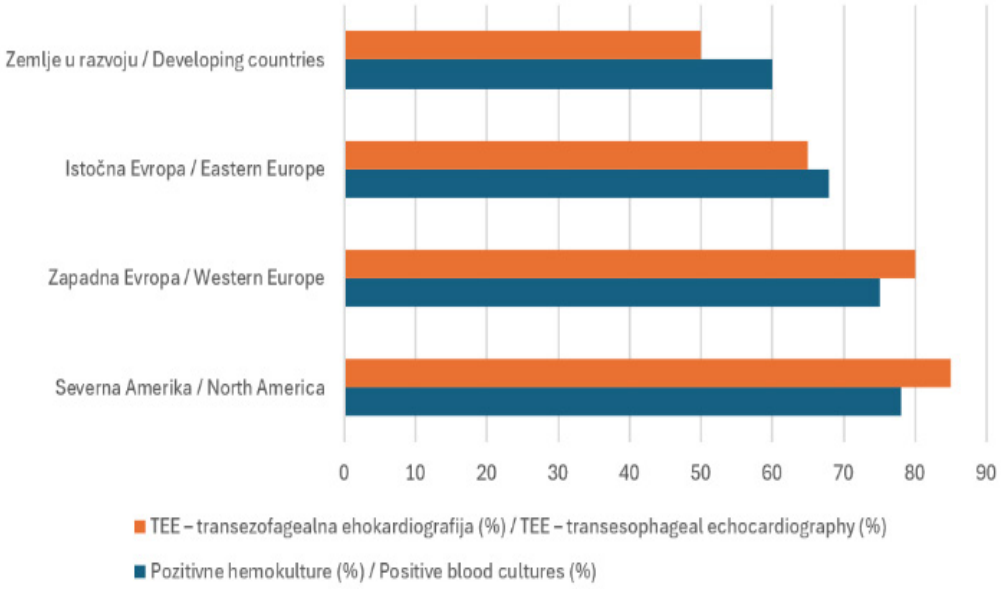
U svim analiziranim regionima, transtorakalna i transezofagealna ehokardiografija predstavljaju osnovne dijagnostičke metode. Međutim, dostupnost naprednih dijagnostičkih procedura značajno varira. Upotreba transezofagealne ehokardiografije (TEE) najčešća je u Severnoj Americi (85% pacijenata) i Zapadnoj Evropi (80%), a zatim u Istočnoj Evropi (65%) i zemljama u razvoju (50%) (grafikon 4). Pozitivne hemokulture pre započinjanja terapije su najčešće u Severnoj Americi (78%) i Zapadnoj Evropi (75%), a zatim u Istočnoj Evropi (68%) i u zemljama u razvoju (60%).

Rezultati pokazuju da je hirurško lečenje najčešće u razvijenim zemljama, što se dovodi u vezu sa boljom dostupnošću kardiohirurških centara i ranijim prepoznavanjem komplikacija. Učestalost

Grafikon 3. Procentualna zastupljenost rezistentnih uzročnika infektivnog endokarditisa među regionima



Grafikon 4. Dijagnostičke metode kod infektivnog endokarditisa po regionima



by Western Europe (30%), Eastern Europe (22%) and developing countries (15%) (Figure 2). Healthcare-associated endocarditis occurs more frequently in the elderly population, as well as in persons with a greater number of comorbidities and more frequent hospitalizations.

The analysis of resistance shows significant regional differences related to the presence of multi-resistant strains, especially in staphylococcal and enterococcal infections. Among Staphylococcus aureus isolates, MRSA is the highest in North America (28%), and somewhat lower in Western Europe (22%), Eastern Europe (18%) and developing countries (12%) (Figure 3). Vancomycin-resistant enterococci (VRE) are dominant in North America (15%), and less present in Western Europe (10%), Eastern Europe (7%) and developing countries (5%).

