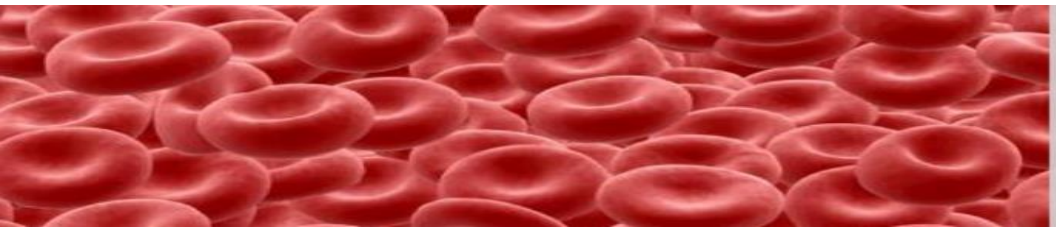
İE'de Oral Antibiyotik Tedavisi: Olabilir mi?

Yasemin Tezer Tekçe



İECG

Sunum Planı

- İE'de antimikrobik tedavi için genel öneriler
- İE hastanede mi tedavi edilmeli, hospitalizasyonu neden ve nasıl azaltırız?
- İE'de parenteral (PE) tedavi gerekli mi, sakıncaları var mı?
- Ne zaman oral tedaviden bahsedebiliriz? Hangi ajanlarla?
- Parenteral başlanmış İE tedavisi oral tedavi ile tamamlanabilir mi?

İE tedavisinde genel görüşler

- 4-6 hafta süre ile hastanede
- Parenteral tedavi
- Hastane içi mortalite gelişmiş ülkelerde %20*, S. aureus'da* %22;
- Türkiye'de %27, *S. aureus*'da %38
- 1 yıllık mortalite gelişmiş ülkelerde %30, yapay kapak ve *S. aureus* İE'de %50
- İE olgularının %25-50 akut dönemde, %20-40'na konvelesan dönemde cerrahi gerekmektedir.
- Günlük vizitlerle, yakın takip; 7/24/4-6 hafta

İE’de Antimikrobik Tedavi

- Zor , belli kurallar…
- Vejetasyonda bakteri savunması yetersiz ve bakteri yoğunluğu çok yüksek
- Vegetasyon içindeki m.o. metabolik aktivitesi yavaş
- Cerrahi gereksinimi?
- Etken izolasyonu, tür düzeyinde tanımlanması, MİK değerinin belirlenmesi, hasta yakınmalarının süresi, tutulan kapağın özellikleri
- GENEL İLKELER; sidal ajanlarla, parenteral yoldan ve uzun süreli

Serap Şimşek-Yavuz Klimik Dergisi 2015;28(2):46-67
Holland TL et al Nat Rev Dis Primers 2017 March
Habib G et al European Heart Journal 2015 August 1-54

İE neden hastanede tedavi edilmeli?

- %20-40 oranlarında görülen mortalite hızlarını azaltmak
- Kardiyak komplikasyonlarının takip ve tedavisi

-Kapaktaki lezyonda kötüleşme

-Apse

-Kalp yetmezliği

-Aritmi, iletim defekti

-Perikardit, miyokardit

- Cerrahi ihtiyacını ve zamanlamasını belirlemek

İE neden hastanede tedavi edilimeli?

- Beraberinde oluşan diğer enfeksiyonların ve komorbiditelerin tedavisi
- Oluşabilecek kardiyak dışı komplikasyonları azaltmak ya da tedavi etmek

-Tedavi başarısızlığı

-Nörolojik komplikasyonlar (emboli..)

-Akut böbrek yetmezliği

-Dalak apsesi

-Tedavi ilişkili komplikasyonlar (ilaç ateşi…)

Hastanede kalış süresi azaltılmalı mı?

- Uzun süreli yatıştan kaynaklanan artmış komplikasyon riski
- Diğer hastaların tedavisindeki pozitif katkı
- Sağlık bakımı ile ilişkili maliyeti azaltmak

PLOS | MEDICINE

ESSAY

An Unsupported Preference for Intravenous Antibiotics

Ho Kwong Li[1], Ambrose Agweyu[2], Mike English[2,3], Philip Bejon[1,3,4]*

Hospitalizasyonu nasıl azaltırız?

- Parenteral tedavi süresini kısaltarak

(2 haftalık tedavi)

- APAT ile
- Sadece oral tedavi ile?
- PE➔PO geçilerek

PE (IV) tedavi gerekli mi?

- IV tedavi sonrası hızlıca tepe değerine ulaşan AB konsantrasyonu en önemli sebep
- ANCAK; beta-laktamlar, glikopeptidler ve makrolidler gibi antimikrobiyaller için tepe değerinden çok MİK değerinin üzerinde geçen süre
- AYRICA; yüksek dozlarda IV verilse bile, MİK değerinin üzerinde geçen süre, biyoyararlanımı iyi olan AB'lerin PO benzer
- Tepe konsantrasyon değerleri önemli olan aminoglikozidler ve kinolonlar için ise; AG oral absorbe olamadığından, kinolonlar PO'da etkili konsantrasyonlara ulaştığından

Li HK et al PLOS Medicine 2015 May 1-7

PE (IV) tedavi gerekli mi?

