

## Sol taraflı endokarditte daptomisin: Tek merkez deneyim

### Daptomycin in the left-sided endocarditis: A single center experience

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#### ÖZET

**Amaç:** Enfektif endokardit, tedavi yaklaşımlarındaki gelişmelere rağmen, yüksek mortalite ve morbidite oranları ile seyretmeye devam etmektedir. Antibiyotik tedavisine dirençli suşların gelişmesiyle beraber, standart antibiyotik rejimleri dışında yeni ajanların etkinliğine yönelik araştırmalar devam etmektedir. Bu ajanlardan biri olan daptomisin stafilokok bakteriyemisi ve sağ taraflı endokardit tedavisi için onay almıştır. Bu çalışmada, sol taraflı enfektif endokardit hastalarında daptomisinin etkinliğini geriye dönük olarak araştırıldı.

**Yöntemler:** Çalışmaya, Duke kriterlerine göre sol taraflı enfektif endokardit tanısı olarak daptomisin tedavisi verilmiş 14 hasta (ortalama yaş 50.9±16.5; dağılım 24-70 yıl) dahil edildi. Sonlanım noktaları klinik iyileşme, mikrobiyolojik eradikasyon ve hastane içi ölüm olarak belirlendi.

**Bulgular:** On üç hastada (%92.8) kan kültürü pozitif ve bir hasta dışında tümünde stafilokoklar izole edildi (%92.3). Daptomisin 6 veya 8 mg/kg/gün dozunda ortalama 40.6±4.4 gün süreyle monoterapi olarak uygulandı. Klinik iyileşme oranı %71.4 mikrobiyolojik eradikasyon oranı ise %85.7 idi. Klinik iyileşme süresi ortalama 8.7±3.2 gün, mikrobiyolojik eradikasyon süresi ise ortalama 11.1±3.6 gün sürdü. Altı hastada ilaca bağlı yan etkiler tespit edildi, ancak hastalarda ilacı bırakma gerekliliği olmadı. On hasta komplikasyonsuz olarak iyileşti. İki hasta tedavi devam ederken kalp yetersizliği ve çoklu organ yetersizliğine bağlı olarak kaybedilirken, iki hasta da erken kardiyak cerrahi gerekliliği nedeniyle ameliyat edildi, ancak ameliyat sonrası erken dönemde hasta kaybedildi.

**Sonuç:** Sol taraflı enfektif endokardit olgularında daptomisin etkinlik ve güvenilirlik açısından standart antibiyotik tedavisine alternatif olabilir.

#### ABSTRACT

**Objective:** Infective endocarditis (IE) carries a high risk of cardiac morbidity and mortality, despite advances in the contemporary armamentarium. Along with the development of antibiotic resistant strains, research focusing on the efficacy of novel agents other than standard antibiotic regimens continues. Daptomycin, one of these antibiotics, is approved for the treatment of *Staphylococcus bacteremia* and right-sided endocarditis. This retrospective study was an investigation of the effectiveness of daptomycin in patients with left-sided IE.

**Methods:** Fourteen patients (mean age 50.9±16.5; range 24 to 70 years) with diagnosis of left-sided IE based on modified Duke criteria received daptomycin as monotherapy. Outcome was evaluated according to clinical improvement, microbiological eradication, and in-hospital mortality.

**Results:** Blood culture was positive in 13 patients (92.8%) and staphylococci were isolated in all but 1 patient (92.3%). Daptomycin was administered as monotherapy at a dose of 6 or 8 mg/kg/day for mean of 40.6±4.4 days. Clinical recovery rate was 71.4% and microbiological eradication rate was 85.7%. Mean duration of clinical recovery was 8.7±3.2 days and duration of microbiological eradication was 11.1±3.6 days. Side effects developed in 6 patients, but drug discontinuation was not required in any patient. Ten patients improved without complications. Two patients were lost due to heart failure and multiple-organ failure while treatment was continuing, and 2 patients died in early cardiac postoperative period.

