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HOSPITAL-ACQUIRED INFECTIONS AND MEASURES FOR SUPPRESSION

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Abstract. *Hospital-acquired infections are infections that patients contract during their stay in a hospital or other healthcare facility. They represent a global health and economic challenge, as they lead to increased mortality, morbidity, and length of hospital stay. According to the European Center for Disease Prevention and Control, more than 3.5 million cases of hospital-acquired infections occur in the European Union and the European Economic Area each year, of which more than 90,000 are fatal. The average incidence is 5-10%, with the highest in intensive care units (9-37%). These are mainly ventilator-associated pneumonia, bloodstream infections, urinary catheter-associated infections, and surgical site infections. The pathogens are bacteria, viruses, fungi, and parasites. To suppress and control, it is important to identify the link between the hospital environment (air, surfaces, staff uniforms) and various pathogens, especially methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, norovirus, Pseudomonas aeruginosa, Clostridium difficile, Acinetobacter, Candida spp. Hospital-acquired infections account for 71% of antibiotic-resistant bacterial infections, including bacteria resistant to last-generation antibiotics such as carbapenem-resistant Enterobacterales. In addition to cleaning and disinfection, it is also important to regularly change and check the effectiveness of disinfectants using both standard indicator strains (test microorganisms) and clinical and ambient hospital-acquired isolates. It is necessary to perform microbiological tests as soon as possible of biological material, i.e. patient samples (swabs, blood, urine), as well as air samples, swabs from staff uniforms, equipment, and surfaces, to isolate and identify the pathogens. Bacterial isolates are also tested for sensitivity to antibiotics using phenotypic and/or genotypic methods. Epidemiological surveillance is mandatory to identify patients with infection or colonization and to assess the risk factors that contributed to its occurrence. It is estimated that 30% and even up to 50% of hospital-acquired infections can be prevented by applying protocols and recommendations for prevention and control.*

Key words: *hospital-acquired infections, epidemiological surveillance, identification, disinfection*

Introduction

Hospital-acquired infections/healthcare-associated infections (HAIs) or nosocomial infections are infections acquired during the utilization of healthcare services (primary, secondary, tertiary), most commonly tertiary/in an inpatient healthcare facility (hospital) that are not present at the time of admission and may manifest within 48 to 72 hours after discharge from the hospital. They also include occupational infections that may affect staff [1] and refer to infections that a patient does not have before admission to the hospital, that do not even exist in latency, and that occur on arrival at the hospital or within 48-72 hours of admission to the hospital [2]. In the European Union and the European Economic Area (EU/EEA), more than 3.5 million cases of HAIs occur annually, causing more than 90,000 deaths [3], while the number is higher in underdeveloped countries with poor sanitary conditions. It is estimated that in highly developed countries, 5-10% of hospitalized patients are infected with HAIs, with 9% to 37% occurring in intensive care units. HAIs are responsible for 71% of antibiotic-resistant bacterial infections, including bacteria that are resistant to last-resort antibiotics, such as carbapenem-resistant *Enterobacteriaceae* (CRE) [3]. They increase morbidity and mortality rates and are associated with invasive procedures and surgical interventions, permanent medical devices, and prostheses [1]. In addition, they are a financial burden for patients and the healthcare system.

There are evidence-based guidelines for the prevention of HAIs (Figure 1). Control measures include identifying patients at risk for HAIs, adhering to hand hygiene, following standard precautions to reduce transmission, and strategies to reduce hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and catheter-associated infections. Prevention of infections in special patient groups (e.g. patients with burns) includes identification of reservoirs of infection and microorganisms, isolation of patients if necessary, selective antibiotic prophylaxis, early removal of necrotic tissue, prevention of tetanus, and nutritional control. Immunocompromised and transplant patients are at greater risk of opportunistic infections. Particular attention must be paid to room ventilation, cleaning, disinfection and decontamination, proper and regular use of personal protective clothing and footwear, and biological/microbiological correctness of food and water. Infection control and epidemiological surveillance teams are formed at the health facility level. A particularly important measure is the management of antibiotics to optimize dosage and the active use of information technologies. The recommendations in these guidelines are intended to support, not replace, good clinical practice [4].