- İyi absorbe olan oral AB'den;

Amoksisilin biyoyararlanımı>%75

Klindamisin biyoyararlanımı %90

Doksisiklin biyoyararlanımı %95

Dokularda etkin konsantrasyona ulaşmakta

- Pekçok infeksiyon hastalığı için randomize kapsamlı çalışma olmamasına rağmen; klinisyenlerin elini güçlü tutma isteği, malpraktis ve dava çekincesi, geri ödeme sorunları nedeniyle oral tedavi tercih edilebilecekken PE tedavi kullanılmakta

Li HK et al PLOS Medicine 2015 May 1-

Journal of Antimicrobial Chemotherapy Advance Access published April 27, 2016

J Antimicrob Chemother
doi:10.1093/jac/dkw129

Journal of Antimicrobial Chemotherapy

What prevents the intravenous to oral antibiotic switch? A qualitative study of hospital doctors' accounts of what influences their clinical practice

Jennifer Broom[1,2], Alex Broom[3], Kate Adams[4] and Stefanie Plage[3]*

Results: Decisions around the choice of iv over oral antibiotics were influenced by three key issues: (i) *consumer-ism*, i.e. participants were concerned about the risk of litigation or complaints if patient expectations were not met; (ii) *hierarchy* of the medical team structure limited opportunities for de-escalation of antibiotics; and (iii) iv antibiotics were perceived as more potent and having significant *mythical qualities*, which participants acknowledged were not necessarily evidence based.

PE (IV) Tedavinin sakıncaları??

- Filebit, ekstravasazyon yaralanmaları, tromboz, lokal ya da sistemik infeksiyon (bakteriyemi)
- Hospitalizasyon süresini dolayısı ile finansal ve hastane bakım ilişkili maliyeti artırmakta

PLOS | MEDICINE

ESSAY

An Unsupported Preference for Intravenous Antibiotics

Ho Kwong Li[1], Ambrose Agweyu[2], Mike English[2,3], Philip Bejon[1,3,4]*

PE (IV) Tedavinin sakıncaları??

- Bakteriyemi riski;

IV periferal %0.1;PICC %2.4; SVK %4.4

- Uzamış hospitalizasyon nedeniyle maliyet

4500 £/gün

- APAT ile maliyet 1800 £/gün
- Günlük tek doz PE olarak seçilebilecek antibiyotikler geniş spektrumlu➔Direnç
- İE'de kateter kullanımı prognoz ile ilişkili

PLOS Medicine | DOI:10.1371/journal.pmed.1001825 May 19, 2015
F.Z. Ahmed et al. / Journal of Hospital Infection 83 (2013) 46–50

Hangi Durumlarda Oral Tedavi?

- Uzun süreli venöz yol girişinin istenmediği durumlar (damardan ilaç kullanımı olan hastalar gibi)

- Venöz yol girişi için uygun olmayan hastalar (hastanın kabul etmemesi gibi..)

When are Oral Antibiotics a Safe and Effective Choice for Bacterial Bloodstream Infections? An Evidence-Based Narrative Review

Andrew J. Hale, MD[1,2*], Graham M. Snyder, MD, SM[3,4], John W. Ahern, PharmD[5,6], George Eliopoulos, MD[3,4], Daniel N. Ricotta, MD[4,7], W. Kemper Alston, MD, MPH[1,2]

- Güçlü klinik çalışmalar YOK;
  - uzman görüşleri

* Kaynak kontrolü

* Patojen ve antimikrobiyal ilişkili faktörler

* Hasta ile ilişkili faktörler

Journal of Hospital Medicine Published Online February 2018

TABLE 3. **Checklist for Using an Oral Antibiotic for Bloodstream Infection**

Bacterial/Antimicrobial Factors

- [ ] Speciation and susceptibilities are available
- [ ] Susceptibilities indicate an oral antibiotic is effective against the pathogen
- [ ] Oral agent is highly bioavailable
- [ ] Oral agent has a low acquired-resistance potential for the given pathogen
- [ ] Oral agent is well-tolerated and has an acceptable safety profile for the pa
- [ ] No serious drug–drug interactions between the selected agent and other r

Patient Factors

- [ ] No allergies or intolerances to the selected agent
- [ ] No impaired gastrointestinal absorption
- [ ] Hemodynamically stable
- [ ] Minimal compliance concerns
- [ ] Patient has received appropriate education and demonstrated understandi importance of compliance
- [ ] Dietary interactions considered (Table 2)
- [ ] Underlying source of bloodstream infection identified and controlled
- [ ] Upon discharge, patient has access to the oral agent
  - [ ] • The pharmacy has the agent available
  - [ ] • The patient is able to get medication from pharmacy before the next d
  - [ ] • Medication copay at the pharmacy is affordable
- [ ] Available for follow-up

- Etken m.o.'nın duyarlılık ve MİK değerleri bilinmeli
- Yüksek biyoyararlanımı olan AB
- AB kazanılmış direnç potansiyeli düşük
- İyi tolere edilebilen, absorbe olan, güvenli
- Ciddi ilaç-ilaç etkileşimi olmayan

- Allerji, intolerans,GIS absorbsiyon problemi olmayan
- HEMODİNAMİK olarak STABİL
- Diyet etkileşimi
- AB temini ve sonrasında takip problemi olmayan
- Kaynak kontrolü??

