Indicaciones, momento y fármaco para el tratamiento con antimicrobianos orales en la EI.

MA Goenaga
SEI. OSI Donostialdea

GUÍON

- ¿Qué sabemos?.¿En qué lo basamos?. Un poco de historia.
- ¿Qué proponen las guías al uso?.
- Hay algo más fuera de las guías. Futuro…
- Conclusiones

REVISIÓN

GUÍON

- ¿Qué sabemos?.¿En qué lo basamos?. Un poco de historia.
- ¿Qué proponen las guías al uso?.
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- Conclusiones

David Durack (1945) en “Endocarditis Past and present: some things I learned over 50 years” ASM 2016, Boston

- Curación MICROBIOLÓGICA
  - Esterilizar la sangre→ rápido HC neg en 48-72h
  - Disminuir la carga bacteriana 10^6→10^2 UFC 3-14 días
  - Esterilizar la válvula---????
- Curación del PACIENTE
- Curación Cardiológica

Un poco de historia. Siglo XX

- Dos primeras décadas del s XX:
  - Reconocimiento patológico/identificación clínica/diagnóstico microbiológico—paciente tipo
  - Enfermedad mortalidad del 100%
- Década de los 30
  - Uso sulfonamidas-----VO

Am J Med 1946 Jul;1(1).

Sulfonamide Therapy of Subacute Bacterial Endocarditis*

JOSEPH SCHEIN,† M.D. *and* GEORGE BAEHR, M.D.
New York, New York

1938

Between 1938, when sulfanilamide was first used for the treatment of subacute bacterial endocarditis, and 1943, when sulfadiazine was replaced by penicillin, ninety-seven patients with the disease were treated with reasonably adequate amounts of one or more of the sulfonamides over a prolonged period. Eighty-one patients received oral therapy, 1.0 to 2.0 Gm. every four hours, for periods ranging from ten days to fourteen weeks.‡ In this group eight were cured—a recovery rate of 9.8 per cent. In two of the recovered patients hyperthermia was employed in addition to sulfonamide therapy.[3]

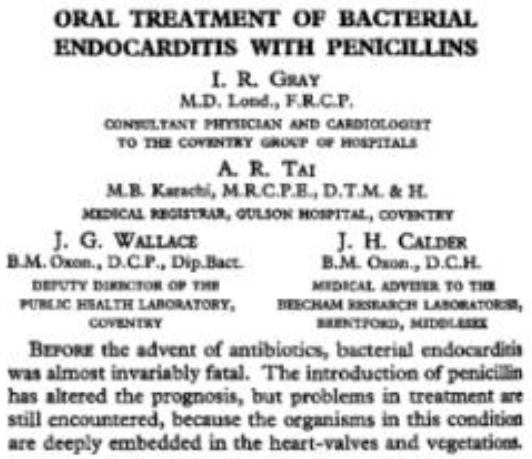
97 pac

81 vo

8 curados

Un poco de historia

- Dos primeras décadas del s XX:
  - reconocimiento patológico/identificación clínica/diagnóstico microbiológico—paciente tipo
  - Enfermedad mortalidad del 100%
- Década de los 30
  - Uso sulfonamidas-----VO
- Década de los 40
  - Introducción de la penicilina—iv-----vo---
- Década 50 y post
  - Aparición de resistencias a penicilina y nuevos antibióticos/papel de la cirugía/ nuevas técnicas de imagen/ cambios perfil de los pacientes



ORAL TREATMENT OF BACTERIAL ENDOCARDITIS WITH PENICILLINS

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BEFORE the advent of antibiotics, bacterial endocarditis was almost invariably fatal. The introduction of penicillin has altered the prognosis, but problems in treatment are still encountered, because the organisms in this condition are deeply embedded in the heart-valves and vegetations.

The Lancet 1964 Jul; 284 (7351): 110-114

Postgrad Med J 1964 Dec;40 Suppl:105-111

TREATMENT OF BACTERIAL ENDOCARDITIS WITH ORAL PENICILLINS

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TABLE I

Details of 13 Patients with Bacterial Endocarditis Treated with Penicillin by Mouth.

No.	Name	Age and sex	Lesions	Blood Culture	M.I.C. in Serum (μg./ml.)	Peak Serum level (μg./ml.)	Treatment	Course
1.	D.O.	59 F	A.R.	Str. fæcalis			Ampicillin 2 g., Erythromycin 2 g., daily	Recovery
2.	A.G.	41 F	M.S., A.R.	Str. fæcalis	4.00		Ampicillin 2.5 g. then 5.0 g., daily	Relapse then recovery, died congestive failure
3.	J.B.	26 M	V.S.D., P.S.	Str. viridans	1.00		Propicillin 1.25 g., daily	Recovery
4.	J.W.	22 M	Fallot	Str. viridans	0.50		Propicillin 2.5 g., daily	Recovery
5.	J.H.	48 M	A.R.	Sterile			Propicillin 1.25 g., daily	Recovery
6.	O.M.	47 F	A.R, M.R.	Str. viridans	0.12		Propicillin 2.5 g., daily	Died. Ruptured aortic valve
7.	E.S.	68 M	A.S.	Str. viridans	0.50	11.00	Propicillin 2.5 g., daily	Recovery
8.	M.L.	26 F	M.S.	Str. viridans Str. pneumoniæ		18.00	Ampicillin 1.0-2.0 g., daily	Penicillin sensitivity Recovery
9.	B.B.	24 M	A. R.	Str. viridans	0.25	18.00	Propicillin 2.5 g., Probenecid 2 g., daily	Infection cured Coronary embolism. Died cardiac failure
10.	V.C.	29 F	M.R.	Str. viridans	0.50	17.50	Probenecid 2 g., Propicillin 2 g. daily	Recovery
11.	J.C.	58 M	A.S.	Sterile		6.10	Propicillin 2.5 g. Probenecid 2 g., daily	Recovery
12.	E.J.	49 F	M.R.	Str. viridans	0.50	17.50	Propicillin 2 g. Probenecid 2 g., daily	Recovery Penicillin sensitivity
13.	A.M.	29 F	A.R., M.R.	Str. viridans	1.00	29.30	Propicillin 2.5 g. Probenecid 2 g., daily	Recovery

Furthermore ampicillin is likely to be much more effective than any of the phenoxypenicillins in infections with *Strept. fæcalis*. These arguments seem to favour ampicillin as the oral penicillin of choice when the diagnosis of bacterial endocarditis is suspected but the result of blood culture is not yet available.

Conclusion

We have treated 13 patients with bacterial endocarditis with oral penicillins, ten with propicillin and three with ampicillin. Infection was controlled in every case but relapse occurred once.

We found a dosage of 500 mg. four-hourly (2.5 g. per day) satisfactory and found that probenecid 0.5 g. six-hourly increased the serum levels considerably.

Between 80 and 90% of the propicillin in serum appeared to be inactivated and we therefore compared serum levels with M.I.C.s estimated in the presence of human serum. Even so the peak serum levels were more than 20 times the M.I.C. in all cases where full data were available.

Although only three of our patients were actually treated with ampicillin, the broad antibacterial spectrum of this antibiotic and the absence of inactivation by serum protein suggest that it is preferable to any of the phenoxypenicillins for the oral treatment of bacterial endocarditis before the results of blood culture and antibiotic sensitivity tests are available. If the organism is found to be highly sensitive, one of the phenoxypenicillins can be substituted.

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MCCARTHY, C. G., FINLAND, M. (1960): *New Engl. J. Med.*, **263**, 215.

1 Conocimiento de agente etiológico
2 superioridad de la ampicilina
3 Importancia de la sensibilidad de los microorganismos a los antibióticos.

