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MRSA in urology

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Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the main pathogen in healthcare-associated infections (HAI) worldwide, especially in hospitals and long-term care facilities. In the field of urology, however, there is a lack of comprehensive studies on MRSA infections. Therefore, urological infections caused by MRSA need to be examined more carefully in clinical trials, because urinary tract infections (UTI) and surgical site infections (SSI) caused by MRSA are both important HAI. Treatment of MRSA infection is usually empirical, but complete eradication of MRSA from the urinary tract is difficult because of complicating factors, such as indwelling catheters. There have been, however, no randomized clinical trials on treatment of the various MRSA infections in urological diseases to date. In recent years, community-associated MRSA (CA-MRSA) has been noted as an emerging pathogen causing SSI in the community. Therefore, we should know how to diagnose and treat such SSI caused by CA-MRSA, although they have been rare in the field of urology.

Keywords: methicillin-resistant S. aureus (MRSA), urology, urinary tract infection, surgical site infection

Summary of recommendations

Epidemology

1. If the rate of MRSA infections is high or increasing, active surveillance is recommended to prevent outbreaks (GoR B).

Pathogenesis of UTI caused by MRSA

2. Considering the multifactorial conditions of UTI caused by MRSA and their toxins further research on pathogenesis of MRSA UTI is needed (GoR C).

3. The potential reservoir of urinary MRSA for healthcare-associated infections (HAI) needs to be considered (GoR B).

Biofilm

4. Two virulence factors, beta-hemolysin and fibronectin-binding protein A, should be recognized in biofilm formation, because they are suggested to be associated with MRSA colonization and infection of the urinary tract (GoR C).

5. Clarithromycin could be considered for combination therapy because it has an inhibitory effect on the glycocalyx and biofilm formation of MRSA (GoR C).

MRSA in surgical site infections

6. The clinical relevance of SSIs caused by MRSA should be perceived, because the isolation rate of MRSA from SSIs was unchanged with regard to duration and type of antimicrobial prophylaxis (GoR B).

7. Preoperative urine culture could be critical for surveillance of MRSA, because MRSA isolated from wounds often correspond to that found in preoperative urine culture. Therefore, preoperative urine culture is also recommended, to exclude MRSA bacteriuria as a risk factor for SSIs in urological surgery (GoR B).

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Treatment

8. Glycopeptides could be used for treatment of MRSA UTI, although there is a lack of data on the treatment outcome and there are not enough data on their cost, toxicity and their availability (GoR C).

9. Daptomycin, a new lipopeptide antimicrobial agent, could be used as an alternative treatment option, because it is considered to be as effective as linezolid or vancomycin (GoR C).

10. In an in vitro study, vancomycin or rifampicin was ineffective in reducing biofilm formation and combined with linezolid both were also ineffective (GoR C).

11. Clarithromycin could be an alternative treatment for MRSA biofilm infection because it has an inhibitory action on the glycocalyx and biofilm of MRSA (GoR C).

12. Combination therapy with vancomycin and clarithromycin might be an alternative treatment option because of their efficacy in UTI caused by MRSA (GoR C).

Community- versus healthcare-acquired MRSA (CA- versus HA-MRSA)

13. Genetic markers can be an important diagnostic tool, because use of genetic markers may make it possible to discriminate between CA-MRSA and HA-MRSA (GoR A).

14. Daptomycin and tigecycline can be used for skin and soft-tissue infections caused by CA-MRSA, because double-blinded clinical trials revealed that daptomycin and tigecycline were equally effective for skin and soft-tissue infections by CA-MRSA (GoR A).

Prevention

15. For the purpose of preventing UTI and SSI caused by MRSA, specific recommendations should be deveoped although there are several educational guidelines for the prevention of UTI and SSI in general (GoR A).

