KLİMİK TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

Bilimle Sağlıkla 33 .Yıl

MRSA Endokarditinde Daptomisin Çünkü….

Dr. Özlem Kurt Azap
Başkent Üniversitesi Tıp Fakültesi
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

Plan

- Daptomisinin kısa tanıtımı
- Endikasyonları/Endikasyon dışı kullanım alanları
- MRSA bakteremisi/endokarditi niçin önemli?
- Vankomisin **vs** Daptomisin: Çalışmalar ve rehberler ne diyor?
- Özet

Tanıdınız mı?

Francis Patrick Tally, M.D.

Frank Tally, the chief scientific officer of Cubist Pharmaceuticals who played a major role in bringing four antibacterial drugs (cefixime, piperacillin/tazobactam, daptomycin and tigecycline) into clinical use, passed away on Sunday 2 October 2006 at the age of 66. Frank succumbed to an acute, overwhelming bacterial infection — infective endocarditis — leading his son, Kevin, to comment in his father's obituary in the Boston Globe that "bacteria put a hit out on him".

His time there made him realize tha
not be satisfied with a career as a 'g
Rhode Island internist' and instead
need not just to practise medicine
to contribute something that would
the practice of medicine in general.

Frank was a success in multiple
endeavours — as an infectious disease physician, performing academic research in molecular microbiology, directing infectious disease research at a large pharmaceutical

to approach science-driven drug discovery ethically and zealously. Frank learned one key lesson in his career that will be carried forward: the drugs that he helped to bring

Frank Tally

Infectious-disease specialist who helped to develop life-saving antibiotics. Born on May 17, 1940, in Providence, RI, USA, he died of acute bacterial infection on Oct 1, 2006, in Boston, MA, USA, aged 66 years.

When the raw data of the most important clinical trial of Frank Tally's drug-development career were unblinded, what should have been a moment of elation for Tally was instead tinged by sadness that the drug was not going to save as many lives as he had hoped. "Despite the fact that the results meant he was personally going to make quite a bit of money, the first thing that came out of his mouth was 'Wow, we have a long way to go'," recalls Praveen Tipirneni, a colleague of Tally's at Cubist Pharmaceuticals, who worked on the approval process for the company's first product daptomycin (Cubicin), which Tally had identified. "Although [the drug] was the best thing available in the world, Frank viewed it as still not as good as it could be for patients", said Tipirneni.

Described by colleagues as "one of the pre-eminent leaders in antibiotic development during the past quarter century", Tally gained his interest in infectious disease during military service in the Vietnam War. As Cubist colleague and friend of 25 years Barry Eisenstein recalls, "he saw some extraordinarily vivid examples of classic infections in the jungles of Vietnam, and witnessed epidemics of the ancient scourges of mankind". These experiences made Tally determined to fight such diseases after returning home.

Once back in the USA, Tally embarked on an infectious-diseases fellowship at the Wadsworth VA Hospital in Los Angeles, CA, before moving to New England Medical Center in Boston, in 1975, to take up a post as professor and senior physician. During these early years in academia, Tally was among the founders of a new biology: anaerobic bacteriology. The field was slow to emerge because of the difficulty of cultivating anaerobic micro-organisms, but it took off after the discovery that these types of bacteria cause many more infections than had previously been thought. According to Eisenstein, "There was a revolution in the 60s and 70s around these organisms and Frank's early fame was to do with being at the heart of that revolution."

In 1987, Tally decided to leave academia and joined Lederle Labs, NY, where he played a key part in developing antibiotics, including Zosyn (piperacillin/tazobactam). He was a talented academic, but Eisenstein speculates that this move may have been driven by frustration at the gap between basic science and clinical practice. "He was an expert at the bench and an expert at the bedside, but it was difficult to get the connection to work", explains Eisenstein. Tally excelled in industry and joined Cubist Pharmaceuticals in 1995, where the crowning achievement of his successful career was the development of daptomycin, now the company's lead drug.

Tally was known for his directness and passion for getting to the scientific truth. "He was a scientist to the heart and working with him we got a respect for the truth of science and the integrity of the data", said Tipirneni. Martin Blaser, a long-time friend of Tally and outgoing President of the Infectious Disease Society of America, with which Tally was heavily involved, regards Tally's greatest contribution as understanding how daptomycin could be used effectively. Blaser explains that Tally "created the prototype of a novel and useful class of antibiotics, in an era with very few innovations in antibacterial agents". Ralph Corey, an infectious disease specialist at Duke University, NC, who worked with Tally on a clinical trial of daptomycin, agrees: "With daptomycin he did something that hadn't been done before. He did a trial, and with that trial created a new way of thinking about bloodstream infections." It was a terrible irony that Tally was eventually killed by the organism he had been fighting for most of his professional life.

[illegible] way "He always wanted to come up with newer and better antimicrobials even though this area has been somewhat abandoned by the pharmaceutical industry". And despite leaving clinical practice almost 30 years ago, Tally never lost sight of the purpose of his endeavours. "In drug development you often see a science side of the world and less of a patient side of the world, but Frank never let go of that focus on the patient and on saving the patients' lives", says Tipirneni.

Tally is survived by his wife Barbara and three children, Kevin, Michaela, and Patrick.

Hannah Brown
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The Lancet

Burası neresi?

Daptomisin

Daptomycin: From the Mountain to the Clinic, with Essential Help from Francis Tally, MD

Barry I. Eisenstein, Frederick B. Oleson, Jr., and Richard H. Baltz

Cubist Pharmaceuticals, Lexington, Massachusetts

Daptomycin has been approved and successfully launched for the treatment of complicated skin and skin-structure infections caused by gram-positive pathogens [1] and bacteremia and right-sided endocarditis due to *Staphylococcus aureus*, including strains that are resistant to methicillin or other antibiotics [2]. The development of the drug, however, was not straightforward; it involved a cast of characters, including scientists at Eli Lilly and at Cubist Pharmaceuticals. Of most importance, the development of daptomycin involved the tenacious leadership of Dr. Francis Tally. As a tribute to Dr. Tally, we attempt to reconstruct the path of daptomycin from the mountain to the clinic.

DISCOVERY OF DAPTOMYCIN

Daptomycin (Figure 1) is a natural product of a soil actinomycete, as are most of the important antibiotics developed in the past 50 years [3]. The producing microorganism, *Streptomyces roseosporus*, was isolated by scientists at Eli Lilly from a soil sample from Mount Ararat (Turkey). This sporulating actinomycete produced a family of lipopeptide antibiotics designated A21987C (Figure 1) [4, 5]. Eli Lilly scientists also isolated ical studies of intravenous (IV) daptomycin during the late 1980s and early 1990s [11]. In the initial phase 1 trials, daptomycin was well tolerated in healthy volunteers at up to 6 mg/kg IV in 2 divided doses per day [9]. For the initial phase 2 clinical trial involving complicated skin and skin-structure infection (SSSI), the scientists at Eli Lilly used a daptomycin treatment regimen of 2 mg/kg given once daily. In later clinical trials, daptomycin was administered twice daily (every 12 h).

