Methicillin-resistant *Staphylococcus aureus* infective endocarditis

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Methicillin was introduced in 1959 to treat penicillin-resistant *S. aureus* infection, however Methicillin-resistant *S. aureus* (MRSA) was reported 2 years later (1). The most common organism identified in acute infective endocarditis (AIE) is still *S. aureus* associated with increased hospital mortality, morbidity and hospitalization. In Germany the proportion of MRSA among *S. aureus* microbiologic examinations was 1.1% in 1990 and dramatically increased to 17.5% by 2001 and reached 21.9% in 2009 (2). Due to the biofilm in AIE, adequate treatment is challenging, including appropriate antibiotic therapy. To improve outcome of AIE early adequate antibiotic therapy is needed, however vancomycin has a decrease microbe clearance and poor clinical response compared with *β*-lactam agents in Methicillin-susceptible *S. aureus*. Today, several reports on clinical failures in MRSA with vancomycin were documented even at MICs <2.0 µg/ml. Current guidelines recommend higher trough vancomycin of 10-20 µg/ml, which will lead to increase complications such as nephrotoxicity (3). Therefore more effective alternative antibiotic treatment is needed to treat MRSA endocarditis and reach sufficient into the biofilm (4). This overview reports recent developments to improve MRSA endocarditis treatment.

Keywords MRSA, active infective endocarditis, biofilm

1. Introduction

Endocarditis was first described in 1885 by Sir William Osler (5), which is a demanding disease in which a high number of patients require surgery due to antibiotic therapy failure (6). Generally active infective endocarditis (AIE) has a high mortality rate and therefore many studies have been performed to identification risk factors, clinical improvements, predictors, including the modified Duke criteria which should guide and improve the treatment of AIE (7). Nevertheless in-hospital mortality has remained high and has not varied substantially during the last decades. Additionally patients risk profiles has increased during the last years and contribute to a continuing high mortality rate.

One important factor in AIE is the caused microorganism of which *Staphylococcus aureus* (*S. aureus)* show a poorer outcome compared to other patients suffering from different microbes. In fact it is an independent risk factor for increased morbidity and mortality (8). Data from the International Collaboration on Endocarditis showed that in-hospital mortality, which occurred in 22.8% of the study patients, was predicted by older age, health-care-associated infection, *S. aureus* infection and complications of PVE, including heart failure, stroke, intra-cardiac abscess and persistent bacteraemia (9). The authors concluded also that complications of PVE strongly predict in-hospital mortality, which remains high despite prompt diagnosis and the frequent use of surgical intervention (10).

S. aureus shows not only higher morbidity and mortality rates, but is also the most common cause of AIE (11,12). The increased complication associated with *S. aureus* is due to the highly invasive character with early tissue infiltration, extending to excessive abscess formation (13). Furthermore Corral et al (14) found that *S. aureus* in native valve endocarditis statistically significantly increased the risk of neurological complications (p=0.024).

In 1959, methicillin was introduced to treat penicillin-resistant *S. aureus* infections, however after two years first methicillin-resistant *S. aureus* (MRSA) were found (1). In Germany the proportion of MRSA among *S. aureus* microbiologic examinations was 1.1% in 1990 and dramatically increased to 17.5% by 2001 and reached 21.9% in 2009 (2). To improve outcome of AIE early adequate antibiotic therapy is needed, however vancomycin which is used in MRSA endocarditis has a decrease microbe clearance and poor clinical response compared with *β*-lactam agents in methicillin-susceptible *S. aureus* (MSSA). Therefore vancomycin should be avoided in patients with MSSA and can only be used after methicillin-resistance has been proven. Furthermore *S. aureus* within the biofilms have several defense mechanisms against antimicrobial agents (15). Therefore several alternative antibiotic therapies have been introduced and forward in guidelines to treat AIE today (16,17). An extreme demanding problem is still the treatment of MRSA endocarditis, which is a combination of surgery and supported by a limited number of antimicrobial agents. To treat AIE adequately it is important to understand the complexity of this disease, starting with the biofilm.

2. The Biofilm

Biofilms have been described as early as 1684 by Anton van Leeuwenhoek, the so-called “animalculi”, in the plaque on his own teeth investigated with his developed microscope. Nevertheless it took almost three hundred years until the theory of biofilm was promulgated (18). The biofilm is defined as "an aggregate of microbial cells adherent to a living

or non-living surface, embedded within a matrix of extracellular polymeric substances of microbial origin" (19). Biofilms are more resistant to antibiotic therapy and are protected by different mechanism such as reduced penetration of antibiotics, protective surface, bacteria within the biofilm are slow growing with reduced DNA synthetic activity, showing stress response gens and antigen expression, increased mutation rates, persister cells, β-lactamase receptors control and decrease infiltration due to be a diffusion barrier (15). *S. aureus* are dominant cause of biofilm-associated infections in which *S. aureus* involves most often host tissues (20), which produce a multi-layered biofilm, including glycocalyx, a specific polysaccharide antigens called polysaccharide intercellular antigen (PIA). Important is the different regulation of Biofilms development in MSSA and MRSA. O'Neill and colleges (21) found that MRSA biofilms are more regulated by SarA and Agr adhesin proteins and *ica* independent, whereas MSSA biofilms development is linked by SarA-regulated PIA and polymeric N-acetyl-glucosamine PNAG.