Un poco de historia

- Hasta nuestros días

- Establecimiento de “las reglas de tto actuales”

Home Treatment of Infective Endocarditis with Oral Amoxicillin

WARREN G. GUNTHEROTH, MD
ANN A. CAMMARANO, MD
WILLIAM M.M. KIRBY, MD

The seriousness of infective endocarditis (IE) has discouraged experimental clinical trials of varying regimens, but occasionally a clincal setting occurs that requires some compromise with the published standards for treatment. Most regimens of treatment of IE require 4 to 6 weeks of parenteral antibiotic therapy, and most routines recommend at least 2 weeks of intravenous treatment. The major exception is penicillin-sensitive streptococcal IE, for which a 4-week course of penicillin may be shortened to 2 weeks by the addition of streptomycin.[1] Gray[2] stands almost alone in recommending simply oral amoxicillin, although he has treated more than 90 patients with as high a success rate as can be claimed for any regimen for IE. We were recently confronted with a clinical situation in which an oral regimen at home was the only acceptable choice.

time. We discussed the alternatives, and the parents chose oral management, even if we could not assure success, at home. We agreed on a brief hospitalization under sedation to obtain further blood cultures and an echocardiogram. No vegetations were observed on ultrasound examination, but the 4 blood cultures all grew out S. sanguis II, *with colony counts ranging from 33 to 69 per milliliter. The bacteria were quite sensitive to a broad range of antibiotic drugs. Because of the advantages of excellent absorption and high levels that could be obtained orally, amoxicillin was chosen, and 1 g was given every 6 hours with probenecid, 500 mg 4 times daily. The patient had no adverse reaction to this regimen and was sent home after only 30 hours in the hospital. She did well, had no gastrointestinal upsets, and completed a full month of therapy successfully. The patient has now been without all medications for over 1 year, with no significant illnesses.*

Although expense was not a consideration in our patient, we compared her hospitalization costs, $846, with those for a patient of similar age who was hospitalized for 18 days, including 14 days of intravenous penicillin and intramuscular streptomycin, at a cost of $9,662. Both patients were successfully treated.

The current practice in the U.S. of parenteral treatment of IE may reflect the earlier experiences with unpredictable absorption of oral penicillin. The intro-

antibiotic therapy, and much more convenient and more likely to be administered by the dentist. We have recently pointed out that parenteral antibiotic drugs as a requirement for dental procedures is difficult to achieve in many parts of the world, and even in the continental U.S.; furthermore, the discomfort adds to the underlying fear of dentists that many patients have.[5]

The seriousness of IE must be respected in the choice of treatment, but if newer antibiotic drugs and regimens can be shown to provide adequate serum levels in relation to the infective agent, the seriousness of the disease is not a logical basis on which to retain prolonged, uncomfortable and expensive regimens.

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Ayuda

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

Awad Al-Omari[1], D William Cameron[2,3,4], Craig Lee[2,4] and Vicente F Corrales-Medina[2,3,4,5*]

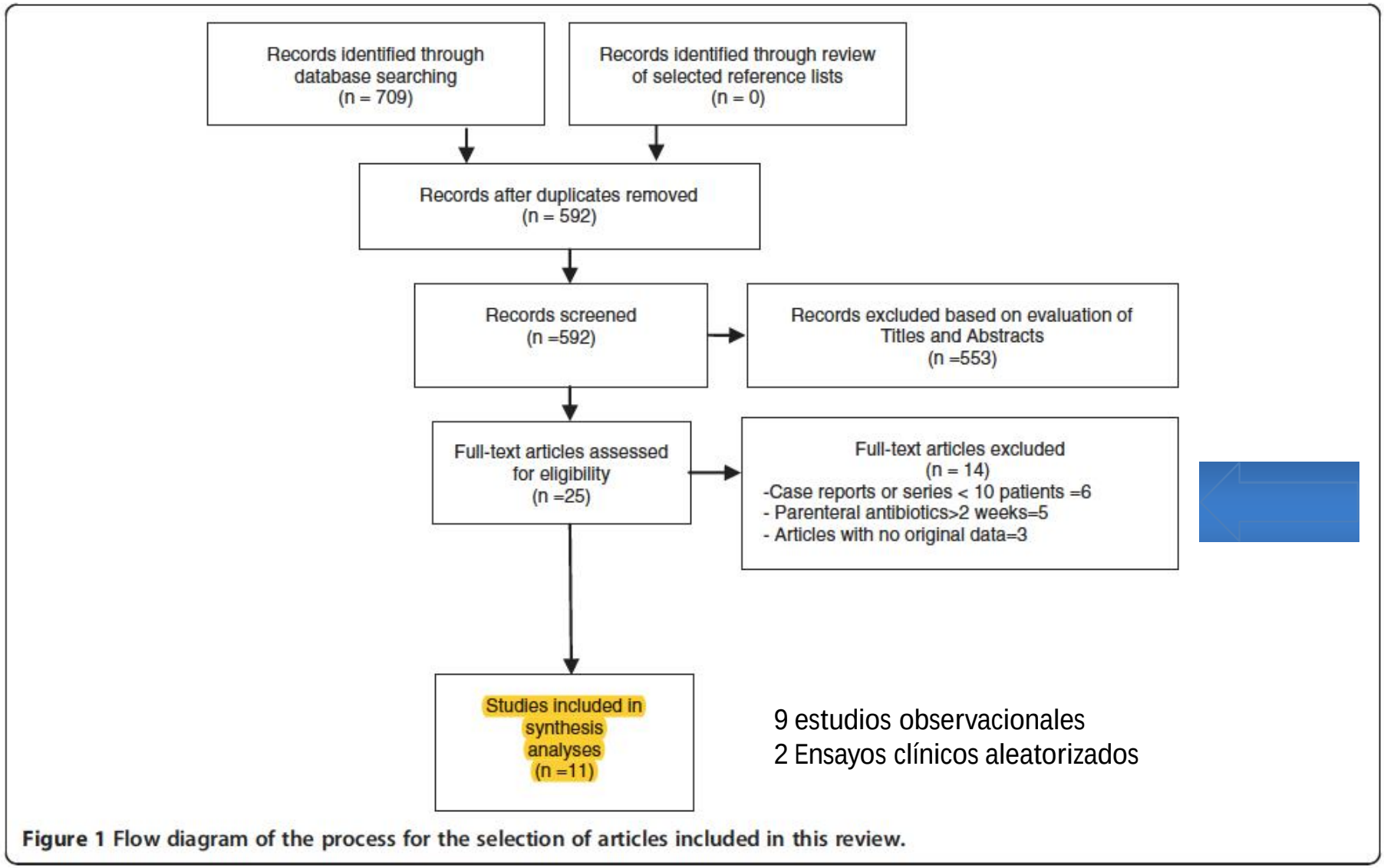

Figure 1 Flow diagram of the process for the selection of articles included in this review.

Búsqueda: MEDLINE 1948-jun 2013; EMBASE 1947-jun 2013; SCOPUS 1960-junio 2013

Table 1 Observational studies of oral antibiotic therapy for infective endocarditis *(Continued)*

Campeau et al, Canada [15] 1963	10 NVIE (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] 1952	11 NVIE (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] 1948	81 NVIE (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%

NVIE denotes cases of native valve infective endocarditis. PVIE denotes cases of prosthetic valve infective endocarditis. IV denotes intravenous. IVDUs denotes intravenous drug users. MSSA denotes methicillin-sensitive *S. aureus*. MRSA denotes methicillin-resistant *S. aureus*. CoNS denotes coagulase-negative staphylococcus. GNB denotes gram-negative bacilli. Unless specified otherwise, all cohorts were primarily of adult patients. All reports reported follow-up ≥3 months.

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] 2007	12 NVIE and 2 PVIE 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] 1989	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] 1988	15 NVIE (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%
Pinchas et al, Israel [12] 1983	11 NVIE (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] 1977	13 NVIE (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, flucloxacillin or erythromycin for 6-8 weeks	100%
Gray et al, UK [14] 1964	13 NVIE (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%

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] 2007	12 NVIE and 2 PVIE 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] 1989	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%
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Table 1 Observational studies of oral antibiotic therapy for infective endocarditis *(Continued)*

Campeau et al, Canada [15] 1963	10 NVIE (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%
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Schein et al, USA [17] 1948	81 NVIE (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%

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V Nativas: 98 + 81

V Protésicas:2

Bacterias: G+/ cult neg

Table 2 Clinical trials of oral antibiotic therapy for infective endocarditis

Reference	Cases	Design	Case definition	Microbiology	Therapy	Results
Heldman et al, USA [18] 1996	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] 1991	30 NVIE (all left-sided), 15 in each arm	Prospective, randomized, open label. 3 to 6-motnh 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

NVIE denotes cases of native valve infective endocarditis. IV denotes intravenous. IM denotes intramuscular. IVDUs denotes intravenous drug users. MSSA denotes methicillin-sensitive *S. aureus*. MRSA denotes methicillin-resistant *S. aureus*. CoNS denotes coagulase-negative staphylococcus. All reports reported follow-up ≥2 months.