1 Introduction

Staphylococcus aureus (*S. aureus*) is part of the normal flora on the human skin and in the nasal cavity. To date, various multidrug resistant (MDR) bacterial pathogens have been identified and methicillin-resistant *S. aureus* (MRSA) is one of the most important. MDR bacterial organisms have been mostly isolated in hospitals or long-term care facilities causing healthcare-associated infections (HAI). MRSA was first isolated in the United Kingdom in 1961 [1], [2] and has become widespread worldwide since then. In Japan, healthcare-associated MRSA (HA-MRSA) infection, including urinary tract infection (UTI) and surgical site infection (SSI), became an issue of clinical importance especially during the period 1980 to 1990. At that time, there were occasional outbreaks of HA-MRSA not only in intensive care units but also in urology wards. Although frequent outbreaks of HA-MRSA in the urology field have occurred rarely in Japan in recent years, the isolation rate of MRSA in the urological field has been either unchanged or increasing [3], [4], [5] despite implementation of the standard precautions advocated by the Centers for Disease Control and Prevention (CDC) of the United States. In this chapter, reports on mainly HA-MRSA isolated from urine or surgical sites in the urology field are reviewed and discussed.

2 Methods

A systematic literature search was performed in PubMed with the following keywords: *MRSA and urinary tract infection*, *MRSA and biofilm*, *MRSA and surgical site infection*, *MRSA and genital infection*, *community-associated MRSA and genital infection*, *MRSA and skin and soft tissue infection* , *MRSA and balanoposthitis*, and keywords above and treatment. Only English publications and Japanese publications with english abstracts were considered. Publications on other infections, such as pneumonia, sepsis and blood stream infection were excluded from the analysis. A total of 8,997 publications were found, which were screened by title and abstract, and finally 32 were included in the analysis.

The studies were rated according to the level of evidence (LoE) and the grade of recommendation (GoR)

using ICUD standards (for details see Preface) [6].

3 Definition

MRSA is defined as strains of *S. aureus* resistant to isoxaszoyl penicillins, such as methicillin and oxacillin. The definition of MRSA should be made according to clinical background at isolation and microbiological characteristic findings. In this chapter, MRSA is defined according to the clinical background or situation at isolation because we focused on clinical MRSA infection. We define both healthcare-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) mostly according to the guidelines developed by the British Society for Antimicrobial Chemotherapy [7]. We mainly focus on HA-MRSA, except in the section on CA-MRSA.

4 Healthcare-associated MRSA (HA-MRSA)

The pattern of transmission is dissemination within healthcare settings. Most HA-MRSA strains are diagnosed in inpatient settings. In general, the medical history shows the history of MRSA colonization, infection, recent surgery, antibiotic use and admission to a hospital or nursing home. When infection occurs in hospitals or healthcare settings, it is hospital or healthcare onset. When it occurs in the community e.g. after hospital discharge, it is community onset [6].

5 Community-associated MRSA (CA-MRSA)

The transmission pattern is just community-associated (CA). Diagnosis is done in outpatient or community settings. Medical history shows no significant history or healthcare contact. When infection occurs in an outpatient or community setting, it means community onset. When it occurs within 48 hours of hospital admission, it means hospital onset. Medical history shows no history of MRSA and patients do not have indwelling catheters [6] (LoE 4, GoR A). However, because *S. aureus* can persist for a longer duration, community-onset infections with possible CA-MRSA may indeed be caused by HA-MRSA.

6 MRSA in urinary tract infection

6.1 Epidemiology

The frequency of *S. aureus* urinary tract infections (UTI), mostly MRSA, has been gradually growing and it is a clinically important issue for HAI worldwide [8], [9]. In particular, bloodstream infection and pneumonia due to MRSA have been frequently observed [10]. The colonization with MRSA might be common in long term care facilities which relates to the relatively high prevalence in patients admitted to acute care geriatric departments (7.6%) compared to the acute care admission prevalence (2.2%) in other departments [11] (LoE 3).

In a report on the isolation rate of UTI bacterial pathogens for urology inpatients in Kobe, Japan [5], the prevalence rates of isolated urinary *S. aureus* were 1.9% from 1983 to 1987, 4.6% from 1988 to 1992, 5.3% from 1993 to 1997, and 6.6% from 1998 to 2002. The rate showed an increasing trend in the past years. The authors noted that the rate of MRSA showed a similar increasing trend and accounted for 82.2% of the entire *S. aureus* population in 2002 (LoE 3).