**Conclusion:** Daptomycin is an effective and safe alternative to standard antibiotic therapy for the treatment of left-sided IE.

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Despite rapid developments in the management and antibiotherapies of infective endocarditis (IE) inpatient mortality rates still range between 16, and 28 percent.<sup>[12]</sup> In patients with infective endocarditis, most frequently detected agents include gram-positive microorganisms (80%). Among gram-positive agents *Staphylococcus aureus* is the most frequently isolated microorganism<sup>[3]</sup> followed by viridans streptococci, and coagulase- negative staphylococci.<sup>[34]</sup> Effectiveness, and reliability of classical antibacterial agents as beta-lactams, rifampycin, gentamicin, and vancomycin in the management of endocarditis of both native, and prosthetic valve have been proved in clinical studies.<sup>[5]</sup> However frequently strains resistant to these treatments have been isolated which decrease treatment success. Daptomycin is one of the relatively new agents whose effectiveness is being investigated in the treatment of infective endocarditis. Daptomycin is a dose-dependent lipopeptide antibiotic which is effective against gram-positive bacteria. Use of daptomycin was approved in cases with *Staphylococcus aureus* bacteremia, and right-sided IE, at daily doses of 6 mg/kg for the first years after its introduction into clinical practice. However in 2015 ESC IE guideline its daily dose is >10 mg/kg<sup>[5-7]</sup>

The aim of this study is to retrospectively evaluate effectiveness of daptomycin in left-sided IE.

## METHODS

A total of 14 patients hospitalized with the diagnosis of left-sided IE based on modified Duke criteria in Ankara Higher Specialization Training and Research Hospital, and treated with daptomycin monotherapy were included in the study. Medical information of the patients were retrieved from archival files, and phone calls made with the patients between May 2010, and May 2012.

For blood cultures, venous blood samples were obtained as recommended in the diagnosis of IE., and implanted on automatic culture systems (BacT/ALERT 3D BioMerieux, France). Antimicrobial susceptibilities of the bacteria were measured using VITEK 2 automated system (BioMerieux, France).

In empirical treatment of acute, and severe IE, if the disease is community-acquired or delayed prosthetic valve endocarditis, and a known methicillin-sensitive *Staphylococcus aureus* (MSSA) or methicillin-resistant -

*Staphylococcus aureus* (MSSA)

is not detected, in consideration of drug-

interaction,

renal, and hepatic functions, ampicillin-gentamicin combination was preferred, if early-onset prosthetic valve IE or advanced healthcare -related endocarditis is presumed, combinations of glycopeptide were preferred in empirical treatment. Treatment was changed based on antibiotic-susceptibility test results.

As antimicrobial agent in patients with prosthetic valve endocarditis with growth of *Staphylococcus aureus* in the culture, and minimum inhibitory concentration (MIC) value of >1 mg/L, daptomycin was preferred. Daptomycin was infused for 30 minutes at daily doses of 6-8 mg/kg. Based on the severity of the transthoracic echocardiographic findings (TTE), in some patients because of its rapid bactericidal effectiveness, its capacity for vegetation, and biofilm activity daily doses of 8 mg were used.. The patients with initial diagnosis of bacteremia whose blood cultures demonstrated growth of *Staphylococcus aureus* were started on daptomycin, and if diagnosis of IE was supported with TTE, and transesophageal echocardiography findings, and modified Duke criteria were met with clinical improvement, then the treatment was continued..

The patients were followed up as for the presence of symptoms of diarrhea, rashes, dizziness, hypotension, and myopathy which was the most important side effect. In patients with symptoms of muscle weakness, myalgia, paresthesia or paralysis, levels of creatinine kinase were measured. Renal functions were controlled at every 48 hours. Cessation of daptomycin treatment was planned if clinical symptoms persisted in patients whose creatinine phosphatase values increased more than 5-fold and in clinically asymptomatic patient whose creatinine phosphatase values increased 10- fold..

The results were evaluated as “clinical improvement”, “microbiological eradication”, and “inpatient mortality”. “Clinical improvement” was defined as improvement of clinical signs, and symptoms, and “microbiological eradication” was described as negative blood cultures obtained after initiation of treatment.

## Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables with numbers, and percentages. For this evaluation IBM SPSS software (IBM

## Abbreviations

IE	Infective endocarditis
MIC	Minimum inhibitory concentration
MRSA	Methicillin -resistant <i>Staphylococcus aureus</i>
TTE	Transthoracic echocardiography

SPSS Statistics for Windows, Version 21.0. Ar- monk, NY: IBM Corp.) was used.

## RESULTS

A total of 14 patients (male, 71.4%) with a mean age of 50.9±16.5 (range, 24-70) years were included in the study. Basic clinical characteristics, and laboratory findings are summarized in Table 1. In 13 patients blood culture positivity was detected, and most frequently (92.9%), staphylococci were isolated. In the first treatment regimens of the patients teicoplanin (n=2), cephazoline (n=2), vancomycin (n=5), combination of ampicillin-gentamycin (n=1) , and daptomycin (n=4) were used. The reason why daptomycin was preferred for the initial treatment in 4 patients was higher MIC values of other agents, and inability to use them because of higher creatinine values. The antibiotic in the starting regimen was changed to daptomycin because of persistent infection (n=7) drug side effects (n=2), clinical deterioration despite no growth in cultures..

Daptomycin was used for a mean period of 40.6±4.4 days at daily doses of 6 mg/kg, and 8 mg/kg in 10, and 4 patients, respectively. Although in 6 patients, daptomycin-related side effects as higher serum creatinine phosphokinase, and serum creatinine values, myopathy, peripheral neuropathy, constipation, and vomiting were observed, in none of these cases, discontinuation of daptomycin treatment was not required at all, and at the termination of the treatment side effects disappeared..

Ten patients were discharged without complication at the end of the treatment. Rates of clinical improvement and microbiological eradication were 71.4%, and 85.7 %, respectively. Mean durations of clinical improvement, and microbiological eradication were 8.7±3.2, and 11.1±3.6 days, respectively. Mortality or serious side effects were not observed in four patients receiving daily doses of 8 mg/kg daptomycin.

Cardiac surgery was performed in four cases at an early stage because of heart valve dysfunction , and related worsened heart insufficiency despite treatment. Two of these patients were lost during early postoperative period, and two patients under medical treatment died because of worsened heart insufficiency and multiple organ failure during preoperative period. (Table 2).

## DISCUSSION

In recent years vancomycin, and rifampicin were started to be used prevalently in the treatment of left-sided

IE, however their side effect profiles, and increase in MIC values started to limit the use of these agents .<sup>[8]</sup>

**Table 1. Demographic, clinical characteristics, and echocardiographic findings of the patients**

	n	Mean ± SD%
Number of patients	14	100
Age (year)		50.9±16.5
Male gender	10	71.4
Concomitant diseases	12	85.7
Diabetes mellitus	3	21.4
Chronic kidney disease	6	42.9
Chronic pulmonary disease	3	21.4
Underlying heart disease	13	92.9
Prosthetic valve	6	42.9
Rheumatismal heart disease	7	50
Physical examination findings		
Fever	10	71.4
Splenomegaly	9	64.3
Clubbing	7	50
Osler nodules	2	14.3
Laboratory values		
Sedimentation rate >50 mm/h	13	92.9
WBC >10,000/mm <sup>3</sup>	11	78.6
Serum creatinine >2 mg/L	6	42.9
Echocardiographic findings		
Size of the vegetation		
<10 mm	4	28.6
10-15 mm	8	57.1
>15 mm	2	14.3
Mobility of the vegetation		
Immobile	1	7.1
Low	9	64.3
Moderate	3	21.4
Serious (it prolapses)	1	7.1
Severe valvular insufficiency	4	28.6
Cardiac abscess	5	35.7
Clinical event		
Neurologic complication	2	14.3
Early stage heart surgery	4	28.5

; SD: Standard deviation.

