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THE IMPORTANCE OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN HUMAN MEDICINE

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Summary

Staphylococcus aureus (*S. aureus*) is one of the most important bacterial opportunistic pathogens in humans. It easily adapts to the various environmental conditions. Very important is rapid development of resistance to different antimicrobial agents. Especially important is the resistance to beta-lactam antibiotics (so called methicillin-resistant *S. aureus*: MRSA). MRSA strains differ according to the setting they cause infections to healthcare-acquired strains, community-acquired strains and animal strains. Healthcare-acquired MRSA strains were responsible for the largest epidemic of healthcare-associated infections that ever occurred in the world; community-acquired MRSA strains are huge problem in USA, not so important in Europe. Animal MRSA strains are new addition to human pathogens, but they are not very frequent. In Croatia, MRSA strains are big problem in hospitals but with the tendency of decreasing in recent years; community-acquired MRSA strains are so far very rare, and infections caused by animal MRSA strains are still not described in humans, although they are present in pig farms.

Keywords: *Staphylococcus aureus*; methicillin resistance; MRSA

S. aureus, in about 20-30% of people is a part of normal flora, most often in the area of the nasal vestibulum, but it may be found in the mucous membrane of the throat, the intestines, on the skin of the perineum, in the armpit and in the groins. *S. aureus* has many different virulence factors, which are responsible for the occurrence of various clinical syndromes. So far more than 30 different virulence factors have been described, which lead to the occurrence of the disease in particular situations [1]. It causes a wide range of infections, from localized skin infections to life-threatening deep abscesses, osteomyelitis, pneumonia, sepsis, and endocarditis, various post-operative infections; *S. aureus* toxins can cause food poisoning, and

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toxic shock syndrome [2,3]. *S. aureus* is a causative agent of about 10-12% of healthcare-associated infections.

S. aureus adapts very easily to various environmental conditions (dessication, high concentrations of salt, low pH). Genomes of about ten strains of *S. aureus* have been completely sequenced and these genomes have been shown to contain a large number of mobile genetic elements, which means they very easily exchange genes horizontally with other microorganisms. This gives them the possibility of adapting to different situations in the environment, as well as in humans, enabling them to be harmless as colonization flora, but also to cause serious infections.

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)

An especially important characteristic of the adaptability of *S. aureus* is the fact that it can obtain very quickly resistance to various antibiotics. Already about ten years after the discovery of penicillin, resistance appeared to penicillin, and today about 80-90% of strains of *S. aureus* produce beta-lactamase which destroys penicillin [4,5]; directly after the introduction of methicillin into clinical practice (1959-1960), the first methicillin resistant *S. aureus* (MRSA) was isolated. In 1961 in the United Kingdom, it was found in the blood of a patient with bacteraemia [6]. MRSA strains differ according to their sensitivity to other anti-staphylococcal antibiotics, but they are most often resistant to most of them. Reduced sensitivity and so-called hetero-resistance to vancomycin, today one of the primary drugs used for treating MRSA infection, was described in 1997 [7], and since 2002 several cases of resistance to vancomycin have been described - but it has not spread further than the few cases described [8,9]. However, an increase in minimal inhibitory concentrations of vancomycin is developing in MRSA strains, which is resulting in a reduction in the effectiveness of that drug too. The occurrence of MRSA strains has even been described to new drugs available in this country, that is, linezolid and daptomycin. MRSA strains have also developed resistance to all other antibiotics used to treat staphylococcal infection (macrolides, lincosamides, streptogramin B, quinolones, cotrimoxazol, rifampicin, fusidic acid).

Resistance to methicillin is mediated by the production of PBP 2a, coded by the gene *mecA*, located within the staphylococcal chromosomal cassette SCC*mec.* PBP 2a, in contrast to PBP in sensitive strains, has a very weak affinity for beta-lactam antibiotics, and MRSA strain is resistant to all beta-lactam antibiotics. To date, 11 types of SCC*mec* [10] have been recognized. SCC*mec* gene has a genetic structure like an island of pathogenesis, which is transferred horizontally from one strain of bacteria to another. Types 1, 2 and 3 have a large SCC*mec*, within which there are

many genes of resistance to other antibiotics, but due to their size they are probably more difficult to transfer, and they have only been transferred to a few clones in the world, and therefore these MRSA strains are mainly clonal. These types of MRSA are widespread in health care institutions. Types 4-11 have smaller SCC*mec*, they are very mobile, contain less or no other resistance gene, and they spread very easily. MRSA strains with these types of SCC*mec* are mainly polyclonal and sensitive to most other antibiotics. They are widespread in the non-hospital (community) population, but in some environments (USA) they are also widespread in hospitals.

