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Daptomycin for the treatment of *Staphylococcus aureus* infections complicated by septic pulmonary emboli☆,☆☆

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ABSTRACT

The management of *Staphylococcus aureus* bacteremia is limited by high rates of methicillin resistance and the paucity of antibiotic agents with proven efficacy in complicated infectious syndromes, such as endocarditis. Vancomycin is the mainstay of therapy; however, salvage therapy is frequently required due to persistence of infection or drug toxicity. Daptomycin is FDA-approved for *S. aureus* bacteremia and right-sided endocarditis, but controversy exists regarding the role of this agent in the setting of septic pulmonary emboli. Sequestration by pulmonary surfactant renders daptomycin ineffective in bronchoalveolar pneumonia; however, the impact of this drug property on efficacy in hematogenous pulmonary infections is unclear. Herein we review the available evidence in order to inform the rationale use of daptomycin in *S. aureus* infections complicated by septic pulmonary emboli.

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1. Introduction

Septic pulmonary emboli (SPE) are a complication of infective endocarditis (IE) most commonly associated with right-sided disease involving the tricuspid or pulmonary valves (Baddour et al., 2015). Right-sided IE represents 10–20% of all endocarditis cases and is characterized by distinctly different risk factors from left-sided disease (Murdoch et al., 2009; Remetz and Quagliarello, 1992). Historically, SPE were primarily associated with intravenous drug use; however, healthcare-associated risk factors have been identified, such as central venous catheters and intravascular devices (Cook et al., 2005; O'Donnell et al., 1995; Wojda et al., 2016). *Staphylococcus aureus* is the most commonly isolated organism in patients with IE and SPE. Due to high bacterial burden and increasing rates of methicillin-resistant *S. aureus* (MRSA), management of this infectious syndrome can be challenging (Baddour et al., 2015).

Daptomycin is approved by the Food and Drug Association (FDA) for right-sided IE and is recommended by the American Heart Association (AHA) and Infectious Diseases Society of America (IDSA) as an alternative to vancomycin for native valve endocarditis due to *S. aureus* (Baddour et al., 2015). While daptomycin appears to be a viable option for patients with right- or left-sided *S. aureus* IE, its utility in the treatment of IE complicated by SPE is controversial. Additionally, use of daptomycin in this setting has been a subject of debate due to known inactivation by pulmonary surfactant (Silverman et al., 2005). The

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significance of this mechanism is of questionable importance due to the hematogenous source of infection. No controlled studies have been designed specifically to evaluate daptomycin in this setting; however, in recent years, several reports detailing use of daptomycin for the treatment of IE complicated by SPE have emerged. Because treatment options for MRSA IE are limited, we sought to evaluate the available literature in order to determine whether daptomycin is a viable option for the treatment of IE complicated by SPE.

2. Treatment options for *S. aureus* infective endocarditis: primary and salvage therapies

The AHA and IDSA guidelines for the treatment of infective endocarditis in adults recommend antistaphylococcal penicillins and vancomycin as the first line agents for IE due to methicillin-susceptible (MSSA) and MRSA, respectively (Baddour et al., 2015). Daptomycin is listed as a first line alternative to vancomycin for native valve MRSA IE; however, it is not currently recommended in patients with valvular prostheses. For patients with MSSA IE and a history of penicillin allergy, cefazolin and vancomycin are the recommended alternatives for non-type I and type I hypersensitivity reactions, respectively. Notably, the guidelines emphasize daptomycin as an alternative to vancomycin for patients with severe allergies due to the increasing evidence of vancomycin inferiority in severe MSSA infections (Baddour et al., 2015).