In all analyzed regions, transthoracic and transesophageal echocardiography are the main diagnostic methods. However, the availability of advanced diagnostic procedures varies considerably. The use of transesophageal echocardiography (TEE) is most common in North America (85% of patients) and Western Europe (80%), followed by Eastern Eu-

Figure 3. Percentage of resistant pathogens in infective endocarditis by regions

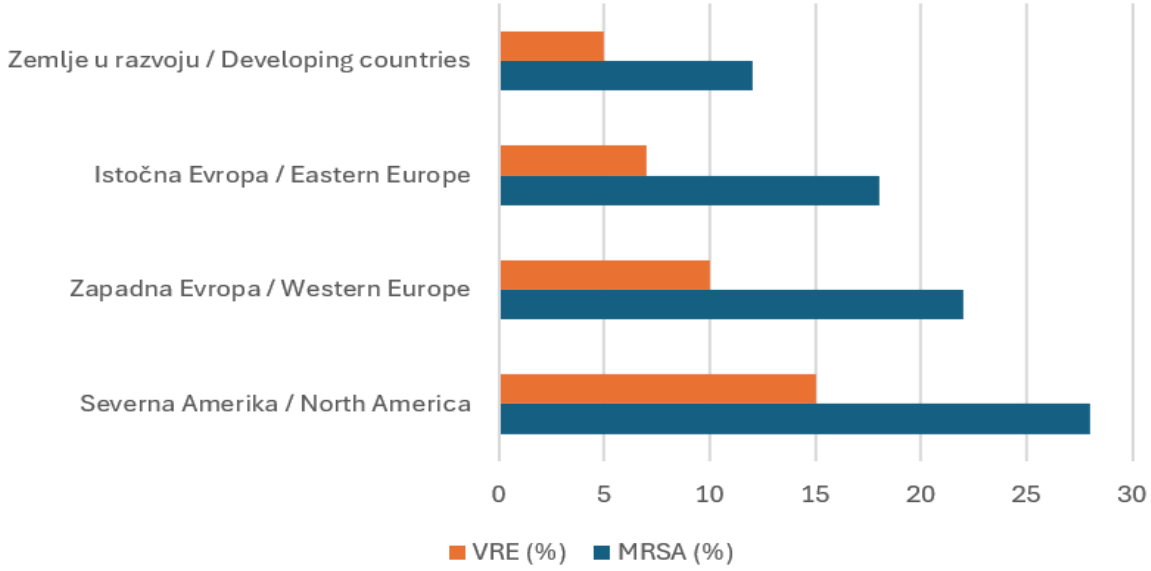
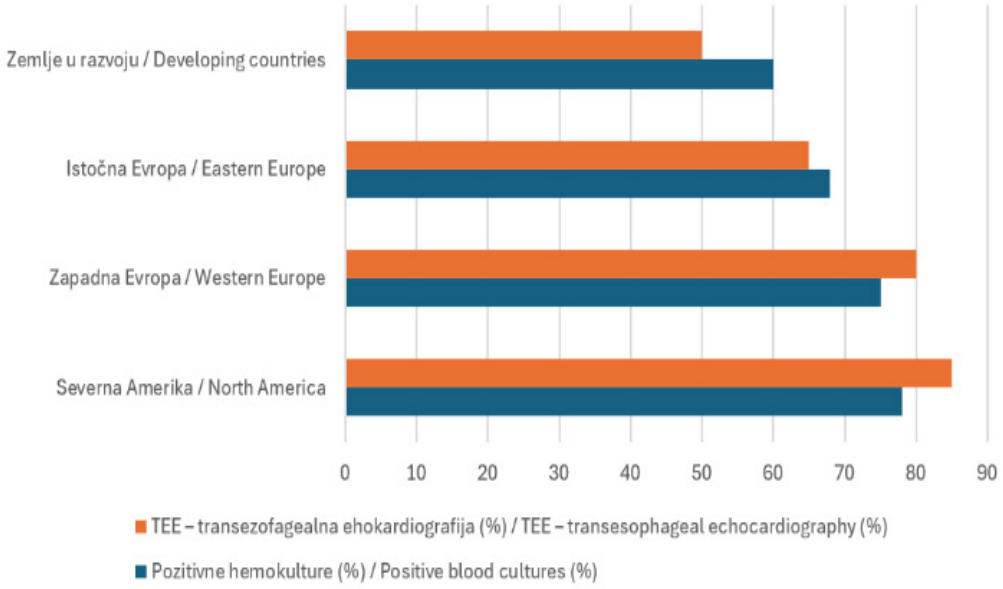