Conclusiones de Al-Omari

- Los ab vo, con buen perfil PK, parecen efectivos en tratar casos seleccionados de EI causados por microorganismos susceptibles.
  - Esto se confirma para **amoxicilina** en altas dosis en casos de infección por estreptococos susceptibles y al **linezolid** en casos de SA (calidad de estudios no alta).
  - La combinación oral de **ciprofloxacino + rifampicina** es una alternativa aceptable (situaciones especiales) para EI derechas, por SA, en UDVP, no complicadas.
- Se necesitan futuras investigaciones para definir el papel de éstos y otros ab (minociclina/doxiciclina/sulfa-trimetro/levoflox/moxiflox/cloxacilina)

Qué sabemos:

- La EI es una enfermedad grave que dejada a su libre evolución tiene un desenlace fatal
- El tratamiento antibiótico cambia esta situación y que por las características de las vegetaciones hacen falta altas concentraciones de fármacos bactericidas(al menos al principio) por tiempos prolongados, combinados a veces :
  - La vía iv:
    - obtiene rápidas concentraciones en sangre y tejidos perfundidos.
    - Puede ser más potente*
    - Hay situaciones clínicas en las que su utilización puede ser muy complicada (alergias/problemas de vías/ duración de los ttos)
- El tratamiento por vía oral, bajo ciertos condicionantes, puede ser una alternativa.

GUÍON

- Introducción. ¿tiene el tema interés?
- ¿Qué sabemos?.¿En qué lo basamos?. Un poco de historia.
- ¿Qué proponen las guías al uso?.
- Hay algo más fuera de las guías. Futuro…
- Conclusiones

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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)

7. Antimicrobial therapy: principles and methods

7.1 General principles

Successful treatment of IE relies on microbial eradication by antimicrobial drugs. Surgery contributes by removing infected material and draining abscesses. Host defences are of little help. This explains why bactericidal regimens are more effective than bacteriostatic therapy, both in animal experiments and in humans.[126,127] Aminoglycosides synergize with cell-wall inhibitors (i.e. beta-lactams and glycopeptides) for bactericidal activity and are useful for shortening the duration of therapy (e.g. oral streptococci) and eradicating problematic organisms (e.g. *Enterococcus* spp.).

Sistema inmune ayuda poco--bactericidas
NO DICE VIA ADMINISTRACIÓN

Table 16 Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group[a]

Table 18 Antibiotic treatment of infective endocarditis due to *Enterococcus* spp.

Table 20 Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification)[a]

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		

Frank Hansen
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Treatment of *Staphylococcus aureus* endocarditis with high doses of trimethoprim/sulfamethoxazole and clindamycin—Preliminary report

Sir,

Infective endocarditis (IE) is still experiencing a high mortality rate even though this rate has been reduced in successive stages thanks to more focused antibiotics and increased indications for cardiac surgery, as is being confirmed in recent studies [1]. Recently, following early surgery the mortality rate at Aix-Marseille Université (Marseille, France) fell to 10% [1]. However, a new increase in the number of deaths in our centre appears to be related to issues of time management and organisation in surgical treatment and, second, to the increase in the number of septic shocks related to *Staphylococcus aureus* [2]. In fact, the early (≤3 months) fatality rate went from 9% (from 2000 to 2006) to 12% (from 2007 to 2008) and to 15% (from 2009 to 2011) ($P = 0.075$ between the first and third groups) (Table 1). This was linked to an increase in *S. aureus* infections from 11% until 2008 to 19% (44 of 226 definite IE) in 2009–2011. Retrospective analysis of a series of 108 cases of definite *S. aureus* IE in our centre from January 2000 to April 2012 showed that this was causing the highest mortality of bacterial IE (22/108; 20.4%). This is independent from meticillin resistance. In contrast, we did not experience any relapse or persistence of infection [3]. We concluded that the problem raised by *S. aureus* endocarditis (besides early surgery) was the risk of immediate septic shock following initiation of treatment as we found 14% early deaths (≤3 months) in these patients. *S. aureus* has the property to secrete toxins that may be induced by oxacillin and depressed by macrolides, in particular clindamycin [4].

Table 1
Fatality rates of infective endocarditis (IE) in Aix-Marseille Université (Marseille, France) and cases of *Staphylococcus aureus* infections.

	2000–2006	2007–2008	2009–2011	2012
Cases	275	172	226	101
Deaths	26 (9%)[a]	21 (12%)	33 (15%)[*,†]	8 (8%)[*]
S. aureus IE	30 (11%)[a]	18 (10%)	44 (19%)	33 (33%)[a]

Significant difference (χ^2 *P*-value) between figures with the same symbol.
[a] $P = 0.09$.
[†] $P = 0.075$.
[‡] $P < 0.001$.

Owing to the importance of this fatality rate and due to the absence of trimethoprim/sulfamethoxazole (STX) resistance in the *S. aureus* isolated from blood cultures in Marseille, we have implemented a preliminary study using SXT (efficient both against meticillin-susceptible and -resistant strains) and clindamycin (to prevent toxic shocks). We included all patients with a diagnosis of *S. aureus* IE. SXT was used 30 years ago in IE at low dosage and recently at higher dosage [5]. Here we prescribed high doses, prescribed for bone and joint infections, that have been found to be well tolerated [5]. This treatment was prescribed intravenously (sulfamethoxazole 4.8 g/trimethoprim 960 mg and clindamycin 1800 mg) and then shifted to a per oral treatment at 7 days of SXT only (sulfamethoxazole 4 g/trimethoprim 800 mg daily for 5 more weeks), stopping clindamycin. This preliminary work began in April 2012. We decided to report it now, as soon as possible, as among the first 31 treated patients (Table 1) we observed only one case of immediate (<24 h) death but no fatalities between the first day and the third month after admission, this being different from our retrospective study ($P < 0.04$). Moreover, the fatality rate of endocarditis from 2012 fell to 8% (8 of 101 cases), lower than the 2 years before ($P = 0.09$) despite a significant increase in *S. aureus* IE ($P < 0.04$).

This work is of course preliminary, being a non-comparative, observational and randomised work comparing a prospective with a retrospective series. However, given the significant early difference between this first work and previous data and the rationality of this treatment, we believe that it is essential to communicate our results. It may have benefited from both a better management (earlier surgery) and antibiotic treatment. However, we believe that this should be the first step for a multicentre, randomised protocol processing IE and for comparing the combination SXT and clindamycin versus the treatments that are currently considered as references [1]. At a time when new expensive antibiotic compounds are being proposed in this indication, such cost-effective and rapidly orally available treatments are all the more interesting.

Funding: None.
Competing interests: None declared.
Ethical approval: Not required.

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.

7.11 Fungi

Fungi are most frequently observed in PVE and in IE affecting i.v. drug abusers (IVDAs) and immunocompromised patients.[198] *Candida* and *Aspergillus* spp. predominate, the latter resulting in BCNIE.[199,200] Mortality is very high (>50%), and treatment necessitates combined antifungal administration and surgical valve replacement.[135,198–200] Antifungal therapy for *Candida* IE includes liposomal amphotericin B (or other lipid formulations) with or without flucytosine or an echinocandin at high doses; and for *Aspergillus* IE, voriconazole is the drug of choice and some experts recommend the addition of an echinocandin or amphotericin B.[135,198,200,201] Suppressive long-term treatment with oral azoles (fluconazole for *Candida* and voriconazole for *Aspergillus*) is recommended, sometimes for life.[135,198,201] Consultation with an ID specialist from the Endocarditis Team is recommended.

12.2 Infective endocarditis affecting cardiac implantable electronic devices

12.2.8 Antimicrobial therapy

Antimicrobial therapy for CDRIE should be individualized and based on culture and susceptibility results if possible (see section 7). Because most CDRIE infections are secondary to staphylococcal species and, of those, up to 50% are methicillin-resistant,[376,392] vancomycin should be administered initially as empirical antibiotic coverage until microbiological results are known. Daptomycin, approved for right-side IE and bacteraemia attributable to *S. aureus*,[168] is a promising molecule to treat CIED infection.[393–395] Before hardware removal, but after blood cultures, i.v. antibiotics should be initiated. There are no clinical trial data to define the optimal duration of antimicrobial therapy. The duration of therapy should be 4–6 weeks in most cases.[362]

At least 2 weeks of parenteral therapy is recommended after extraction of an infected device for patients with bloodstream infection. Patients with sustained (>24 h) positive blood cultures despite CIED removal and appropriate antimicrobial therapy should receive parenteral therapy for at least 4 weeks.[362,366]

12.4 Right-sided infective endocarditis

Alternatively, when conventional i.v. route therapy is not possible, right-sided *S. aureus* IE in IVDAs may also be treated with oral ciprofloxacin [750 mg bis in die (b.i.d.)] plus rifampicin (300 mg b.i.d.) provided that the strain is fully susceptible to both drugs, the case is uncomplicated and patient adherence is monitored carefully.[439]

439. Al Omari A, Cameron DW, Lee C, Corrales-Medina VF. Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review. *BMC Infect Dis* 2014;**14**:140.

(*Circulation*. 2015;132:1435-1486. DOI: 10.1161/CIR.0000000000000296.)