Clinical outcomes data and therapeutic options for the salvage treatment of MRSA IE are limited. Vancomycin remains the mainstay of therapy; however, its use is complicated by slow bactericidal activity, need for frequent therapeutic drug monitoring, and risk of significant toxicity – most notably nephrotoxicity. Daptomycin has numerous additional advantages, including once daily dosing in normal renal function, rapid bactericidal activity, few adverse effects, and bacterial biofilm penetration at high doses (Smith et al., 2014). Linezolid offers the convenience of a highly bioavailable oral dosage form, but its use is limited by bacteriostatic activity, drug–drug interactions, and potential for serious myelosuppression and neuropathy with prolonged therapy (Zahedi Bialvaei et al., 2017). Additionally, outcomes with linezolid in patients with *S. aureus* IE have been disappointing (Baddour et al., 2015; Britt et al., 2015; Falagas et al., 2006; Munoz et al., 2007; Schwalm et al., 2004). Quinupristin-dalfopristin retains activity against MRSA; however, experience in IE is limited to case reports and therapy is frequently limited by significant arthralgias/myalgias (Drew et al., 2000; Sander et al., 2002). Telavancin, a lipoglycopeptide, has been used in small case reports and case series for salvage treatment of MRSA IE (Marcos and Camins, 2010; Nace and Lorber, 2010; Ruggero et al., 2015). Trimethoprim-sulfamethoxazole is frequently active in vitro against MRSA; however, it was inferior to vancomycin in a randomized controlled trial of intravenous drug users with severe staphylococcal infections (Markowitz et al., 1992). Ceftaroline is a promising new antibiotic with preliminary data demonstrating efficacy in complicated *S. aureus* infections; however, there are currently insufficient data to recommend routine use in IE (Casapao et al., 2014; Ho et al., 2012; Lin et al., 2013; Zasowski et al., 2017). Daptomycin in combination with beta-lactams, including ceftaroline, or trimethoprim-sulfamethoxazole may be useful in salvage therapy; however, available outcomes data are limited.

3. History of daptomycin for pulmonary source infections: animal models and clinical trials

It is now widely known that daptomycin is ineffective for the treatment of pulmonary source infections due to binding and sequestration within pulmonary surfactant (Silverman et al., 2005). However, daptomycin was initially investigated in animal models of *S. aureus* lung infection with promising results (Kephart and Esposito, 1988; Verghese et al., 1988). In a hamster model of MRSA pneumonia, both daptomycin and vancomycin increased animal survival relative to placebo ($P < 0.01$) with no difference in efficacy between the two drugs ($P > 0.05$) (Kephart and Esposito, 1988). Additionally, only daptomycin increased pulmonary bacterial clearance over placebo at both high and low inocula. In another hamster model of pneumonia, daptomycin effectively increased survival of animals infected with one MRSA strain but failed against a second strain (Verghese et al., 1988). Finally, in a distinctly different murine pulmonary infection model of inhalation anthrax, daptomycin improved animal survival to day 43 over placebo ($P < 0.01$) and demonstrated similar efficacy to ciprofloxacin ($p > 0.30$) (Heine et al., 2010).

Based on these data, two phase III studies were conducted to assess the safety and efficacy of daptomycin in the treatment of community-acquired pneumonia (CAP) (Pertel et al., 2008). These randomized, double-blind trials enrolled patients with CAP who required hospitalization and at least 5 days of intravenous antibiotic therapy. Patients were randomized to either daptomycin (4 mg/kg) or ceftriaxone (2 g) administered with the option to use open-label aztreonam for suspected or confirmed gram-negative pathogens. The primary outcome was clinical success measured seven days after completion of therapy. At the conclusion of the first study, daptomycin failed to demonstrate non-inferiority and enrollment in the second study was terminated. The pooled data demonstrated that clinical success with daptomycin was inferior to ceftriaxone in both the intention to treat (70.9% vs 77.4%; 95% confidence interval [CI] for difference, −12.4% to −0.6%) and clinically evaluable populations (79.4% vs 87.9%; 95% CI for difference, −13.8% to −4.2%).

To investigate the mechanism underlying this unexpected failure of daptomycin, Cubist conducted multiple in vitro and animal model studies of daptomycin in pulmonary infections (Silverman et al., 2005). First, mice were intranasally infected with *S. pneumoniae* or MRSA to produce a model of bronchial-alveolar pneumonia. In this model, daptomycin failed to reduce the pulmonary bacterial load of both *S. pneumoniae* and MRSA at 24 hours while ceftriaxone demonstrated bactericidal activity against *S. pneumoniae*. Next, a rat model of hematogenous pneumonia was produced with both MSSA and MRSA and, in this model, daptomycin led to a numerically greater reduction in pulmonary bacterial load at day seven than either nafcillin against MSSA or vancomycin against MRSA.

The discrepancy between daptomycin activity in bronchial-alveolar and hematogenous models of pneumonia led the investigators to conclude that it was likely a factor specific to the environment of the interior airway that led to the failure of daptomycin in pneumonia trials (Silverman et al., 2005). Pulmonary surfactant is a component unique to the interior airway made up primarily of lipids and protein, similar to a bacterial cell membrane, which they hypothesized may be able to bind and sequester daptomycin. To investigate this interaction, daptomycin susceptibility testing was performed against *S. pneumoniae* in 1% and 10% surfactant with resulting 16–32- and 100-fold decreases in potency, respectively. Finally, a fluorescence assay confirmed daptomycin binding and sequestration in pulmonary surfactant.