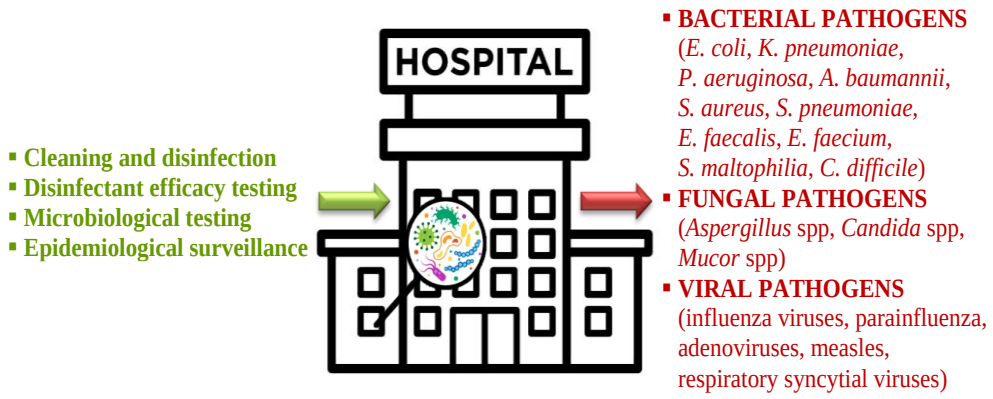

Figure 1. Measures in the fight against the most common HAIs pathogens

ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp) are the most common causes of HAIs worldwide. Most isolates exhibit multidrug resistance (MDR), one of the three major threats to global public health, usually caused by overuse/overprescription of drugs and inappropriate use of antimicrobials. Understanding the resistance mechanisms of these bacteria is crucial for the development of new antimicrobial agents or other alternative means to combat this major challenge in clinical practice. It could help predict the underlying or even unknown resistance mechanisms that could be applied to other multidrug-resistant pathogens [5]. One potential source of pathogens is hospital waste, with 20-25% of this waste being hazardous waste [6].

Chain of infection and measures for prevention and control

For an infection to occur, there must generally be a chain of infection (Vogralik's chain) consisting of six links: (1) infectious agent (bacteria, fungi, viruses, parasites), (2) reservoir of infection (dirty-contaminated surfaces and equipment, humans, animals, insects, soil, food, water, air), (3) susceptible host (any person, especially patients), (4) portal of entry for an infectious agent (skin injuries/cuts, respiratory tract, mucous membranes), (5) portal of exit of the infection (open wound/skin injury, splatter of body fluids, aerosol), and (6) mode of transmission of the infection (by direct or indirect contact, ingestion or inhalation) [7]. Breaking any link in the chain of infection contributes to the prevention of infectious diseases. The first step is to know how the chain of infection works in healthcare settings and then to break one or more links to prevent spread or transmission [7].

According to the Centers for Disease Control and Prevention (CDC), infection control prevents or stops its spread in healthcare settings and is essential to a safe healthcare environment. To suppress and prevent HAIs, measures are taken at various levels: (1) strengthening host resistance (immunization and treatment of underlying disease), (2) acting on the infectious agent (diagnosis and treatment, antimicrobial management), (3) acting on the reservoir of infection (cleaning, disinfection, sterilization, pest

control), (4) acting on portal of exit (wearing masks), (5) preventing transmission (hand hygiene, personal protective equipment, food safety, cleaning, disinfection, sterilization, isolation), and (6) acting on portal of entry (hand hygiene, personal protection, equipment, personal hygiene, first aid, removal of catheters and tubes) [7].

Brief overview and comparison of HAIs

Raoofi et al. [2] conducted a systematic review and meta-analysis of the global prevalence of HAIs between 2000 and June 2021 and found that the annual growth rate was 0.06%. The prevalence of these infections was reported to be 5% in North America and some parts of Europe and about 40% in some Asian, Latin American, and African countries, with the prevalence in Central Africa being 0.27% higher than in other parts of the world. The most common pathogen was *Escherichia coli*, followed by coagulase-negative *Staphylococcus* spp and *P. aeruginosa*. The highest infection rates were recorded in transplant, neonatal, and intensive care units.