MRSA strains may be divided into three groups according to the environment where they are causing the infection: MRSA in health care institutions (hospital acquired MRSA), MRSA in the community (community acquired MRSA) and MRSA related to animals.

MRSA IN HEALTH CARE INSTITUTIONS

Since the appearance of the first strains in 1961, MRSA has been spread very quickly in hospitals all over the world. In 1963 it was isolated in Denmark, at the same time also in other European countries, and in Australia and the USA. The first MRSA epidemic was described in 1963 [11]. Data from the SENTRY program (1997-1999) [12], showed that the spread of MRSA differs in various parts of the world: 46% in the Pacific area, 34% in the USA, 35% in Latin America, 26% in Europe, and only 6% in Canada. Also, the variations were very great within each individual region, for example between Australia (27%) and Japan (70%) and in Europe between the Netherlands (<2%) and Portugal (54%).

Today MRSA is one of the most common causes of healthcare-associated infection, causing 40-70% of staphylococcal infections in intensive care units [12]. Healthcare-associated MRSA is a truly opportunistic pathogen, which causes infection in otherwise seriously ill patients, patients after major surgery, patients on haemodialysis, patients with a indwelling catheters, stomas, and bed sores, but also inhabitants of nursing homes. In these patients MRSA mainly causes post-surgical wound infections, pneumonia or sepsis.

Taking the world as a whole, MRSA was responsible for the largest epidemic of healthcare-associated infections that ever occurred in the world [13,14,15]. Therefore it is an important not only public health, but also political problem in the entire world. In hospital conditions it spreads very easily from patient to patient, mainly by the hands of health workers [16], but it may spread through contaminated objects and also by air [17]. The scope of the spread of MRSA is shown in the example of the USA: in intensive care units MRSA was isolated in only 2% of staphylococcal infec-

tions in 1974, in 1992 in 36% and in 2003 in as many as 64% [18]. A major problem is the fact that infections caused by MRSA have a significantly higher mortality rate than those caused by sensitive staphylococcus [19,20]. Moreover, healthcare-associated infections caused by MRSA significantly increase the costs of hospital treatment [21].

PREVENTION OF HEALTHCARE-ASSOCIATED INFECTIONS BY MRSA STRAINS

Since the problem of infection by MRSA strains in hospital is very large, various preventive measures are taken, of which some have been shown to be very effective, whilst for others there is less evidence, but they are undertaken on the basis of the experience of some institutions or states. All these measures are included in guidelines which hospitals keep to, with more or less success. Many countries have national guidelines, including Croatia [22,23,24]. With strict adherence to guidelines, many states in the world have recorded a reduction in the frequency of infection by MRSA strains. The most important preventive measures are included in a "bundle" of measures [25,26,27,28,29], which consist of the following procedures: hand hygiene, decontamination of the environment and equipment, active selection of carriers on admission to hospital, contact isolation for colonized and infected patients (isolation in single bed rooms), and the application of bundle care procedures for central vascular catheters.

In the past twenty or so years, MRSA has also been spread to nursing homes and other long-term care facilities, where some residents are bed-ridden. This is not unusual, since serious staphylococcal infections are often found in older persons. The elderly, when they are admitted to hospital, are easily infected with strains of MRSA, and return to the nursing home as carriers. In nursing homes there is sometimes a very high percentage of MRSA carriers (7-46%) [30,31]. It has not been explained how far these MRSA carriers may infect other residents, but it has been shown that an MRSA carrier is an important risk factor for the occurrence of serious infection [32], infections in diabetics or patients with occlusive vascular disease [33] amongst those residents.

COMMUNITY ACQUIRED MRSA

MRSA strains appeared about ten years ago in the community, causing infections in otherwise healthy people [34,35,36,37]. This did not happen however by the MRSA "leaving" the hospital, as was shown by further research: MRSA strains

in the community are different from those in hospitals in terms of bacteriological characteristics and the clinical syndromes they most often cause. As has already been mentioned, community acquired MRSA is not multi-resistant, the strains are mainly polyclonal (the exception is the clone USA 300, which is very widespread in the USA) [36,38]. The SCC*mec* types are from IV to VI and more recently up to XI (10). Community strains of MRSA very often produce Panton-Valentine toxin [36,37,39,40] which makes them highly pathogenic, especially if they also possess other pathogenic factors, such as strain USA 300 [41,42]. Most often they cause infection of the skin and soft tissues, but also serious and often fatal necrotizing pneumonia [43,44], necrotizing fasciitis and infections of the bones and joints [42,45]. In the USA, community acquired MRSA spreads very quickly, and since these patients are very often hospitalized due to a serious form of the infection, strains of MRSA and especially USA 300 are also widespread in hospitals, especially paediatric wards [40]. In Europe community acquired MRSA is not a significant problem at the moment [46].

