

UDK 616.98
Review article
Received: 5 October 2011
Accepted: 14 December 2011

CLINICAL ASPECTS OF INFECTIONS CAUSED BY METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

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Summary

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important cause of nosocomial infections. Clinical presentation of infections is determined by the way of the acquisition of the pathogen then by virulence factors itself. In the intensive care units MRSA causes blood stream infections (BSI) associated with the use of venous lines as well as ventilator-associated pneumonia (VAP). MRSA is prone to form biofilm on implanted foreign materials like orthopaedic and other prostheses, catheters, artificial heart valves and cause persistent infections of surrounding tissues which are difficult to treat. It is difficult to eradicate infection without extraction of these materials. MRSA is weaker inductor of general inflammatory reaction than MSSA. Increase in patient's mortality and morbidity is associated more with a delay of appropriate antibiotic treatment than severity of infection. New antibiotics like linezolid, daptomycin, tygecycline, ceftarolin, ceftobiprol are available nowadays for the treatment of these infections. Although glycopeptides are still the first line treatment of MRSA infections, increase of minimal inhibitory concentrations (MIC creep) is associated with poorer outcome.

Keywords: MRSA; clinical aspects

Health - care associated methicillin-resistant *Staphylococcus aureus* (MRSA) infections still represent an important threat for patients welfare all around the world [1]. Although recently a gradual decrease in the incidence of nosocomial MRSA infections is reported [2], new aspects in the epidemiology of MRSA infections showed that the burden of MRSA associated infections still exists and substantially increases patients' morbidity and mortality. Two major factors are: 1) the increasing

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number of outpatients with extensive healthcare contact, and 2) the emergence of community-acquired (CA) clones of methicillin-resistant staphylococci. Since the number of patients treated as outpatients increases, an increasing prevalence of health-care-associated (HCA) is reported [3]. CA infections has been registered both in the United States and Europe [4].

The objective of this review is to present the problem of HCA MRSA, since CA MRSA infections are still uncommon. The most common nosocomial-infections are primary blood-stream infections including endocarditis, associated with central venous catheters, artificial valves or intracardiac devices, pneumonia and postoperative infections like meningitis/ventriculitis or osteomyelitis.

PRIMARY BLOOD STREAM INFECTIONS

Central-venous-catheter (CVC) associated blood stream infections still represent a major threat to critically ill patients, but also for other patients who require a prolonged use of CVC like cancer or haematological patients. The incidence of MRSA infections is a significant indicator of a poorer infection control, since MRSA infections are generally exogenous infections spread on the hands of ICU personal. Coagulase-negative staphylococci are the most common pathogens associated with such infections, but MRSA still cause about 5 to 11% of these infections [5]. Insertion of CVC increases the risk of MRSA bacteraemia about 35 times [6]. MRSA bacteraemia significantly increases the risk of hospital death about three times, particularly in elderly patients [7]. Two meta-analyses examined mortality associated with MSSA and MRSA infections. MRSA infection was associated with an increase in the risk of death, compared with MSSA infection in both analyses [8,9]. The reason was not MRSA infection *per se* but delay of appropriate therapy.

The risk of MRSA infections depends on insertion site. It is more common with femoral or jugular CVC than subclavian pathway [10]. The incidence of MRSA CVC associated bacteraemia is significantly reduced in countries where rigorous preventive measures had been applied.

MRSA is the major pathogen associated with health-care associated endocarditis which represents a growing problem due to the greater number of invasive procedures applied in patients burdened with serious comorbidities [11]. This is the biggest study regarding staphylococcal infective endocarditis (IE). Most patients with health care-associated *S. aureus* IE (131 patients, 60.1%) acquired the infection outside of the hospital. MRSA IE was more common in the United States (37.2%) and Brazil (37.5%) than in Europe/Middle East (23.7%) and Australia/ New Zealand (15.5%). Interestingly, haemodialysis was a very common exposure preceding endo-