Daptomisin

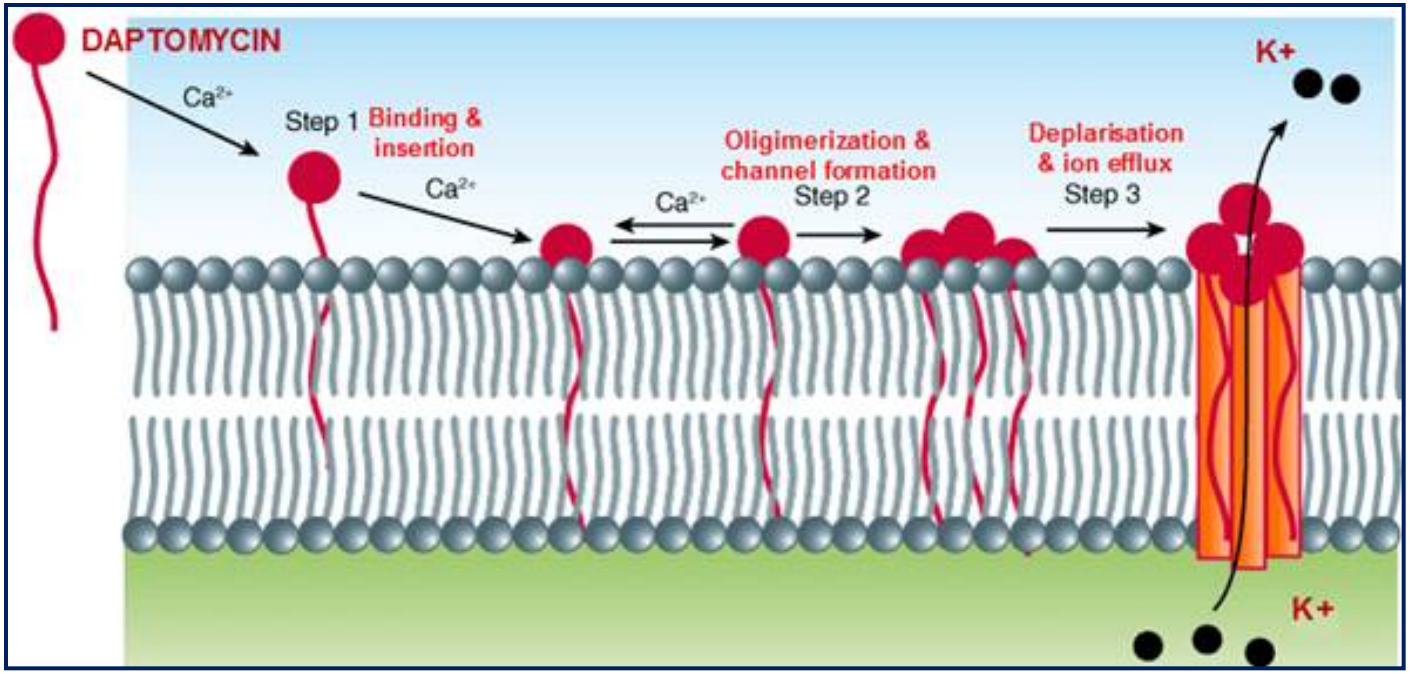
Table 1. Effect of Daptomycin Dosing Regimen on Microscopic Musculoskeletal Findings in Dogs

Dosage	Peak serum creatine phosphokinase level, IU/L	No. of muscle sites affected[a]
0 mg/kg every 8 h	265	1
25 mg/kg every 24 h	~990	3
75 mg/kg every 24 h	~990	8
25 mg/kg every 8 h	~4000	15

[a] Twenty-eight sites were evaluated (7 sites evaluated in each of 4 dogs). Microscopic findings indicated only minimal musculoskeletal degeneration.

Clinical Infectious Diseases 2010; 50:S10–5

Daptomisin- Etki Mekanizması



- Lipopeptit yapıda
- Hücre membranına bağlanır (Kalsiyuma bağımlı bir aşama)
- Membranda potasyum kanalları oluşur
- Hücre lizise uğramadan, membran depolarizasyonu nedeniyle ölür

Daptomisin

KISA ÜRÜN BİLGİSİ

1. BEŞERİ TIBBİ ÜRÜNÜN ADI

CUBICIN 500 mg enjeksiyonluk çözelti için toz içeren flakon.

4 KLİNİK ÖZELLİKLER

4.1 Terapötik endikasyonlar

CUBICIN, erişkinlerde metisiline duyarlı ve metisiline dirençli izolatların neden olduğu sağ kalp enfektif endokarditi, Staphylococcus aureus'un neden olduğu bakteriyemiler ve komplike deri ve yumuşak doku enfeksiyonlarının tedavisinde endikedir. CUBICIN'in Staphylococcus aureus'a bağlı sol kalp endokarditi olan hastalarda etkinliği kanıtlanmamıştır.

CUBICIN yalnızca Gram pozitif bakterilere karşı aktiftir. Gram negatif ve/veya bazı anaerobik bakteri tiplerinden şüphelenilen karma enfeksiyonlarda, CUBICIN uygun bir antibakteriyel ajanla/ajanlarla birlikte uygulanmalıdır.

Antibakteriyel ajanların uygun kullanımıyla ilgili resmi kılavuzlar göz önünde bulundurulmalıdır.

CUBICIN pnömoni tedavisinde endike değildir (bkz. bölüm 4.4).

