Endocarditis and the new ESC guidelines

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Disclosure

(Potentiële) Belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Geen
Sponsoring of onderzoeksgeld	Geen
Honorarium of andere (financiële) vergoeding	Geen
Aandeelhouder	Geen
Andere relatie, namelijk …	Geen

Casuïstiek 1

SEH
63-year old man crashed his car after syncope
Admitted to neurology ward for observation, n.a.

Consultation cardiology because of syncope

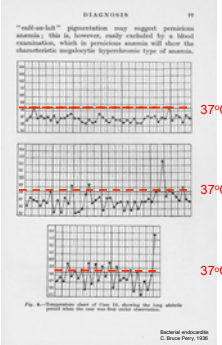
History:
no abnormalities, just some weight loss, attributed to excercise

Physical examination
Body temp 37 C, diastol murmur gr 2/4 pm apex

Casuïstiek 1

16.4 echocardiography: AOI, mobile structure in LVOT

Casuïstiek 1



Casuïstiek 1

16.4 echocardiography: AOI, mobile structure in LVOT

17.4 blood cultures 2x
18.4 blood cultures 2x

Enterococcus faecalis 4/4 blood cultures (7/8 bottles)

Definite endocarditis

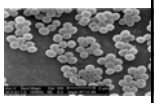
Major criteria

1. Blood cultures positive for IE
   - a. Typical m.o. ≥ 2 blood cultures
   - b. M.o. consistent with IE from persistently positive blood cultures
   - c. Positive blood culture for Coxiella burnetii or phase IgG ab >1:800
2. Imaging positive for IE
   - a. Echocardiogram positive for IE

Minor criteria

1. Predisposing heart condition or injection drug use
2. Temperature > 38C
3. Vascular phenomena
4. Immunological phenomena (glomerulonephritis, RF, Roth's spots, Osler)
5. Blood culture not meeting major criterion or serological evidence

Enterococcal endocarditis



- ~ 10% of infective endocarditis
  - 90% *Enterococcus faecalis*
  - 95% low level gentamicin resistance
- Mean age > 65 years
- Comorbidities
- Guidelines (ESC 2009):
  - ampicillin + gentamicin (when no high-level genta resistance)
  - 4 to 6 weeks (2-3 wks might be considered i.c.o toxicity)
  - gentamicin 3 mg/kg/day in 2-3 doses

THE AMERICAN JOURNAL of MEDICINE
1948;4:671-89

Penicillin-resistant Non-hemolytic Streptococcal Subacute Bacterial Endocarditis*

WILLIAM H. CLARK, M.D., SERGIUS BRYNER, M.D. and LOWELL A. KANTZ, M.D.
San Francisco, California

- Many relapses in genus Enterococcus SBE
- Large daily doses of penicillin should be used
- Streptomycin & penicillin combined may be effective

THE AMERICAN JOURNAL of MEDICINE
1951;10:278-99

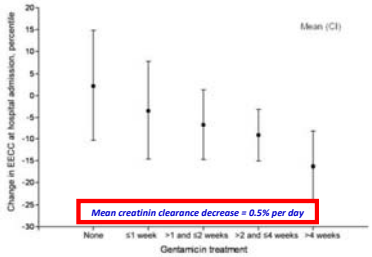
Treatment of Enterococcal Endocarditis and Bacteremia*

Results of Combined Therapy with Penicillin and Streptomycin

WILLIAM C. ROBBINS, M.D.† and RALPH TOMPSETT, M.D.

- 0.5 million U penicillin i.m.(!) every 2 hrs, & 0.5 gm streptomycin i.m.(!) four times daily Continued for 28 to 42 days
- "Results of the combined treatment were striking" (n = 7)

Aminoglycosides and nephrotoxicity



Bucholtz e.a. Clin Infect Dis 2009

Amoxicillin plus gentamicin for 14 days

Reference, author	Year of study	No. of episodes	Cure, %[a]	Antibiotic therapy in cured episodes, median days	
					Aminoglycoside[c]
[5] Geraci and Martin	1954	14	50	38	38
[6] Vogler et al.	1962	13	77	—	—
[7] Mandell et al.	1970	36	83	42[d]	42[d]
[8] Moellering et al.	1974	14	57	36	24
[9] Wilson et al.	1984	56	88	28[d]	28[d]
[10] Rice et al.	1991[e]	40	73	39[d]	35[d]
Present study	2002	100	78x E. faecalis	42	15 (0 - > 49 days)

[a] Cure implies no death during treatment and no relapse at follow-up.
[b] Cell wall–active agents implicates
[c] Aminoglycoside implicates streptomycin, gentamicin, tobramycin, or netilmicin.
[d] Mean.
[e] Antibiotic therapy includes all treated patients.