Figure 4. Diagnostic methods in infective endocarditis by regions

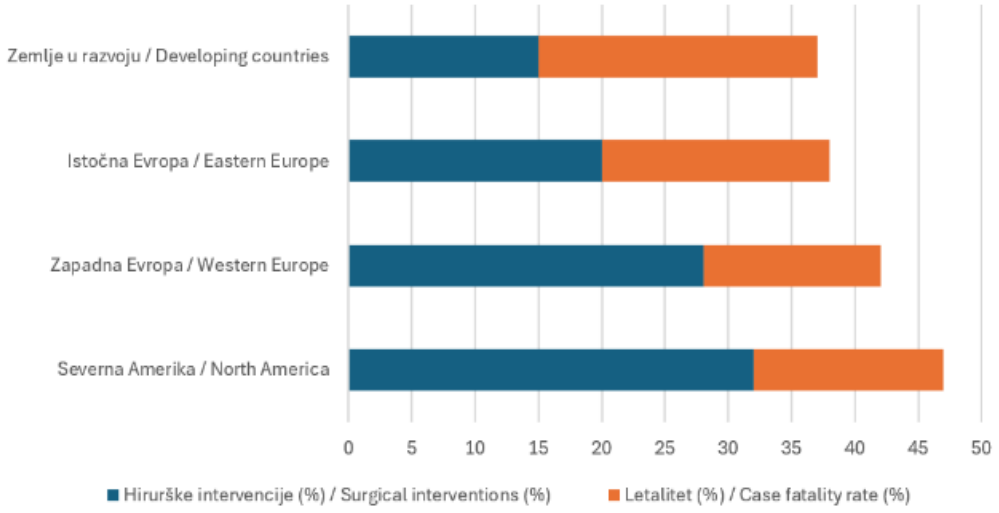


hirurških intervencija je najveća u Severnoj Americi (32%), zatim u Zapadnoj Evropi (28%), Istočnoj Evropi (20%) i u zemljama u razvoju (15%) (grafikon 5). Hospitalni letalitet usled infektivnog endokarditisa je bio najviši u Istočnoj Evropi (18%) i u zemljama u razvoju (22%), dok je niži u Severnoj Americi (15%) i u Zapadnoj Evropi (14%).

Diskusija

Rezultati ovog rada ukazuju na izražene i kompleksne regionalne razlike u etiologiji, epidemiologiji, dijagnostici, terapijskim pristupima i ishodima infektivnog endokarditisa u 21. veku. Ove razlike predstavljaju posledicu delovanja brojnih faktora, uključujući demografske promene, nivo razvoja zdravstvenog sistema, dostupnost savremenih dijagnostičkih i terapijskih procedura, kao i globalni

Grafikon 5. Učestalost hirurških intervencija i letalitet kod infektivnog endokarditisa (%)



porast antimikrobne rezistencije kao jednog od najvećih izazova. Jedan od najznačajnijih nalaza odnosi se na promenu etiološkog spektra infektivnog endokarditisa. U razvijenim zemljama Severne Amerike i Zapadne Evrope, *Staphylococcus aureus* se jasno izdvaja kao najčešći uzročnik, što predstavlja značajan pomak u odnosu na ranije decenije, kada su streptokoki viridans grupe bili najčešći patogeni. Ova promena može se dovesti u vezu sa starenjem populacije, visokom učestalošću hroničnih bolesti, čestom primenom intravaskularnih katetera, hemodijalize i implantabilnih kardijalnih uređaja (5). Takođe, porast intravenske upotrebe droga u pojedinim regionima dodatno doprinosi većoj učestalosti stafilokoknog endokarditisa, naročito kod mlađih pacijenata (10).