Klinik Kullanım Alanları

Onaylı endikasyonlar

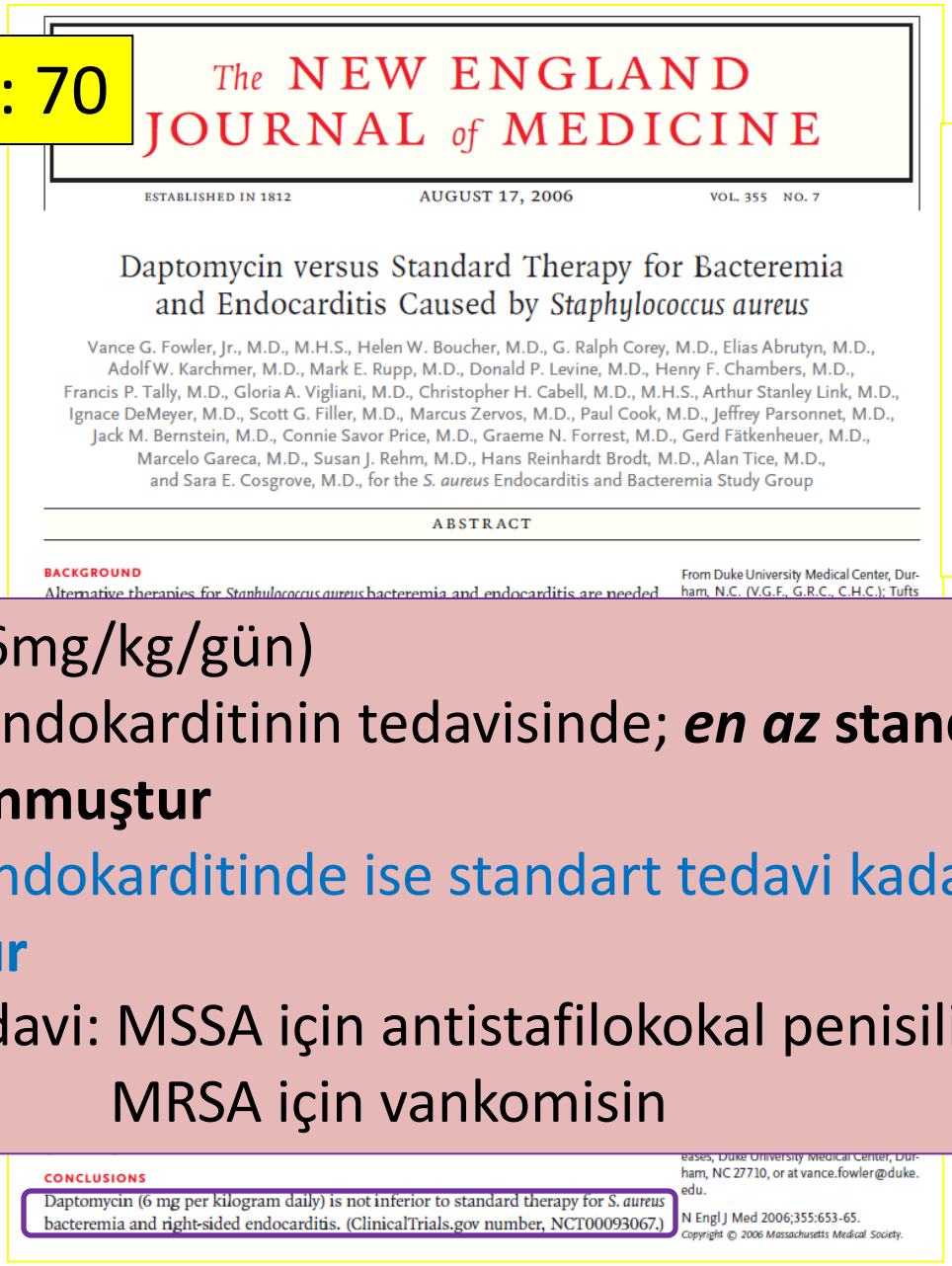
- *S.aureus'*un etken olduğu bakteremi
- *S.aureus*'un etken olduğu ***sağ*** kalp endokarditi
- Komplike deri ve yumuşak doku enfeksiyonları

- *S.aureus'*un veya enterokokların etken olduğu sol kalp endokarditi
- MRSA'nın etken olduğu septik artrit, osteomyelit
- Vertebral osteomyelit
- Diyabetik ayak enfeksiyonları
- Stafilokokların veya enterokokların etken olduğu protez enf.
- VRE enfeksiyonları

- Protez kapak endokarditinde de zaman zaman kullanıyoruz

- Pnömonide kullanılmaz!

Etki Faktörü: 70



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 17, 2006 VOL. 355 NO. 7

Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

Vance G. Fowler, Jr., M.D., M.H.S., Helen W. Boucher, M.D., G. Ralph Corey, M.D., Elias Abrutyn, M.D., Adolf W. Karchmer, M.D., Mark E. Rupp, M.D., Donald P. Levine, M.D., Henry F. Chambers, M.D., Francis P. Tally, M.D., Gloria A. Vigliani, M.D., Christopher H. Cabell, M.D., M.H.S., Arthur Stanley Link, M.D., Ignace DeMeyer, M.D., Scott G. Filler, M.D., Marcus Zervos, M.D., Paul Cook, M.D., Jeffrey Parsonnet, M.D., Jack M. Bernstein, M.D., Connie Savor Price, M.D., Graeme N. Forrest, M.D., Gerd Fätkenheuer, M.D., Marcelo Gareca, M.D., Susan J. Rehm, M.D., Hans Reinhardt Brodt, M.D., Alan Tice, M.D., and Sara E. Cosgrove, M.D., for the *S. aureus* Endocarditis and Bacteremia Study Group

ABSTRACT

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Alternative therapies for *Staphylococcus aureus* bacteremia and endocarditis are needed

From Duke University Medical Center, Durham, N.C. (V.G.F., G.R.C., C.H.C.); Tufts

Patients received daptomycin (Cubicin, Cubist Pharmaceuticals) (6 mg per kilogram of body weight intravenously once daily) or standard therapy with either vancomycin (1 g every 12 hours with appropriate dose adjustment) or an antistaphylococcal penicillin (nafcillin, oxacillin, or flucloxacillin) (2 g every 4 hours), depending on the susceptibility of the causative strain to methicillin. The duration of therapy was determined by the investigator on the basis of the working diagnosis. All patients who were randomly assigned to standard treatment and patients with left-sided endocarditis who were assigned to daptomycin were to receive gentamicin (1 mg per kilogram intravenously every eight hours or adjusted on the basis of renal function) for the first four days.

CONCLUSIONS

Daptomycin (6 mg per kilogram daily) is not inferior to standard therapy for *S. aureus* bacteremia and right-sided endocarditis. (ClinicalTrials.gov number, NCT00093067.)

eases, Duke University Medical Center, Durham, NC 27710, or at vance.fowler@duke.edu.

N Engl J Med 2006;355:653-65.

Daptomisin (6mg/kg/gün)

- **Sağ kapak** endokarditinin tedavisinde; ***en az*** **standart tedavi kadar etkili bulunmuştur**
- **Sol kapak** endokarditinde ise standart tedavi kadar etkili **bulunmamıştır**
- Standart tedavi: MSSA için antistafilokokal penisilin, MRSA için vankomisin

Olgular

Table 1. (Continued.)