The history of the discovery of interaction between daptomycin and pulmonary surfactant is instructive when considering its clinical use for pulmonary infections. A notable finding of the animal data summarized above is that daptomycin was universally effective against pulmonary infections associated with a hematogenous source or significant pulmonary tissue disruption. The hamster models of *S. aureus* pulmonary infection were associated with necrotizing pneumonia, severe tissue disruption, and bacteremia (Kephart and Esposito, 1988; Verghese et al., 1988). Similarly, early dissemination of infection beyond the interior of the lungs occurred in the murine model of inhalation anthrax (Heine et al., 2007). Similarly, daptomycin provided a numerically greater reduction in the pulmonary burden of *S. aureus* than either nafcillin or vancomycin in the hematogenous pneumonia model performed by Cubist (Silverman et al., 2005). Therefore, it seems reasonable to conclude that in animal models of hematogenous pulmonary infection or pulmonary infections associated with significant tissue

disruption, daptomycin was at least as effective as comparator antimicrobials. This finding is mechanistically plausible given an infection that arises from hematogenous dissemination and extension from the vascular endothelium to the adjacent lung parenchyma accompanied by only minimal invasion to the alveolar space. The interaction with daptomycin and pulmonary surfactant, then, should have little bearing on the efficacy of daptomycin in eradicating the primary foci of infection. A study designed to test this hypothesis using a murine model of hematogenous pulmonary infection, created using MRSA enclosed in agar beads introduced as artificial septic emboli, found daptomycin to be more effective than either placebo (94% vs 0%, $p < 0.001$) or vancomycin (94% vs 52.9%, $p = 0.008$) in improving animal survival (Harada et al., 2013). These animal model data coupled with a clear pathophysiologic rationale provide a reasonable basis for the clinical use and evaluation of daptomycin for hematogenous pulmonary infections.

4. Clinical use of daptomycin in infections complicated by septic pulmonary emboli: clinical trial data and case reports

Daptomycin has demonstrated efficacy in hematogenous source pulmonary infections in animals; however, clinical outcomes data in human patients are less readily available. Infective endocarditis is an infectious syndrome with a shortage of robust data from well-designed, controlled, prospective clinical trials to guide practice. As such, there is only one prospective, randomized, controlled study which directly compares daptomycin to standard therapy for the treatment of *S. aureus* bacteremia and endocarditis and includes a subset of patients with septic pulmonary emboli (Fowler et al., 2006).

The landmark Fowler study was an open-label, randomized, non-inferiority study of patients with *S. aureus* bacteremia, including bacteremia complicated by right sided endocarditis (Fowler et al., 2006). Left-sided endocarditis was an exclusion criterion until a protocol amendment in the second to last year of the study period. Eligible patients were randomized to daptomycin or comparator therapy, which consisted of vancomycin or an anti-staphylococcal penicillin. Gentamicin was added for the first four days of therapy in all patients in the comparator arm and for patients randomized to daptomycin with left-sided endocarditis. The primary outcome was clinical success at follow-up. The study included 120 patients treated with daptomycin and 115 with comparator therapy in the primary analysis. Of these, only 35 (14.9%) and 18 (7.7%) had right- and left-sided IE, respectively. Daptomycin was non-inferior to standard therapy for uncomplicated (42.7% vs 39.3%; +3.4%, 95% CI -8.9 to 15.7%) and complicated *S. aureus* bacteremia (43.3% vs 37.7%; +5.6%, 95% CI -11.8 to 23.1%), but failed to meet non-inferiority in any subgroups with IE. Despite the lack of statistically significant outcomes in *S. aureus* IE, daptomycin earned FDA-approval for complicated bacteremia and right-sided IE based on the pooled results of those two subgroups [34/79 (43%) vs 30/77 (39%); +4.1%, 95% CI -11.3 to 19.5%)].