In a report examining how to determine the number of newly diagnosed cases of MRSA detected in a urology ward in Portsmouth, UK [12], the ratios of the number of newly diagnosed MRSA cases to total urological admissions were 0.82 in 2000, 0.89 in 2001, 1.00 in 2002, 0.67 in 2003, and 0.79 in 2004. The origins of isolates were urinary indwelling devices and urine, including three catheters, six nephrostomy tips, 19 suprapubic catheter tips, six urine samples from catheter, and 11 midstream urine samples. Other origins were wounds, nose, genitalia, groin, blood cultures, leg ulcers, sputum, and bronchoscopic lavage fluid. The proportion of MRSA isolates of urinary origin was 38.8% (45 of 116). They concluded that the number of new cases of MRSA remained constant and low acquisition rates were found (LoE 3).

The isolation rates of urinary MRSA varied among hospitals and facilities. Therefore we should track the isolation rates of urinary MRSA by surveillance of urinary pathogens and undertake standard precautions to prevent MRSA outbreaks (GoR B). If the rate of MRSA infection is relatively high or increasing, active surveillance cultures might be needed for effective prevention of outbreaks [13] (LoE 1a, GoR B).

6.2 Virulence in urinary tract

S. aureus strains, including MRSA (57%), isolated from patients with UTI were analyzed, and the prevalence of toxins and adhesion factors were determined [14]. Staphylococcal enterotoxin (SE) A (63%), SE D (20%), toxic shock syndrome toxin-1 (8.5%) and staphylococcal bicomponent leukotoxin LukE/LukD (60%) were produced by the isolates. In addition, *S. aureus* UTI has been found to be associated with implanted catheters and biomaterials. Adhesin factors, including clumping factor B (clfb), elastin-binding protein (ebp) and laminin-binding protein (lbp) are possibly involved in colonization on urinary catheters. In general, the pathogenesis of urinary MRSA is multifactorial and toxins causing UTI have not been clearly determined yet (LoE 3).

In a cohort study at a long-term care Veterans Affairs facility [15], 82% of 102 patients had urinary tract catheterization. In addition, 33% of the patients had symptomatic UTI with initial isolation of *S. aureus* and 13% were bacteremic. In this study, 86% of the initial urine cultures were MRSA-positive. Persistent carriers of urinary MRSA colonization were found to be at high risk for subsequent UTI and bacteremia. Therefore, the pathogenesis of urinary MRSA might be associated with urinary indwelling catheters and there was a relatively high prevalence of asymptomatic patients with urinary MRSA. In the patients with asymptomatic urinary MRSA, we should be aware of urinary MRSA being a potential reservoir for HAI (LoE 2, GoR B).

In a recent review of the pathogenesis of MRSA [16], selected virulence factors of *S. aureus* were investigated. Microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) are important surface proteins that can bind molecules such as collagen, fibronectin, and fibrinogen. MSCRAMMs might initiate catheter infections as well as endocarditis, osteomyelitis, septic arthritis and prosthetic-device infections. According to Muder et al. [16] there are no specific risk factors for UTI caused by MRSA except for urinary catheter or instrumentation (LoE 1a). The virulence of MRSA in the urinary tract depends on urinary catheters or instruments. Therefore UTI caused by MRSA can always be considered as complicated UTI. There are no definite virulence factors of MRSA reported for uncomplicated UTI to date.

6.3 Biofilm

Although there are relatively many patients with asymptomatic urinary MRSA, it rarely leads to severe systemic infection or febrile UTI, but occasionally it can lead to serious bacteremia. Biofilm formation in the urinary tract or on a urinary indwelling device is considered the main cause for asymptomatic bacteriuria (ABU). The mechanisms of biofilm formation in the urinary tract or on the urinary indwelling device [17] are as follows: once bacterial adhesion is completed on the surface of a foreign body such as a urinary catheter, a glycocalyx consisting of polysaccharides is produced outside the bacterial cells. Finally, the condition results in biofilm formation. The biofilm is considered to be antimicrobial-resistant, allowing bacteria to escape the host defense against infection and to escape the actions of antimicrobials. Two virulence factors, beta-hemolysin and fibronectin-binding protein A, were suggested to be associated with MRSA colonization and infection of the urinary tract [18] (LoE 2b). In an experimental study [17], the results suggested that clarithromycin had an inhibitory action on the glycocalyx and biofilm of MRSA (LoE 2b).