Chen and Zou [8] conducted a retrospective cohort study of VAP and HAP caused by the Gram-negative bacteria *Stenotrophomonas maltophilia* (SM) and *K. pneumoniae* (KP) in patients admitted to the intensive care unit with a diagnosis of SM-HAP/VAP or KP-HAP/VAP between June 2019 and June 2021 and compared the differences between them in terms of mortality, duration of ventilation, length of hospital stay, and risk factors for infection. The primary outcome was 28-day mortality, which was 16.7% due to *S. maltophilia* and 15.9% due to *K. pneumoniae*. It was concluded that SM-HAP/VAP or KP-HAP/VAP patients in the intensive care unit have a similar prognosis in terms of mortality, total duration of mechanical ventilation and ventilator use, total length of stay in the intensive care unit, and hospitalization.

Analysis of 35 relevant publications on HAIs in Africa between 2010 and 2017 revealed that *Klebsiella* spp, *S. aureus*, *E. coli*, and *Pseudomonas* spp were the most common pathogens reported in the bloodstream, urinary tract (catheter-associated) and surgical site infections and as a cause of pneumonia. Among HAIs, methicillin-resistant *S. aureus* (MRSA; 3.9-56.8%) and beta-lactamase-producing Gram-negative bacilli (1.9-53.0%) were the most frequently reported antimicrobial-resistant pathogens, which is a consequence and evidence of inadequate surveillance of HAIs in Africa and the emergence of antimicrobial resistance in pathogens [9].

The proportion of Gram-negative bacteria causing VAP ranges from 76.13 to 95.3%, with the most common MDR pneumonia pathogens being *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa*. Ampicillin, tetracyclines, amoxicillin-clavulanic acid, cephalosporins, and carbapenems have been shown to be highly resistant in most studies. Risk factors include: previous MDR-Gram-negative bacteria infection, older age, use of broad-spectrum antibiotics, high incidence of local antibiotic resistance, prolonged hospitalization, intensive care unit admission, mechanical ventilation, and immunosuppression. *S. maltophilia* is a serious cause of HAP/VAP in mechanically ventilated patients with hematologic malignancies due to its ability of biofilm formation, site adhesion in respiratory devices, and intrinsic and acquired drug

resistance mechanisms. Therapeutically, effective combination therapies targeting pandrug-resistant strains and drug-resistant genes, antibiofilm agents, gene-based vaccinations, and pathogen-specific lymphocytes should be developed [10].

Bacterial pathogens

According to the European Center for Disease Prevention and Control (ECDC), the most common bacterial species are: *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *S. aureus*, *Streptococcus pneumoniae*, *E. faecalis*, and *E. faecium* [11].

E. coli is a Gram-negative bacteria that causes many diarrheal diseases, including travelers' diarrhea and dysentery, uncomplicated cystitis, and other extraintestinal diseases, including pneumonia, bacteremia, and abdominal infections such as spontaneous bacterial peritonitis [12]. Many hospitals worldwide have reported the spread of carbapenemase-producing strains, especially *E. coli* and *K. pneumoniae*, and these species are the main cause of HAIs [13-15]. The status of nosocomial carbapenem-resistant *E. coli* and *K. pneumoniae*, the most common carbapenemase type, the antibiotic treatments used depending on the carbapenemase type, and the most effective patient management strategies for controlling CRE were analyzed in the United Kingdom between 2009 and 2021 [15]. It has been shown that: (1) the total number of carbapenem-resistant *E. coli* was 1083 and carbapenem-resistant *K. pneumoniae* was 2053 in more than 63 United Kingdom hospitals, (2) KPC was the predominant carbapenemase produced by *K. pneumoniae*, (3) the treatment options considered depended on the type of carbapenemase, and (4) *K. pneumoniae* showed greater resistance to treatment options, i.e. Colistin, than other carbapenemases. Carbapenem is the drug of first choice in the treatment of nosocomial *E. coli* infections. However, carbapenem-resistant *E. coli* began to emerge, mainly due to the production of carbapenemases, decreased antibiotic permeability (increased efflux pump and lack of porin presence), and altered carbapenem binding sites.