Given the lack of robust data available for daptomycin in *S. aureus* bacteremia and IE, multiple *post hoc* analyses have been conducted from the original Fowler trial (Kanafani et al., 2010; Rehm et al., 2008). One such study analyzed the outcomes all patients with IE, as defined by the Duke criteria, and specifically assessed the subgroup of patients with right-sided IE and SPE (Kanafani et al., 2010). This analysis demonstrated similar outcomes irrespective of treatment assignment, 42% (6/10) success with daptomycin and 44% (6/9) with comparator therapy, but is limited by the small subset of enrolled patients with SPE.

Clinical experience with daptomycin in patients with IE and SPE has been mixed (Cunha et al., 2005; Gomez et al., 2010; Hagiya et al., 2013; Liu et al., 2008; Zainah et al., 2013). Gomez and colleagues describe a series of four patients treated with daptomycin and rifampin for MRSA bacteremia complicated by SPE without documented IE (Gomez et al., 2010). Three of the four patients had a history of intravenous drug use. All patients were initially treated with vancomycin and were switched to daptomycin with rifampin due to persistent bacteremia or leukocytosis. Duration of bacteremia prior to daptomycin was 7–9 days with one patient clearing prior to changing therapy. Bacteremia cleared in 2–3 days following initiation of daptomycin and rifampin. All four patients achieved clinical resolution with daptomycin and rifampin; however, one patient died after discharge, though this was not believed to be due to infection. The authors did not describe follow-up imaging to assess for SPE resolution.

Cunha and colleagues describe a 33-year-old pregnant woman who developed line-associated MSSA bacteremia and endocarditis (Cunha et al., 2005). Initial chest radiograph was suggestive of SPE. Echocardiography demonstrated a large tricuspid vegetation and she was managed with cefazolin. Blood cultures cleared after the third week of therapy but inflammatory markers continued to increase. During the fourth week of therapy, the patient developed hemoptysis and pleuritic chest pain; however, imaging demonstrated no change in size of the vegetation or emboli. The patient was switched to daptomycin and treated for a total of 7 weeks with normalization of inflammatory markers and resolution of the echocardiogrphic abnormalities. No further information was provided regarding SPE resolution.

Despite the promising results described above, clinical failure of daptomycin for the treatment of SPE has also been documented. One case report described an 86-year-old patient who developed cavitary pulmonary disease while on treatment with daptomycin for right-sided IE (Liu et al., 2008). The patient initially developed MRSA bacteremia after central line placement and tip culture obtained from the line was positive. Bacteremia persisted for the first 18 days of hospitalization and echocardiography demonstrated vegetations in the right atrium and on the tricuspid valve near the implantable cardioverter-defibrillator (ICD) leads. The ICD was removed and therapy changed from vancomycin and rifampin to daptomycin and rifampin. The patient continued to have fevers and a chest CT scan demonstrated multiple pulmonary cavitary lesions which were not present on previous chest radiographs. Therapy was changed to linezolid and fusidic acid with resolution of bacteremia and fevers after 5 days of treatment. This combination was continued for an additional 10 days followed by teicoplanin for 2 weeks with complete resolution of lung lesions per imaging.

A similar case occurred in a 73-year-old male with SPE due to catheter-related MRSA bacteremia (Hagiya et al., 2013). The patient was receiving total parenteral nutrition and developed MRSA bacteremia. Scans demonstrated cavity-forming consolidations suggestive of SPE. Bacteremia persisted despite 5 days of vancomycin therapy and catheter removal; therefore, therapy was escalated to daptomycin. After over a week of daptomycin therapy, the patient developed respiratory failure requiring intubation and intensive care unit admission. He was found to have a massive pleural effusion which grew MRSA following drainage. Given SPE as the suspected source of persistent bacteremia, therapy was changed to linezolid. The bacteremia cleared; however, the patient's condition did not improve. On autopsy the patient was found to have right internal jugular vein thrombosis and necrotizing pancreatitis with abscess formation, but, notably, all cultures obtained were sterile. Examination of the lungs did reveal large cavities which the authors state is indicative of a SPE.

A complicated case of IE is reported in a 24-year-old female intravenous drug user who presented with MRSA bacteremia, multi-valve IE, and emboli to the lungs and central nervous system (Zainah et al., 2013). Due to acute kidney injury, the patient was initially managed with daptomycin. Bacteremia cleared after 6 days of therapy; however, chest CT imaging demonstrated progression of the pulmonary cavitary lesions. Despite these findings, the patient continued to improve and therapy was continued. On hospital day 11, the patient became febrile and chest radiography demonstrated diffuse airspace disease. Therapy was switched to ceftaroline. Repeat imaging on hospital day 17 demonstrated an improvement in pulmonary disease and the patient was successfully treated with 6 weeks of therapy.