TABLE 1. **Penetration of Select Oral Antimicrobials to Tissue Sites**[7,44]

Antimicrobial	Bloodstream bioavailability	Lung	Liver	Urinary Tract	Prostate	Bone	GI	Skin	Bile	CSF	Synovial
Ciprofloxacin	70%	++	+++	+++	+++	+++	+++	+++	+++	+	+++
Levofloxacin	99%	+++	+++	+++	+++	+++	+++	+++	+++	+	+++
Moxifloxacin	90%	+++	+++	+++	+++	+++	+++	+++	+++	+	+++
Trimethoprim-Sulfamethoxazole	90%	++	++	+++	++	++	++	+++	++	+	++
Doxycycline	95%	++	++	++	++	++	++	++	++	+	++
Minocycline	95%	++	++	++	++	++	++	++	++	+	++
Linezolid	99%	+++	++	+++	++	++	++	+++	++	++	++
Metronidazole	90%	++	+++	++	++	++	++	++	++	++	++
Clindamycin	90%	++	++	++	++	++	++	++	++	+	++
Ampicillin	50%	+	++	++	+	++	++	++	++	++	+
Penicillin V	50%	++	++	++	+	++	++	++	++	++	+
Amoxicillin	85%	+	++	++	+	++	++	++	++	++	+
Cephalexin	60%	++	++	++	++	++	++	++	++	+	++

Journal of Hospital Medicine Published Online February 2018

İE’de ??

Oral tedavide kriterler APAT'a benzer mi?

Phase of treatment	Guidelines for use
Critical phase (weeks 0–2)	• Complications occur during this phase • Preferred inpatient treatment during this phase • Consider OPAT if: oral streptococci or *Streptococcus bovis*,[a] native valve,[b] patient stable, no complications
Continuation phase (beyond week 2)	• Consider OPAT if medically stable • Do not consider OPAT if: HF, concerning echocardiographic features, neurological signs, or renal impairment
Essential for OPAT	• Educate patient and staff • Regular post-discharge evaluation (nurses 1/day, physician[c] in charge 1 or 2/week)[d] • Prefer physician-directed programme, not home-infusion model

European Heart Journal Advance Access published August 29, 2015
European Heart Journal
doi:10.1093/eurheartj/ehv319
ESC GUIDELINES

2015 ESC Guidelines for the management of infective endocarditis

The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)

European Heart Journal Advance Access published August 29, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv319

2015 ESC Guidelines for the management of infective endocarditis

The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)

Table 15 Predictors of poor outcome in patients with infective endocarditis

Patient characteristics • [illegible] • [illegible] • [illegible] • [illegible] ...ary
C • [illegible] • [illegible] • [illegible] • [illegible] • Septic shock
Microorganism • *Staphylococcus aureus* • Fungi • Non-HACEK Gram-negative bacilli
Echocardiographic findings • Periannular complications • Severe left-sided valve regurgitation • Low left ventricular ejection fraction • Pulmonary hypertension • Large vegetations • Severe prosthetic valve dysfunction • Premature mitral valve closure and other signs of elevated diastolic pressures

İE'de oral antibiyotik tedavisi düşünemeyeceğimiz hasta grubu

European Heart Journal Advance Access published August 29, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv319

2015 ESC Guidelines for the management of infective endocarditis

The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)

Table 19 Antibiotic treatment of blood culture-negative infective endocarditis (adapted from Brouqui *et al.*[193])

Pathogens	Proposed therapy[a]	Treatment outcome
Brucella spp.	Doxycycline (200 mg/24 h) plus cotrimoxazole (960 mg/12 h) plus rifampin (300–600/24 h) for ≥3–6 months[b] orally	Treatment success defined as an antibody titre <1:60. Some authors recommend adding gentamicin for the first 3 weeks.
C. burnetii (agent of Q fever)	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h)[c] orally (>18 months of treatment)	Treatment success defined as anti-phase I IgG titre <1:200, and IgA and IgM titres <1:50.
Bartonella spp.[d]	Doxycycline 100 mg/12 h orally for 4 weeks plus gentamicin (3 mg/24 h) i.v. for 2 weeks	Treatment success expected in ≥90%.
Legionella spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 weeks or clarithromycin (500 mg/12 h) i.v. for 2 weeks, then orally for 4 weeks plus rifampin (300–1200 mg/24 h)	Optimal treatment unknown.
Mycoplasma spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 months[e]	Optimal treatment unknown.
T. whipplei (agent of Whipple's disease)[f]	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h)[c] orally for ≥18 months	Long-term treatment, optimal duration unknown.

Oral Ajanlarla Tedavi

- Klavuzlarda verilerin azlığı ve etkinlikteki kaygılar nedeniyle klavuzlarda nadiren bahsedilmektedir.
- Oral tedavi ile yer değiştirme de önerilmemektedir.
- Ancak damar yolu ile ilaç kullananlarda oral tedavinin güvenli bir seçenek olabileceğinden bahsedilmektedir.
- Oral tedavinin uygunluğu, kullanılacak antimikrobiyalin biyoyararlanımı ve hastaya ilişkin faktörlere bağlıdır.
- Damar yolu ile verildiğine yakın, biyoyararlanımı yüksek olan, hastanın tolere edebildiği, GIS absorbsiyonu sorun olmayan ajanlar kullanılabilir.
- Siprofloksasin, linezolid, rifampisin gibi…

J Antimicrob Chemother 2012; **67**: 269–289
doi:10.1093/jac/dkr450 Advance Access publication 14 November 2011

Journal of Antimicrobial Chemotherapy

Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy

F. Kate Gould[1*], David W. Denning[2], Tom S. J. Elliott[3], Juliet Foweraker[4], John D. Perry[1], Bernard D. Prendergast[5], Jonathan A. T. Sandoe[6], Michael J. Spry[1] and Richard W. Watkin[7]

Oral Ajanlarla Tedavi

- Son klavuzlardaki ortak görüş; Oral ajanların etkinliği ve güvenirliliği konusunda yeterli bilgi yok
- Parenteral başlanmış ilaçların belli bir süre sonra orale geçilmesi konusunda bazı çalışmalar olmakla birlikte….
- Tedavi süresi genelde 4-6 hafta
- Ancak viridans streptokoklar ve MSSA'nın neden olduğu sağ kalp doğal kapak İE'de 2 haftalık kombinasyon tedavisi
- Komplike seyir izleyen, yakınmaları 3 aydan uzun süren olgularda, yapay kapak varlığında kısa süreli tedavi önerilmez.