Nasuprot tome, u zemljama sa nižim i srednjim prihodima i dalje je izražena visoka učestalost streptokoknog endokarditisa, što se delimično može objasniti perzistencijom reumatske bolesti srca kao značajnog predisponirajućeg faktora (9). Nedovoljna dostupnost preventivne zdravstvene zaštite, ograničen pristup redovnoj stomatološkoj nezi i kasno lečenje infekcija gornjih disajnih puteva dodatno povećavaju rizik od nastanka bolesti. Ovi nalazi naglašavaju značaj socijalnih i ekonomskih determinanti zdravlja u formiranju globalne epidemiologije infektivnog endokarditisa.

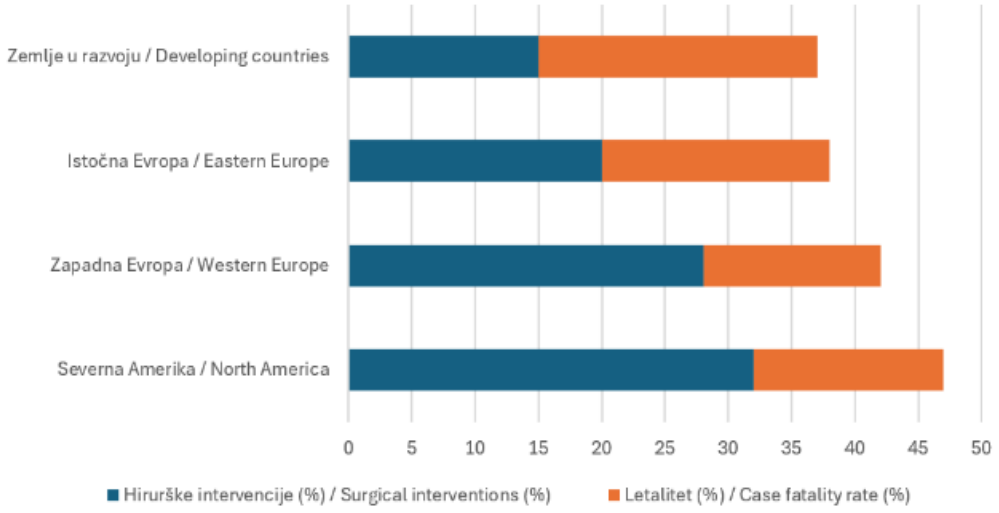
Problem antimikrobne rezistencije predstavlja jedan od najvećih izazova u savremenom lečenju infektivnog endokarditisa u 21. veku. Rezultati istraživanja ukazuju na višu učestalost meticilin-rezistentnog *Staphylococcus aureus* (MRSA), globalno najvažnijeg rezistentnog patogena u infektivnom endokarditisu, koji je povezan sa većom stopom komplikacija, dužom hospitalizacijom i povećanom smrtnošću, kao i na prisustvo vankomicin-rezistentnih enterokoka u razvijenim regionima, naročito u Severnoj Americi. Ovaj trend se može povezati sa dugogodišnjom i često nekontrolisanom primenom antibiotika, kako u bolničkim uslovima, tako i u ambulantnoj praksi. Antimikrobna rezistencija značajno komplikuje terapijski pristup, produžava trajanje hospitalizacije i povećava rizik od neželjenih ishoda, uključujući smrtni ishod (6).

U regionima sa ograničenim resursima, niža do-

rope (65%) and developing countries (50%) (Figure 4). Positive blood cultures before starting the therapy are most common in North America (78%) and Western Europe (75%), followed by Eastern Europe (68%) and developing countries (60%).

The results show that surgical treatment is most common in developed countries, which is associated with better availability of cardiac surgery centers and earlier recognition of complications. The frequency of surgical interventions is highest in North America (32%), and much lower in Western Europe (28%), Eastern Europe (20%) and in developing countries (15%) (Figure 5). Hospital mortality caused by infective endocarditis was highest in Eastern Europe (18%) and in developing countries (22%), while it was much lower in North America (15%) and Western Europe (14%).