5. Discussion and conclusions

The use of daptomycin in patients with infections complicated by SPE remains controversial. Pre-clinical studies have elucidated the mechanism underlying the failure of daptomycin in bronchoalveolar pneumonia and have demonstrated consistent efficacy in models of hematogenous source pulmonary infection (Silverman et al., 2005). These data establish a mechanistic rationale for the use of daptomycin in infections confined to the pulmonary vasculature and parenchyma. Clinically, the use of daptomycin for right-sided endocarditis complicated by SPE is supported by a subset of patients from a large, randomized, controlled trial comparing daptomycin to standard of care (Fowler et al., 2006). This study led to the FDA-approval of daptomycin for right-sided *S. aureus* IE and its inclusion in the 2015 AHA and IDSA guidelines as an alternative to standard therapy for *S. aureus* native valve disease (Baddour et al., 2015). Additionally, these data informed the guideline panel's strong statement regarding the use of daptomycin for IE complicated by SPE and "the distinct pathogenesis of this syndrome as opposed to traditional pneumonia".

However, the significant limitations of these data must be acknowledged. The subset of patients in in the Fowler trial with right-sided IE and SPE was small, 10 treated with daptomycin and 9 with comparator therapies, which greatly limits the generalizability of the findings (Kanafani et al., 2010). However, it is important to note that the overall proportion of patients with right-sided IE include in this trial was small, 19 treated with daptomycin and 16 with comparator therapies, indicating that over half of the patients with right-sided disease had SPE (Fowler et al., 2006). Additionally, FDA-approval for right-sided endocarditis was obtained based on pooled results of patients with right-sided IE and those with complicated bacteremia and it should be noted that large majority of patients in that analysis had bacteremia without IE. The high clinical cure rates in right-sided IE in the recently published registry experience with daptomycin for IE should also be considered as, although not included in the analysis, many of the patients with right-sided disease likely also had SPE (Guleri et al., 2015).

Case reports and case series have been inconclusive with published cases both for and against daptomycin for SPE (Cunha et al., 2005; Gomez et al., 2010; Hagiya et al., 2013; Liu et al., 2008; Zainah et al., 2013). Taken together, it is difficult to discount the experience highlighted by the cases of clinical failure presented here. They represent a cautionary tale, reminiscent of the once promising therapeutic for pneumonia, which bears consideration. Other treatment considerations, such as optimal dosing and the role of daptomycin combination therapy for treatment of IE, have not yet been fully elucidated and may play a role in the success of this agent.

In the era of heightened emphasis on antimicrobial stewardship, daptomycin is generally viewed as an antibiotic of last resort. Most patients treated with daptomycin for *S. aureus* IE will have relative or absolute contraindications to the standard therapy with an antistaphylococcal beta-lactam or vancomycin. These contraindications are generally related to adverse effects or concern for treatment failure with the primary therapeutics. Daptomycin may be viewed as salvage therapy for *S. aureus* IE, which has important implications if alternatives or adjuncts require consideration when SPE are present. The addition of an anti-staphylococcal antibiotics targeted at pulmonary disease to daptomycin would exposure the patient to potentially greater adverse effects. The available therapies in this setting would be linezolid or ceftaroline. Linezolid is not recommended for *S. aureus* IE due to poor outcomes as monotherapy and has the theoretical potential for antagonism with daptomycin due to bacteriostatic activity (Baddour et al., 2015; Falagas et al., 2006; Munoz et al., 2007). Ceftaroline is a promising therapeutic for MRSA infections but is currently lacking in outcomes data evaluating its use as monotherapy for IE. Combination therapy with ceftaroline and daptomycin provides potent anti-MRSA activity but incurs significant cost with the potential for collateral damage owing to expanded gram-negative spectrum of activity of ceftaroline (Casapao et al., 2014; Ho et al., 2012; Lin et al., 2013; Zasowski et al., 2017).

Based on the considerations listed above, it is reasonable to consider use of daptomycin as monotherapy for hematogenous source infections with SPE at the higher doses and durations recommended by the AHA and IDSA guidelines. However, if daptomycin is used as monotherapy for the treatment of infections with SPE, there should be a low threshold to adjust therapy if clinical improvement is not seen or progression of disease is noted. Further research into better characterizing SPE as a complication of IE and the role of daptomycin in the management of these infections is desperately needed.

