



EuroValve
January 26-27, 2017

Case-based session. Infective Endocarditis.
Applying the new guidelines.

A case of large vegetation with neurological complication.

María Nazarena Pizzi
Hospital Universitari Vall d'Hebron
Barcelona.

www.eurovalvecongress.com



EuroValve

January 26-27, 2017

I have **no financial relationships** to disclose.

www.eurovalvecongress.com



CLINICAL PRESENTATION

A 74 year old man with no cardiovascular history

Admitted to a Community Hospital due to 5 months of :

- Fever
 - Constitutional syndrome (fatigue, poor appetite, weight loss of 10 kg).
 - Progressive exercise-induced dyspnea (no other signs of heart failure).
-
- BLOOD CULTURES 6/6: *Streptococcus sanguis* (viridans group *Streptococcus*)

23-05-16

Community
Hospital

27-05-16

(+) Blood Cultures



TOE AT THE COMMUNITY HOSPITAL

- **Myxomatous mitral valve degeneration.**
- **Large and mobile vegetation** of 6 x 22 mm on the atrial aspect of the posterior leaflet.
- **Severe mitral regurgitation** (ERO by PISA of 68 mm²).
- Mild dilatation of the LV with normal systolic function.





EuroValve

January 26-27, 2017
Crowne Plaza Barcelona Fira Center, SPAIN

ON ADMISSION

Major criteria

1. Blood cultures positive for IE

- Typical microorganisms consistent with IE from 2 separate blood cultures:
 - *Viridans streptococci*, *Streptococcus gallolyticus* (*Streptococcus bovis*), *HACEK* group, *Staphylococcus aureus*; or
 - Community-acquired enterococci, in the absence of a primary focus; or
- Microorganisms consistent with IE from persistently positive blood cultures:
 - ≥ 2 positive blood cultures of blood samples drawn >12 h apart; or
 - All of 3 or a majority of ≥ 4 separate cultures of blood (with first and last samples drawn ≥ 1 h apart); or
- Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titre $>1:800$

2. Imaging positive for IE

- Echocardiogram positive for IE:
 - Vegetation;
 - Abscess, pseudoaneurysm, intracardiac fistula;
 - Valvular perforation or aneurysm;
 - New partial dehiscence of prosthetic valve.
- Abnormal activity around the site of prosthetic valve implantation detected by ^{18}F -FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT.
- Definite paravalvular lesions by cardiac CT.

European Society of Cardiology 2015 modified criteria
for the diagnosis of infective endocarditis



Minor criteria

- Predisposition such as predisposing heart condition, or injection drug use.
- Fever defined as temperature $>38^\circ\text{C}$.
- Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
- Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
- Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

