Daptomycin treatment in patients with resistant staphylococcal periprosthetic joint infection

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Abstract

Background: Resistant staphylococcal organisms remain a serious problem in the treatment of periprosthetic joint infection (PJI). Higher failure rates have been reported when vancomycin was used. The purpose of this study was to assess the clinical dosage, effect, and safety of daptomycin in patients with resistant staphylococcal PJI.

Methods: We retrospectively enrolled patients with hip or knee PJI who were treated with daptomycin in our institution (n = 16) from January 2013 to December 2014 with a minimum follow-up of 2 years. The patients received daptomycin when glycopeptide could not be used due to multiple resistance, any adverse reaction, chronic kidney disease stage 3 or worse, and previous treatment failure with glycopeptide or empirical therapy.

Results: These patients received daptomycin at a median dose of 8.3 mg/kg per day for a median duration of 14 days. The overall treatment success rate was 87.5% (14 of 16 cases) after a median follow-up period of 27 months. In the subgroups of acute and chronic PJI, the success rate was 80% and 91%, respectively. One patient developed asymptomatic transient serum aspartate transaminase (AST) elevation. No severe side effects such as myositis, acute renal failure due to rhabdomyolysis or eosinophilic pneumonia were found in our series.

Conclusion: Relatively high daptomycin doses combined with adequate surgical intervention were effective in treating resistant staphylococcal PJI. Daptomycin is an option worthy of consideration in PJI patients for whom glycopeptide treatment is unsuitable. Further prospective randomized comparative study is needed in the future.

Keywords: Daptomycin, Prosthetic joint infection, Staphylococcus aureus, Resistant
vancomycin or teicoplanin. Higher treatment failure was noted when intravenous vancomycin had been administered in cases of resistant staphylococcal PJI with minimum inhibitory concentrations (MICs) > 1.5 mg/L [10, 11].

Daptomycin is a newer option for the treatment of PJI owing to its excellent bactericidal activity against gram-positive bacteria, especially MDR strains [12]. The modest advantage of daptomycin over other drugs reflects the presence of a higher fraction of surface or near-surface organisms in an in vitro model; these organisms would be expected to be remain susceptible to the rapid cidal activity of daptomycin [13]. Furthermore, daptomycin penetrates bone effectively and disrupts multiple bacterial plasma membrane functions without penetrating the cytoplasm [14]. The clinical efficacy and safety of daptomycin have been proven in patients with renal impairment, especially patients with vancomycin-associated nephrotoxicity [15]. However, few studies have investigated daptomycin as a possible option for the treatment of resistant staphylococcal PJI [16, 17]. We believe daptomycin to be effective and well-tolerated in patients with PJI caused by resistant staphylococcal organisms. The study aimed to review clinical practice in terms of daptomycin treatment, with specific emphasis on its clinical outcome, safety, and tolerability in patients with resistant staphylococcal PJI.

**Methods**

We retrospectively enrolled patients with hip or knee PJI who were treated with daptomycin in our institute from January 2013 to December 2014 with a minimum follow-up of 2 years. We recorded patient demographics, comorbidities, the estimated glomerular filtration rate (eGFR) [18], the location of the prosthesis, type of PJI, surgical methods, microbiological results, dosages and treatment duration, in addition to the reason for daptomycin treatment, its side effects and clinical efficacy. All patients were classified based on the Tsukayama classification [5], which categorizes PJI according to the duration from prosthesis implantation.

Standard protocols for PJI treatment were adopted. For type II and type III acute infection, urgent surgical debridement with exchange of mobile parts and prosthesis retention were performed, followed by systemic antibiotic therapy for 4–6 weeks. In type IV chronic infection, a two-stage reimplantation protocol was adopted as previously described [19]. In the first stage, the operative procedure included removal of the implant, aggressive debridement of the joint and insertion of a high-dose, antibiotic-loaded cement spacer or beads for topical antibiotic delivery. To effectively target the causative pathogen and deliver antibiotic treatment, joint synovial fluid was collected in a blood culture bottle, in addition to 3 to 4 sets of tissue cultures. The causative microorganism was confirmed if at least two positive samples of the same microorganism were identified or matched to blood, joint synovial fluid, or tissue culture. After the culture results were known, an infectious disease specialist was consulted to recommend appropriate antibiotics.