AHA Scientific Statement

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

Endorsed by the Infectious Diseases Society of America

Larry M. Baddour, MD, FAHA, Chair; Walter R. Wilson, MD; Arnold S. Bayer, MD; Vance G. Fowler, Jr, MD, MHS; Imad M. Tleyjeh, MD, MSc; Michael J. Rybak, PharmD, MPH; Bruno Barsic, MD, PhD; Peter B. Lockhart, DDS; Michael H. Gewitz, MD, FAHA; Matthew E. Levison, MD; Ann F. Bolger, MD, FAHA; James M. Steckelberg, MD; Robert S. Baltimore, MD; Anne M. Fink, PhD, RN; Patrick O'Gara, MD, FAHA; Kathryn A. Taubert, PhD, FAHA; on behalf of the American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council

Antimicrobial Therapy

Therapeutic Principles

The primary goal of antibiotic treatment is to eradicate infection, including sterilizing vegetations, although the unique characteristics of infected vegetations can pose a variety of challenges. These characteristics include focal infection with high bacterial density, slow rate of bacterial growth within biofilms, and low microorganism metabolic activity.[72] Host characteristics such as impaired immunity also contribute to challenges in therapeutics. In addition, antibiotics may fail to eradicate infection as a result of increased binding of the drug to serum proteins, perturbations of antibiotic penetration into the vegetation, and unique antibiotic pharmacokinetic/pharmacodynamic (PK/PD)

Drug Penetration

The penetration of antibiotics is a significant issue in the treatment of IE because cardiac vegetations, which are composed of layers of fibrin and platelets, pose a considerable mechanical barrier between the antibiotic and the embedded

ESTREPTOCOCOS/ESTAFILOCOCOS

Table 7. Therapy of NVE Caused by Highly Penicillin-Susceptible VGS and *Streptococcus gallolyticus (bovis)*

Table 8. Therapy of NVE Caused by Strains of VGS and *Streptococcus gallolyticus (bovis)* Relatively Resistant to Penicillin

Table 9. Therapy for Endocarditis Involving a Prosthetic Valve or Other Prosthetic Material Caused by VGS and *Streptococcus gallolyticus (bovis)*

Table 10. Therapy for NVE Caused by Staphylococci

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		

ENTEROCOCOS

Table 12. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* Species Caused by Strains Susceptible to Penicillin and Gentamicin in Patients Who Can Tolerate β-Lactam Therapy*

Table 13. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* species Caused by a Strain Susceptible to Penicillin and Resistant to Aminoglycosides or Streptomycin-Susceptible Gentamicin-Resistant in Patients Able to Tolerate β-Lactam Therapy*

Table 14. Vancomycin-Containing Regimens for Vancomycin- and Aminoglycoside-Susceptible Penicillin-Resistant *Enterococcus* Species for Native or Prosthetic Valve (or Other Prosthetic Material) IE in Patients Unable to Tolerate β-Lactam

Table 15. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* Species Caused by Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Linezolid Or Daptomycin	600 mg IV or orally every 12 h 10–12 mg/kg per dose	>6 >6	*Class IIb; Level of Evidence C* *Class IIb; Level of Evidence C*	Linezolid use may be associated with potentially severe bone marrow suppression, neuropathy, and numerous drug interactions. Patients with IE caused by these strains should be treated by a care team including specialists in infectious diseases, cardiology, cardiac surgery, clinical pharmacy, and, in children, pediatrics. Cardiac valve replacement may be necessary for cure.

HACEK

Table 16. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Caused by HACEK Microorganisms

Regimen	Dose and Route	Duration, wk	Strength of Recommendation	Comments
Ceftriaxone sodium*	2 g/24 h IV or IM in 1 dose	4	*Class IIa; Level of Evidence B*	Preferred therapy: cefotaxime or another third- or fourth-generation cephalosporin may be substituted.
Or				
Ampicillin sodium	2 g IV every 4 h		*Class IIa; Level of Evidence B*	Ampicillin sodium may be an option if the growth of the isolate is sufficient to permit in vitro susceptibility results.
Or				
Ciprofloxacin†	1000 mg/24 h orally or 800 mg/24 h IV in 2 equally divided doses		*Class IIb; Level of Evidence C*	Fluoroquinolone therapy‡ may be considered for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted; fluoroquinolones generally is not recommended for patients <18 y old. Treatment for 6 wk is reasonable in patients with PVE (*Class IIa; Level of Evidence C*).

Fungi

Recommendations

1. **Valve surgery should be done in most cases of fungal IE (*Class I; Level of Evidence B*).**
2. **After completion of initial parenteral therapy, lifelong suppressive therapy with an oral azole is reasonable (*Class IIa; Level of Evidence B*).**

Outpatient Therapy

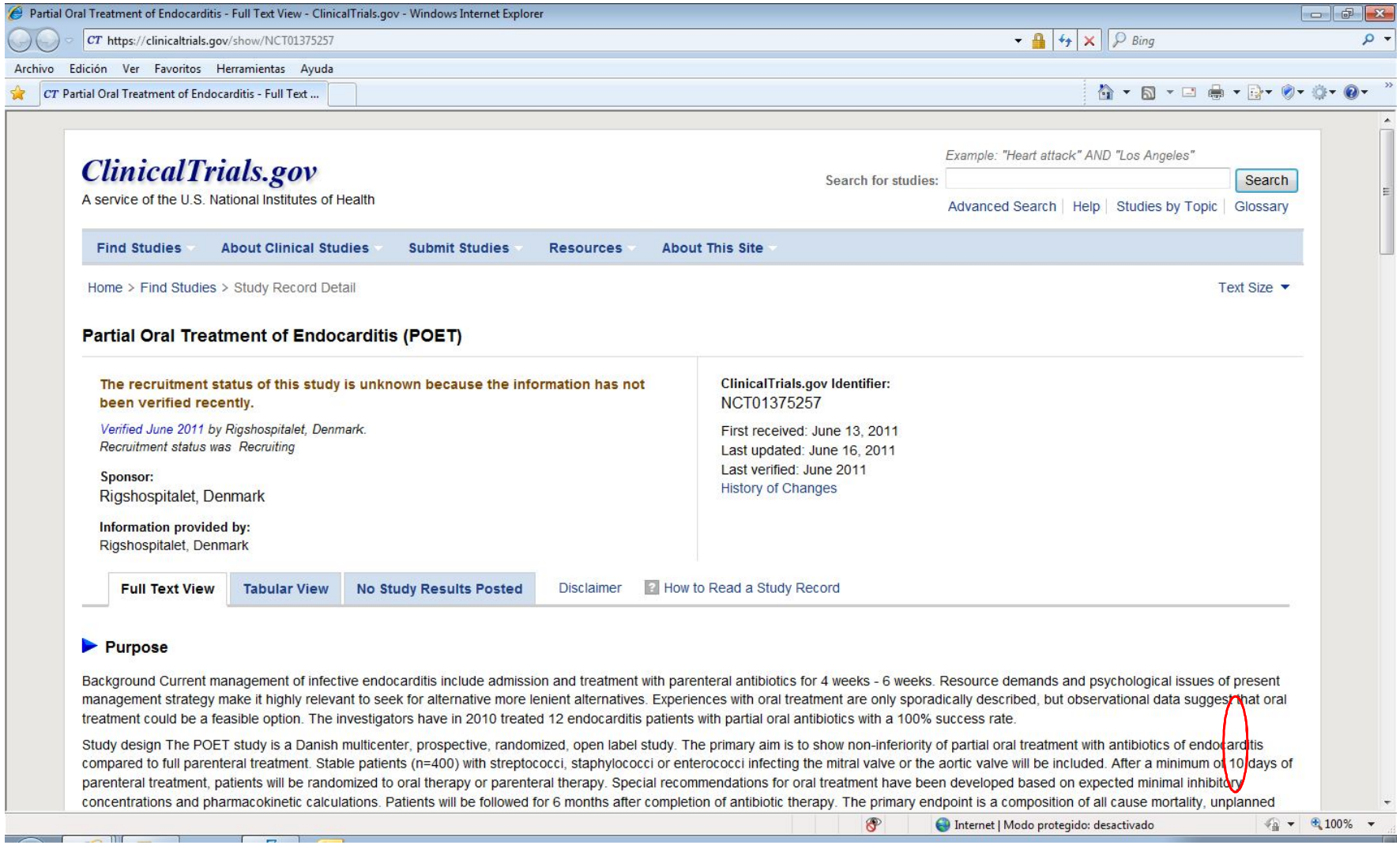
Outpatient parenteral antibiotic therapy (OPAT) is efficacious, safe, and cost-effective for a variety of infections,[323–325] including IE that requires prolonged parenteral therapy in hospitalized patients who otherwise no longer require inpatient care but do require continued parenteral antimicrobial therapy. Antibiotic regimens recommended for IE vary widely and often require ≥4 weeks of therapy, generally given by the intravenous route. Absorption of orally administered antimicrobial agents may be unreliable, and such a strategy is generally not recommended as sole therapy for IE. Several other aspects of OPAT such as drug stability at room temperature; frequency of drug dosing; access to ancillary equipment, including ambulatory pumps; insurance coverage; and whether the patient has a history of IDU can all affect the ultimate use of OPAT.

