THE EVALUATION AND MANAGEMENT OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)

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Abstract

This article is devoted to analysis of relevant information about methicillin-resistant Staphylococcus aureus, infections that it causes and available detection and treatment. The main danger that MRSA presents is due to its antibiotic resistance, high virulence and contact transmission route. Available treatment of MRSA associated infections consists of antibiotics, like vancomycin and daptomycin. New treatment and prevention methods are in development.

Keywords: *methicillin-resistant Staphylococcus aureus, MRSA, prevention, detection, treatment*

Introductions. As antimicrobial resistance is still a worldwide problem, methicillin-resistant *Staphylococcus aureus* (MRSA) remains a subject of great concern. Methicillin-susceptible *Staphylococcus aureus* (MSSA) is a Gram-positive, coagulase-positive non-motile spherically shaped bacteria, which is a part of human normal microbiome [1]. It colonizes primarily nasal mucosa and can be found in one-third of human population [2]. It is believed, that MRSA arose after introduction of methicillin, by horizontal transfer of a mobile genetic element designated staphylococcal cassette chromosome *mec* (SCC*mec*). SCC*mec* contains gene *mecA,* which encodes penicillinbinding protein 2a (PBP2a). This enzyme is responsible for crosslinking the peptidoglycans in the bacterial cell wall and has a low affinity for β-lactams, making MRSA resistant to almost every antibiotic in this class [3].

Methicillin-resistant *Staphylococcus aureus* causes healthcare-associated/acquired MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA). MRSA is prevalent in hospitals, nursing homes and in correctional facilities [4]. It resided on surfaces, including improperly sterilized medical devices. In tight, crowded or badly cleaned spaces, any object could be a fomite (an object that can carry or transmit disease).

The aim of this work was to gather and summarize information regarding MRSA infections, challenges and treatment options.

Materials and methods. Information about methicillin-resistant *Staphylococcus aureus* was gathered through search on NCBI, PubMed and Google Scholar with relevant keywords. Information was thoroughly analyzed and summarized.

Results and discussion. Methicillin-resistant *Staphylococcus aureus* causes different types of infections, ranging from mild to severe and life threatening. This include skin and soft tissue infections (SSTI), bone and joint infections (osteomyelitis), pneumonia (including hospital-acquired), bacteremia, endocarditis. Treatment is somewhat difficult, as MRSA can be simultaneously resistant to other antibiotics, like vancomycin, has many virulence factors, and is easily transmitted by contact with carriers or fomites. Virulence factors include adhesion proteins,

chemotaxis inhibitory proteins, various enzymes such as proteases, lipases, hyaluronidase, staphylokinase, catalase, nucleases, lipases, coagulase, catalase, proteases, collagenases, β-lactamases, and elastases which help the *S. aureus* in causing infection in host. Except these virulence factors, MRSA also contains different mobile genetic elements (MGEs). It also produces a range of toxins: exotoxins, enterotoxins, TSST-1, hemolysin toxins and Panton-Valentine leukocidin toxins [5]. MRSA infection can rapidly develop and worsen, if no treatment is applied. MRSA is able to form biofilms, which reduce efficiency of drug treatments [6].

Like most infections, MRSA infections are more prevalent and severe in people, who belong to risk groups, such as: immunocompromised people, people who recently received a transplant or a prosthesis, previously infected people, athletes, diabetics, intravenous drug users, people over 60 years old, people living in communal housing, prison and jail inmates, users of quinolone antibiotics.

Because methicillin-resistant *Staphylococcus aureus* can inhabit nasal cavities, human carriers might not have any symptoms, while actively spreading pathogens and being at a higher risk of developing MRSA associated infections. To determine if person is a carrier, risk factor based screening is recommended. Patients are screened if they belong to risk factor group, and staff is screened if it`s suspected, that a staff member is a source of MRSA. Universal screening is not widely used, as it increases cost of treatment and puts additional strain onto laboratories. However, if possible economically and technologically, universal screening can be beneficial to prevent HA-MRSA [7].

Detection and identification of methicillin-resistant *Staphylococcus aureus* consists of analysis of clinical or screening samples, collected from patient. If patient shows symptoms of infection, specimens of purulent discharge, deep tissues, sputum and blood can be collected. For screening, swabs from nasal cavities, throat and perineum are taken. There are studies showing increased effectiveness of MRSA detection by screening 2-3 sites of probable colonization [1, 3]. Screening at the discharge from hospital rather than only standard admission screening is also effective in prevention of HA-MRSA [8].