Daptomycin was indicated if the patient’s condition met any one of the following criteria: glycopeptide antibiotics could not be used due to resistance or any adverse reaction such as allergy or phlebitis; vancomycin MIC > 1.5 mg/L; previous treatment failure with intravenous glycopeptide; empirical therapy in cases of suspected MDR Gram-positive cocci PJI; and chronic kidney disease (CKD) stage 3 or worse (eGFR < 60 mL/min/1.73m²) [16]. Daptomycin treatment in every case was initiated after consultation with infectious disease specialists, and the dosage and duration were also based on specialist guidance. Based on the recent Infectious Diseases Society of America guidelines and clinical reports [16, 17, 20], daptomycin may be administered as an alternative option to manage resistant staphylococcal PJI at a dose ≥ 6 mg/kg per day. In patients with advanced renal insufficiency (stage 4 or worse), daptomycin should be administered every 48 h [21].

All patients had received oral antibiotics following parenteral antibiotics after discharge. The median period of oral antibiotic treatment after discharge was 35 days (range: 6–65 days). The oral antibiotic combinations included sulfamethoxazole/trimethoprim and rifampicin or fusidic acid and rifampicin. The criteria for reimplantation surgery included a reduced erythrocyte sedimentation rate (ESR), return to near-normal C-reactive protein (CRP) level, and a satisfactory wound status. All reimplantations were performed after a 2-week antibiotic holiday without elevation of ESR and CRP. After prophylaxis with intravenous 1 g vancomycin, new prostheses were reimplanted with 1 g daptomycin in a pack of 40 g of bone cement [Stryker Orthopaedics, Mahwah, New Jersey] for knee or hip prosthesis fixation if cement fixation was needed in the second stage. After reimplantation, the patients received systemic antibiotics until the intraoperative culture results showed negative finding. No further oral antibiotics were administered after discharge.

A successful clinical outcome after daptomycin therapy was defined as resolution of clinical signs and symptoms and/or no prolonged suppressive oral antibiotic treatment, and CRP and ESR levels that had returned to the normal range at the last follow-up. Failure was defined as an inadequate response to therapy, worsening or new/recurrent signs and symptoms, the need for a change of parenteral antibiotic therapy or prolonged suppressive oral antibiotic treatment, a positive culture at the end of therapy, or the requirement for re-operation [22]. Prolonged suppressive oral antibiotic treatment was defined as oral antibiotic therapy prescribed for a duration longer than 6 months...
Patients were assessed weekly for daptomycin adverse effects following initiation of daptomycin treatment, including serum creatine phosphokinase (CPK), liver enzymes, and other associated blood parameters. Other adverse effects, including low blood pressure, high blood pressure, swelling, insomnia, rash, diarrhea, abdominal pain, eosinophilia and eosinophilic pneumonia, dyspnea, fever, hypersensitivity, myopathy and rhabdomyolysis, were also monitored.