The timing for transition from inpatient antibiotic therapy to OPAT and patient exclusion criteria have been critically evaluated by Andrews and von Reyn.[326] These guidelines are based on the local availability of medical care in the outpatient setting and risk factors and timing of potential adverse outcomes that would be best managed in the inpatient setting.

GUÍON

- Introducción. ¿tiene el tema interés?
- ¿Qué sabemos?.¿En qué lo basamos?. Un poco de historia.
- ¿Qué proponen las guías al uso?.
- Hay algo más fuera de las guías. Futuro…
- Conclusiones

POET STUDY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Text Size
Partial Oral Treatment of Endocarditis (POET)
The recruitment status of this study is unknown because the information has not been verified recently.
Verified June 2011 by Rigshospitalet, Denmark.
Recruitment status was Recruiting
Sponsor:
Rigshospitalet, Denmark
Information provided by:
Rigshospitalet, Denmark
ClinicalTrials.gov Identifier:
NCT01375257
First received: June 13, 2011
Last updated: June 16, 2011
Last verified: June 2011
History of Changes
Full Text View
Tabular View
No Study Results Posted
Disclaimer
How to Read a Study Record
Purpose
Background Current management of infective endocarditis include admission and treatment with parenteral antibiotics for 4 weeks - 6 weeks. Resource demands and psychological issues of present management strategy make it highly relevant to seek for alternative more lenient alternatives. Experiences with oral treatment are only sporadically described, but observational data suggest that oral treatment could be a feasible option. The investigators have in 2010 treated 12 endocarditis patients with partial oral antibiotics with a 100% success rate.
Study design The POET study is a Danish multicenter, prospective, randomized, open label study. The primary aim is to show non-inferiority of partial oral treatment with antibiotics of endocarditis compared to full parenteral treatment. Stable patients (n=400) with streptococci, staphylococci or enterococci infecting the mitral valve or the aortic valve will be included. After a minimum of 10 days of parenteral treatment, patients will be randomized to oral therapy or parenteral therapy. Special recommendations for oral treatment have been developed based on expected minimal inhibitory concentrations and pharmacokinetic calculations. Patients will be followed for 6 months after completion of antibiotic therapy. The primary endpoint is a composition of all cause mortality, unplanned
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POET

- Estudio Danés multicéntrico. EECC Fase IV
- Fecha inicio 2011
- Objetivo: demostrar la NO inferioridad de utilizar antibióticos por vo durante una parte del tratamiento (tras al menos 10 días de tratamiento iv) *VS* a que todo el tratamiento antibiótico sea por iv en las EI.
- Diana: 400 pacientes

Condition	Intervention	Phase
Endocarditis	Drug: Oral treatment with antibiotics for endocarditis Drug: Guideline treatment with parenteral antibiotics	Phase 4

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Partial Oral Treatment of Endocarditis

Resource links provided by NLM:

MedlinePlus related topics: Antibiotics Endocarditis

U.S. FDA Resources

Further study details as provided by Rigshospitalet, Denmark:

Primary Outcome Measures:

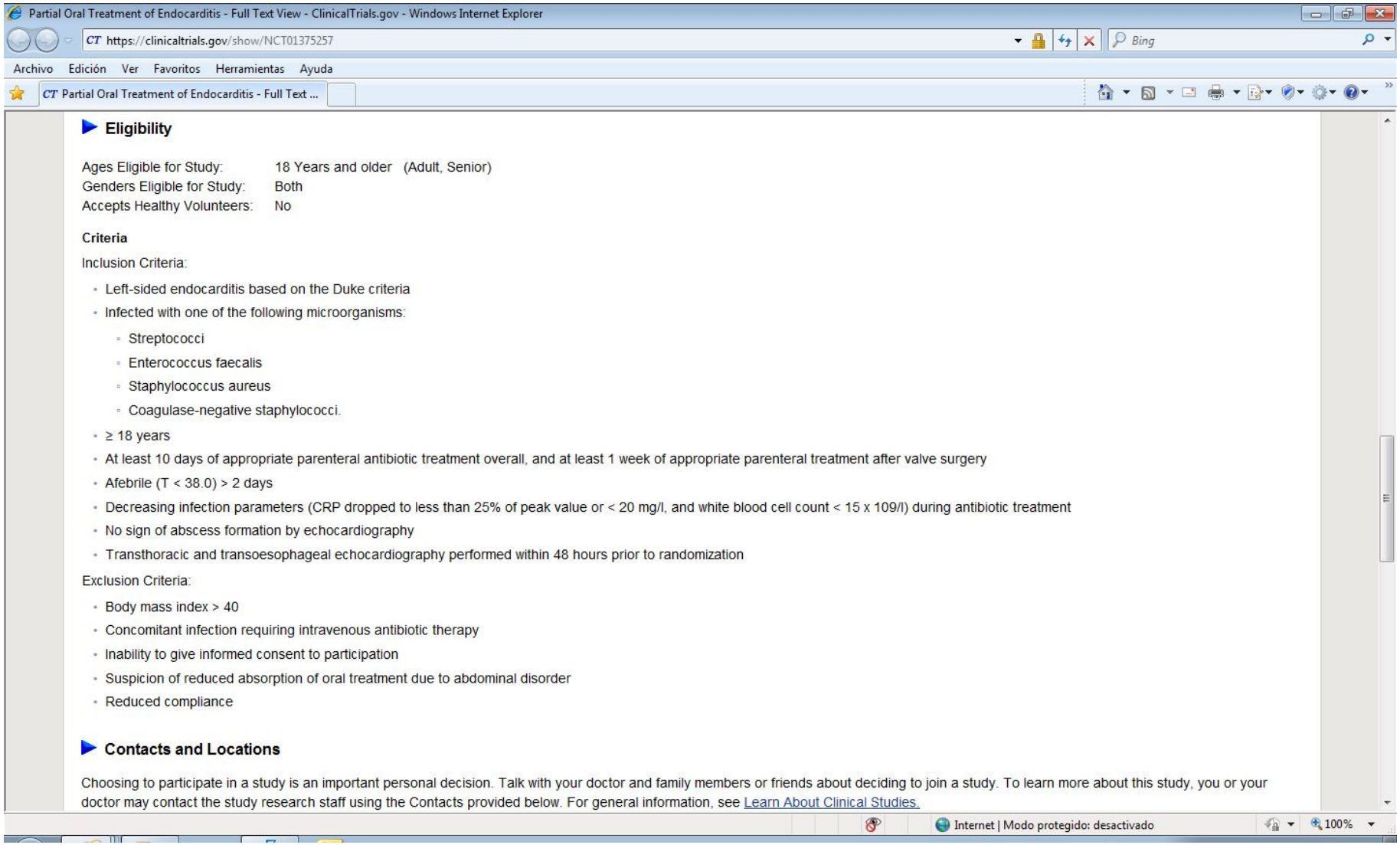
- The primary endpoint is a composite endpoint including all cause mortality, unplanned cardiac surgery, embolic events and relapse of positive blood cultures with the primary pathogen [Time Frame: Approximately 7 months. From randomisation until 6 months after end of study medication] [Designated as safety issue: Yes]

Secondary Outcome Measures:

- Quality of life [Time Frame: Approximately 7 months. From randomisation until 6 months after end of study medication] [Designated as safety issue: No]

  QOL performed during the study and after completion of the study

- Cost of treatment [Time Frame: Approximately 7 months. From randomisation until 6 months after end of study medication] [Designated as safety issue: No]
- Duration of antibiotic therapy [Time Frame: 4 weeks] [Designated as safety issue: No]
- Number of cerebral infarcts [Time Frame: Approximately 7 months. From randomisation until 6 months after end of study medication] [Designated as safety issue: No]