L. Olaison et al. Clin Infect Dis 2002;34:159-66

Amoxicilline plus ceftriaxone synergistic for *E. faecalis*

- In vitro
- In vivo
- Observational human studies
  - Galdavà e.a. Ann Int Med 2007;146:574-79

Clin Infect Dis. 2013;56:1261-8

Observational, nonrandomized, comparative multicenter cohort study

	Ampicillin + Ceftriaxone (n=159)	Ampicillin + gentamicin (n=87)	P-value
Duration of therapy			
overall in survivors	42 (39-46)	42 (35-44)	.122
days untill surgery	11 (6-22)	9 (3-22)	.34
Adverse Events			
rash/fever	1%	-	.46
leukopenia	0.6%	-	.46
new renal failure	-	23%	<.001
vestibular toxicity	-	2%	.055
Surgery			
active phase of infection	58%	65%	.39
follow-up	3%	9%	.09
In-hospital mortality			
Overall	26%	25%	.85
Without indication for surgery	12%	12%	.98
Operated	19%	29%	.29
Not operated (with indication)	62%	42%	.16

Casuïstiek 1

Treatment

1 = amoxicillin plus gentamicin 4 – 6* weeks

2 = amoxicillin plus ceftriaxone 6 weeks

Gentamicin:

1 = 4 – 6 weeks

2 = 2 weeks**

1 = 3 mg/kg/day in 2 -3 doses

2 = 3 mg/kg/day in 1 dose

* Symptoms > 3m or PVE

** 'Some experts recommend gentamicin for only 2 weeks (IIa, B)

Casuïstiek 2

32-year old man is bitten by guinea pig

10 days later: fever, facial palsy left, hemiparesis right side

CT-scan: cerebral (septic) emboli

Blood cultures: *S. aureus* (2/2, 4 bottles)

Casuïstiek 2

TEE:

aoi, dubious vegetation mitral valve

Therapy

1. = flucloxacilline plus gentamicin (ESC 2009)

Endocarditis door *S. aureus*

- In-vitro
  - synergism flucloxacillin - gentamicin
- In-vivo
  - shortens duration bacteremia
  - no differences in morbidity and mortality
- Patients with *S. aureus* endocarditis, randomized
  - no differences in morbidity and mortality (Korzeniowsk 1982, Ribera 1996)
- Aminoglycoside no longer indicated for patients with native valve endocarditis by *S. aureus* (ESC 2015)

Casuïstiek 2

- 5 days of antimicrobial therapy and still fever
- Blood cultures remain positive
- repeat TEE: aoi, abces aortic root, vegetation MV

Casuïstiek 2

Operation

non-coronary cusp perforated

Vegetations mitral and aortic valve

Prosthetic valves implanted

Postoperative antibiotic regimen:

1 = that recommended for PVE

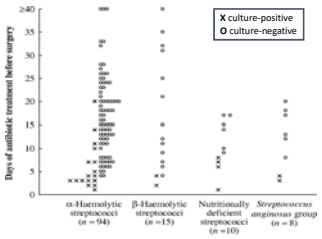
2 = that recommended for NVE

Postoperative antibiotic regimen

Surgical data limited and ambiguous

- Patients, who are operated late in the course of the disease and using antimicrobial therapy but who already completed the standard antimicrobial regimen
- Patients, operated early in the course of the disease and using antimicrobial therapy, but who did not yet complete the standard antimicrobial regimen

Duration of treatment before surgery and valve culture results



J Antimicrob Chemother 2005;55:234

Postoperative antibiotic regimen

Surgical data limited and ambiguous

- Patients, who are operated late in the course of the disease and using antimicrobial therapy but who already completed the standard antimicrobial regimen
- Patients, operated early in the course of the disease and using antimicrobial therapy, but who did not yet complete the standard antimicrobial regimen
- Variable information about Gram stains, culture results, use of PCR, duration of postoperative treatment
- Changing terminology and definitions
  relapse, recurrent, continuing, treatment failure, persisting, second episode, etc

Post-operative treatment ESC

- In NVE needing valve replacement by a prosthesis during antibiotic therapy, the post-operative antibiotic regimen should be that recommended for NVE, not for PVE.
- In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery.
- After surgery, a new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.

AHA Scientific Statement

Endorsed by the Infectious Diseases Society of America

Infective Endocarditis

The counting of days of recommended duration of therapy should begin on the first day on which blood cultures were negative in cases in which blood cultures were initially positive.

There is a lack of consensus as to whether the postoperative treatment regimen should be one that is recommended for prosthetic valve treatment rather than one that is recommended for native valve treatment

If the resected tissue is culture positive, then an entire course of antimicrobial therapy is recommended after valve resection.

If the resected tissue is culture negative, then the recommended duration of prosthetic valve treatment should be given less the number of days of treatment administered for native valve infection before valve replacement.

In regimens that contain combination antimicrobial therapy, it is important to administer agents at the same time or temporally close together to maximize the synergistic killing effect on an infecting pathogen.

Class CII: consensus of experts (C); conflicting evidence, a divergence of opinion, or both about the usefulness/efficacy of a procedure or treatment (II).

Circulation. 2015;132:00-00. DOI: 10.1161/CIR.0000000000000296.