MRSA detection is carried by phenotypic methods, like cultivation on selective or non-selective media, utilization of disk diffusion method with oxacillin or cefoxitin, which induces *mec*A. Alternatively, antigen–antibody based latex agglutination test is used, for detection of PBP2a by anti-PBP2a antibody. Non-phenotypic methods include multiplex real-time PCR assays and matrix assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) [1]. Chromogenic medium, like CHROMagar and chromID agar are able to help detect MRSA in screening. Combination of these mediums can be used in resource-restricted facilities, like military medical field camps [9]. Different strains or clonal complexes of MRSA can be identified by (staphylococcal protein A)-typing (*spa*-typing) [3].

Detection of methicillin-resistant *Staphylococcus aureus* is not the only obstacle in fighting MRSA associated infections. Treatment presents some problems

too, mainly multiple drug resistance. Main concern causes vancomycin resistance, as it is a first line of treatment for many MRSA infections [10]. Linezolid resistance is pretty common, daptomycin and ceftaroline resistances are rare, but it can occur [11]. It appears as if for the past 10 years clindamycin and levofloxacin resistance grew stronger [12].

Modern treatment of methicillin-resistant *Staphylococcus aureus* associated infections includes administration or application of antibiotics. Different conditions require different antibiotics and administration route: severe skin and soft tissue infections (SSTI) are usually treated with intravenous vancomycin, daptomycin and linezolid. Clindamycin, trimethoprim–sulfamethoxazole and doxycycline are alternatives for mild or moderate conditions. Skin abscesses also require drainage. Severe MRSA infections are treated with vancomycin or daptomycin (for bacteremia) and vancomycin or linezolid for hospital-acquired pneumonia. As soon as patient gets better, the administration route for linezolid can be switched to oral. In Europe, including Ukraine, teicoplanin is commonly used as a non-inferior alternative to vancomycin. Serious prolonged cases of bacteremia are treated with combination therapy. Vancomycin and gentamicin can be used together, but this combination is considered inferior to daptomycin alone [1]. Daptomycin has good synergy with antistaphylococcal β-lactams [13].

Prevention of methicillin-resistant *Staphylococcus aureus* associated infections is a vital part in battling these bacteria. Good hygiene practice, proper hospital practices and protocols, antimicrobial agents and control of carrier patients are part of prevention tactics. Decolonization plays a huge role as an intervention, control and prevention. Most decolonization strategies use topical agents applied to the nostrils. Mupirocin is the principal agent and is often combined with chlorhexidine bathing [1]. The polyketide antibiotic batumin synthesized by the producer strain *Pseudomonas batumici* has a high selective activity against staphylococci, which determines the prospects for its medical application in the treatment of staphylococcal infections and the control of the nasal carriage of this pathogen. All investigated staphylococci strains, including MRSA, regardless of the source of their isolation and sensitivity to different antibiotics, were sensitive to the batumin [14].

One promising treatment is bacteriophages. Bacteriophages live in dynamic relationships with bacteria and have coevolved over time. Given this coevolution, bacteriophages have developed innate ability penetrate biofilms and lyse bacteria inside biofilms. Bacteriophages also have the ability to disrupt the biofilm's extracellular matrix with the use of depolymerase enzymes, so they can be used to treat chronic and acute MRSA infections [15].

Conclusions. Methicillin-resistant *Staphylococcus aureus* related infections raise concern due to MRSA high virulence, ability to develop resistance to drugs, including vancomycin, contact transmission and severity of infections. Several methods of MRSA detection and differentiation are in use, including cultivation on selective and chromogenic medium, multiplex real-time PCR, MALDI-TOF mass spectrometry and *spa*-typing. Treatment consists of antibiotic drugs like vancomycin, daptomycin, linezolid, clindamycin, trimethoprim–sulfamethoxazole, doxycycline

and teicoplanin. Combination therapy is also utilized. Prevention includes decolonization with chlorhexidine, mupirocin and batumin. Novel treatments are being developed and implemented, like bacteriophage therapy.

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