Partial Oral Treatment of Endocarditis - Full Text View - ClinicalTrials.gov - Windows Internet Explorer
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Partial Oral Treatment of Endocarditis - Full Text ...
Eligibility
Ages Eligible for Study: 18 Years and older (Adult, Senior)
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No
Criteria
Inclusion Criteria:
Left-sided endocarditis based on the Duke criteria
Infected with one of the following microorganisms:
Streptococci
Enterococcus faecalis
Staphylococcus aureus
Coagulase-negative staphylococci.
≥ 18 years
At least 10 days of appropriate parenteral antibiotic treatment overall, and at least 1 week of appropriate parenteral treatment after valve surgery
Afebrile (T < 38.0) > 2 days
Decreasing infection parameters (CRP dropped to less than 25% of peak value or < 20 mg/l, and white blood cell count < 15 x 109/l) during antibiotic treatment
No sign of abscess formation by echocardiography
Transthoracic and transoesophageal echocardiography performed within 48 hours prior to randomization
Exclusion Criteria:
Body mass index > 40
Concomitant infection requiring intravenous antibiotic therapy
Inability to give informed consent to participation
Suspicion of reduced absorption of oral treatment due to abdominal disorder
Reduced compliance
Contacts and Locations
Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.
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Partial oral treatment of endocarditis

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Background Guidelines for the treatment of left-sided infective endocarditis (IE) recommend 4 to 6 weeks of intravenous antibiotics. Conversion from intravenous to oral antibiotics in clinically stabilized patients could reduce the side effects associated with intravenous treatment and shorten the length of hospital stay. Evidence supporting partial oral therapy as an alternative to the routinely recommended continued parenteral therapy is scarce, although observational data suggest that this strategy may be safe and effective.

Study Design This is a noninferiority, multicenter, prospective, randomized, open-label study of partial oral treatment with antibiotics compared with full parenteral treatment in left-sided IE. Stable patients (n = 400) with streptococci, staphylococci, or enterococci infecting the mitral valve or the aortic valve will be included. After a minimum of 10 days of parenteral treatment, stable patients are randomized to oral therapy or unchanged parenteral therapy. Recommendations for oral treatment have been developed based on minimum inhibitory concentrations and pharmacokinetic calculations. Patients will be followed up for 6 months after completion of antibiotic therapy. The primary end point is a composition of all-cause mortality, unplanned cardiac surgery, embolic events, and relapse of positive blood cultures with the primary pathogen.

Conclusion The Partial Oral Treatment of Endocarditis study tests the hypothesis that partial oral antibiotic treatment is as efficient and safe as parenteral therapy in left-sided IE. The trial is justified by a review of the literature, by pharmacokinetic calculations, and by our own experience. (Am Heart J 2013;165:116-22.)

12 pacientes

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	β-Hemolytic streptococci group G	Prosthetic biological mitral valve	Fusidic acid and rifampicin	13 d/28 d	No	Success
Male	75	*Staphylococcus epidermidis*	Aortic and mitral valve	Linezolid and moxifloxacin	17 d/30 d	Yes, prosthetic biological mitral and aortic valve	Success
Male	62	*S aureus*	Mitral valve	Fusidic acid and linezolid	17 d/24 d	No	Success
Male	56	*S aureus*	Prosthetic biological mitral valve	Fusidic acid and rifampicin	29 d/15 d	No	Success
Female	74	*Streptococcus sanguinis*	Mitral valve	Linezolid and moxifloxacin	15 d/17 d	No	Success
Male	54	*S aureus*	Aortic valve	Rifampicine and linezolid	29 d/15 d	Yes, prosthetic biological aortic valve	Success
Male	78	*Enterococcus faecalis*	Prosthetic biological mitral valve	Linezolid	20 d/10 d	No	Success
Male	67	Coagulase-negative *Staphylococcus*	Pacemaker electrode	Rifampicin and linezolid	36 d/16 d	Yes, removal of infected electrode	Success
Female	65	β-Hemolytic streptococci group C	Aortic valve	Rifampicin and linezolid	24 d/6 d	Yes, prosthetic 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

Table III. Inclusion and exclusion criteria

Inclusion criteria
Left-sided endocarditis based on the Duke criteria
Infected with one of the following microorganisms:
Streptococci
E faecalis
S aureus
Coagulase-negative staphylococci
≥18 y
≥10 d of appropriate parenteral antibiotic treatment overall and at least 1 wk of appropriate parenteral treatment after valve surgery
T <38.0°C >2 d
C-reactive protein dropped to <25% of peak value or <20 mg/L, and white blood cell count <15 x 10^9/L during antibiotic treatment
No sign of abscess formation revealed by echocardiography
Transthoracic and transesophageal echocardiography performed within 48 h of randomization
Exclusion criteria
Body mass index >40
Concomitant infection requiring intravenous antibiotic therapy
Inability to give informed consent to participation
Suspicion of reduced absorption of oral treatment due to abdominal disorder
Reduced compliance