Jefferson et al (22) studied the reduced penetration of glycopeptide antibiotic e.g. vancomycin into viable *S. aureus* within a biofilm using confocal scanning laser microscopy with fluorescently labeled derivative of vancomycin. This study suggests that, whereas planktonic bacteria were rapidly exposed to a full bolus of vancomycin, the bacteria in the deeper layers were exposed to a gradually increasing dose of the drug. Therefore bacteria living within a biofilm undergo stress induced metabolic or transcriptional changes that increase resistance to the antibiotic. PNAG, an important component of the *S. aureus* biofilm matrix, was not involved in the observed decrease in the rate of vancomycin penetration.

Rani et al (23) investigated different patterns of DNA replication and protein synthetic activity of staphylococcal biofilms by using inducible green fluorescent protein construct. His study suggested that staphylococcal biofilms contain cells in at least four distinct states: growing aerobically, growing fermentation, dead, and dormant. The variety of activity states represented in a biofilm may contribute to the special ecology and tolerance to antimicrobial agents of biofilms.

Bagge et al (24) showed that patients suffer from cystic lung fibrosis, who are generally colonized with *Pseudomonas aeruginosa* biofilms, show an effect on subinhibitory concentrations of a *β*-lactam antibiotic, such as imipenem. In total 34 genes showed statistically significant differential expression in response to imipenem, induced or repressed in biofilms exposed to imipenem compared to the controls. The strong impact was induced by *ampC*, which codes for chromosomal *β*-lactamase.

Oliver A et al (25) investigated chronic infections in patients with cystic lung fibrosis caused by P. aeruginosa, having increased adaption on antibiotic therapy. This was explained by spontaneous mutation rates, in this study found by 36% with hypermutable (mutator) strains and the evolution of antibiotic resistance.

Lechner et al (26) studied bacterial persister cells, which are non- or slow-growing reversible phenotypic variants of the wild type, showing an increased tolerate to bactericidal antibiotics. This study investigated *S. aureus* persister levels by monitoring colony-forming unit counts of planktonically grown cells treated with different antimicrobials over time. The study showed that *S. aureus* in the stationary phase are equivalent to persister cells, as not all of these cells showed antibiotic tolerance.

Bagge et al (27) studied the expression of chromosomal AmpC *β*-lactamase in P. aeruginosa regulation by the activity of an amidase, AmpD. Some P. aeruginosa strains show resistant variants isolated from in vivo and in vitro biofilms for mutations in ampD leading to high-level expression of chromosomal *β*-lactamase. Identical mutation in Enterobacter cloacae were found of AmpR which cause a 450-fold higher AmpC expression. This pathway can also lead to an increase antimicrobial resistance in biofilms.

Xu et al (28) investigated the effect of decrease infiltration due to be a diffusion barrier for antimicrobial agents. De Beer et al (29) evaluated the penetration of chlorine into biofilms during an ongoing infection. This study showed the deactivation of antimicrobial agents in the upper surface layers of the biofilm before the deeper layer were reached. A recent study of Singh et al (30) evaluated the penetration of different antibiotics such as oxacillin, cefotaxime and vancomycin in *S. aureus* and *S. epidermidis* biofilms, finding similar results.

3. Antibiotic therapy options

The different antimicrobial agents to treat MRSA endocarditis are limited, however the success of the treatment is not only depending on selecting the correct substance but timing of an appropriate antibiotic therapy is also essential. The Tarragona strategy says “hit hard and early” (31), which will have an enormous influence on the mortality. Schramm et al (32) found in a multi-variant analysis that inappropriate antimicrobial treatment is one independent risk factor for hospital mortality (adjusted Odds Ratio (OR) 1.92 with 95% confidence interval (CI) 1.48-2.50; p-value 0.013). Cheong HS et al (33) showed that inappropriate antibiotic therapy will have a negative influence on the survival curve at the Kaplan-Meier analyses (p=0.050). Furthermore the working mechanism of an antimicrobial agent is important, showing a bacteriostatic or bactericidal affect (34). Pankey GA et al (35) demonstrated the advantages of bacteriostatic over bactericidal activity who will avoid toxic shock syndrome due to exotoxins or part of the microbial components. On the other hand there activity is not active and limited against microbes and less affective in biofilm, which are available in AIE.