Characteristic	Daptomycin (N=120)	Standard Therapy (N=115)
Baseline pathogen — no. (%)		
Infection with MRSA	45 (37.5)	44 (38.3)
Diagnosis according to adjudication committee — no. (%)		
Baseline diagnosis		
Definite endocarditis	17 (14.2)	20 (17.4)
Possible endocarditis	73 (60.8)	71 (61.7)
Not endocarditis	30 (25.0)	24 (20.9)
Final diagnosis		
Uncomplicated bacteremia	32 (26.7)	29 (25.2)
Complicated bacteremia	60 (50.0)	61 (53.0)
Uncomplicated right-sided endocarditis	6 (5.0)	4 (3.5)
Complicated right-sided endocarditis	13 (10.8)	12 (10.4)
Left-sided endocarditis	9 (7.5)	9 (7.8)

Daptomisin - Duyarlılık - Doz

EUCAST 2019:

- Stafilokoklar ve Streptokoklar için:

  Disk diffüzyon için sınır değer YOK

  MİK ≤ 1 µg/mL duyarlı

- Enterokoklar için: Sınır değer YOK

Daptomisine tedavi altında direnç gelişmesini önlemek için

- Yüksek dozda kullanım (**8-12** mg/kg/gün)
- **Kombinasyon** tedavisi

Endokarditte daptomisin kullanımına ilişkin…

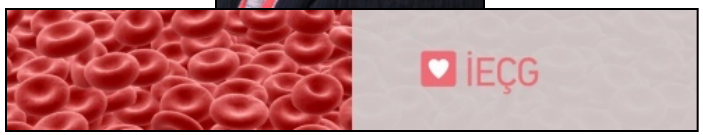
Turk Kardiyol Dern Ars 2017;45(4):303-307 doi: 10.5543/tkda.2017.79168

Davetli Editöryal Yorum / *Invited Editorial*

İnfektif endokarditin tedavisinde daptomisin: Ne zaman kullanalım?

Daptomycin for the treatment of infective endocarditis: When do we use it?

Dr. Serap Şimşek Yavuz



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S.aureus Bakteremisi- Mortalite

Etki Faktörü: 17

Predictors of Mortality in *Staphylococcus aureus* Bacteremia

Sebastian J. van Hal,[a,b] Slade O. Jensen,[b,c] Vikram L. Vaska,[d] Björn A. Espedido,[b,c] David L. Paterson,[d] and Iain B. Gosbell[a,b,c]

and Infectious Diseases, Sydney South West Pathology Service—Liverpool, South Western Sydney Local Health Network, Sydney, New
iotic Resistance and Mobile Elements Group, Microbiology and Infectious Diseases Unit, School of Medicine, University of Western Sydney,
ustralia[b]; Ingham Institute of Applied Medical Research, Sydney, New South Wales, Australia[c]; and The University of Queensland, UQ Centre
, Herston, Queensland, Australia[d]

AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

Review

Predictors of Mortality in *Staphylococcus aureus* Bacteremia

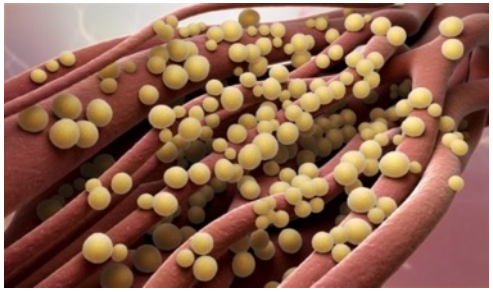
Sebastian J. van Hal, Slade O. Jensen, Vikram L. Vaska, Björn A. Espedido, David L. Paterson, Iain B. Gosbell

DOI: 10.1128/CMR.05022-11

SUMMARY

Staphylococcus aureus bacteremia (SAB) is an important infection with an incidence rate ranging from 20 to 50 cases/100,000 population per year. Between 10% and 30% of these patients will die from SAB. Comparatively, this accounts for a greater number of deaths than for AIDS, tuberculosis, and viral hepatitis combined. Multiple factors influence outcomes for SAB patients. The most consistent predictor of mortality is age, with older patients being twice as likely to die. Except for the presence of comorbidities, the impacts of other host factors, including gender, ethnicity, socioeconomic status, and immune status, are unclear. Pathogen-host interactions, especially the presence of shock and the source of SAB, are strong predictors of outcomes. Although antibiotic resistance may be associated with increased mortality, questions remain as to whether this reflects pathogen-specific factors or poorer responses to antibiotic therapy, namely, vancomycin. Optimal management relies on starting appropriate

April 2012 Volume 25 Number 2 p. 362–386



MRSA Bakteremisinde Mortalite

Predictive factors for mortality in patients with methicillin-resistant *Staphylococcus aureus* bloodstream infection: impact on outcome of host microorganism and therapy

O. Gasch[1], M. Camoez[1], M. A. Dominguez[1], B. Padilla[2], V. Pintado[3], B. Almirante[4], J. Molina[5], F. Lopez-Medrano[6], E. Ruiz[7], J. A. Martinez[8], E. Bereciartua[9], F. Rodriguez-Lopez[10], C. Fernandez-Mazarrasa[11], M. A.Goenaga[12], N. Benito[13], J. Rodriguez-Baño[14], E. Espejo[15], M. Pujol[1] and on behalf of REIPI/GEIH Study Groups*

Mortality related to methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (BSI) remains high, despite changes in the epidemiology. To analyze the current predictive factors for mortality we conducted a prospective study in a large cohort of patients with MRSA-BSI from 21 Spanish hospitals. Epidemiology, clinical data, therapy and outcome were recorded. All MRSA strains were analysed, including susceptibility to antibiotics and molecular characterization. Vancomycin MICs (V-MIC) were tested by the *E*-test and microdilution methods. Time until death was the dependent variable in a Cox regression analysis. Overall, 579 episodes were included. Acquisition was nosocomial in 59% and vascular catheter was the most frequent source (38%). A dominant PFGE genotype was found in 368 (67%) isolates, which belonged to Clonal Complex (CC)5 and carried SCCmecIV and *agr*2. Microdilution V-MIC50 and V-MIC90 were 0.7 and 1.0 mg/L, respectively. Initial therapy was appropriate in 66% of episodes. Overall mortality was observed in 179 (32%) episodes. The Cox-regression analysis identified age >70 years (HR 1.88), previous fatal disease (HR 2.16), Pitt score >1 (HR 3.45), high-risk source (HR 1.85) and inappropriate initial treatment (HR 1.39) as independent predictive factors for mortality. CC5 and CC22 (HR 0.52 and 0.45) were associated with significantly lower mortality rates than CC8. V-MIC $\geq$ 1.5 did not have a significant impact on mortality, regardless of the method used to assess it.

- 579 MRSA bakteremi olgusu
- Mortalite: **%32**

Etki Faktörü: 3,9

Clin Microbiol Infect 2013; 19: 1049–1057

Endokardit-Mortalite

Etki Faktörü: 59

Infective endocarditis

Thomas J Cahill, Bernard D Prendergast

Lancet 2016; 387: 882–93
Published Online
September 2, 2015
http://dx.doi.org/10.1016/
S0140-6736(15)00067-7

Department of Cardiology,

Infective endocarditis occurs worldwide, and is defined by infection of a native or prosthetic heart valve, the endocardial surface, or an indwelling cardiac device. The causes and epidemiology of the disease have evolved in recent decades with a doubling of the average patient age and an increased prevalence in patients with indwelling cardiac devices. The microbiology of the disease has also changed, and staphylococci, most often associated with health-care contact and invasive procedures, have overtaken streptococci as the most common cause of the disease. Although novel diagnostic and therapeutic strategies have emerged, 1 year mortality has not improved and remains at 30%, which is worse than