7 MRSA in surgical site infections

SSIs are strongly associated with morbidity and mortality for inpatients as HAI occur despite standard precautions. SSIs caused by MRSA are common in urology wards [3], [19]. Two transmission manners are hypothesized. One is preoperative dissemination from MRSA bacteriuria, with MRSA endogenously transmitted from the urinary tract to the wound. The other is exogenous contact transmission from hand to hand by the medical staff.

In a study [3], [4] on SSIs of open urological operations, the results showed that the most frequently isolated pathogen was MRSA. The isolation rate of MRSA from SSIs was unchanged regarding duration and type of antimicrobial prophylaxis. The frequencies of MRSA isolation from SSI were 73.3% in an uncontrolled antimicrobial prophylaxis group and 93.3% in a controlled antimicrobial prophylaxis group (LoE 2b). In addition, SSIs for radical cystectomy with urinary diversion using the small intestine, considered a contaminated operation by the CDC guidelines, were surveyed and reported [19]. The results showed that the overall incidence of SSIs was 33% and MRSA was the most frequently isolated bacterium, accounting for 38% of the isolated pathogens. This study showed that MRSA isolated from

wounds tended to correspond to that in preoperative infected urine (LoE 3). Another report [20] also showed that MRSA was frequently associated with SSI of open urological surgery and preoperative UTI was the most important risk factor for SSI (LoE 3).

There have been a few reports about SSIs of urological surgeries according to the classification of the CDC guideline; however, those reports indicated that MRSA was the organism most frequently isolated from wound SSIs. Preoperative MRSA bacteriuria is considered to be one of the risk factors for SSIs in urological surgery (LoE 3). As we know, the rate of SSI in clean or clean-contaminated surgery is much lower than that in contaminated surgery [3], [21]. Therefore, SSIs of urological surgeries caused by MRSA are mainly related to contaminated surgery such as radical cystectomy with urinary diversion as described in previous reports [3], [19], [20]. Unfortunately, no effective antimicrobial prophylaxis regimen against SSI caused by MRSA has been established yet. Because MRSA isolation rates are highly variable among medical centers, not every urologist may have a problem with SSI caused by MRSA. However, since MRSA is an important pathogen in HAI, we should establish effective standard precautions.

8 Treatment

Surprisingly few studies of antimicrobial treatment for UTI caused by MRSA have been performed to date. Applicable anti-MRSA drugs are generally likely to vary in each country or region. In addition, the frequency of uncomplicated UTI caused by MRSA is not high enough to establish a standard treatment regimen. In Japan, there are five applicable antimicrobial agents for MRSA infection, including UTI: vancomycin, teicoplanin, arbekacin, linezolid, and daptomycin. Regrettably, there have been no randomized controlled studies with these antimicrobial agents [22] although such studies might lead to favorable treatment outcomes.

In the guidelines of the United Kingdom [23], tetracycline is recommended as the first-line treatment regimen for UTI caused by susceptible MRSA. The guidelines state that there is a lack of data on the treatment outcomes of glycopeptides for UTI caused by MRSA and not enough data on their cost, toxicity and the availability of other agents. Therefore, well designed basic, clinical and epidemiological studies on UTI caused by MRSA are needed (LoE 4, GoR C). In patients with MRSA bacteremia due to severe febrile UTI, a minimum treatment duration of 14 days with glycopeptides or linezolid is recommended in the guidelines [Liu et al. 2011 CID-IDSA guidelines].

In an in vitro study daptomycin, a lipopeptide antibiotic [24], was considered to be as effective as linezolid or vancomycin (LoE 2b, GoR C). Unfortunately, there has been no clinical study with daptomycin in the field of urology, so it should be studied in clinical trials in the future.

In the clinical situation, it is almost impossible to eradicate urinary MRSA completely from the catheterized urinary tract. Exchange of the urinary catheter is one possible procedure to eradicate urinary MRSA, but the complicated urinary tract condition generally makes eradication of MRSA difficult, because it is closely associated with biofilm formation on the urinary catheter. An in vitro study [25] revealed that treatment with vancomycin or rifampicin to reduce biofilm growth was ineffective and treatment with linezolid was also ineffective [26] (LoE 2b, GoR C). Another study [17] revealed that clarithromycin had an inhibitory action on the glycocalyx and biofilm of MRSA and that combination therapy with vancomycin and clarithromycin might be efficacious for UTI caused by MRSA (LoE 2b, GoR C).