4. Vancomycin

Vancomycin is the golden standard in MRSA AIE treatment, generally used in combination with other antimicrobial agents. Although this agent is widely applied, it only limited penetrates tissue or biofilm, slow bactericidal activity, and having adverse effect such as Red man syndrome, neutropenia, thrombocytopenia and renal failure (36). Soriano et al (37) studied the influence of minimal inhibitory concentration (MIC) on MRSA bacteremia. In a logistic regression model this study showed that MICs of > 2 µg/mL had a significant higher failure rate (OR, 3.62; 95% CI 1.20-10.9). Lodise and colleges (38) compared the outcome between low and high vancomycin MICs in bacteremia with MIC ≥ 1.5 µg/mL (n=66) and MIC < 1.5 µg/mL (n=26) and an overall failure rate of respectively 36.4% versus 15.4% (p=0.49) and hospitalization duration stay of respectively median 21 (range 9-43) and 11 (range 9-17) (p=0.02). Switch to alternative antibiotic therapy was in 20% and 2% respectively needed. This results showed a trend, however was not statistically significant. Vancomycin resistant S. aureus is very rare, however the number of patients vancomycin-intermediate (VISA) and heterogeneous VISA are growing (39,40).

5. Teicoplanin

Teicoplanin is a semisynthetic glycopeptides, similar to vancomycin, however has no renal toxicity. There are studies which show equal results with teicoplanin and vancomycin, however teicoplanin is generally better tolerated. Rolston et al (41) performed a prospective, randomized, double-blind study comparing teicoplanin and vancomycin for the treatment of gram-positive bacteremias in neutropenic patients. This study showed also showed more adverse reactions occurred more often in the vancomycin group (31%) than in the teicoplanin group (9%; P = .06). Huang et al (42) performed so far the only retrospective study using teicoplanin versus vancomycin in MRSA endocarditis, however could not find any statistical significant difference in hospital mortality rate and therapy failure.

6. Tigecycline

Tigecycline is a glycylcycline antimicrobial agent with bacteriostatic elect against S. aureus including MRSA. This aantibiotic has limted side-effects, however meanly voting and nausea which can be dose limited. Due to the peak serum concentration it is only limited effective in bacteremia (36). On MRSA endocarditis there are no studies available.

7. Linezolid

Linezolid is an oxazolidinone is bacteriostatic against staphylococci. The advantage of this antimicrobial agent is the availability for oral and intravenouse application. There are some disadvantages of linazolid as it is limited to 28 days of application. Bone marrow suppression, thrombocytopenia and irreversible sensory and motory polyneuropathy have been reported as side-effects (36). Wilcox et al (43) showed in a Phase 3 study using linezolid in catheter-associated bacteremia a higher mortality then with vancomycin.

8. Telavancin

Telavancin is a lipoglycoprptide with needs to be applicated once a day. It is effective against MRSA, however also against VISA and VRSA. No clinical studies are available on MRSA endocarditis, however Smith et al showed some superiority in a range of in vitro biofilms models of multi-resistant *S. aureus* (44).

9. Daptomycin

Daptomycin is a cyclic lipopeptide with rapid bactericidal effect against S. aureus including MRSA. Although it is bactericidal it does not release endotoxin which will lead to toxic shock syndrome. The side effect of daptomycin is rabdomyolysis. Fowler et al (45) showed a similar effect on complicated bacteremia from daptomycin versus combined standard therapy, however there was a significant decrease on renal complications. A recent study of Dohmen et al (4) showed favourable results of daptomycin in Endocardtis including a high number of patients with MRSA endocarditis. Today there are several studies on daptomycin use in resistant and multi-resistant endocarditis which has also been included in several guidelines (16,17).

10. Surgical options

Current guidelines suggest that if surgery is performed short-term mortality will be decrease, in patients with specific symptoms or organisms; however it is unclear when surgery should be performed (46). Head et al (46) performed a meta-analysis on the current data available on medical or surgical therapy in AIE. These data support that surgery can decrease in-hospital mortality with an overall odds ratio of 0.47 (CI 0.38-0.58). however a marked statistically significant heterogeneity was found (I^2 =65%, p= 0.005) which means there is an excessive variation of compared results.

The first clinical trail, so called ENDOVAL is a randomized prospective multi-centre study to compare medical and surgery treatment in patients suffering from AIE. (47)

AIE caused by *S. aureus* are challenging and complicated due to large vegetations and embolic manifestations with increased mortality and if a multi-resistant *S. aureus* is found, surgery will always be indicated (46).

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