carditis. Comparison of MRSA and MSSA infections showed that persistent bacteraemia was more common in patients with MRSA IE (42.6% vs. 8.8%), but there was no difference in in-hospital mortality (29.8% vs. 23.3%). An Australian study showed that a higher number of patients with MRSA IE was subdued to cardiac surgery (59%) but the mortality remained very high (66%) [12]. During the last decade the number of patients with cardiac intraventricular devices increased. Most intravascular device infections are thought to result from skin flora contamination during implantation [13]. Infection of the subcutaneous portion of the device can subsequently track to deeper intravascular tissues. Infection that involves the intravascular or intracardiac portion of these devices carries a high morbidity and mortality. Despite appropriate antibiotic therapy, cure of infection is frequently possible only with device removal. MRSA might be a significant pathogen associated with these infections although coagulase-negative staphylococci prevail.

VENTILATOR-ASSOCIATED PNEUMONIA

MRSA is an important pathogen associated with the development of VAP. The epidemiology of MRSA pneumonia varies across countries. Methicillin resistance in *S. aureus* ventilator associated pneumonia (VAP) ranged between 37 % in German, 54 % in the US American and 78 % in Asian and Latin American ICUs [14]. Crude hospital mortality in studies performed after 2005 varies between 27 % and 59 % and attributable MRSA pneumonia mortality at 40%. Diagnosis of VAP requires beside x-ray of the chest a prompt microbiological diagnosis (Gram staining of the appropriate respiratory specimen, determination of the number of colony-forming units per millilitre, and permanent and prompt contact with clinicians). Close cooperation between microbiologist and clinician results in better timing of appropriate therapy which further improves patients' outcome. Risk factors associated with MRSA VAP were older age, medical patients, more comorbidities. Consequences were prolonged hospitalization and significantly increased cost [15].

POSTOPERATIVE INFECTIONS

Meningitis

MRSA is an important pathogen associated with postoperative and shunt-meningitis. *S. aureus* is cause of shunt meningitis in about one third of patients. Beside presence of fever and signs of meningitis, shunt infections may result in peritonitis in patients with ventriculoperitoneal shunts or right-sided endocarditis in ventriculoatrial shunts. Usually infections are slowly progressing [16]. Removal of the shunt

is necessary for eradication of infection. Existing shunt is replaced with external ventricular drainage, and intensively treated. After resolving of meningitis, permanent shunt is implanted again.

Osteomyelitis

Osteomyelitis after surgical interventions is usually caused by coagulase-negative staphylococci. All bones may be affected. There is no large epidemiologic study to estimate the true incidence of MRSA osteomyelitis among postoperative patients. Rather, small case-series are presented. Prolonged antibiotic use is mandatory in these patients, often with combined antibiotic regimens since replacement of artificial materials is often impossible.

TREATMENT

Early appropriate antibiotic therapy is the cornerstone of successful therapy and positive patients' outcome. Early studies showed that mortality directly related to pneumonia was significantly higher among patients with MRSA episodes (RR = 20.72, 95% CI = 2.78-154.35) [17]. Subsequent studies showed that a delay in appropriate treatment was the major contributing factor of a poor outcome. more than MRSA infection per se, particularly after adjustments for other contributing factors. However, only a half of patients with MRSA bacteraemia received an appropriate empirical therapy [18]. In a study of Zahar et al. the crude hospital mortality rate was higher for MRSA-infected patients than for MSSA-infected patients (59.4% vs. 40%; $P = .024$), but this difference disappeared after controlling for time in the ICU before VAP and parameters imbalanced at ICU admission (odds ratio [OR], 1.23; 95% confidence interval [CI], 0.49-3.12; $P = .7$) and remained unchanged after further adjustments for initial treatment adequacy and polymicrobial VAP (OR, 0.98; 95% CI, 0.36-2.66) [19]. Appropriate empirical antibiotic treatment has also a significant survival benefit in MRSA bacteraemia. Pooling of six studies using adequate methodology for the adjusted analysis resulted in an OR of 1.98 (95% CI 1.62-2.44) for a delay of appropriate therapy [20]. These data suggest that early diagnosis of MRSA infection and wide-spectrum therapy with subsequent de-escalation in settings where MRSA infections are common are mandatory [21].