Prognosis and ongoing care

The in-hospital mortality of infective endocarditis is estimated at around 20%, increasing to 25–30% at 6 months, although this mortality varies substantially according to the infecting organism and clinical circumstances.[1,2,89,90] The most important adverse prognostic factors are old age, prosthetic valve endocarditis, heart failure, paravalvular complication, stroke, and infection with *S aureus*. Improved patient-

Staphylococcus aureus Native Valve Infective Endocarditis: Report of 566 Episodes from the International Collaboration on Endocarditis Merged Database

José M. Miro,[1] Ignasi Anguera,[2] Christopher H. Cabell,[7] Anita Y. Chen,[7] Judith A. Stafford,[7] G. Ralph Corey,[7] Lars Olaison,[3] Susannah Eykyn,[4] Bruno Hoen,[5] Elias Abrutyn,[8] Didier Raoult,[6] Arnold Bayer,[9] Vance G. Fowler, Jr.,[7] and the International Collaboration on Endocarditis Merged Database Study Group[a]

Background. *Staphylococcus aureus* native valve infective endocarditis (SA-NVIE) is not completely understood. The objective of this investigation was to describe the characteristics of a large, international cohort of patients with SA-NVIE.

Methods. The International Collaboration on Endocarditis Merged Database (ICE-MD) is a combination of 7 existing electronic databases from 5 countries that contains data on 2212 cases of definite infective endocarditis (IE).

Results. Of patients with native valve IE, 566 patients (34%) had IE due to *S. aureus*, and 1074 patients had IE due to pathogens other than *S. aureus* (non–SA-NVIE). Patients with *S. aureus* IE were more likely to die (20% vs. 12%; $P < .001$), to experience an embolic ev
event (20% vs. 13%; $P < .001$) and were less lik
with non–SA-NVIE. Multivariate analysis of p
95% confidence interval [CI], 1.1–1.7), perian
95% CI, 2.3–6.7), and absence of surgical thera
associated with mortality in patients with SA-N
characteristics by multivariate analysis, geogra
patients with SA-NVIE ($P < .001$).

Conclusions. *S. aureus* is an important and common cause of IE. The outcome of SA-NVIE is worse than that of non–SA-NVIE. Several clinical parameters are independently associated with mortality for patients with SA-NVIE. The clinical characteristics and outcome of SA-NVIE vary significantly by geographic region, although the reasons for such regional variations in outcomes of SA-NVIE are unknown and are probably multifactorial. A large, prospective, multinational cohort study of patients with IE is now under way to further investigate these observations.

- 566 *S.aureus* endokarditi olgusu
- Mortalite: **%20**

Etki Faktörü: 9.1

Clinical Infectious Diseases 2005; 41:507–14

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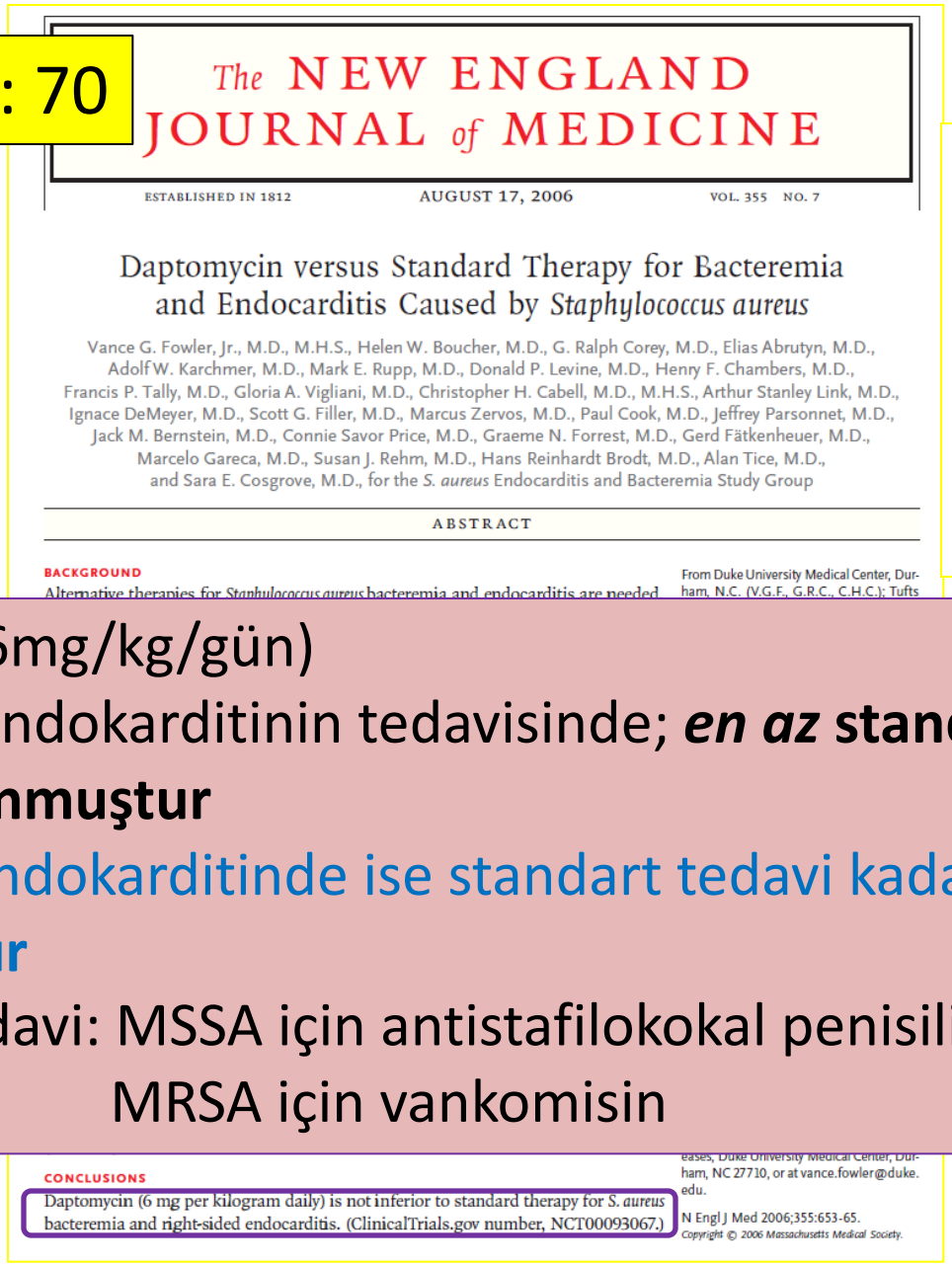
Etki Faktörü: 70



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Daptomycin for the treatment of infective endocarditis: results from a European registry

- Sol ve sağ kapak endokarditi, retrospektif
- Daha çok tedaviye yanıtsız olgular
- MRSA, MSSA
- 6 mg/kg, ≥8 mg/kg
- Klinik başarı (6mg/kg): %80
  - Sağ kalpte: %91
  - Sol kalpte: %76
  - MSSA'da %84
  - MRSA'da % 81
- Klinik başarı (8mg/kg): %90
  - Sağ kalpte: %91
  - Sol kalpte: %76