2 major + 1 minor CRITERIA

DEFINITIVE COMMUNITY-ACQUIRED NATIVE VALVE ENDOCARDITIS



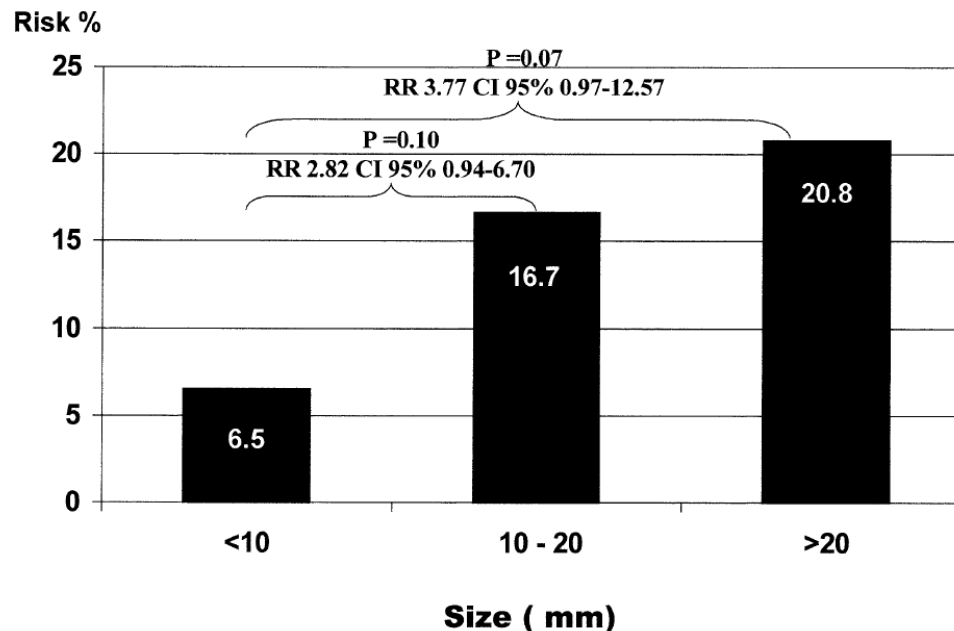
EuroValve

January 26-27, 2017
Crowne Plaza Barcelona Fira Center, SPAIN

ON ADMISSION

RISK FACTORS OF EMBOLISM: VEGETATION CHARACTERISTICS

- **SIZE:** > 10 mm, specially > 15 mm + **significant mobility** (very high > 3 cm)
- **MOBILITY**
- **LOCATION:** **mitral** valve
- **EVOLUTION:** size increment under antibiotic therapy.



HIGH EMBOLIC RISK



EuroValve

January 26-27, 2017
Crowne Plaza Barcelona Fira Center, SPAIN

ON ADMISSION



Indications and timing of surgery in left-sided valve infective endocarditis

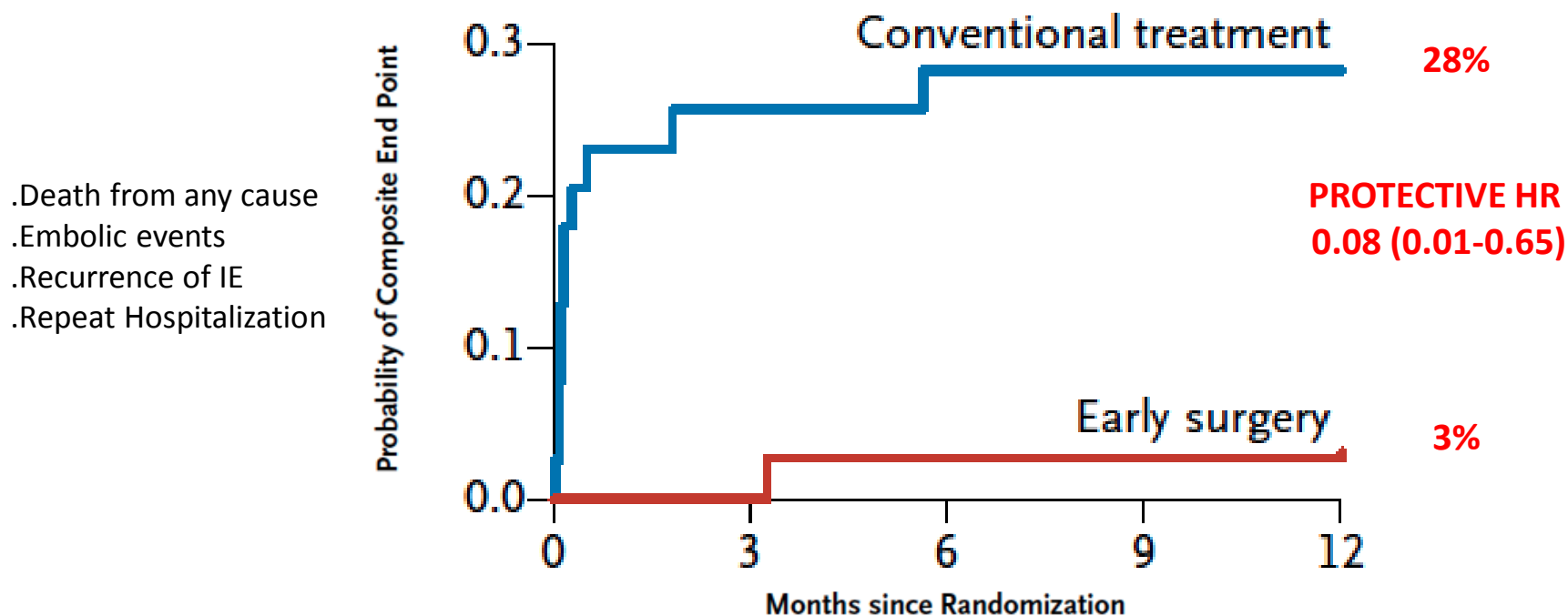
3. Prevention of embolism			
Aortic or mitral NVE or PVE with persistent vegetations > 10 mm after one or more embolic episode despite appropriate antibiotic therapy	Urgent	I	B
Aortic or mitral NVE with vegetations > 10 mm, associated with severe valve stenosis or regurgitation, and low operative risk	Urgent	IIa	B
Aortic or mitral NVE or PVE with isolated very large vegetations (> 30 mm)	Urgent	IIa	B
Aortic or mitral NVE or PVE with isolated large vegetations (> 15 mm) and no other indication for surgery ^e	Urgent	IIb	C