Table 1 Observational studies of oral antibiotic therapy for infective endocarditis

Reference	Cases	Design	Case definition	Microbiology	Assessment of antibiotic susceptibility	Therapy	Cure
Colli et al, Italy [9]	12 NVE and 2 PVE requiring acute valve replacement(all left-sided)	Retrospective. Mean follow-up was 20.8 ± 7 months	By Duke criteria	MRSA (60%) *S. viridans* (30%) *Enterococcus sp.* (10%)	Yes	IV vancomycin for 5.3 ± 3.4 days followed by oral linezolid for 3 weeks	100%
Dworkin et al, USA [10]	13 IVDUs with NVE (all right-sided with no systemic metastasis)	Prospective. 4-week follow-up	≥2 positive blood cultures AND any of the following: Vegetations on echocardiogram (definite – 3 cases) OR pulmonary infiltrates/ effusion or tricuspid insufficiency murmur (probable – 6 cases) OR no other identifiable source for the infection (possible – 1 case)	*S. aureus* (100%)	Yes	IV ciprofloxacin and oral rifampin for 1 week followed by oral ciprofloxacin and oral rifampin for 3 weeks	77%
Chetty et al, South Africa [11]	15 NVE (right-sided vs. left-sided not specified, all cases were considered uncomplicated)	Prospective. 3-year follow-up	Characteristics clinical features AND any of the following: Positive blood cultures OR vegetations on echocardiogram	*Streptococcus sp.* (60%) Culture negative (40%)	Yes	High dose oral amoxycillin for 6 weeks (47% also received probenecid)	87%

2007

1989

1988

Al-Omari et al. BMC Infectious Diseases 2014, 14:140

Table 1 Observational studies of oral antibiotic therapy for infective endocarditis

Reference	Cases	Design	Case definition	Microbiology	Assessment of antibiotic susceptibility	Therapy	Cure
Pinchas et al, Israel [12]	11 NVE (all left-sided, considered uncomplicated)	Prospective. Follow-up varied from 3 months to 12 years	Fever AND pre-existing valvular heart disease AND multiple positive blood cultures	*S. viridans* (100%)	Yes	High dose oral ampicillin for 6 weeks with probenecid for the first 4 weeks. IM streptomycin for the first 2 weeks	90%
Phillips et al, UK [13]	13 NVE (right-sided vs. left-sided not specified) – all children	Retrospective. Follow-up varied from 1-15 years	Pre-existing valvular disease AND characteristic clinical features AND positive blood cultures	*S. viridans* (62%) *Staphylococcus sp.* (23%) Other streptococci or *Enterococcus sp.* (15%)	Yes	IV therapy for < 2 weeks (92% ≤3 days) followed by oral penicillin V, ampicillin, cloxacillin, fludoxacillin or erythromycin for 6-8 weeks	100%
Gray et al, UK [14]	13 NVE (right-sided vs. left-sided not specified)	Retrospective. 3-month follow-up	Not specified	*S. viridans.* (62%) *E. faecalis* (1%) Culture negative (37%)	Yes	Oral ampicillin or propicillin (with or without probenecid) for 6 weeks	92%

1983

1977

1964

Al-Omari et al. BMC Infectious Diseases 2014, 14:140

Table 1 Observational studies of oral antibiotic therapy for infective endocarditis

Reference	Cases	Design	Case definition	Microbiology	Assessment of antibiotic susceptibility	Therapy	Cure
Campeau et al, Canada [15]	10 NVE (right-sided vs. left-sided not specified)	Retrospective. Follow-up varied from 6-30 months	Pre-existing valvular disease AND Characteristic clinical features AND ≥2 positive blood cultures	*S. viridans* (60%) *E. faecalis* (30%) Anaerobic bacteria (10%)	Yes	Oral phenithicillin for 4-6 weeks (IM streptomycin for the first 2 weeks in 6 cases, concomitant probenecid in 2 cases)	80%
Friedberg et al, USA [16]	11 NVE (right-sided vs. left-sided not specified)	Retrospective. Follow-up not specified	Pre-existing rheumatic valvular disease AND Unexplained fever for ≥2½ weeks	*S. viridans* (55%) *E. faecalis* (18%) Culture negative (27%)	Yes	Oral Aureomycin for 5-8 weeks	36%
Schein et al, USA [17]	81 NVE (right-side vs. left-sided not specified)	Retrospective. Follow-up varied from 2-8 years	Not specified	*Streptococcus sp.* (94%) *S. aureus* (1%) *Enterococcus sp.* (1%) *H. influenza* (4%)	Not specified	Oral sulfonamides (sulfanilamide, sulfapyridine, sulfathiazole or sulfadiazine) for 10 days-14 weeks	10%