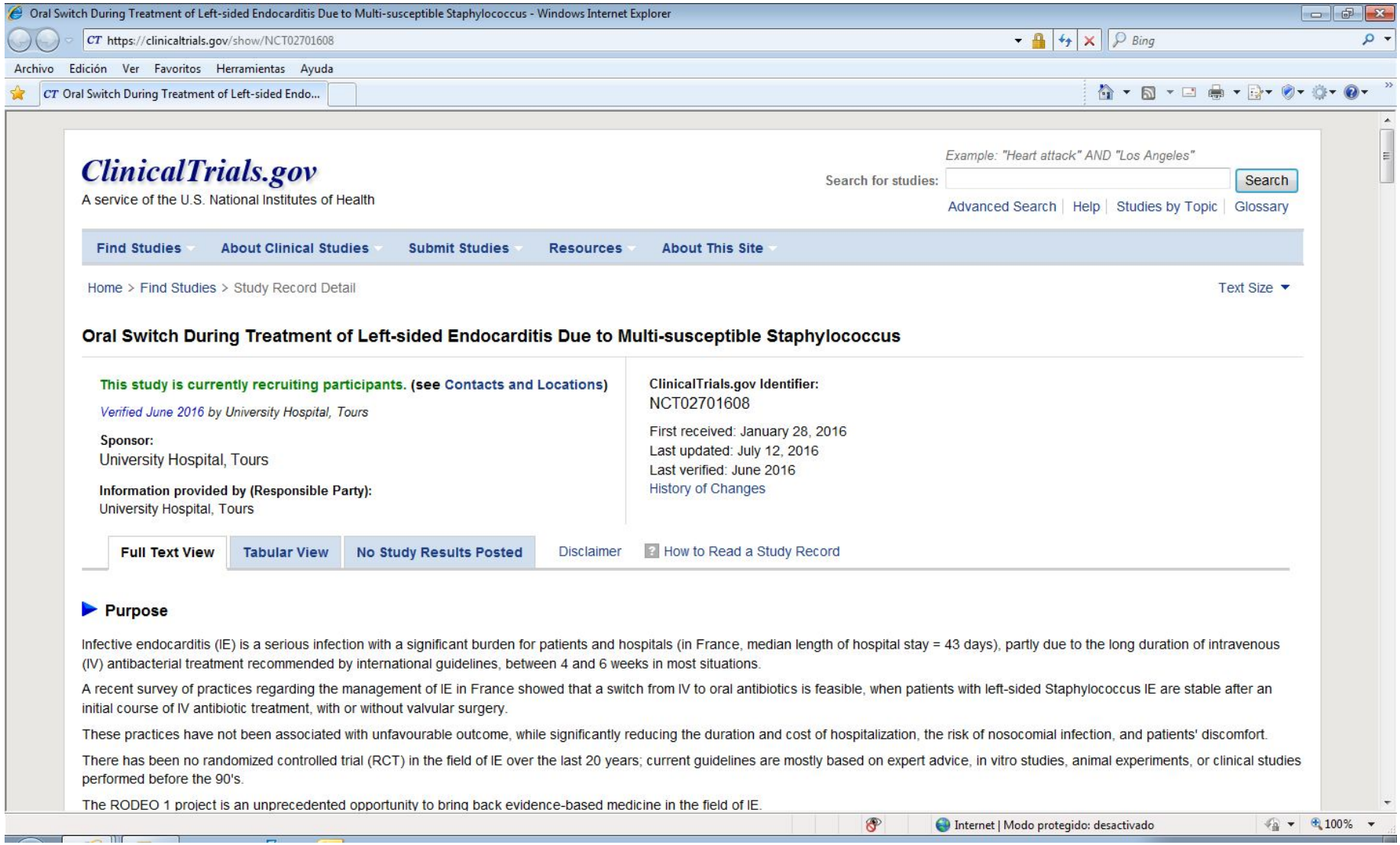
Status of the study

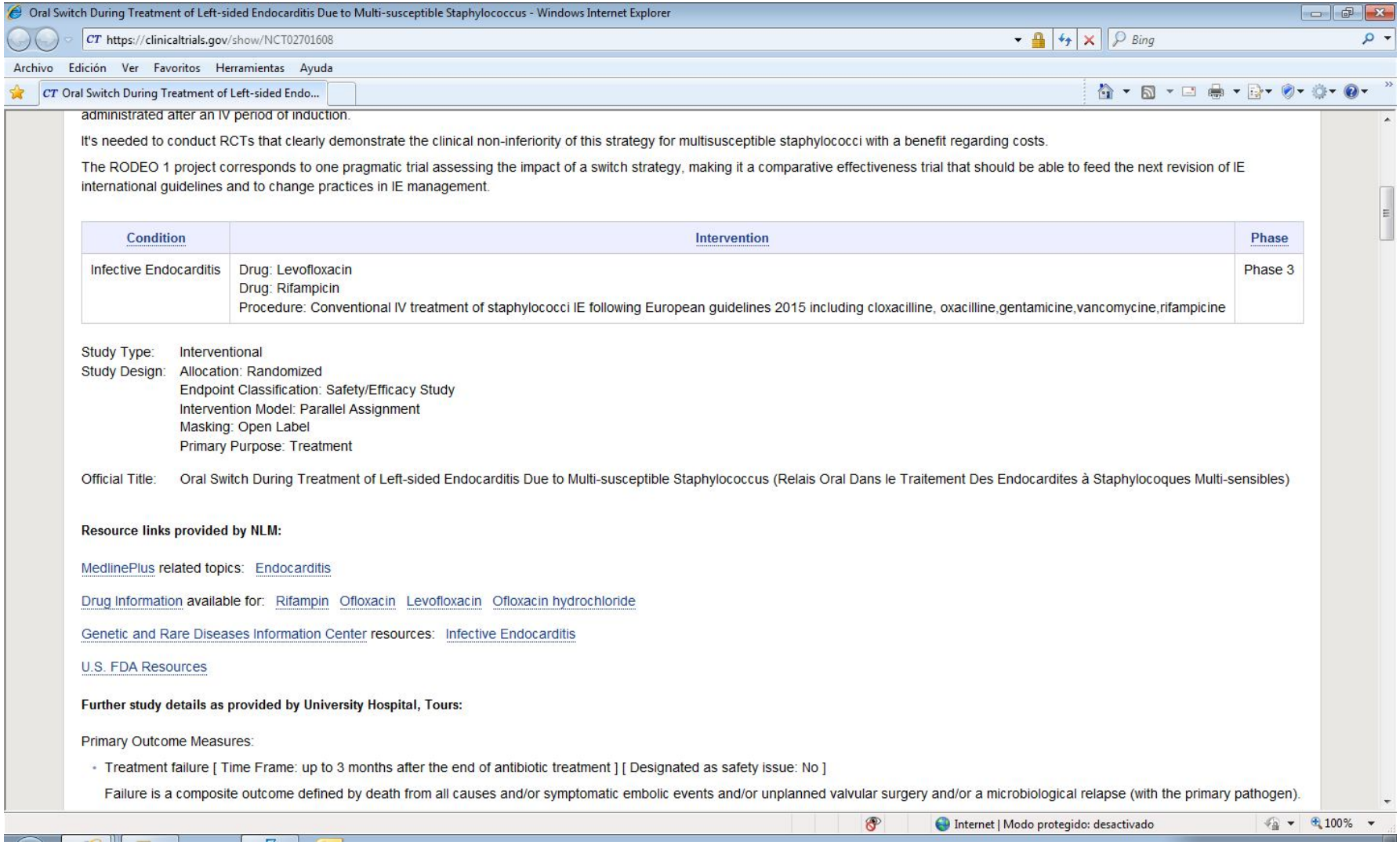
Five centers have begun inclusion, 46 patients having been included in the study to date (July 20, 2012).

One patient randomized to parenteral treatment has experienced a primary end point (unplanned cardiac surgery). One of the patients has switched from oral to parenteral therapy due to nausea.

The last center will initiate inclusion within the forthcoming 2 months.

RODEO 1 STUDY





administrated after an IV period of induction.

It's needed to conduct RCTs that clearly demonstrate the clinical non-inferiority of this strategy for multisusceptible staphylococci with a benefit regarding costs.

The RODEO 1 project corresponds to one pragmatic trial assessing the impact of a switch strategy, making it a comparative effectiveness trial that should be able to feed the next revision of IE international guidelines and to change practices in IE management.

Condition	Intervention	Phase
Infective Endocarditis	Drug: Levofloxacin Drug: Rifampicin Procedure: Conventional IV treatment of staphylococci IE following European guidelines 2015 including cloxacilline, oxacilline,gentamicine,vancomycine,rifampicine	Phase 3

Study Type: Interventional

Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Oral Switch During Treatment of Left-sided Endocarditis Due to Multi-susceptible Staphylococcus (Relais Oral Dans le Traitement Des Endocardites à Staphylocoques Multi-sensibles)

Resource links provided by NLM:

MedlinePlus related topics: Endocarditis

Drug Information available for: Rifampin Ofloxacin Levofloxacin Ofloxacin hydrochloride

Genetic and Rare Diseases Information Center resources: Infective Endocarditis

U.S. FDA Resources

Further study details as provided by University Hospital, Tours:

Primary Outcome Measures:

- Treatment failure [Time Frame: up to 3 months after the end of antibiotic treatment] [Designated as safety issue: No]

  Failure is a composite outcome defined by death from all causes and/or symptomatic embolic events and/or unplanned valvular surgery and/or a microbiological relapse (with the primary pathogen).

Estimated Enrollment:	324
Study Start Date:	March 2016
Estimated Study Completion Date:	October 2019
Estimated Primary Completion Date:	October 2019 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Oral switch treatment Oral switch to the combination of levofloxacin and rifampicin	Drug: Levofloxacin levofloxacin 500 mg x1/day (for patients ≤70kg) or levofloxacin 750 mg x1/day (for patients >70kg) Other Name: Fluoroquinolones Drug: Rifampicin rifampicin 600mg x1/day (for patients ≤70kg) or rifampicin 900mg x1/day (for patients >70kg)
Active Comparator: Conventional IV treatment according to european guidelines Conventional IV treatment of staphylococci IE (European guidelines 2015)	Procedure: Conventional IV treatment of staphylococci IE following European guidelines 2015 including cloxacilline, oxacilline,gentamicine,vancomycine,rifampicine Conventional IV treatment of staphylococci IE following European guidelines 2015 including cloxacilline, oxacilline,gentamicine,vancomycine,rifampicine

Detailed Description:

The RODEO 1 study is designed to determine the safety and efficacy of partial oral treatment of IE compared with traditional full-length parenteral treatment. Our primary objective is to demonstrate that in patients with left-sided multi-susceptible Staphylococcus who have received at least 10 days of IV antibiotic treatment with or without valvular surgery, a switch to an oral combination of rifampicin and fluoroquinolones between Day 10 and Day 28 after initiation of the IV antibiotic treatment, is not inferior to the continuation of the conventional IV antibiotic treatment regarding to treatment failure within 3 months after the end of antibiotic treatment.

Nationwide, noninferiority, multicenter, randomized, controlled, open-label trials.

Randomisation will only be offered to patients who have received at least 10 days of IV conventional antibiotic treatment of IE, and fulfil the inclusion criteria.

Randomisation will take place between Day 10 and Day 28 after initiation of parenteral antibiotic therapy or valvular surgery, thus ensuring to have at least 14 days of oral therapy in the experimental group.

Patients will be eligible whether they have undergone valvular surgery or not. This will imply that surgery procedure prior to randomisation will be heterogeneous, but randomisation will be stratified on the requirement of valvular surgery as part of the treatment of the current episode of IE or not.