Drug-related side effects, and higher MIC values are related to treatment failure, and mortality <sup>[9,10]</sup> Especially in cases where nephrotoxic effects of vancomycin emerge, switch to an effective, and reliable alternative agent

is a must , Our study results suggest that daptomycin may be a good alternative in such cases.

Table 2. Clinical characteristics, isolated microorganisms, MIC values, antimicrobial treatment and treatment results

Patient#	Gender	Age	Valve	Size of the vegetation (mm)	Valvular type	Blood culture	MIC value of daptomycin (µg/ml)	MIC value of Vancomycin (µg/ml)	Initial antibacterial treatment, and its duration (day)	Dose of daptomycin, and duration of treatment (day)	Treatment outcome
1	Male	65	MV	12	NV	MRCoNS	<0.5	1	Teicoplanin(5)	6mg/kg/d	Death
2	Male	69	MV	8	NV	MRCoNS	<0.5	1	Teicoplanin (4)	6mg/kg/d	Improvement
3	Male	43	MV	12	NV	MSSA	<0.5	1	Cephazolin (5)	6mg/kg/d	Improvement
4	Male	45	MV	20	NV				Vancomycin (7)	6mg/kg/d	Death
5	Female	69	MV	14	NV	MRSA	<0.5	2	Vancomycin (7)	6mg/kg/d	Improvement
6	Male	24	MV	14	NV	ARE	<0.5	<1	Ampr+Genta	6mg/kg/d	Improvement
7	Male	38	AV	15	PV	MSSA	<0.5	<1	Cephazolin (5)	6mg/kg/d	Death
8	Male	55	MV	8	PV	MSSA	<0.5	<1	Daptomycin	8mg/kg/d	Improvement
9	Male	45	AV	9	PV	MRCoNS	<0.5	2	Daptomycin	8 mg/kg/d	Improvement
10	Male	64	MV	11	PV	MRSA	<0.5	2	Vancomycin(7)	6mg/kg/d	Improvement
11	Female	36	AV	9	PV	MRSA	<0.5	2	Vancomycin(5)	8 mg/kg/d	Improvement
12	Female	65	AV	18	PV	MSSA	<0.5	<1	Daptomycin	8 mg/kg/d	Improvement
13	Male	25	MV	12	PV	MRCoNS	<0.5	<1	Vancomycin (7)	8 mg/kg/d	Improvement
14	Female	70	MV	14	PV	MRCoNS	<0.5	<1	Daptomycin	6mg/kg/d	Death

MIC: minimum inhibitory concentration; MV: mitral valve; NV: native valve; PV: prosthetic valve; MRCoNS: methicillin-resistant coagulase –negative staphylococci; MSSA: methicillin-sensitive *Staphylococcus aureus*; ARE: ampicillin-resistant enterococcus; MRSA: methicillin resistant staphylococcus aureus, AV: aortic valve

In a study Kaya et al. [11] reported that in cases with IE the most important reason for switching from vancomycin to daptomycin was vancomycin-related side effects. However in our study the most important reason of switching to daptomycin treatment was inability to get any response to treatment with other agents.

Daptomyvin has been approved by European Medical Agency (EMA) and US Food and Drug Association (FDA) for the treatment of *Staphylococcus aureus* bacteremia in cases with right-sided IE. [12] Previous studies had demonstrated effectiveness of daptomycin in the treatment of staphylococcal IE equivalent to beta-lactam antibiotics, and vancomycin. [13] In a multicenter retrospective study high doses of daptomycin (>8 mg/kg/d) were detected to be successful in rescue treatment in patients with MRSA, and vancomycin-resistant enterococcal (VRE) . However in this study 61% of the cases consisted of right-sided IE patients. [14] In a study conducted in Spain on *Staphylococcus aureus* endocarditis, when compared with standard antibiotherapy, first-line use of daptomycin at doses ranging between 6, and 8 mg/kg was found to be more effective. [15] In another study on mostly MRSA cases, daptomycin was used at daily doses of 6 mg/kg, and its effectiveness in the treatment of left-sided IE was reported [13] In a cohort study with left-sided , treatment –resistant IE daptomycin at average daily doses of Sol 9.2 mg/kg achieved an acceptable effectiveness. [16] In a study performed recently on the effect of daptomycin on gram-positive bacteria, daptomycin was found to be very effective, and a distinct side effect was not reported during short-lived (only 2 minutes) infusions. (DAPTODOM study). [17]