1963

1952

1948

Al-Omari et al. BMC Infectious Diseases 2014, 14:140

Table 2 Clinical trials of oral antibiotic therapy for infective endocarditis

Reference	Cases	Design	Case definition	Microbiology	Therapy	Results
Heldman et al, USA [18]	85 IVDUs with NVIE (all right-sided with no systemic metastases), 40 in the oral therapy arm and 45 in the IV therapy arm	Prospective, randomized, open label. 1-month follow-up	- ≥2 positive blood cultures AND any of the following: Valvular vegetations on echocardiogram (definite – 15 cases) OR evidence of pulmonary emboli on chest X-ray or tricuspid insufficiency murmur (probable – 26 cases) OR no other identifiable source for the infection (possible – 44 cases)	MRSA (5%) MSSA (89%) CoNS (6%)	Oral ciprofloxacin and rifampin for 4 weeks vs. IV oxacillin or vancomycin (IV gentamicin for the first 5 days) for 4 weeks	Cure rate: 90% (oral therapy) vs. 91% (IV therapy), $p = 0.9$ Treatment toxicity: 3% (oral therapy) vs. 62% (IV therapy), $p < 0.001$
Stamboulian et al, Argentine [19]	30 NVIE (all left-sided), 15 in each arm	Prospective, randomized, open label. 3 to 6-month follow-up	- ≥2 positive blood cultures AND any of the following: New or changing regurgitant murmur OR predisposing heart disease OR vascular phenomena OR valvular vegetation on echocardiogram	S. viridans (50%) S. bovis (50%)	IV or IM ceftriaxone for 2 weeks followed by high dose oral amoxicillin for 2 weeks vs. IV or IM ceftriaxone for 4 weeks	Cure rate: 100% in both arms. Treatment toxicity not reported

1996

1991

Al-Omari et al. BMC Infectious Diseases 2014, 14:140

Al-Omari *et al. BMC Infectious Diseases* 2014, **14**:140
http://www.biomedcentral.com/1471-2334/14/140

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review

- Raporlanmış yayınlarda oral tedavi ile kür oranları %77-100

- Kısıtlı kanıtlara rağmen, küçük bir klinik araştırmada PO Cip+Rif tedavisi, komplike olmayan, IVDU daki *S. aureus* etkenli sağ kalp İE'de konvansiyel PE tedavi kadar etkin ve daha az yan etki

- AB'lerin başarısı; m.o.'nın duyarlılığına, AB'in farmokokinetik özelliklerine (biyoyararlanım, dağılım ve vegetasyonda etkili konsantrasyonuna), uygun AB tedavi süresine bağlı bulunmuş

Al-Omari et al. BMC Infectious Diseases 2014, 14:140
http://www.biomedcentral.com/1471-2334/14/140

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review

- PO ampisilin farmokokinetik profili suboptimal olmasına rağmen cevap alınması, çalışmanın yapıldığı dönemlerde streptokokların beta laktamlara yüksek duyarlılık göstermesi ve yüksek dozların probenesid ile desteklenmesi

- PO amoksisislin >%90 biyoyararlanımı, düşük serum Pro. bağlanma%17, dokuya iyi penetrasyon

- Amoksisiline probenesid eklenmesi tepe ve vadi konsantrasyonlarını%30'dan 4 kata kadar artırmakta

- Bir gözlemsel çalışmada streptokok İE'de amoksisilin ile %80 başarı; 1 klinik araştırmada ise, PE tedavi sonrası 2 haftalık yüksek doz amoksisilin ile tam başarı

Al-Omari et al. BMC Infectious Diseases 2014, 14:140
http://www.biomedcentral.com/1471-2334/14/140

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review

- IVDU'larda, *S. aureus* etkenli sağ kalp İE'de kullanılan PO siprofloksasin;
bakterisidal, %70 biyoyararlanımı, serum proteinlerine bağlanma%30
ANCAK deneysel çalışmalarda tedavi sırasında direnç problemi
Rifampisin;
S. aureus için bakterisidal, biyoyararlanımı tam,çok az serum proteinlerine bağlanma
ANCAK tedavi sırasında kendiliğinden direnç, direnç bariyeri düşük
- Tebas P ve ark 1991'de bildirdikleri bir İE olgusunda Rif+ Cip kombinasyonuna erken direnç gelişimi

Başka hangi ajanlar PO tedavide?

- Levofloksasin ve moksifloksasin *S. aureus* için bakterisidal
- Siprofloksasinde olduğu gibi in –vivo direnç nadir
- Deneysel hayvan modelleri ve olgu raporlarında etkin
- PO aureomisin sulfanomid ve eritromisin geçmişte diğer kullanılan ajanlar
- Minosiklin ve doksisiklin
- TMP-SMX, biyoyararlanımı iyi ancak *S. aureus* sağ kalp İE PE vankomisinden daha düşük etkinlik

Haemophilus parainfluenzae aortic prosthetic valve endocarditis (PVE) successfully treated with oral levofloxacin

Burke A. Cunha, MD [a,b,*], Kunal Brahmbhatt, MD [a], Muhammad Raza, MBBS [a]

Beta-Laktam allerjisi nedeniyle, 5 gün levofloksasin IV tedavi sonrası PO levofloksasin ile kür!

Table 1
Oral antibiotic therapy of endocarditis.