Carbapenem-resistant *K. pneumoniae* is an important cause of pneumonia, surgical site infections, bloodstream and urinary tract infections and meningitis, leading to high morbidity and mortality [15]. *Klebsiella* spp are capsular strains that are intrinsically (naturally) resistant to ampicillin and other aminopenicillins and can acquire resistance to cephalosporins, aztreonam, and carbapenem through the production of extended-spectrum beta-lactamases (ESBL) [16, 17]. Capsular strains usually cause severe nosocomial infections, as their capsule is an important virulence factor and prevents antibiotics from entering the cell [18].

Among Gram-negative bacteria, *P. aeruginosa* is the most common MDR bacterial pathogen that causes HAP/VAP and has intrinsic resistance to many antimicrobial agents [19, 20]. In the empirical treatment of MDR *P. aeruginosa*, conventional antipseudomonal beta-lactam antibiotics have been used alone or in combination with other agents from a different class of antibiotics (e.g. cefiderocol) to increase efficacy. Some MDR isolates of *P. aeruginosa* are sensitive to polymyxin B only. Bacteriophages are promising candidates for the control of recurrent infections

caused by MDR *P. aeruginosa* due to their high specificity and ability to avoid conventional antibiotic resistance mechanisms [21].

Acinetobacter spp. cause a broad spectrum of clinical infections. More than 85% of isolates are sensitive to carbapenems, but resistance is increasing due to IMP-type metalloenzymes or OXA-type carbapenemases, and the ability to form biofilms [22]. Sulbactam is used as an alternative therapy that has an antibacterial effect on *Acinetobacter* spp [23]. Outbreaks of carbapenem-resistant *A. baumannii* infections are difficult to control and sometimes require the temporary closure of the ward to clean and disinfect the area. A novel multimodal approach with improved personal and environmental hygiene without ward closure, cohorting or temporary admission restrictions was implemented to control a fatal outbreak in the intensive care unit [24].

MRSA is one of the most important and earliest detected bacteria in infants and children with cystic fibrosis, with 70.6 colonized/infected patients and an average age at first infection of 3.6 years [25], persisting in the lungs for many years despite antibiotic intervention [26].

S. pneumoniae and *Haemophilus influenzae* are community-acquired infections that usually cause early HAP in patients without other risk factors. Many strains of *S. pneumoniae* are resistant to penicillin and some of them to cephalosporins, macrolides, tetracyclines, and clindamycin and all MDR strains are sensitive to vancomycin, linezolid, and fluoroquinolones [27-29]. Conjugate vaccines targeting capsular serotypes are also effective in preventing *S. pneumoniae* infections [30]. Resistance of *H. influenzae* to antibiotics other than penicillin and ampicillin is so rare that it does not pose a problem for therapy [29].

Enterococci, especially *E. faecalis* and *E. faecium*, cause infectious diseases that are associated with high mortality and morbidity. *Enterococcus* spp. is characterized by low susceptibility to many antimicrobial drugs, including aminoglycosides, cephalosporins, and sulfonamides and, in the case of *E. faecium*, low doses of penicillin and ampicillin. Due to the limited therapeutic options, vancomycin is often used to treat enterococcal infections, especially *E. faecium* [31].

In addition to the most common bacterial strains that cause HAIs, some others that contribute to a lesser extent are also worth mentioning. *S. maltophilia* is a pathogen that colonizes the respiratory tract, is resistant to carbapenems due to the presence of metallo-beta-lactamase, and is most likely sensitive to trimethoprim-sulfamethoxazole, ticarcillin-clavulanate or fluoroquinolone [32]. *C. difficile* is a Gram-positive, sporogenous bacterium that is the most common cause of diarrhea and pseudomembranous colitis, in some cases with a fatal outcome. *C. difficile* infection can also be caused by intestinal dysbacteriosis as a result of prolonged antibiotic therapy. In addition, more and more virulent strains that are resistant to antibiotics have emerged in recent years. Therefore, current guidelines for the treatment of *C. difficile* infections recommend the use of antibiotics (metronidazole, vancomycin, and fidaxomicin) and alternative antimicrobial strategies (bacteriophages, endolysin, monoclonal antibodies, fecal microbiota transplantation, vaccination) [33].