Etki Faktörü: 5.2

J Antimicrob Chemother 2013; **68**: 936–942

A multicentre evaluation of the effectiveness and safety of high-dose daptomycin for the treatment of infective endocarditis

Ravina Kullar[1]†, Anthony M. Casapao[1], Susan L. Davis[1,2], Donald P. Levine[1,3], Jing J. Zhao[4], Christopher W. Crank[5], John Segreti[6], George Sakoulas[7], Sara E. Cosgrove[8] and Michael J. Rybak[1,3]*

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Division of

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Wayne State University, 259 Mack

Received 3 Ap

Objectives: Despite sign
high morbidity and mort
as ≥8 mg/kg/day, in pat

Methods: This was a m
haemodialysis, with blo
of IE, who received dapt

Results: Seventy patien
with left-sided IE (LIE)
bone/joint infection bei
Pathogens were isolat
common organism (84.
daptomycin dose was
9.3 mg/kg/day, respecti
gens isolated (n=64), th
55 (85.9%) achieved c
creatine phosphokinase elevations.

Conclusions: Patients with both RIE and LIE had successful outcomes with high-dose daptomycin therapy. Additional clinical trials evaluating high daptomycin dosages in patients with IE are warranted.

70 endokardit olgusu, retrospektif

- 33 sağ kalp
  35 sol kalp
  2 hem sağ hem sol kalp
- 65 olguda kurtarma tedavisi
- 64'ü *S.aureus*
- 9.8 mg/kg/gün
- Bakteriyel eradikasyon: %89
- Klinik başarı: %90

Etki Faktörü: 5.2

J Antimicrob Chemother 2013; **68**: 2921–2926

High-Dose Daptomycin Therapy for Left-Sided Infective Endocarditis: a Prospective Study from the International Collaboration on Endocarditis

Manuela Carugati,[a,d] Arnold S. Bayer,[b] Josè M. Miró,[c] Lawrence P. Park,[d] Armenio C. Guimarães,[e] Athanasios Skoutelis,[f] Claudio Q. Fortes,[g] Emanuele Durante-Mangoni,[h] Margaret M. Hannan,[i] Francisco Nacinovich,[j] Nuria Fernández-Hidalgo,[k] Paolo Grossi,[l] Ru-San Tan,[m] Thomas Holland,[d] Vance G. Fowler, Jr.,[d] Ralph G. Corey,[d] Vivian H. Chu,[d] on behalf of the International Collaboration on Endocarditis

Department of Clinical Science, University of Milan, Luigi Sacco Hospital, Milan, Italy[a]; LA Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance and

- Sol kalp endokarditi, 1112 olgu, prospektif kohort
- 9.2 mg/kg/gün daptomisin
- Hızlı bakteremi klirensi
- Yan etkide artış yok
- Standart tedaviye alternatif olabilecek kadar etkili

dian daptomycin dose was 9.2 mg/kg of body weight/day. Two-thirds of the patients treated with daptomycin had failed a previous antibiotic regimen. In-hospital and 6-month mortalities were similar in the two cohorts. In cohort A, median time to clearance of methicillin-resistant *S. aureus* (MRSA) bacteremia was 1.0 day, irrespective of daptomycin dose, representing a significantly faster bacteremia clearance compared to SOC (1.0 versus 5.0 days; $P < 0.01$). Regimens with higher daptomycin doses were not associated with increased incidence of AEs. In conclusion, higher-dose daptomycin may be an effective and safe alternative to SOC in the treatment of left-sided IE due to common Gram-positive pathogens.

Etki Faktörü: 4.7

December 2013 Volume 57 Number 12 Antimicrobial Agents and Chemotherapy p. 6213–6222

Turk Kardiyol Dern Ars 2017;45(4):310-315 doi: 10.5543/tkda.2017.60784

Sol taraflı endokarditte daptomisin: Tek merkez deneyim

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

Dr. Burak Açar,[1] Dr. Yasemin Tezer Tekçe,[2] Dr. Çağrı Yayla,[1] Dr. Sefa Ünal,[1]
Dr. Ahmet Göktuğ Ertem,[1] Dr. Bihter Şentürk,[3] Dr.Özlem Özcan Çelebi,[1] Dr. Sinan Aydoğdu[1]

Clinics of Cardiology[1], and Infection Diseases[2] Turkey Higher Specialization Training and Research Hospital Ankara
[3] Department of Cardiology, 9 Eylül University, Faculty of Medicine, Izmir

Yöntemler: Çalışmaya, Duke kriterlerine göre sol taraflı enfektif endokardit tanısı alarak 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 pozitifti 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 uygula
%71.4 mikrobiyolojik eradikasyon
iyileşme süresi ortalama 8.7±3.2 g
yon süresi ise ortalama 11.1±3.6 g
bağlı yan etkiler tespit edildi, anca
gerekliliği olmadı. On hasta komplik
hasta tedavi devam ederken kalp
yetersizliğine bağlı olarak kaybedilirken, iki hasta da erken kardiyak cerrahi gerekliliği nedeniyle ameliyat edildi, ancak ameliyat sonrası erken dönemde hasta kaybedildi.

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

- 13 olgu
- Klinik iyileşme: %71
- Mikrobiyolojik eradikasyon: %85

Vankomisin MİK değeri - Daptomisin kullanımı

EUCAST kriterleri

S.aureus - Vankomisin:

≤ 2 µg/mL ise duyarlı

> 2 µg/mL ise dirençli

Vankomisin MİK değeri ≥ 2 µg/mL olan suşlarda tedavide daptomisin tercih edilmelidir

IDSA MRSA Bakteremi Rehberi

IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

III. What is the management of MRSA bacteremia and infective endocarditis?

Bacteremia and Infective Endocarditis, Native Valve

19. For adults with uncomplicated bacteremia (defined as patients with positive blood culture results and the following: exclusion of endocarditis; no implanted prostheses; follow-up blood cultures performed on specimens obtained 2–4 days after the initial set that do not grow MRSA; defervescence within 72 h of initiating effective therapy; and no evidence of metastatic sites of infection), vancomycin (**A-II**) or daptomycin 6 mg/kg/dose IV once daily (**AI**) for at least 2 weeks. For complicated bacteremia (defined as patients with positive blood culture results who do not meet criteria for uncomplicated bacteremia), 4–6 weeks of therapy is recommended, depending on the extent of infection. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (**B-III**).

20. For adults with infective endocarditis, IV vancomycin (**A-II**) or daptomycin 6 mg/kg/dose IV once daily (**A-I**) for 6 weeks is recommended. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (**B-III**).