**Results**

Sixteen patients were treated with daptomycin for resistant staphylococcal PJI during the study period and completed follow-up for at least 2 years; one patient was excluded due to loss to follow-up within 6 months. The median age of the 16 patients was 66.5 years (range: 52–86 years). The types of infection were as follows: 5 patients with acute infection (type II and III) who had received surgical debridement and implant retention; and 11 patients with chronic infection (type IV) who had received two-stage reimplantation (Table 1). Methicillin-resistant *Staphylococcus aureus* (MRSA) accounted for 62.5%, and methicillin-resistant coagulase-negative Staphylococci (MRCoNS) for 37.5%. The reasons for using daptomycin included vancomycin MIC > 1.5 mg/L in 1 case, previous glycopeptide failure in 3 cases, and MRSA resistance. The treatment was shifted to teicoplanin, and severe, persistent symptoms were noted after 21 days of daptomycin therapy (8.3 mg/kg per day). The patient's CRP and ESR levels reached the normal ranges. Finally, the patient recovered well, and no recurrent infection occurred during a 34-month follow-up period. The patient’s CRP and ESR levels reached the normal ranges. Finally, the patient recovered well, and no recurrent infection occurred during a 34-month follow-up period. The other case of treatment failure (Patient 10) was a 60-year-old male who underwent resection arthroplasty of the left hip for chronic PJI. After the surgery, daptomycin therapy (6.3 mg/kg per day) was instigated, but persistently high CRP and ESR levels with left thigh erythema and pus discharge were noted after 21 days of daptomycin therapy. The treatment was shifted to teicoplanin, and several debridements were performed. After a six-month follow-up period, the patient’s clinical symptoms had improved, and the CRP and ESR levels had reached the normal ranges. Thus, reimplantation surgery was performed, and no recurrent infection occurred within a 24-month follow-up period.

**Discussion**

Vancomycin has been considered the first choice parenteral antibiotic for the treatment of resistant...
| Patients | Surgical procedure    | Pathogen     | DAP Reason   | DAP dosage (mg/kg/day) | DAP duration (days) | Total parental antibiotics (days) | Total time under DAP (%) | Adverse effects | Outcome | Follow-up (months) |
|----------|----------------------|--------------|--------------|------------------------|---------------------|-----------------------------------|--------------------------|-----------------|---------|-------------------|
| 1        | two-stage reimplantation | MRSA      | intolerance  | 10                     | 10                  | 13                                | 77                       | none            | success | 26                |
| 2        | two-stage reimplantation | MRSA      | intolerance  | 8.3                    | 18                  | 35                                | 51                       | none            | success | 27                |
| 3        | two-stage reimplantation | MRCoNS  | CKD stage 5 | 3.3                    | 12                  | 15                                | 80                       | none            | success | 25                |
| 4        | DAIR         | MRCoNS  | intolerance  | 8.3                    | 23                  | 23                                | 100                      | none            | success | 41                |
| 5        | two-stage reimplantation | MRSA    | CKD stage 3 | 7.7                    | 18                  | 13                                | 100                      | none            | success | 23                |
| 6        | DAIR         | MRSA    | teicoplanin failure | 10.6                  | 11                  | 21                                | 52                       | AST elevation | success | 25                |
| 7        | two-stage reimplantation | MRCoNS | intolerance  | 8.3                    | 12                  | 26                                | 46                       | none            | success | 27                |
| 8        | two-stage reimplantation | MRSA    | intolerance  | 7.2                    | 18                  | 49                                | 37                       | none            | success | 24                |
| 9        | DAIR         | MRSA    | vancomycin MIC >1.5 mg/L | 10                    | 27                  | 32                                | 84                       | none            | success | 26                |
| 10       | two-stage reimplantation | MRSA    | empirical    | 6.3                    | 21                  | 33                                | 64                       | none            | failure  | 24                |
| 11       | two-stage reimplantation | MRCoNS | intolerance  | 10                     | 13                  | 36                                | 36                       | none            | success | 34                |
| 12       | two-stage reimplantation | MRSA    | teicoplanin failure | 6.7                    | 14                  | 39                                | 36                       | none            | success | 36                |
| 13       | DAIR         | MRSA    | intolerance  | 7.4                    | 14                  | 20                                | 70                       | none            | success | 29                |
| 14       | two-stage reimplantation | MRCoNS | intolerance  | 8.3                    | 16                  | 22                                | 73                       | none            | success | 36                |
| 15       | DAIR         | MRSA    | empirical    | 8.3                    | 26                  | 66                                | 39                       | none            | failure  | 34                |
| 16       | two-stage reimplantation | MRCoNS | empirical    | 10.6                   | 11                  | 19                                | 58                       | none            | success | 42                |