Figure 5. Frequency of surgical interventions and case fatality rate in infective endocarditis (%)



Discussion

The results of this study point to pronounced and complex regional differences related to etiology, epidemiology, diagnostics, therapeutic approaches and outcomes of infective endocarditis in the 21st century. These differences are the result of the action of numerous factors, including demographic changes, the level of development of the health system, the availability of modern diagnostic and therapeutic procedures, as well as the global increase in antimicrobial resistance as the biggest challenge. One of the most significant findings refers to the change in the etiological spectrum of infective endocarditis. In developed countries of North America and Western Europe, *Staphylococcus aureus* clearly stands out as the most common causative agent, which represents a significant shift compared to previous decades, when viridans streptococci were the most common pathogens. The change can be associated with the aging of the population, the high frequency of chronic diseases, the frequent use of intravascular catheters, hemodialysis and implantable cardiac devices (5). Also, the increase in intravenous drug use in certain regions additionally contributes to the higher frequency of staphylococcal endocarditis, especially in younger patients (10).

In contrast, in low- and middle-income countries, high frequency of streptococcal endocarditis is still pronounced, which can be partly explained by the persistence of rheumatic heart disease as a significant predisposing factor (9). The insufficient availability of preventive health care, limited access to regular dental care and late treatment of upper respiratory tract infections further increase the risk of developing the disease.

The problem of antimicrobial resistance represents one of the greatest challenges in the modern treatment of infective endocarditis in the 21st century. Research results point to the higher frequency of methicillin-resistant *Staphylococcus aureus (MRSA)*, the most important resistant pathogen in infective endocarditis at the global level, which is associated with a higher rate of complications, longer hospitalization and high mortality, and vancomycin-resistant enterococci in developed regions, especially in North America. This trend can be associated with the long-term and often uncontrolled use of antibiotics, both in hospital conditions and in outpa-

kumentovana stopa rezistencije ne mora pokazati realno stanje, već može biti posledica malog broja mikrobioloških analiza i ograničene laboratorijske infrastrukture. U takvim uslovima, empirijska terapija se često sprovodi bez preciznog poznavanja uzročnika i njegove osetljivosti, što može doprineti neuspehu terapije i daljem razvoju rezistencije. Ovi nalazi ukazuju na potrebu za jačanjem mikrobioloških kapaciteta i standardizacijom dijagnostičkih procedura na globalnom nivou (11).

Dijagnostika infektivnog endokarditisa predstavlja poseban izazov zbog često nespecifičnih kliničkih simptoma i varijabilnog toka bolesti. U razvijenim zdravstvenim sistemima, široka dostupnost transezofagealne ehokardiografije, naprednih slikovnih metoda i savremenih laboratorijskih testova omogućava ranije i preciznije postavljanje dijagnoze. Suprotno tome, u regionima sa slabije razvijenom zdravstvenom infrastrukturom, dijagnoza se često postavlja kasno, kada su već prisutne ozbiljne komplikacije poput embolijskih događaja ili srčane insuficijencije (12). Ovakva kašnjenja direktno utiču na lošije terapijske ishode i višu stopu mortaliteta (1,11).

Terapijski pristupi infektivnom endokarditisu značajno variraju širom sveta zbog dostupnosti resursa, finansijskih ograničenja i zdravstvenih sistema. U razvijenim zemljama, multidisciplinarni timski pristup, koji uključuje kardiologe, mikrobiologe, infektologe i kardiohirurge, postaje standard u lečenju infektivnog endokarditisa (1). Ovakav pristup omogućava pravovremeno donošenje odluka o hirurškoj intervenciji, optimizaciju antimikrobne terapije i bolju kontrolu komplikacija. U regionima sa ograničenim resursima, ovakav model lečenja često nije dostupan, što može predstavljati veliki problem za tok bolesti.