To date, there have been no well performed clinical trials for the treatment of UTI caused by HA-MRSA or for the inhibition of MRSA biofilm formation on urinary catheters. Current treatments for these conditions tend to be in general empirical.

9 CA-MRSA

CA-MRSA has been especially noted as a pathogen causing skin and soft-tissue infections in the community. In the field of urology, a few special genital or perineal infections might be related to CA-MRSA. However, there has been an epidemic of CA-MRSA in recent years. Therefore, we should know how to diagnose and treat the skin and soft-tissue infections caused by this pathogen.

Use of genetic markers may make it possible to discriminate between CA- and HA-MRSA [27] (LoE 4, GoR A). In the United States, CA-MRSA has the staphylococcal cassette chromosome (SCC) *mec* type IV and the gene for Panton-Valentine leukocidin (PVL) [27] (LoE 4, GoR A).

10 Balanoposthitis caused by CA-MRSA

There has been just one published case clearly caused by MRSA to date [28]. The history revealed that i an insulin dependent diabetic male balanoposthitis was caused by HA-MRSA. In contrast we treated one case with balanoposthitis caused by CA-MRSA as determined by clinical history (no inpatient or outpatient history), although SCC mec type IV and the gene for PVL could not be examined (LoE 3, GoR C).

To date, skin infections caused by CA-MRSA have not been a critical issue in urology. However, impetigo, folliculitis, furuncles, and abscesses caused by CA-MRSA are epidemic worldwide. We should be aware that such infections could occur also in urology in the future.

11 Treatment for CA-MRSA skin and soft-tissue infections

There are four US Food and Drug Administration (FDA)-approved anti-MRSA drugs: vancomycin, linezolid, daptomycin, and tigecycline. Vancomycin is a standard drug for SSI caused by CA-MRSA [27]. Therefore, clinical trials were carried out by comparing the other drugs with vancomycin. An open-label clinical trial revealed that the cure rate for CA-MRSA infections was higher in the group treated with linezolid (88.6%) than in that with vancomycin (66.9%) [29]. Double-blinded clinical trials revealed that daptomycin and tigecycline were equally effective for skin and soft-tissue infections caused by CA-MRSA [30], [31] (LoE 1b, GoR A). In addition, oral antimicrobial agents such as trimethoprim-sulfamethoxazole, doxycycline, minocycline, rifampin, clindamycin, and fusidic acid are also recommended; however, clinical trials in the field of urology are lacking.

12 Prevention

Prevention of both UTI and surgical site infection caused by MRSA is most important especially in the urology ward of healthcare settings. There are several educational guidelines for prevention of UTI and surgical site infection [32], [33] (LoE 1a, GoR A). These guidelines are commonly available for almost all nosocomial pathogens of HAI including HA-MRSA. Although those are not the guidelines for the prevention of particular MRSA transmission, the detailed content can also cover the field of urology. It is strongly recommended that urologists peruse these guidelines.

13 Further research

There is a lack of comprehensive studies of MRSA infection in the field of urology, although UTI caused by MRSA is an important origin of HAI and surgical site infections.

14 Conclusions

Urinary MRSA is a potential reservoir for HAI. If the rate of MRSA infection is high or increasing, active surveillance might be important for effective prevention of outbreaks. The pathogenesis of urinary MRSA is multifactorial and toxins causing urinary tract infections have not been clearly determined yet. MRSA is frequently associated with SSI of open urological surgery and preoperative MRSA bacteriuria is considered to be one of the risk factors for SSIs in urological surgery.

There is a lack of data on the treatment of UTI caused by MRSA with glycopeptides, e.g. vancomycin, and with other agents, such as linezolid and daptomycin. In an in vitro study, treatment with vancomycin, rifampicin, or linezolid was ineffective to reduce biofilm growth. Clarithromycin had an inhibitory effect on the glycocalyx and biofilm of MRSA in contrast to the agents mentioned before. Therefore a combination therapy with vancomycin and clarithromycin might be efficacious for the treatment of UTI caused by MRSA. Daptomycin and tigecycline were equally effective for SSI caused by CA-MRSA. There are several educational guidelines for prevention of UTI and SSI.

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