Bakteremi için

- Vankomisin (A-II)
- Daptomisin 6 mg/kg (A-I)
  8-10 mg/kg (B-III)

Endokardit için

- Vankomisin (A-II)
- Daptomisin 6 mg/kg (A-I)
  8-10 mg/kg (B-III)

Clinical Infectious Diseases 2011;52(3):e18–e55

Avrupa Endokardit Rehberi

Table 17 Antibiotic treatment of infective endocarditis due to *Staphylococcus* spp.

Antibiotic	Dosage and route	Duration (weeks)	Class[i]	Level[j]	Ref.[k]	Comments
Native valves						
Methicillin-susceptible staphylococci						
(Flu)cloxacillin *or* oxacillin	12 g/day i.v. in 4–6 doses	4–6	I	B	6,8, 128, 135, 136, 158	Gentamicin addition is not recommended because clinical benefit has not been demonstrated and there is increased renal toxicity
	Paediatric doses:[g] 200–300 mg/kg/day i.v. in 4–6 equally divided doses					
Alternative therapy* Cotrimoxazole[a]	Sulfamethoxazole 4800 mg/day and Trimethoprim 960 mg/day (i.v. in 4–6 doses)	1 i.v. + 5 oral intake	IIb	C		*for *Stahylococcus aureus*
with						
Clindamycin	1800mg/day i.v. in 3 doses	1	IIb	C		
	Paediatric doses:[g] Sulfamethoxazole 60 mg/kg/day and Trimethoprim 12 mg/kg/day (i.v. in 2 doses) Clindamycin 40 mg/kg/day (i.v. in 3 doses)					
Penicillin-allergic patients[h] ***or methicillin-resistant staphylococci***						
Vancomycin[b] **	30–60 mg/kg/day i.v. in 2–3 doses	4–6	I	B	6,8, 135, 136	**Cephalosporins** (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis
	Paediatric doses:[g] 40 mg/kg/day i.v. in 2–3 equally divided doses					
Alternative therapy**: Daptomycin[c,d]	10 mg/kg/day i.v. once daily	4–6	IIa	C		**Daptomycin** is superior to vancomycin for MSSA and MRSA bacteraemia with vancomycin MIC > 1 mg/L
	Paediatric doses:[g] 10 mg/kg/day i.v. once daily					
Alternative therapy* Cotrimoxazole[a]	Sulfamethoxazole 4800 mg/day and Trimethoprim 960 mg/day (i.v. in 4–6 doses)	1 i.v. + 5 oral intake	IIb	C		*for *Stahylococcus aureus*
with						
Clindamycin	1800mg/day IV in 3 doses	1	IIb	C		

Avrupa Endokardit Rehberi

Prosthetic valves						
Methicillin-susceptible staphylococci						
(Flu)cloxacillin *or* oxacillin with Rifampin[e] and Gentamicin[f]	12 g/day i.v. in 4–6 doses	≥ 6	I	B	6,8, 135, 136	Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts. Gentamicin can be given in a single daily dose in order to reduce renal toxicity
	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I	B		
	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B		
	Paediatric doses:[g] Oxacillin and (flu)cloxacillin as above Rifampin 20 mg/kg/day i.v. or orally in 3 equally divided doses					
Penicillin-allergic patients[h] and methicillin-resistant staphylococci						
Vancomycin[b] with Rifampin[e] and Gentamicin[f]	30–60 mg/kg/day i.v. in 2–3 doses	≥ 6	I	B	6,8, 135, 136	**Cephalosporins** (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis. Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts. Gentamicin can be given in a single daily dose in order to reduce renal toxicity
	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I	B		
	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B		
	Paediatric dosing:[g] As above					

AUC = area under the curve; C_{min} = minimum concentration; IE = infective endocarditis; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*; PVE = prosthetic valve endocarditis.
[a]Renal function, serum Cotrimoxazole concentrations should be monitored once/week (twice/week in patients with renal failure); [b]Serum trough vancomycin levels (C_{min}) should be ≥ 20 mg/L. A vancomycin AUC/MIC >400 is recommended for MRSA infections; [c]Monitor plasma CPK levels at least once a week. Some experts recommend adding cloxacillin (2 g/4 h i.v.) or fosfomycin (2 g/6 h i.v.) to daptomycin in order to increase activity and avoid the development of daptomycin resistance; [d]Daptomycin and fosfomycin are not available in some European countries; [e]Rifampin is believed to play a special role in prosthetic device infection because it helps eradicate bacteria attached to foreign material.[157] The sole use of rifampin is associated with a high frequency of microbial resistance and is not recommended. Rifampin increases the hepatic metabolism of warfarin and other drugs; [f]Renal function and serum gentamicin concentrations should be monitored once/week (twice/week in patients with renal failure); [g]Paediatric doses should not exceed adult doses; [h]Penicillin desensitization can be attempted in stable patients; [i]Class of recommendation; [j]Level of evidence; [k]Reference(s) supporting recommendations.
** No clinical benefit of adding rifampicin or gentamicin

European Heart Journal (2015) **36**, 3075–3123

ABD Endokardit Rehberi

Table 10. Therapy for NVE Caused by Staphylococci

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 4–6 equally divided doses	6	*Class I; Level of Evidence C*	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk (see text).
For penicillin-allergic (nonanaphylactoid type) patients				Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin.
Cefazolin*	6 g/24 h IV in 3 equally divided doses	6	*Class I; Level of Evidence B*	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases.
Oxacillin-resistant strains				
Vancomycin§	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class I; Level of Evidence C*	Adjust vancomycin dose to achieve trough concentration of 10–20 μg/mL (see text for vancomycin alternatives).
Daptomycin	≥8 mg/kg/dose	6	*Class IIb; Level of Evidence B*	Await additional study data to define optimal dosing.

IE indicates infective endocarditis; IV, intravenous; and NVE, native valve infective endocarditis.
*Doses recommended are for patients with normal renal function.
§For specific dosing adjustment and issues concerning vancomycin, see Table 7 footnotes.

Circulation. 2015;132:1435-1486.

ABD Endokardit Rehberi

Table 11. Therapy for Endocarditis Involving a Prosthetic Valve or Other Prosthetic Material Caused by Staphylococci

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 6 equally divided doses	≥6	*Class I; Level of Evidence B*	Vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics (see Table 5 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin in patients with non–immediate-type hypersensitivity reactions to penicillins.
Plus				
Rifampin	900 mg per 24 h IV or orally in 3 equally divided doses	≥6		
Plus				
Gentamicin†	3 mg/kg per 24 h IV or IM in 2 or 3 equally divided doses	2		
Oxacillin-resistant strains				
Vancomycin	30 mg/kg 24 h in 2 equally divided doses	≥6	*Class I; Level of Evidence B*	Adjust vancomycin to a trough concentration of 10–20 μg/mL. (see text for gentamicin alternatives)
Plus				
Rifampin	900 mg/24 h IV/PO in 3 equally divided doses	≥6		
Plus				
Gentamicin	3 mg/kg per 24 h IV/IM in 2 or 3 equally divided doses	2		

IM indicates intramuscular; and IV, intravenous.
*Doses recommended are for patients with normal renal function.
†Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing. See Table 7 for appropriate dose of gentamicin.