EU-CORE European Kubisin registration study was conducted in eight European countries for a period of 30 months, and 1127 patients were included in the study. [18] In this study treatment success rate of daptomycin in *Staphylococcus aureus* endocarditis (complete or partial improvement) was reported as 81 percent. [19] In a real-life meta-analysis published in 2016 which evaluated EUROCORE and CORE records, treatment success of daptomycin was estimated as 75.4 percent. [20] In this meta-analysis it was indicated that effectiveness, and success rates of higher doses of daptomycin (> 6mg/kg/d) in IE increased without any serious side effects or toxicity.

In our study success rate in achieving clinical improvement was nearly 71 % which approximated to the success rates indicated above. Studies have demonstrated that especially vancomycin is effective in patients with higher MIC values, and survival rates were much higher in these patients. [14,21,22] In this study improvement was achieved in 6 of 7 cases (%85.7), while in six patients with MIC value of < 1 mg/L only milder degree of improvement was achieved.(n=6; 66.6%)

Effective dose range of dapsomycin is still debatable. In patients with both right-, and left-sided IE successful outcomes have been obtained generally with daily doses over 8 mg/kg. In a study by Durante-Mangoni et al.[23] daptomycin was administered at a daily dose of 8.2 mg/kg to 102 IE patients with serious comorbidities, and the patients were evaluated as for side effects. At the end of the study, effectiveness, and safety of daptomycin treatment in patients with serious comorbidities were reported. Even though serious renal and hepatic dysfunction were not observed, eosinophilia was observed in 15 % of the patients. In 3 cases among them interstitial eosinophilic pneumonia was seen which mandated monitorization of levels of eosinophils in patients who received high doses of daptomycin. In a study on rabbits with induced aortic valve endocarditis, daily doses of 18 mg/kg daptomycin (equivalent to 10 mg/kg/d in human beings) demonstrated significant decrease in the size of vegetations when compared with the controls.[24] These findings suggest that in left-sided IE, high doses of daptomycin may be more effective. Indeed 2015 ESC guideline recommended use of daptomycin at least at a single daily dose of .10 mg/kg or over , and with combination so as to prevent development of resistance..[5] In our study daptomycin was given at a daily dose of 6-8 mg/kg and as a monotherapy based on the outcomes of case series, and studies performed at that time. On the other hand treatment success rates are within acceptable levels . Besides treatment response was achieved faster with prompt clinical improvement , and microbiological eradication .Though daptomycin induced side effects in nearly half of the cases (42.8%) the patients could maintain their treatment, and mortality, and morbidity related to side effects did not occur.

Inpatient mortality was observed in four (28.5%) cases Two of them had undergone operations because of

surgical indication at an early stage, and the other two cases were lost because of worsened heart insufficiency , and multiorgan deficiency developed during their medical treatment In various studies IE –related inpatient mortality rates change between 15, and 30 percent..[5] Though mortality rate of 28.5% in our study appears to be a little bit higher, our study group consisting of considerably higher risk (almost all of them had staphylococcal endocarditis, 6 cases with prosthetic valve endocarditis, 5 patients with diagnosis of periannular abscess , and 10 cases with vegetations larger than 10 mm in diameter) may explain this higher rate.

Although our results support the use of daptomycin in left-sided IE caused by gram-positive bacteria,, smaller number of patients, and retrospective design of our study are the most important limitations of our study. Larger scale, randomized studies will shed light on the use of daptomycin in the left-sided endocarditis..

### ***Conflict of Interest: None***

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**Anahtar sözcükler:** Daptomisin; sol taraflı infektif endokardit; *S.aureus*.

**Keywords:** Daptomycin; left sided infective endocarditis; *S.aureus*