DAP Daptomycin, MRSA Methicillin-resistant Staphylococcus aureus, MRCoNS Methicillin-resistant coagulase-negative staphylococci, CKD chronic kidney disease, MIC Minimum inhibitory concentration, AST Aspartate aminotransferase; intolerance, allergy to glycopeptide or phlebitis
staphylococcal PJI [4]; however, vancomycin has not been demonstrated to result in a favorable outcome in patients with methicillin-resistant staphylococcal PJI [24]. Furthermore, a risk of vancomycin-induced nephrotoxicity in the population with chronic kidney disease has also been reported [25]. In a recent meta-analysis study related to MRSA-infected patients, high vancomycin trough levels were recognized as an independent factor associated with risk of nephrotoxicity [26]. For the above reasons, vancomycin is not optimal for the treatment of resistant staphylococcal PJI in patients with CKD. Daptomycin is indicated when vancomycin or teicoplanin cannot be used due to intolerance, allergy, or previous treatment failure, or in patients with poor renal function. In our study, two patients with CKD were successfully treated with daptomycin without acute kidney injury. Daptomycin, at a median dose of 6.0 mg/kg administered every 24 h or 48 h, showed efficacy and safety in patients with renal impairment. The authors concluded that daptomycin is a safe and effective therapeutic agent for use in patients with renal impairment for whom previous treatment had failed or in those who cannot tolerate vancomycin.

There were some limitations of our study. First, the lack of randomized comparative information limited the clinical results. Second, the data pool was too small to obtain statistically-significant results. Third, in chronic infection cases, the component of antibiotic-loaded cement spacer or beads used was not the same in each case. Fourth, the duration of oral antibiotic therapy following parenteral antibiotics varied in this study in the first stage, and postoperative oral antibiotics were not prescribed after reimplantation. Oral antibiotics can effectively suppress manifestations of residual infection, and some studies have suggested that postoperative oral antibiotics can effectively reduce the re-infection rate following two-stage revision arthroplasty [27]. Finally, we did not provide information regarding the drugs or the concentrations of antibiotic-impregnated cement routinely used in the two-stage procedure.

The overall success rate of treatment of resistant PJI in this study was 87.5%. In the subgroup of acute PJI cases, treatment with daptomycin, debridement and prosthesis retention was successful in 80% of patients, and for chronic cases, the success rate increased to 91%. The success rate of daptomycin treatment for PJI has varied greatly among different reports in the literature, from 54.5% to 78.6% (Table 3) [16, 17, 21, 28, 29]. The reason for this variability may be related to an inadequate dosage of daptomycin prescribed in some studies. For example, Rao et al. used daptomycin at a median dosage of 4 mg/kg per day in 11 cases, and achieved a lower success rate of 54.5% [21]. Antony et al. reported a 38% success rate among patients treated with 4 mg/kg per 24 or 48 h as compared with a 77% success rate among patients who received daptomycin at 6 mg/kg per day [26]. Byren et al. [17] used daptomycin at 6 or 8 mg/kg per day for 6 weeks in a randomized trial during the two-stage reimplantation process, and found that the higher-dose group (8 mg/kg per day) exhibited a higher treatment success rate than the lower-dose (6 mg/kg per day) group. Other clinical studies also supported the efficacy and safety of higher daptomycin doses up to 8 mg/kg per day or more [30, 31]. In our study, patients who received an adequate dosage of daptomycin with suitable surgical intervention for the treatment of PJI (median dosage of 8.3 mg/kg per day) had successful outcomes. However, in 50% of patients (2 of 4) in whom treatment failed when daptomycin was administered for empirical reasons, following shifting to teicoplanin therapy, success was achieved. This would seem to suggest that daptomycin is problematic as a first-line treatment, and that the treatment outcome may be impacted by the initial antibiotic, multiple surgical procedures, and further oral therapy. We believe that daptomycin cannot replace glycopeptide for the treatment of resistant staphylococcal PJI, but it is an option worthy of consideration.