Type of Infective Endocarditis (IE)	Usual Pathogens	Usual IV antibiotic	Equivalent PO antibiotic	Oral bioavailability	Usual MIC of Pathogens	Peak serum concentration
Subacute bacterial endocarditis (SBE)	*Viridans streptococci*	• Penicillin or	Cephalexin 1 g (PO) q6h or	99%	<1 mcg/ml	36 mcg/ml
		• Cefazolin or	Amoxicillin 1 g (PO) q8h or	90%	<1 mcg/ml	16 mcg/ml
		• Ceftriaxone	Levofloxacin 500 mg	100%	<1 mcg/ml	5 mcg/ml
	Haemophilus sp.	• Ceftriaxone	Levofloxacin 500 mg	100%	<1 mcg/ml	5 mcg/ml
Acute bacterial endocarditis (ABE)	*S. aureus* (MSSA)	• Nafcillin or	Cephalexin 1 g (PO) q6h or	99%	<2 mcg/ml	36 mcg/ml
		• Cefazolin	Linezolid 600 mg (PO) q12h	100%	<1 mcg/ml	20 mcg/ml
	S. aureus (MRSA)	• Daptomycin or	Levofloxacin 500 mg or	100%	<1 mcg/ml	20 mcg/ml
		• Vancomycin or	Minocycline 100 mg (PO) q12h or	100%	<1 mcg/ml	20 mcg/ml
		• Minocycline or	Linezolid 600 mg (PO) q12h or	95%	<1 mcg/ml	4 mcg/ml
		• Linezolid	Levofloxacin 500 mg	100%	<1 mcg/ml	20 mcg/ml

Case Report

Successful Oral Ciprofloxacin Therapy of *Neisseria elongata* Endocarditis

David A. Herbert, MD[1]

Annals of Pharmacotherapy
2014, Vol. 48(11) 1529–1530

DOI: 10.1177/1060028014545355
aop.sagepub.com
SAGE

Nativ mitral kapak endokarditi,
PE(IV) tedaviyi reddeden hasta PO 2x750mg siprofloksasin ile …

Linezolid ?

- Biyayararlanımı >%99, serum proteinlerine bağlanma oranı %30
- Ciddi gram pozitif kok enfeksiyonlarda etkili
- Diğer ajanlara dirençli İE etkenlerinde başarı %63.6-79
- Cerrahi uygulanan 14 İE olgusunda, vankomisin PE tedavi sonrası PO linezolid ile başarılı sonuçlar alınmıştır
- Ancak vankomisin dirençli *E. faecalis* etkenli İE'de sonuç alınamadığı da raporlanmıştır.

Vardakas KZ et al Current Drug Metabolism 2009;10:2-12

Colli A et al Ann Thorac Surg 2007;84:87-91

Al-Omari et al BMC Infectious Diseases 2014;14:140

Journal of Infection (2005) 51, e213-e215

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www.elsevierhealth.com/journals/jinf

CASE REPORT

Successful treatment of MRSA native valve endocarditis with oral linezolid therapy: a case report

N. Nathani[a,*], P. Iles[b], T.S.J. Elliott[c]

- Kronik ciddi astım atakları nedeniyle son 7 yılda 20 kez hospitalize
- Ciddi venöz tromboz ve kateter ilişkili MRSA bakteriyemi atakları vankomisin ile kontrol edilemeyen klinik tablo

- Pulmoner ve trikuspid nativ kapak İE

- Kateter için uygun yol bulunamadığından Linezolid PO ile 3 haftalık tedavi

PE’den PO’e geçiş tedavisi

Clinical Microbiology and Infection 22 (2016) 607–612

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Switch to oral antibiotics in the treatment of infective endocarditis is not associated with increased risk of mortality in non–severely ill patients☆

A. Mzabi [1,2], S. Kernéis [1,2,3], C. Richaud [1,2,3], I. Podglajen [1,2,3], M.-P. Fernandez-Gerlinger [1,2,3], J.-L. Mainardi [1,2,3,4,*]

- 426 İE olgusu; %87 kesin, %13 olası
- 2000-2012 yılları arasında retrospektif kohort
- En az 7 günlük PE tedavi sonrası PO tedavi ile devam edilen
- Günlük; hastanın genel durumu, kliniği, ateş kontrolü, CRP değerlerinde düşme, kan kültürlerinde üreme olmaması, lökositoz ve cre değerlerinin normalizasyonun takibi sonrası
- Hastaların 214'de (%50) de PO tedaviye geçiş

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- PO grupta daha az komorbidite, ve ciddi seyir (kalp yetmezliği, şok, serebral emboli gibi)
- PO grupta daha az *S. aureus* etkenli
- Ortalama PO tedaviye geçiş süresi 21 gün

*streptokoklar için 14 gün, *S. aureus* için 28 gün, enterokoklar için 28 gün , diğer m.o.'lar için 21 gün sonra PO geçiş

- PO geçiş yapılanların %50'ne amoksisilin, diğerleri amoksisilin ve/veya rifampisin ile klindamisin ya da kinolon kombinasyonu

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- PO tedaviye geçiş yapılanlarla PE tedavisi devam edenlerde mortalite oranlarında anlamlı fark YOK
- Takiplerde PO grupta relaps ve reinfeksiyon oranlarında artmış risk YOK

ELSEVIER
FULL-TEXT ARTICLE

Am Heart J. 2013 Feb;165(2):116-22. doi: 10.1016/j.ahj.2012.11.006. Epub 2013 Jan 3.

Partial oral treatment of endocarditis.

Iversen K[1], Høst N, Bruun NE, Elming H, Pump B, Christensen JJ, Gill S, Rosenvinge F, Wiggers H, Fuursted K, Holst-Hansen C, Korup E, Schønheyder HC, Hassager C, Høfsten D, Larsen JH, Moser C, Ihlemann N, Bundgaard H.