MRSA RELATED TO ANIMALS

MRSA is also known as a pathogen in the field of veterinary medicine, found in various animals, from pets to livestock, horses, pigs, poultry, exotic animals, and as a cause of infection and colonizing flora in healthy animals [8]. In Europe this is an increasing problem, especially in connection with colonized pigs (MRSA strains of the sequenced type (ST) 398) from whom it is transferred and causes infections in pig farmers, veterinarians and workers in slaughter houses [46,48]. MRSA has also been found in meat from domestic animals [49], but the authors of that paper did not find the clone ST 398, but only types which may be found in both people and pigs. The MRSA clone ST 398 was discovered for the first time in the Netherlands in 2003, and since then it has been found in other parts of the world, in other European countries, in Asia and the USA [50]. For now, however, this type of MRSA is responsible for a very small proportion of MRSA infections in people [50]. In the Republic of Croatia MRSA strains have also been found in dust on pig farms [51].

MRSA IN THE REPUBLIC OF CROATIA

In Croatia the first report of the importance of MRSA strains was published in 1997 [52]. At the end of the 1990's work began in the Republic of Croatia to systematically monitor the appearance of MRSA as part of the Committee for Monitoring Resistance of Bacteria to Antibiotics of the Academy of Medical Science of Croatia (HAMZ), and also as part of the European Union project EARSS (European Anti-

microbial Resistance Surveillance System, today part of ECDC - monitoring isolates from the blood of patients with bacteraemia). In a study by EARSS for 2005-2006 in the Republic of Croatia, of 745 staphylococcal blood isolates from patients, it was shown that in male patients MRSA was found more often (46%) than in females (30%), that the highest frequency occurred at an older age (14% from 0-4 years, 20% from 5-19 years, 32% from 20-64 years and 45% at more than 65 years). It occurred most often on surgical wards (73%), in intensive care units (64%) and in medical wards (22%). Eighteen of the largest hospitals in Croatia took part in the EARSS project, and MRSA appeared in a wide range of percentages: from 0% to 65%. MRSA strains isolated in Croatia were characterized on a molecular level and found their place in the epidemiological picture of MRSA isolates in Europe [53,54,55].

In the Republic of Croatia, the frequency of MRSA in 2010 was 16% (Annual Report of the HAMZ Committee for Antimicrobial Resistance Surveillance), which is much lower than in previous years (25% in 2007). Also, data from the report on hospital infections (Annual Report of the Ministry of health and social welfare Committee for Prevention and Control of Hospital Infections) show that the incidence of MRSA in clinical hospitals has decreased: the median in clinical hospitals fell from 0.66 patients per 1000 patient days in 2007 to 0.12 patients per 1000 patient days in 2010.

Community acquired MRSA was described for the first time in this country in 2005 [56], but so far the number of these strains is small and these strains were mainly isolated from patients with minor skin and soft tissue infections [57].

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Sažetak

Značenje meticilin-rezistentnih sojeva *Staphylococcus aureus* (MRSA) u humanoj medicini

Staphylococcus aureus (*S. aureus*) jedan je od najznačajnijih bakterijskih oportunističkih patogena u ljudi. Vrlo se lako adaptira na različite uvjete u okolini, a posebno je važno njegovo brzo stjecanje otpornosti na različite antibiotike. Osobito je važna otpornost na betalaktamske antibiotike (takozvani meticilin-rezistentni *S. aureus*: MRSA). Sojevi MRSA-e razlikuju se prema sredini u kojoj uzrokuju infekcije: bolnički stečeni, stečeni u izvanbolničkoj populaciji te oni povezani s domaćim životinjama. Bolnički MRSA izazvao je najveću epidemiju bolničkih infekcija ikada opisanu u svijetu; izvanbolnički MRSA velik je problem u SAD-u, manji u Europi. Životinjski sojevi MRSA-e novi su dodatak ljudskim patogenima, no ne s velikom učestalošću u svijetu. U Republici Hrvatskoj MRSA je velik problem u bolničkim ustanovama, s laganom tendencijom smanjenja posljednjih godina. Izvanbolnički MRSA zasad je vrlo rijedak, a infekcije životinjskim sojevima, premda su dokazane na svinjogojskim farmama, nisu još opisane.

Ključne riječi: *Staphylococcus aureus*; otpornost na meticilin; MRSA