Daptomycin has been reported to be well-tolerated in several clinical trials with a wide therapeutic dosage window. However, it can occasionally cause adverse effects,

| Study                  | No of patients | Daptomycin dose (median, mg/kg/day) | Daptomycin duration (median, days) | Adverse event (%) | Success rate (%) |
|-----------------------|----------------|-----------------------------------|-----------------------------------|------------------|------------------|
| Antony et al. [20] (2006) | 8              | 6.0                               | 42                                | 6.5              | 75.0             |
| Rao et al. [21] (2006)   | 11             | 4.0                               | 42                                | NA               | 54.5             |
| Antony et al. [28] (2009) | 30            | 6.0                               | 37                                | 3.3              | 66.7             |
| Corona et al. [16] (2012) | 14            | 6.6                               | 44                                | 21.4             | 78.6             |
| Byren et al. [17] (2012)  | 24             | 6.0                               | 42                                | 8.0              | 58.3             |
|                        | 13             | 8.0                               | 42                                | 16.7             | 60.9             |
| Our study              | 16             | 8.3                               | 14                                | 6.3              | 87.5             |
such as elevation of liver enzyme and CPK levels, myalgia, rhabdomyolysis, and acute renal failure [32]. In addition, concomitant use of daptomycin and statins carries concern regarding potential synergistic musculoskeletal toxicity [33]. The adverse effects are fewer if a shorter course of systemic daptomycin is prescribed [19]. Regular monitoring of serum creatine and CPK levels along with symptoms of myopathy would be a useful strategy in patients receiving daptomycin treatment. In our short patient series, we observed one case of asymptomatic AST elevation judged as directly associated with daptomycin administration at a dosage of 10.6 mg/kg per day, as the patient was not taking statins or any medication related to the side effect of myositis (Patient 6). In this patient, the AST level normalized rapidly, and clinically-acceptable tolerability to daptomycin was observed. Otherwise, no eosinophilic pneumonia was noted in our patients, but we are aware that this is a potentially deadly complication if not well-managed.

To date, the development of resistance to daptomycin of Staphylococcus aureus has been a concern. A number of factors are associated with loss of daptomycin susceptibility in Staphylococcus aureus. A recent review identified 62 clinical cases in 36 case reports in which daptomycin resistance was observed. In that review, 40 cases occurred after glycopeptide therapy and 15 after vancomycin and/or daptomycin therapy [34]. Another study demonstrated that under a daptomycin dose of <6 mg/kg per day, previous use of teicoplanin and a longer treatment duration were potential risk factors for decreased susceptibility to daptomycin [35]. The mechanism might be due to alterations of the bacterial cell membrane and cell wall [36].

Conclusion
In our practice, daptomycin combined with suitable surgical intervention had a high success rate in treating resistant staphylococcal PJI. Daptomycin could be a treatment option for patients with these infections, especially in those with chronic kidney disease or intolerance to glycopeptide antibiotics. Further prospective randomized comparative study is needed in the future. Otherwise, we should pay attention to potential serious adverse events and monitor the serum liver enzyme and CPK levels closely.

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Availability of data and materials
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Authors’ contributions
YJC and MSL was involved in conception and design of the study, YJC and CHL collected and analyzed the data together with PCL. FCK and YJC were involved in literature search, in drafting the manuscript and finalizing the version to be published. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The protocols used in this retrospective study was reviewed and approved by the institutional review board of Chang Gung Medical Foundation. According to the Taiwanese national legislation, patient consent is not required in retrospective studies.

Consent for publication
Not applicable.

Competing interests
All the authors declared that they have no competing interests.

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Abbreviations
AST: Serum aspartate transaminase; CKD: Chronic kidney disease; CPK: Serum creatine phosphokinase; CRP: C-reactive protein; DAP: Daptomycin; eGFR: Estimated glomerular filtration rate; ESR: Ethyrsocyte sedimentation rate; MDR: Multi-drug-resistant; MIC: Minimum inhibitory concentration; MRCoNS: Methicillin-resistant coagulase-negative Staphylococci; MRSA: Methicillin-resistant Staphylococcus aureus; PJI: Periprosthetic joint infection
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