Hirurško lečenje predstavlja ključni terapijski modalitet kod određenog broja pacijenata, naročito onih sa teškim valvularnim oštećenjima, perzistentnom bakterijemijom ili ponovljenim embolijskim događajima. Više od 50% pacijenata sa infektivnim endokarditisom u razvijenim zemljama podvrgava se hirurškoj intervenciji (9). Veća učestalost hirurških intervencija u razvijenim zemljama može ukazivati na bolju dostupnost specijalizovanih centara, ali i na agresivniji terapijski pristup. S druge strane, niže stope hirurškog lečenja u zemljama u razvoju često su posledica kasnog upućivanja pacijenata ili nedostatka tehničkih i kadrovskih kapaciteta, što negativno utiče na prognozu.

Mortalitet povezan sa infektivnim endokarditisom i dalje ostaje visok širom sveta, uprkos napretku medicine (6,9). Veće stope smrtnosti u regionima sa slabije razvijenim zdravstvenim sistemima naglašavaju značaj ranog prepoznavanja bolesti, adekvatne terapije i organizacije zdravstvene zaštite. Ovi podaci ukazuju na potrebu za globalnim strategijama koje bi unapredile prevenciju, dijagnostiku i lečenje infektivnog endokarditisa, uz uvažavanje lokalnih specifičnosti.

Neka istraživanja ukazuju da infektivni endokarditis više nije bolest mlađih osoba sa urođenim srčanim manama (kako je bilo u prošlosti), već sve češće pogađa stariju populaciju (iznad 65–70 godina) (13). Kod starijih osoba glavni faktori rizika su degenerativne promene zalistaka, dijabetes, maligniteti i češći kontakti sa zdravstvenim sistemom (bolničke infekcije). Ovi pacijenti često imaju atipične simptome, što dovodi do kasnijeg postavljanja dijagnoze. Stariji pacijenti ređe se upućuju na hirurško lečenje zbog visokog rizika i komorbiditeta i imaju lošiju prognozu u poređenju sa mlađom populacijom.

Prevencija infektivnog endokarditisa predstavlja važan, ali često zanemaren aspekt zdravstvene zaštite. Edukacija pacijenata sa visokim rizikom, racionalna primena antibiotika i unapređenje bolničke kontrole infekcija ključni su elementi u smanjenju incidencije bolesti (1,8). Takođe, kontinuirana edukacija zdravstvenih radnika o savremenim smernicama i obrascima rezistencije može doprineti boljem upravljanju ovom bolešću.

Uprkos značajnom napretku u razumevanju patogeneze i terapije infektivnog endokarditisa, rezultati ovog rada jasno ukazuju da regionalne razlike i dalje predstavljaju ozbiljan izazov (10). Razvoj međunarodnih vodiča koji uzimaju u obzir lokalnu epidemiologiju i obrasce rezistencije, kao i jačanje zdravstvenih sistema u nerazvijenim regionima, predstavljaju ključne korake ka smanjenju globalnog tereta ove bolesti. Dalja istraživanja, međunarodna saradnja i ulaganje u zdravstvenu infrastrukturu neophodni su za unapređenje ishoda i kvaliteta života pacijenata obolelih od infektivnog endokarditisa.

Zaključak

Rezultati istraživanja potvrđuju da je infektivni endokarditis u 21. veku doživeo značajnu epidemiološku transformaciju, obeleženu dominacijom stafilokoka i porastom rezistentnih sojeva u razvijenim regionima. Ipak, perzistencija reumatske bolesti srca i ograničeni dijagnostički resursi u zemljama u

tient practice. Antimicrobial resistance significantly complicates the therapeutic approach, prolongs the duration of hospitalization and increases the risk of adverse outcomes, including mortality (6).

In regions with limited resources, the lower registered resistance rate may not reflect the real situation, but may be the consequence of a small number of microbiological analyses and limited laboratory infrastructure. In these conditions, empiric therapy is often implemented without precise knowledge of the causative agent and its sensitivity, which could contribute to the failure of therapy and the further development of resistance. These findings point to the need to strengthen microbiological capacities and standardize diagnostic procedures at the global level (11).