- Noninferiority çalışması
- Nativ ve prostetik sol kalp İE
- En az 10 gün PE tedavi sonrası PO
- Oral ya da venöz yoldan verilen AB serum konsantrasyonları likit kromotografi ile
- Tablet sayıları kontrollü
- Oral tedavi parenteral uygulanan tedavi kadar etkili ve güvenli

Partial oral treatment of endocarditis

Kasper Iversen, MD, DMSc,[a] Nis Høst, MD, PhD,[b] Niels Eske Bruun, MD, DMSc,[c] Hanne Elming, MD, PhD,[d]

American Heart Journal
Volume 165, Number 2

Table I. Key clinical features for patients treated with oral antibiotics for infective endocarditis

Gender	Age	Microbial pathogen	Valve(s)/ material involved	Oral medication	Treatment duration (parental/peroral)	Surgery	Outcome
Male	43						Success
Male	75					ogical lve	Success
Male	62						Success
Male	56						Success
Female	74						Success
Male	54					ogical	Success
Male	78						Success
Male	67					rected	Success
Female	65	streptococci group C				ic biological aortic valve	Success
Female	44	*Staphylococcus lugdunesis*	Pacemaker electrode	Penicillin and linezolid	35 d/14 d	Yes, removal of infected electrode	Success
Male	67	*Salmonella*	Aortic valve	Ciprofloxacin	42 d/21 d	Yes, prosthetic biological aortic valve	Success
Male	74	Coagulase-negative *Staphylococcus*	Aortic and mitral valve	Penicillin	40 d/5 d	Yes, prosthetic biological aortic and mitral valve	Success

Tercih edilen AB'ler, IV ve PO formları eşit değerlerde farmokokinetik özellik

Addressing Concerns about Changing the Route of Antimicrobial Administration from Intravenous to Oral in Adult Inpatients

Lizanne Béïque and Rosemary Zvonar

Table 1. Comparison of Usual Total Daily Dose* by Intravenous (IV) and Oral Route of Administration for Selected Antimicrobial Agents[22,26]

Medication	Total Daily Dose by IV Route	Total Daily Dose by Oral Route	
		Administered	Reaching Systemic Circulation (Approximate)†
High bioavailability and oral dose similar to IV dose			
Levofloxacin	0.75 g	0.75 g	0.75 g
Linezolid	1.2 g	1.2 g	1.2 g
Lower bioavailability that can be compensated by higher oral dose			
Ciprofloxacin	0.8 g	1 g	0.75 g
High bioavailability and oral dose lower than IV dose			
Clindamycin	2.7g	1.8 g	1.6 g
Ampicillin (IV) and amoxicillin (oral)‡	12 g	1.5 g	1.2 g
Cefazolin (IV) and cephalexin (oral)‡	6 g	4 g	3.6 g
Lower bioavailability and oral dose lower than IV dose			
Penicillin	24 MU	6.4 MU	4.2 MU
Cefuroxime	4.5 g	1 g	0.45 g
Cloxacillin	12 g	2 g	1 g

Can J Hosp Pharm. 2015;68(4):318-26

Box 2. Potential Benefits of Changing the Route of Administration from Intravenous (IV) to Oral

For the patient

Lower risk of adverse events related to IV route:

- Infiltration or extravasation of antimicrobial agent, hematoma, thrombosis, thrombophlebitis[13]
- Catheter-related infections and bacteremia[14,15]
- Pain or discomfort[16]
- Fluid overload in fluid-restricted patients, such as some patients with renal or cardiac disease

Increased ease of mobility[16]

Better quality of life (some patients feel less "medicalized")

Earlier discharge from the hospital,[17-20] thereby decreasing the risk of hospital-acquired infections

For the health care team

Pharmacy:

- Shorter medication preparation time

Nursing:

- Reduced time required to administer and monitor antimicrobial agents
- No risk of needlestick injuries

For the hospital and the environment

Lower costs:

- Drug acquisition cost for oral form generally lower than IV form
- Shorter preparation and administration time for antimicrobial agent
- Reduced length of stay
- Reduced rate of hospital-acquired infections
- Saving of "bed-days" from earlier discharge

Reduced waste (e.g., tubing, expired IV bags)

Can J Hosp Pharm. 2015;68(4):318-26

Oral treatment of Infective Endocarditis

P. Muñoz, V. González-Ramallo, M.E. García Leoni, M. Valerio, A. Fernández-Cruz, B. Pinilla, M. Martínez-Sellés, G. Cuerpo, A. Vena, E. Bouza on behalf of Grupo de Apoyo a la Endocarditis Infecciosa del Gregorio Marañón (GAME).
Hospital General Universitario Gregorio Marañón

INTRODUCTION

- Outpatient Parenteral treatment (OPAT) of IE is being increasingly used, with very acceptable rates of hospital readmissions (10-26%) and relapses.
- However, information on oral treatment of infective endocarditis (IE), mainly left-sided, is very scarce.
- Oral drugs with excellent bioavailability are now available, which, theoretically, could allow an early discharge of selected IE patients.

OBJECTIVES

- Our goals were to analyse the frequency and the outcome of IE patients who completed their therapy as outpatients with oral drugs.

METHODS

- Setting: 1,550 bed tertiary care institution attending a population of 750,000 inhabitants in Madrid, Spain. OPAT services available.
- The 435 patients in the HGUGM GAME prospective cohort of Infectious Endocarditis (2008-2016) were analysed. Information was prospectively recorded in a pre-established clinical form. IE was defined according to the modified Duke criteria.