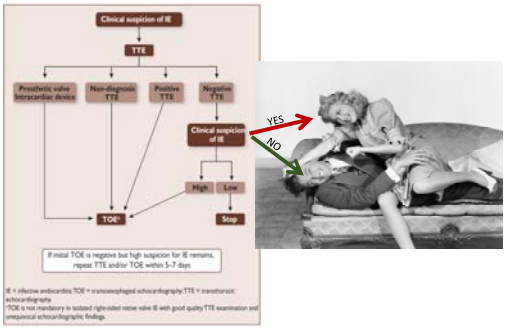
Infective endocarditis - diagnosis

- Presentation highly variable
  - Subacute or chronic disease with low-grade intermittent fever, malaise, weight loss, arthralgia, myalgia, backpain, etc
  - Acute and rapidly progressive infection
- No pathognomonic physical signs
  - Fever ~ 90%, heart murmur ~ 85%, embolic phenomena ~ 25%
- No pathognomic laboratory findings
- No pathognomic imaging findings

Infective endocarditis - diagnosis

Imaging

- Echocardiography
  - False negative, false positive (marantic vegetations – SLE, malignancy)
- Nuclear imaging (^{18}FDG-PET/CT scan)
  - NVE – low sensitivity
  - PVE – preliminary data, not to be used as a first line or confirmatory imaging
  - Diagnostic work-up of extra cardiac manifestations in endocarditis?
- MSCT (multislice CT)
  - Perivalvular extension
- MRI
  - Increased likelihood of detecting cerebral emboli → adds minor Duke criterion



Endocarditis diagnosis

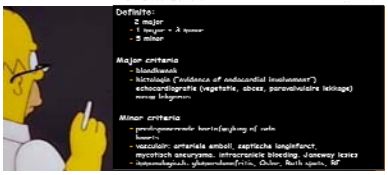
Signs and symptoms, imaging, lab results: nothing is pathognomonic

Infective endocarditis – histology → no gold standard

Proposed histologic criteria
Major criteria – Vegetation – Inflammatory infiltrate with polymorphnuclear cells – Microorganisms demonstrated in tissues by (immuno-)histology
Minor criteria – Mononuclear cell infiltrate of the valve – Necrosis – Neovascularization – Fibrosis – Calcification
Definite IE: 2 major criteria
Possible IE: 1 major and 2 minor criteria
Rejected IE: no major criterion

Lepidi e.a. Infect Dis Clin N Am 2002;16:339-361

Infective endocarditis - diagnosis



(modified) Duke criteria for endocarditis[1,2]

- Primary purpose: research, not for clinical decisions
- Specific, not sensitive (60% to 89%[3])

[1]Durack e.a., Am J Med 1994;96:200
[2]Li e.a., CID 2000;30:633
[3]Van der Vaart, Van der Meer. Int J Antimicrob Agents 2013;41

Diagnosis of infective endocarditis

- These criteria are useful, but they do not replace the clinical judgement – ESC 2015
- The Duke criteria are meant to be a guide for diagnosing IE and must not replace clinical judgement – AHA 2015

Duke criteria, modified by ESC 2015

Major criteria

a. Typical m.o. ≥ 2 blood cultures
b. M.o. consistent with IE from persistently positive blood cultures
c. Positive blood culture for Coxiella burnetii or phase IgG ab >1:800

a. Echocardiogram positive for IE
b. Abnormal activity around site of prosthetic valve implantation (PET/CT) >3 months after implantation
c. Definite paravalvular lesion by cardiac CT

Minor criteria

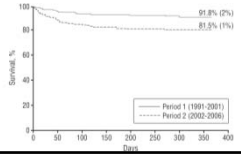
1. Predisposing heart condition or injection drug use
2. Temperature > 38C
3. Vascular phenomena (including those detected by imaging on
4. Immunological phenomena (glomerulonephritis, RF, Roth's spots, Osler)
5. Blood culture not meeting major criterion or serological evidence

The Endocarditis Team

- Disease with very many different aspects
  - Cardiac, infectious, neurological, rheumatological, etc
- High level of expertise needed from practitioners
  - Cardiologists, cardiac surgeons, ID specialists, microbiologists, neurologists, radiologists, nuclear medicine specialists, etc.
- The need for a collaborative approach – the 'Endocarditis Team'

The Endocarditis Team

333 patients with definite endocarditis			
Characteristic	**Period 1 (1991-2001) (n=173)**	**Period 2 (2002-2006) (n=160)**	***P* Value (Period 1 vs Period 2)**
Age, mean (SD), y	57.3 (15.8)	61.6 (16.0)	0.02
Charlson comorbidity index >2	8.7%	26.9%	<0.001
Renal failure	26.6%	15.6%	0.01
Appropriate antimicrobial drug & duration	22.7%	61.8%	<0.001
Compliance with surgical indications	88.4%	95.2%	0.04
Mortality			
• In-hospital	12.7%	4.4%	0.001
• 1-y	18.5%	8.2%	<.001



Modified from Bothelo-Nevers e.a. Arch Intern Med 2009;169:1290-8

Take home message

- Endocarditis is a syndrome diagnosis, nothing is pathognomonic
- Duke criteria is no substitution for clinical judgement
- The treatment of enterococcal endocarditis with amoxicillin & ceftriaxone is associated with much less morbidity than treatment with gentamicin
- There is no room for gentamicin in the treatment of native valve endocarditis by S. aureus
- Treatment of endocarditis is team work

The endocarditis team