***Circulation*. 2015;132:1435-1486.**

Ulusal Uzlaşı Raporumuzda…

Tablo 23. Stafilokoksik İnfektif Endokarditlerin Antimikrobik Tedavisi (3,65,207)

Mikroorganizma	Antimikrobik	Günlük Doz, Doz Aralığı, Uygulama Yolu	Süre (Hafta) Doğal Kapak	Süre (Hafta) Yapay Kapak	Yorum
Metisiline duyarlı stafilokoklar*	Nafsilin veya	12 gr, 6 dozda, İV	4-6	≥6	Ülkemizde nafsilin ve flukloksasilin bulunamamaktadır.
	Flukloksasilin veya	12 gr, 6 dozda, İV	4-6	≥6	
	Sefazolin†	6 gr, 3 dozda, İV	4-6	≥6	
	+				
	Gentamisin	3 mg/kg, tek doz, İV	Verilmez	2	
	+				
	Rifampisin‡	900 mg, tek doz, oral/İV	Verilmez	≥6	
	Daptomisin§ veya	8-12 mg/kg, tek doz, İV	4-6	≥6	Sadece β-laktamları tolere edemeyen veya β-laktam alerjisi olan hastalarda kullanılmalıdır.
	Vankomisin	30 mg/kg/gün, 2 dozda, İV	4-6	≥6	

§ Daptomisinin, seftarolin, sefazolin, seftriakson, trimetoprim-sülfametoksazol (345) veya fosfomisinle kombine edilmesi düşünülebilir

Ulusal Uzlaşı Raporumuzda…

52 *Klimik Derg.* 2019; 32(Suppl. 1): 2-116

Tablo 23. Stafilokoksik İnfektif Endokarditlerin Antimikrobik Tedavisi (3,65,207)

Mikroorganizma	Antimikrobik	Günlük Doz, Doz Aralığı, Uygulama Yolu	Süre (Hafta) Doğal Kapak	Süre (Hafta) Yapay Kapak	Yorum
Metisiline dirençli vankomisine duyarlı (MIC ≤2 µg/ml) stafilokoklar	Vankomisin[‖]	30 mg/kg/gün, 2 dozda İV	4-6	≥6	Kardiyak veya ekstrakardiyak tüm apse odakları uygun cerrahi girişimlerle kontrol altına alınmalıdır.
	+				
	Gentamisin[¶] (duyarlıysa)	3 mg/kg, tek doz, İV	Verilmez	2	
	+				
	Rifampisin (duyarlıysa)	900 mg, 3 doz, oral-İV	Verilmez	≥6	
	Daptomisin[§]	8-12 mg/kg, tek doz, İV	4-6		

§ Daptomisinin, seftarolin, sefazolin, seftriakson, trimetoprim-sülfametoksazol (345) veya fosfomisinle kombine edilmesi düşünülebilir

MRSA Endokarditi için Seçenekler

- Vankomisin
- Daptomisin
- Daptomisin + Ampisilin
- Daptomisin + Sefazolin
- Daptomisin + Ko-trimoksazol
- Daptomisin + Fosfomisin
- ….

Koagülaz negatif stafilokoklar…

Soru: *S.aureus* için olan öneriler koagülaz negatif stafilokoklar için de geçerli mi?

Yanıt: EVET

Avrupa Rehberi ve bizim uzlaşı raporumuz:

- MSSA ve MS-KNS için

  Antistafilokokal penisilin veya 1. kuşak sefalosporin

- MRSA ve MR-KNS için: Vankomisin veya Daptomisin

ABD Rehberi:

- MSSA ve MS-KNS için

  Antistafilokokal penisilin veya 1. kuşak sefalosporin

- MRSA için Vankomisin veya Daptomisin
- MR-KNS için Vankomisin

Striking "Seesaw Effect" between Daptomycin Nonsusceptibility and β-Lactam Susceptibility in *Staphylococcus haemolyticus*

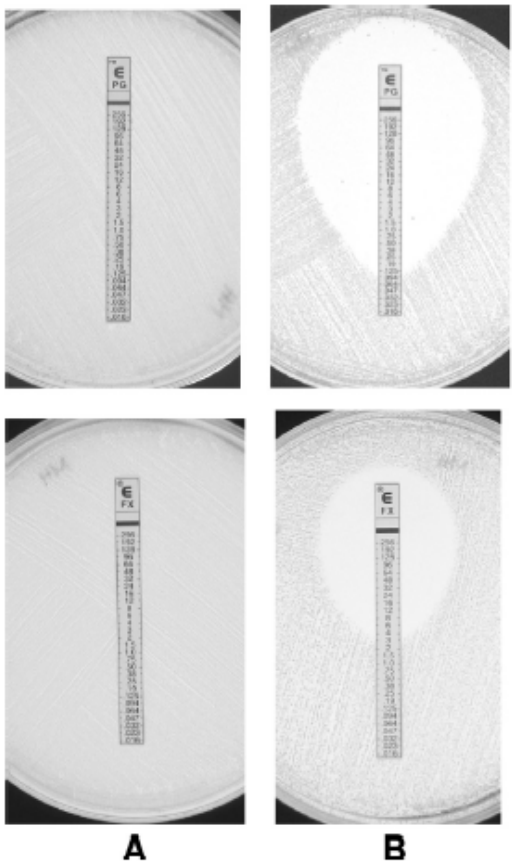

FIG. 1. Diffusion tests using Etest strips (penicillin and cefoxitin). (A) Clinical isolate of daptomycin-susceptible *S. haemolyticus* (parent strain). (B) Daptomycin-nonsusceptible laboratory derivative.

Tahterevalli etkisi

Daptomisinin MİK değer yükseldikçe Beta laktam antibiyotiklerin MİK değeri düşüyor

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2011, p. 2495–2497

ÖZET- 1

- MRSA endokarditinin mortalitesi %30 civarındadır
- Mevcut yayınların niteliği nedeniyle daptomisin ile tedavi edilen olgulara ilişkin veriler tedavi rehberlerindeki önerilere tam olarak yansıtılamamaktadır
- Vankomisin, uzun yıllardır kullanılmasına rağmen stafilokoklarda halen vankomisine direnç oranlarının düşük olması vankomisini cazip hale getirmektedir. Ancak vankomisinin bakterisidal etkinliğinin yavaş olduğu ve nefrotoksik olduğu da akılda tutulmalıdır.

ÖZET- 2

- Daptomisin, MRSA endokarditinde en az 8 mg/kg dozunda kullanılmalıdır
- Daptomisin kullanımı sırasında haftada en az bir kez serum kreatinin kinaz düzeyine bakılmalıdır
- Daptomisin, ampisilin, sefazolin, ko-trimoksazol veya fosfomisin ile kombine kullanılabilir