Fungal pathogens

In contrast to bacteria and viruses, fungi are not dominant pathogens in humans and are mostly associated with immunocompromised individuals, patients undergoing cancer therapy, and long-term and frequent antibiotic therapy. They have developed various mechanisms to evade the host's immune response, including the secretion of proteases, toxins, and superantigens. According to Shah et al. [34], over 150 million people suffer from severe fungal infections, causing more than one million deaths annually. The World Health Organization (WHO) has published a list of 19 priority fungal pathogens, which are classified into 3 categories: critical priority (*Aspergillus fumigatus*, *C. albicans*, *C. auris*), high priority (*C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *Fusarium* spp, *Histoplasma* spp, *Mucorales* spp, mycetoma causing fungi), and medium priority (*C. krusei*, *Coccidiodes* spp, *Cryptococcus gattii*, *Lomentospora prolificans*, *Scedosporium* spp, *Paracoccidiodes* spp, *Pneumocystis jirovecii*, *Talaromyces marneffei*) [35]. *Aspergillus* spp, *Candida* spp, and *Mucor* spp are the most common causes of fungal infections in the hospital and their control requires the use of conventional antimycotics.

Viral pathogens

Viral infections account for 1-5% of all HAIs [36]. Epidemics of pneumonia caused by influenza viruses, parainfluenza, adenoviruses, measles, and respiratory syncytial viruses are well-known and usually occur seasonally. Influenza A is probably the most common cause of pneumonia in adult patients and is transmitted directly (from person to person when infected individuals sneeze, cough or speak) or indirectly [37]. The use of an influenza vaccine together with prophylaxis and early antiviral therapy with amantadine, rimantadine or one of the neuraminidase inhibitors (oseltamivir and zanamivir) drastically reduces the spread of influenza in hospitals and healthcare facilities [38].

Contamination of the environment and preventive measures

The most important source of pathogens in healthcare facilities is the patient, who is colonized or infected and can shed microorganisms from the body, bedding, and clothing and contaminate surrounding surfaces and portable equipment. It is known that pathogens can persist on surfaces for a few hours to a few days, while sporogenous forms can persist for months [39]. Studies have shown that if a patient is infected with microorganisms, the risk of infection is increased in a newly admitted patient staying in the same room [40]. Preventive measures include improving cleaning and disinfection, disinfectant efficacy testing, microbiological testing, and epidemiological surveillance [41-45].

Regular cleaning and disinfection of environmental surfaces and disinfection/sterilization of medical equipment and accessories are carried out in accordance with the Guideline for Disinfection and Sterilization in Healthcare

Facilities [42] using prescribed standard procedures and effective disinfectants. To select the most effective disinfectant and to destroy/inactivate clinical isolates (from biological material of patients) and isolates from the environment (air, surfaces, equipment), it is recommended to perform microbiological monitoring, isolation, identification, and testing the effectiveness of the disinfectants by determining the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) using standard test strains (indicator strains) (e.g. *E. coli* ATCC 11229, *S. aureus* ATCC 6538, *P. aeruginosa* ATCC 15442, *C. albicans* ATCC 10231 or 2091, *A. brasiliensis* ATCC 16404, *B. subtilis* ATCC 19659), and in particular isolates from the healthcare facility [46]. Disinfectant efficacy testing can be performed: (1) *in vitro* to demonstrate the efficacy of selected chemicals/biocides against isolates from the environment (bacteria, fungi, and viruses) and (2) *in situ* to demonstrate the ability of disinfectants to reduce and control microorganisms by monitoring the environment under worst-case conditions with expected microbial concentrations before and after application of the disinfectant (e.g. planned area closure, construction, maintenance, etc.) [46, 47]. It is also recommended to change the type of disinfectant regularly to avoid the development of resistance of microorganisms to the disinfectant.

Cleaning/disinfection and sterilization of medical equipment is based on the Spaulding classification: (a) critical equipment/device (surgical instruments, implants, biopsy instruments, foot care equipment, eye and dental equipment) must be sterilized, therefore cleaning is followed by sterilization, (b) semi-critical equipment/device (respiratory therapy equipment, anesthesia equipment, tonometer) prefer sterilization or cleaning followed by high-level disinfection (as a minimum), and c) non-critical equipment/device (ECG machines, oximeters, bedpans, urinals, commodes) prefer cleaning followed by low-level disinfection (in some cases, cleaning alone is acceptable) [48].