References

Baddour LM, Wilson WR, Bayer AS, Fowler Jr VG, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and Management of Complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132(15):1435–86.

Britt NS, Potter EM, Patel N, Steed ME. Comparison of the effectiveness and safety of linezolid and Daptomycin in vancomycin-resistant Enterococcal bloodstream infection: a National Cohort Study of veterans affairs patients. Clin Infect Dis 2015;61(6):871–8.

Casapao AM, Davis SL, Barr VO, Klinker KP, Goff DA, Barber KE, et al. Large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy. Antimicrob Agents Chemother 2014;58(5):2541–6.

Cook RJ, Ashton RW, Aughenbaugh GL, Ryu JH. Septic pulmonary embolism: presenting features and clinical course of 14 patients. Chest 2005;128(1):162–6.

Cunha BA, Hamid N, Kessler H, Parchuri S. Daptomycin cure after cefazolin treatment failure of methicillin-sensitive Staphylococcus aureus (MSSA) tricuspid valve acute bacterial endocarditis from a peripherally inserted central catheter (PICC) line. Heart Lung 2005;34(6):442–7.

Drew RH, Perfect JR, Srinath L, Kurkimilis E, Dowzicky M, Talbot GH. Treatment of methicillin-resistant staphylococcus aureus infections with quinupristin-dalfopristin in patients intolerant of or failing prior therapy. For the Synercid emergency-use study group. J Antimicrob Chemother 2000;46(5):775–84.

Falagas ME, Manta KG, Ntziora F, Vardakas KZ. Linezolid for the treatment of patients with endocarditis: a systematic review of the published evidence. J Antimicrob Chemother 2006;58(2):273–80.

Fowler Jr VG, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med 2006;355(7):653–65.

Gomez EO, Jafary A, Dever LL. Daptomycin and rifampin for the treatment of methicillin-resistant Staphylococcus aureus septic pulmonary emboli in the absence of endocarditis. Microb Drug Resist 2010;16(3):241–4.

Guleri A, Utili R, Dohmen P, Petrosillo N, Piper C, Pathan R, et al. Daptomycin for the treatment of infective endocarditis: results from European Cubicin((R)) outcomes registry and experience (EU-CORE). Infect Dis Ther 2015;4(3):283–96.

Hagiya H, Hagioka S, Otsuka F. Ineffectiveness of daptomycin in the treatment of septic pulmonary emboli and persistent bacteremia caused by methicillin-resistant Staphylococcus aureus. Intern Med 2013;52(22):2577–82.

Harada Y, Yanagihara K, Yamada K, Migiyama Y, Nagaoka K, Morinaga Y, et al. In vivo efficacy of daptomycin against methicillin-resistant Staphylococcus aureus in a mouse model of hematogenous pulmonary infection. Antimicrob Agents Chemother 2013;57(6):2841–4.

Heine HS, Bassett J, Miller L, Hartings JM, Ivins BE, Pitt ML, et al. Determination of antibiotic efficacy against bacillus anthracis in a mouse aerosol challenge model. Antimicrob Agents Chemother 2007;51(4):1373–9.

Heine HS, Bassett J, Miller L, Purcell BK, Byrne WR. Efficacy of Daptomycin against bacillus anthracis in a murine model of anthrax spore inhalation. Antimicrob Agents Chemother 2010;54(10):4471–3.

Ho TT, Cadena J, Childs LM, Gonzalez-Velez M, Lewis II JS. Methicillin-resistant Staphylococcus aureus bacteraemia and endocarditis treated with ceftaroline salvage therapy. J Antimicrob Chemother 2012;67(5):1267–70.

Kanafani Z, Boucher H, Fowler V, Cabell C, Hoen B, Miro JM, et al. Daptomycin compared to standard therapy for the treatment of native valve endocarditis. Enferm Infecc Microbiol Clin 2010;28(8):498–503.

Kephart PA, Esposito AL. Comparison of the investigational drug, LY146032, with vancomycin in experimental pneumonia due to methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother 1988;21(1):33–9.

Lin JC, Aung G, Thomas A, Jahng M, Johns S, Fierer J. The use of ceftaroline fosamil in methicillin-resistant *Staphylococcus aureus* endocarditis and deep-seated MRSA infections: a retrospective case series of 10 patients. J Infect Chemother 2013;19(1):42–9.