MRSA infections are still difficult-to-treat infections. For many years glycopeptides (vancomycin or teicoplanin) were the antibiotics of choice in the treatment of MRSA infections. Even today they are still first line therapy due to their safety and acceptable costs. However, since these agents have large molecules, accumulation in tissues, penetration of blood-brain barrier might represent a problem [22]. That is

why a need for other potent antibiotics led companies to develop many other drugs. Another potential problem in the treatment of MRSA infections is a phenomena of creeping (increase in the MIC values but still within sensitivity limits) vancomycin minimal inhibitory concentration (MIC) values which resulted with more treatment failures of glycopeptide therapy. That is why it seems prudent to treat infections caused by MRSA strains with MIC values above 1 mg/L with other antibiotics – daptomycin for blood-stream infections and endocarditis and linezolid for pneumonia. However, all studies did not uniformly support negative impact of raised MICs on outcome.

Currently, vancomycin remains the gold-standard treatment option for MRSA infections. In situations that limit its use, consideration of patient-specific parameters, cost, and relevant clinical data demonstrating drug safety and efficacy should be employed for the selection of the appropriate alternative agent [23].

Antibiotics presently used in the treatment of MRSA infections are presented on Table 2.

MRSA infections are world-wide still an important cause of health-care associated infections. They spilled over into community and there is a growing number of patients admitted into hospitals with MRSA infections not acquired during the health-care process. Effective preventive measures decrease but do not eliminate MRSA infections. CA-MRSA infections caused by particular MRSA strains are not in Croatia as common as in USA but a constant alert is necessary to recognize outbreak of these infection.

Table 1. Antibiotics for the treatment of MRSA infections

Vancomycin
Teicoplanin
Linezolid
Daptomycin
Tigecyclin
Telavancin
Quinipristin-dalfipristin
Ceftaroline

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Sažetak

Spektar infekcija uzrokovanih meticilin-rezistentnim sojevima *Staphylococcus aureus*

Infekcije MRSA-om važan su uzročnik bolničkih infekcija. Spektar bolesti koje MRSA izaziva određen je više načinom akvizicije tijekom raznih oblika medicinske skrbi nego patogenetskim značajkama samog organizma. Invazivni zahvati nose rizik infekcija MRSA-om. Glavni su način širenja ruke osoblja, pa su infekcije MRSA-om pokazatelj egzogenog akviriranja bolničke infekcije. Na kirurškim odjelima važan su uzročnik infekcija rana, tkiva i mekih česti. U jedinicama intenzivne medicine uzročnik su infekcija krvotoka povezanih s primjenom centralnih venskih katetera i pneumonija povezanih s provođenjem strojnog disanja, odnosno intubacije. Infekcije MRSA-om velik su problem kod ugradnje stranih materijala jer, zbog stvaranja biofilma, lako koloniziraju proteze, drenažne katetere ili umjetne zalistke te uzrokuju perzistentne infekcije okolnog tkiva koje je vrlo teško liječiti. Zbog toga je potrebno zamijeniti te materijale, što nije laka odluka niti je to uvijek moguće učiniti. Za razliku od infekcija MSSA-om, infekcije MRSA-om povezane su sa slabijom indukcijom opće upalne reakcije. Iako su povezane sa znatnim povećanjem morbiditeta i smrtnosti, ove posljedice infekcija MRSA-om više su posljedica neprepoznavanja ili kašnjenja ispravnog antibiotskog liječenja nego težine infekcije. Danas na raspolaganju imamo čitav spektar novijih antibiotika (linezolid, daptomicin, tigeciklin, ceftarolin, ceftobiprol) kojima se, uz glikopeptide, možemo uspješno suprotstaviti infekcijama MRSA-om, ali rastući je problem smanjenje osjetljivosti na vankomicin, što ima bitne kliničke posljedice.

Ključne riječi: MRSA; spektar infekcija