Eligibility

Ages Eligible for Study: 18 Years and older (Adult, Senior)

Eligibility

Ages Eligible for Study:	18 Years and older (Adult, Senior)
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Left-sided IE (Defined according to Duke criteria) on native or prosthetic valve
- due to one isolate of Staphylococcus sp. (S. aureus or coagulase negative staphylococci, CNS) susceptible to levofloxacin and rifampicin
- in an adult ≥18 year old
- appropriate parenteral antibiotics treatment received for at least 10 days
- in case of valvular surgery, appropriate parenteral antibiotics treatment received for at least 10 days after valvular surgery
- planned duration of antibiotics will extend for at least 14 days at the time of randomisation i.e. a potential switch to oral treatment between Day 10 and Day 28 thus ensuring to have at least 14 days of oral therapy remaining in the experimental group
- apyrexia (temperature < 38°C) at each time point during the last 48 hours (at least two measures/day) at the time of randomisation
- blood cultures have been sterile for at least 5 days at the time of randomisation
- informed, written consent obtained from patient
- subject covered by or having the rights to French social security

Exclusion Criteria:

- body mass index <15 kg/m² or > 40 kg/m²
- creatinine clearance < 60 ml/min
- patient unable or unwilling to take oral treatment (digestive intolerance, significant malabsorption) at the time of randomisation
- expected difficulties regarding compliance with oral antibiotic treatment or follow-up (e.g. severe cognitive impairment, severe psychiatric disease...)
- patient without entourage to support and watch him at discharge
- valvular surgery planned within the next 6 months
- for patients with cardiac devices (pace-maker, implantable cardiac defibrillator) and suspected device-related IE (vegetation on the leads) if removal of the device was not performed
- breast feeding or pregnant women, or women on childbearing age without effective contraception
- expected duration of follow-up < 7 months at the time of randomisation (e.g. expected life expectancy < 7 months, patient living abroad...)
- past medical history of IE in the last 3 months
- other infection requiring parenteral antibiotic therapy
- patient with contra-indication to oral antibiotics administered in the experimental arm (i.e. fluoroquinolones or rifampicin) - including anticipated non-manageable drug interactions with rifampicin, and allergy.

OTRAS EXPERIENCIAS

Clinical Microbiology and Infection

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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,]. ✉

Cohorte 426 casos EI (2000-2012)
Edad dº mediana 64,5 años (R 7-98 años)
25% EI asociadas a cuidados sanitarios
Etiología: estreptococos orales 23%; *S. aureus* 19%.
Mortalidad en seguimiento 22%
Tras una inicial fase de tto iv→ 50% pac -vo mediana 21 d tras dº (R: 0-70 d)
Ab utilizados: amoxicilina sola 109 casos, en combinación con clindamicina, quinolonas, rifampicina en 46 casos más.
En análisis multivariante el paso a vo NO se asoció con un aumento en el riesgo de mortalidad.

Table 2

	Oral antibiotic switch (n=214)	Exclusive intravenous route (n=212)	*P**
Definite endocarditis	179 (84)	190 (90)	0.09
Men	149 (70)	142 (67)	0.60
Median age, years (range)	65 (7-98)	64 (12-93)	0.62
History of previous episode of IE	20 (9)	17 (8)	0.73
Congenital heart disease	20 (9)	15 (7)	0.48
Left heart endocarditis	161 (75)	174 (82)	0.10
Right heart endocarditis	15 (7)	12 (6)	0.69
Pacemaker endocarditis	33 (15)	19 (9)	0.05
Intracardiac device	5 (2)	7 (3)	0.57
Native valve endocarditis	125 (58)	137 (65)	0.20
Prosthetic valve endocarditis	51 (24)	49 (23)	0.91
Diabetes	15 (7)	30 (14)	0.02
Chronic renal failure	17 (8)	29 (14)	0.06
Cirrhosis	4 (2)	12 (6)	0.04
Immunosuppression	25 (12)	34 (16)	0.20
Fever > 38°C	183 (86)	183 (86)	0.89
Acute heart failure	60 (28)	94 (44)	$<10^{-4}$
Shock	9 (4)	36 (17)	$<10^{-4}$
Cerebral emboli	27 (13)	42 (20)	0.05
Median CRP, mg/L (range)	81 (10-512)	88 (10-525)	0.06
Serum creatinine > 100 μmol/L	76 (36)	110 (52)	$<10^{-4}$
Surgery	120 (56)	126 (59)	0.49
Streptococci	91 (43)	80 (38)	0.32
Coagulase-negative staphylococci	26 (12)	22 (10)	0.64
Enterococci	23 (11)	26 (12)	0.65
Staphylococcus aureus	28 (13)	53 (25)	0.002
Susceptibility			0.12
Methicillin-susceptible *S. aureus*	26 (12)	41 (19)	
Methicillin-resistant *S. aureus*	2 (1)	12 (6)	

Table 3

Microorganism	Antibiotics
Streptococci (n=91)	Amoxicillin (n=84; 92%)
	Amoxicillin - Clindamycin (n=4; 4%)
	Amoxicillin - Rifampin (n=3; 3%)
Staphylococci (n=54)	Clindamycin - (Rifampin or Fluoroquinolone) (n=15; 28%)
	Fluoroquinolone - Rifampin (n=13; 24%)
	Amoxicillin - (Rifampin or Fluoroquinolone or Clindamycin) (n=9; 17%)
	Fluoroquinolone (n=4; 7%)
	Amoxicillin (n=4; 7%)
	Clindamycin (n=4; 7%)
	Rifampin - (Bactrim or Doxycycline) (n=2; 4%)
	Linezolide (n=2; 4%)
	Rifampin (n=1; 2%)
Enterococci (n=23)	Amoxicillin (n=21; 91%)
	Amoxicillin - Rifampin (n=2; 9%)

TÍTULO: Tratamiento oral de la Endocarditis Infecciosa

NOMBRE/S Y APELLIDO/S DEL AUTOR/ES: P. Muñoz[1], V. González-Ramallo[1], M.E. García Leoni[1], M. Valerio[1], A. Fernández-Cruz[1], G. Mariscal[1], B. Pinilla[1], M. Martínez-Sellés[1], G. Cuerpo[1], E. Bouza[1] en nombre del Grupo de Apoyo a la Endocarditis Infecciosa del Gregorio Marañón (GAME).

Periodo:2008-2016-----435 episodios-→**44 tto vo (10%)**
Media edad 59 años. Adq comunitaria 61%
Etiología: SA 34%; *S. viridans* 16%; BGN 11%; SCN 9%; *C. burnetti* 6,8%; anaerobios 6,8%; hongos 4,6%; CULTIVO NEGATIVO 4,6%; *E. fecalis*, *S. pneumoniae* y *Ureaplasma spp* 2,3%

Complicaciones previas: Mtt sépticas 12 casos; IQ 29 casos
Fármacos: quinolonas 66%; resto cotrimoxazol 9%; linezolid, cloroquina+ doxi 6,5%; azoles, cefalosporinas 4,6% y rifampicina 13,6%
Duración media tto: 19,5 días
Reingreso 15 pacientes (34%): 2 recidiva precoz
Mortalidad al año 4,5%

GUÍON

- Introducción. ¿tiene el tema interés?
- ¿Qué sabemos?.¿En qué lo basamos?. Un poco de historia.
- ¿Qué proponen las guías al uso?.
- Hay algo más fuera de las guías. Futuro…
- Conclusiones

Indicaciones, momento y fármaco

- El tratamiento con ab orales **es efectivo en tratar casos seleccionados de EI (nivel de evidencia bajo) si:**

  - Estabilidad clínica y no problemas con absorción GI
  - No presencia de complicaciones valvulares (ETT/ETE)
  - Etiología conocida (no empírico)
  - Conocimiento y entendimiento de la situación por parte del paciente (CI?)
  - Fácil control clínico
  - Dificultad para mantener tto iv

- **¿Qué EI? (VN (con/sin IQ)/**VP**/**dispositivo**)**
  - 1 EI derechas por, *S. aureus,* no complicadas en UDVP (EC con cipro+rif)
  - 2 EI válvula nativa
    - Bacterias intracelulares
    - Estreptococos sensibles a penicilina (amoxicilina a dosis altas)
    - *S. aureus* sensibles a linezolid
    - Otras: enterococos R a Peni/vanco con linezolid
  - 3 Tratamiento supresor cuando un material protésico no se ha podido retirar/hongos.

  - **Ptes resultados estudios POET/RODEO**

indicaciones, Momento y fármaco

- No como tratamiento empírico
- **COMO INICIO**: posibles casos EI derecha no complicada por *S. aureus*…
- **COMO CONTINUACIÓN**: En EI causadas por bacterias no intracelulares, al menos tras 10-14 días de tratamiento iv con rápida y buena respuesta clínica.
- En EI por agentes intracelulares. No hay estudios, pero podría ser antes.
- **COMO supresión**: tras ciclo tto iv completo

indicaciones, momento y Fármaco

- Activo contra agente etiológico e idealmente biopelícula
- Buen perfil PK (biodisponibilidad-sangre/tejido/distribución/eliminación)
- Seguro (toxicidades)
- Precio….
- Experiencias con: **amoxicilina, ciprofloxacino**, levofloxacino, moxifloxacino, **linezolid, cotrimoxazol**, doxiciclina, minociclina, rifampicina. Fluconazol
- Futuro tedizolid (menor toxicidad…)

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GRACIAS POR SU ATENCIÓN