Liu CY, Wang JL, Huang YT, Hsueh PR. Development of multiple lung abscesses during daptomycin treatment for right-sided endocarditis caused by meticillin-resistant Staphylococcus aureus. Int J Antimicrob Agents 2008;32(6):544–5.

Marcos LA, Camins BC. Successful treatment of vancomycin-intermediate Staphylococcus aureus pacemaker lead infective endocarditis with telavancin. Antimicrob Agents Chemother 2010;54(12):5376–8.

Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of Staphylococcus aureus infection. Ann Intern Med 1992;117(5):390–8.

Munoz P, Rodriguez-Creixems M, Moreno M, Marin M, Ramallo V, Bouza E, et al. Linezolid therapy for infective endocarditis. Clin Microbiol Infect 2007;13(2):211–5.

Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler Jr VG, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the international collaboration on endocarditis-prospective cohort study. Arch Intern Med 2009;169(5):463–73.

Nace H, Lorber B. Successful treatment of methicillin-resistant Staphylococcus aureus endocarditis with telavancin. J Antimicrob Chemother 2010;65(6):1315–6.

O'Donnell AE, Selig J, Aravamuthan M, Richardson MS. Pulmonary complications associated with illicit drug use. An update. Chest 1995;108(2):460–3.

Pertel PE, Bernardo P, Fogarty C, Matthews P, Northland R, Benvenuto M, et al. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis 2008;46(8):1142–51.

Rehm SJ, Boucher H, Levine D, Campion M, Eisenstein BI, Vigliani GA, et al. Daptomycin versus vancomycin plus gentamicin for treatment of bacteraemia and endocarditis due to Staphylococcus aureus: subset analysis of patients infected with methicillin-resistant isolates. J Antimicrob Chemother 2008;62(6):1413–21.

Remetz MS, Quagliarello V. Endovascular infections arising from right-sided heart structures. Cardiol Clin 1992;10(1):137–49.

Ruggero MA, Peaper DR, Topal JE. Telavancin for refractory methicillin-resistant Staphylococcus aureus bacteremia and infective endocarditis. Infect Dis (Lond) 2015;47(6):379–84.

Sander A, Beiderlinden M, Schmid EN, Peters J. Clinical experience with quinupristin-dalfopristin as rescue treatment of critically ill patients infected with methicillin-resistant staphylococci. Intensive Care Med 2002;28(8):1157–60.

Schwalm JD, El-Helou P, Lee CH. Clinical outcome with oral linezolid and rifampin following recurrent methicillin-resistant Staphylococcus aureus bacteremia despite prolonged vancomycin treatment. Can J Infect Dis 2004;15(2):97–100.

Silverman JA, Mortin LI, Vanpraagh AD, Li T, Alder J. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. J Infect Dis 2005;191(12):2149–52.

Smith JR, Claeys KC, Barber KE, Rybak MJ. High-dose daptomycin therapy for staphylococcal endocarditis and when to apply it. Curr Infect Dis Rep 2014;16(10), 429.

Verghese A, Haire C, Franzus B, Smith K. LY146032 in a hamster model of Staphylococcus aureus pneumonia–effect on in vivo clearance and mortality and in vitro opsonophagocytic killing. Chemotherapy 1988;34(6):497–503.

Wojda TR, Cornejo K, Lin A, Cipriano A, Nanda S, Amortegui JD, et al. Septic Embolism: A Potentially Devastating Complication of Infective Endocarditis. In: Firstenberg MS, editor. Contemporary Challenges in Endocarditis. Rijeka: InTech; 2016. (p. Ch. 08).

Zahedi Bialvaei A, Rahbar M, Yousefi M, Asgharzadeh M, Samadi Kafil H. Linezolid: a promising option in the treatment of gram-positives. J Antimicrob Chemother 2017;72(2):354–64.

Zainah H, Zervos M, Stephane W, Chamas Alhelo S, Alkhoury G, Weinmann A. Daptomycin failure for treatment of pulmonary septic emboli in native tricuspid and mitral valve methicillin-resistant Staphylococcus aureus endocarditis. Case Rep Infect Dis 2013;2013, 653582.

Zasowski EJ, Trinh TD, Claeys KC, Casapao AM, Sabagha N, Lagnf AM, et al. Multicenter Observational Study of Ceftaroline Fosamil for Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections. Antimicrob Agents Chemother 2017;61(2). (pii: e02015-16).