The diagnosis of infective endocarditis is a particular challenge due to frequently non-specific clinical symptoms and variable course of the disease. In developed healthcare systems, the wide availability of transesophageal echocardiography, advanced imaging methods, and modern laboratory tests enable earlier and more accurate diagnosis. In contrast, in regions with a less developed healthcare infrastructure, diagnosis is often established late, when serious complications such as embolic events or heart failure are already present (12). Such delays directly influence worse therapeutic outcomes and a higher mortality rate (1,11).

Therapeutic approaches to infective endocarditis vary significantly worldwide due to the availability of resources, financial constraints, and healthcare systems. In developed countries, a multidisciplinary team approach, which includes cardiologists, microbiologists, infectious disease specialists and cardiac surgeons, is becoming the standard in the treatment of infective endocarditis (1). This approach enables timely decision making on surgical intervention, optimization of antimicrobial therapy and better control of complications. In regions with limited resources, this model of treatment is often not available, which can be a major problem for the course of the disease.

Surgical treatment is a key form of therapy in a certain number of patients, especially those with severe valvular damage, persistent bacteremia, or repeated embolic events. More than 50% of patients with infective endocarditis in developed countries undergo surgical intervention (9). A higher frequency of surgical interventions in developed countries may indicate a better availability of specialized centers, but also a more aggressive therapeutic approach. On the other hand, lower rates of surgical treatment in developing countries are often the result of late referral of patients or lack of technical and personnel capacity, which negatively affects the prognosis.

Mortality associated with infective endocarditis remains high worldwide, despite medical advances (6,9). Higher mortality rates in regions with less developed health systems emphasize the significance of early disease recognition, adequate therapy and organization of health care. These data indicate the need for global strategies that would improve the prevention, diagnosis and treatment of infective endocarditis, while respecting local specificities.

Some studies indicate that infective endocarditis is no longer a disease of young people with congenital disorders (as it was in the past), but increasingly a disease of the elderly (over 65 or 70 years old) (13). In the elderly, the main risk factors are degenerative changes in the valves, diabetes, malignancies and more frequent contacts with the healthcare system (hospital infections). Thus, elderly people often have atypical symptoms, which leads to a later diagnosis. Elderly patients are less likely to undergo a surgery (due to high surgical risk and comorbidities) and have a worse prognosis compared to younger population.

The prevention of infective endocarditis is an important but often neglected aspect of healthcare. The education of high-risk patients, the rational use of antibiotics and the improvement of hospital control of infections are key elements in reducing the incidence of disease (1,8). Also, the continuous education of healthcare workers about modern guidelines and resistant patterns can contribute to better management of this disease.

Despite significant progress in the understanding of pathogenesis and treatment of infective endocarditis, the results of this study clearly indicate that regional differences remain a serious challenge (10). The development of international guidelines that take into account the local epidemiology and patterns of resistance, as well as the strengthening of healthcare systems in developing regions, are key steps towards reducing the global burden of this disease. Further research, international cooperation and investment in health infrastructure are necessary to improve the outcome and quality of life of patients with infective endocarditis.

razvoju ukazuju na duboke globalne nejednakosti u ishodima lečenja. Multidisciplinarni timski pristup i pravovremena hirurška intervencija ostaju ključni faktori za smanjenje visokog mortaliteta, ali njihova dostupnost direktno zavisi od nivoa ekonomskog razvoja zdravstvenih sistema. Konačno, unapređenje ishoda zahteva globalnu standardizaciju protokola i jačanje preventivnih strategija uz obavezno uvažavanje lokalnih specifičnosti mikrobiološkog profila rezistencije.

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Conclusion

The research results confirm that in the 21st century, infective endocarditis has experienced a significant epidemiological transformation, marked by the dominance of staphylococci and the rise of resistant strains in developed regions. However, the persistence of rheumatic heart disease and limited diagnostic resources in developing counties point to profound global inequalities related to treatment outcomes. A multidisciplinary team approach and timely surgical intervention remain key factors for reducing high mortality, but their availability directly depends on the level of economic development of healthcare systems. Finally, the improvement of outcomes requires global standardization protocols and strengthening of preventive strategies with mandatory consideration of local specificities of the microbiological profile of resistance.

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