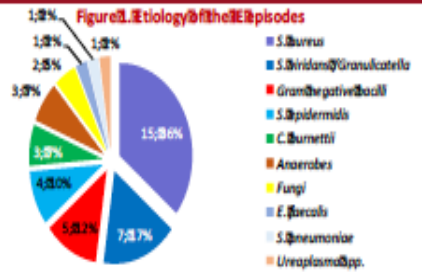
RESULTS

Overall 10% of the IE episodes (n= 44) completed IE treatment ONLY with ORAL antimicrobials for at least 25% of the therapeutic course as outpatients.

General characteristics of patients that received oral therapy

- Mean age was 59 years old (SD 21) and 30 patients (68%) were male.
- Etiology: *S. aureus* (15; 34%) predominated, followed by *S. viridans/ Granulicatella* spp. (7; 16) (Figure 1). Two patients had unknown etiology.
- Infection was mainly community-acquired (27; 61.4%).
- Infected sites were: native valves (22, 50%), prosthetic valves (13; 29.5%) and intra-cardiac material (9; 20.5%).

Figure 1. Etiology of the IE episodes



S. aureus (15; 34%) (2 of them were MRSA), *S. viridans* / Granulicatella spp. (7; 16%), Gram negative rods (5; 11.4%), *S. epidermidis* (4; 9%), *C. burnetii* (3; 6.8%), anaerobes (3; 6.8%), fungi (2; 4.5%), *E. faecalis*, *S. pneumoniae* and *Ureaplasma* spp. (1 each).

- Most episodes involved the left heart (aortic 15; 34.1% / mitral 17; 38.6%)
- Distant septic metastasis were detected in 12 (27.3%) patients (4 spleen, 4 lung, 3 CNS, 2 spondylodiscitis).
- Heart surgery was performed in 29 patients (66%).

Oral Treatment

- Median duration of oral outpatient therapy was 19.5 days (IQR 14-41) and corresponded to 46% of the IE treatment.
- Most commonly used oral drugs were: quinolones (29; 66%), mainly levofloxacin (22), followed by cotrimoxazole (4), linezolid (3), chloroquine-doxycycline (3), azoles (2), cephalosporins (2) and rifampin (6).

Clinical Outcome

- Readmission (after a median of 41 days; IQR 19-83) was required in 15 patients (34%). None was related to failure of therapy: pacemaker implantation (2), BSI of other origin, spondylodiscitis, respiratory insufficiency, Leishmaniasis, pneumonia, bleeding, anticoagulation adjustment, tachycardia, neoplasia and heart transplantation (1 each).
- There were two early relapses (*Aspergillus* endocarditis and *S. viridans* IE), but those patients had left hospital early, against medical advice.
- One-year mortality was 4.5%, but none of the patients died because of the endocarditis.

Comparison of patients that received oral versus IV treatment

- Patients that received oral treatment had less comorbidities, received more valvular surgery and required more hospital re-admissions. (Table 1)
- Mortality at one-year follow up was similar in both groups.

Variables	Oral (N=44)	IV (N=391)	P
Age, median (IQR)	65 (50-76)	71 (58-78)	0.053
Sex (Males)	30 (68.2)	244 (62.4)	0.452
Comorbidities			
Heart failure	8 (18.2)	141 (36.1)	0.055
Hypertension	16 (36.4)	235 (60.1)	0.005
Dislipemia	17 (38.6)	161 (41.3)	0.809
Moderate / severe chronic renal disease	3 (6.8)	69 (17.6)	0.067
Charlsons comorbidity index, mean (SD)	3.5 (2.4)	5.3 (2.8)	<0.01
Affected valve			
Aortic	15 (34.1)	159 (40.7)	0.399
Mitral	17 (38.6)	208 (53.2)	0.067
Prosthetic	15 (29.5)	148 (37.9)	0.279
Native	24 (54.5)	223 (57)	0.752
Endovascular device	9 (20.5)	39 (10)	0.035
Etiology			
S. epidermidis	3 (6.8)	49 (12.5)	0.268
S. aureus	15 (34.1)	103 (26.3)	0.273
Enterococcus spp.	1 (2.3)	59 (15.1)	0.019
Streptococcus spp.	6 (13.6)	98 (25.1)	0.092
Others	16 (36.4)	46 (11.8)	<0.01
New heart failure	10 (22.7)	168 (43.1)	0.021
Persistant bacteremia	5 (11.4)	44 (11.3)	0.796
IE surgical treatment	29 (65.9)	172 (44.0)	0.006
Inhospital stay, median (IQR)	30 (22-47)	32 (17-52)	0.923
Early re-infection	2 (4.5)	2 (0.5)	0.068
Readmission	15 (34.9)	48 (19.4)	0.022
One year mortality	2 (4.5)	23 (5.8)	0.984

CONCLUSIONS

- Our series suggests that it is safe and feasible to complete the treatment of selected complex episodes of endocarditis with outpatient oral regimes.
- The rate of readmissions is similar to patients treated with OPAT, and is not related to treatment failure.

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Journal of Antimicrobial Chemotherapy (2006) 57, 819–824
doi:10.1093/jac/dkl087
Advance Access publication 20 March 2006

JAC

Antimicrobial treatment of infective endocarditis caused by viridans

İE'de oral tedavi pek yakın değil gibi ama, parenteral tedaviden oral tedaviye geçiş BELKİ….

Table 1. Medi

Penicillin (million units)	lapsed or died fection [no. (%)]
First trial	
1	
0.5	
0.25	
Second trial	
0.1	
0.25	
0.5	

'Choosing Wisely'
BİLGECE SEÇİM…

Teşekkürler…