Microbiological testing of biological material, i.e. patient samples (swabs, blood, urine), as well as air samples, swabs from staff uniforms, equipment, and surfaces, must be performed as soon as possible to isolate and identify the pathogens [43, 44]. The next step is to test the sensitivity of bacterial isolates to antibiotics using phenotypic and/or genotypic methods [49] and to classify them accordingly as multidrug-resistant (MDR; resistant to at least one antibiotic from three or more groups of antibacterial drugs that are active for a specific type of microbial genus), extensively drug-resistant (XDR; resistant to one or more antibiotics in all groups of antibiotics) or pandrug-resistant (PDR; resistant to all antibiotics in all groups of antibiotics that are active for a specific genus) [50].

Epidemiological surveillance involves the systematic collection, analysis, interpretation, and dissemination of health data to improve the quality of patient care, detect changes in patterns of HAIs, and develop prevention and control strategies [45]. Surveillance programs should be evaluated regularly to ensure that they provide relevant information in an efficient and effective manner and that existing human resources are sufficient to achieve program objectives.

Conclusion

HAIs cannot be avoided, but it is possible to greatly reduce and/or accelerate their eradication by constantly monitoring patients, staff, and hospital facilities, evaluating the effectiveness of the facility's contamination control strategy, and quickly implementing appropriate protective measures when infections occur.

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INTRAHOSPITALNE INFEKCIJE I MJERE ZA SUZBIJANJE

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Sažetak. *Intrahospitalne infekcije su infekcije koje su pacijenti stekli tokom boravka u bolnici ili drugoj zdravstvenoj ustanovi. Predstavljaju zdravstveni i ekonomski izazov na globalnom nivou jer dovode do povećanog mortaliteta, morbiditeta i vremena boravka u bolnici. Prema podacima Evropskog centra za prevenciju i kontrolu bolesti, godišnje se javlja više od 3,5 miliona slučajeva intrahospitalnih infekcija u Evropskoj uniji i Evropskom ekonomskom prostoru, od kojih je više od 90 000 sa letalnim ishodom. Prosječna učestalost je 5-10%, pri čemu je najveća u jedinicama intenzivne njege (9-37%). Uglavnom su to pneumonije povezane sa ventilatorom, infekcije krvotoka, infekcije povezane sa urinarnim kateterom i infekcije hirurškog mjesta. Uzročnici su bakterije, virusi, gljivice i paraziti. U cilju suzbijanja i kontrole, važno je utvrditi povezanost između bolničkog okruženja (vazduh, površine, radna odjeća zaposlenih) i različitih patogena, posebno meticilin rezistentnog Staphylococcus aureus, vankomicin rezistentnih enterokoka, norovirusa, Pseudomonas aeruginosa, Clostridium difficile, Acinetobacter, Candida spp. Intrahospitalne infekcije čine 71% slučajeva infekcija bakterijama otpornim na antibiotike, uključujući bakterije otporne na antibiotike poslednjeg izbora, kao što su Enterobacterales otporne na karbapenem. Osim čišćenja i dezinfekcije, značajna je i periodična promjena i provjera efikasnosti dezinfekcionih sredstava kako prema standardnim indikator sojevima (test mikroorganizmima) tako i kliničkim i ambijentalnim intrahospitalnim izolatima. Potrebno je što prije uraditi mikrobiološka ispitivanja biološkog materijala tj. uzoraka pacijenata (briseva, krvi, urina), kao i uzoraka vazduha, briseva radnih odijela zaposlenih, opreme i površina, da bi se izolovao i identifikovao uzročnik infekcije. U slučaju bakterijskih izolata, ispituje se i osjetljivost na antibiotike fenotipskim i/ili genotipskim metodama. Obavezan je epidemiološki nadzor radi identifikacije bolesnika koji imaju infekciju ili kolonizaciju, kao i sagledavanje faktora rizika koji su doprinijeli njenom nastanku. Procjena je da se primjenom protokola i preporuka za sprečavanje i suzbijanje može sprečiti 30%, pa čak i do 50% intrahospitalnih infekcija.*

Ključne riječi*: intrahospitalne infekcije, epidemiološki nadzor, identifikacija, dezinfekcija*