INDICATION OF SURGERY FOR EMBOLISM PREVENTION



Early Surgery (48 hours) versus Conventional Treatment for Infective Endocarditis to prevent System Embolism

Large vegetations: > 10 mm (70%) - > 15 mm (30%) + severe valve disease





EuroValve

January 26-27, 2017
Crowne Plaza Barcelona Fira Center, SPAIN



ON ADMISSION

Predictors of poor outcome in patients with infective endocarditis

Patient characteristics

- Older age
- Prosthetic valve IE
- Diabetes mellitus
- Comorbidity (e.g., frailty, immunosuppression, renal or pulmonary disease)

Clinical complications of IE

- Heart failure
- Renal failure
- >Moderate area of ischaemic stroke
- Brain haemorrhage
- 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



INDICATIONS FOR HEART TEAM EVALUATION

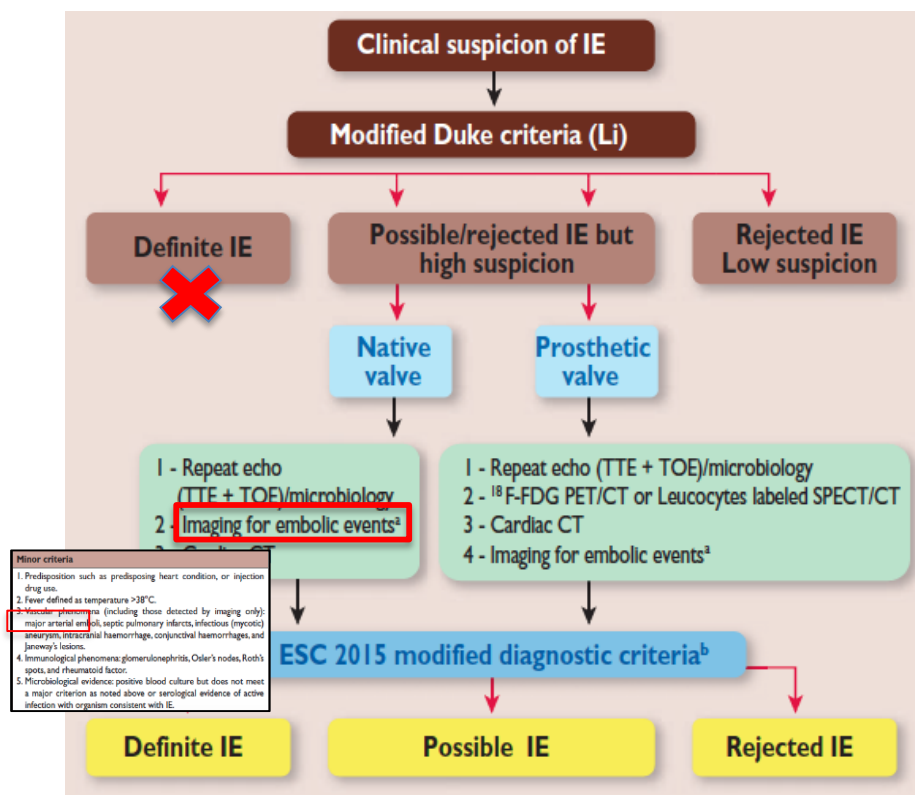
Habib G, et al. Eur Heart J 2015;36(44):3075-3128.



THE PATIENT WAS **NOT** TRANSFERRED: **CONSERVATIVE STRATEGY**

ANTIBIOTIC TREATMENT

Ceftriaxone 2gr/24hs + Gentamicin 80 mg/8hs



Thoracic-abdominal CT

Two splenic embolisms

- 4 cm in the inferior pole
- 1.4 cm in the anterior aspect.



6 DAYS AFTER ANTIBIOTIC ONSET

NEUROLOGICAL SYMPTOMS

- Confusion and somnolence.
- No clear neurological deficits

Brain CT:

- Acute ischemic frontal cortico-subcortical
- Small haemorrhagic lesions in the left occipital lobule.

23-05-16

Community
Hospital

27-05-16

*Streptococcus
Sanguis + ATB*

ECHO:

Large Vegetation
Severe MI

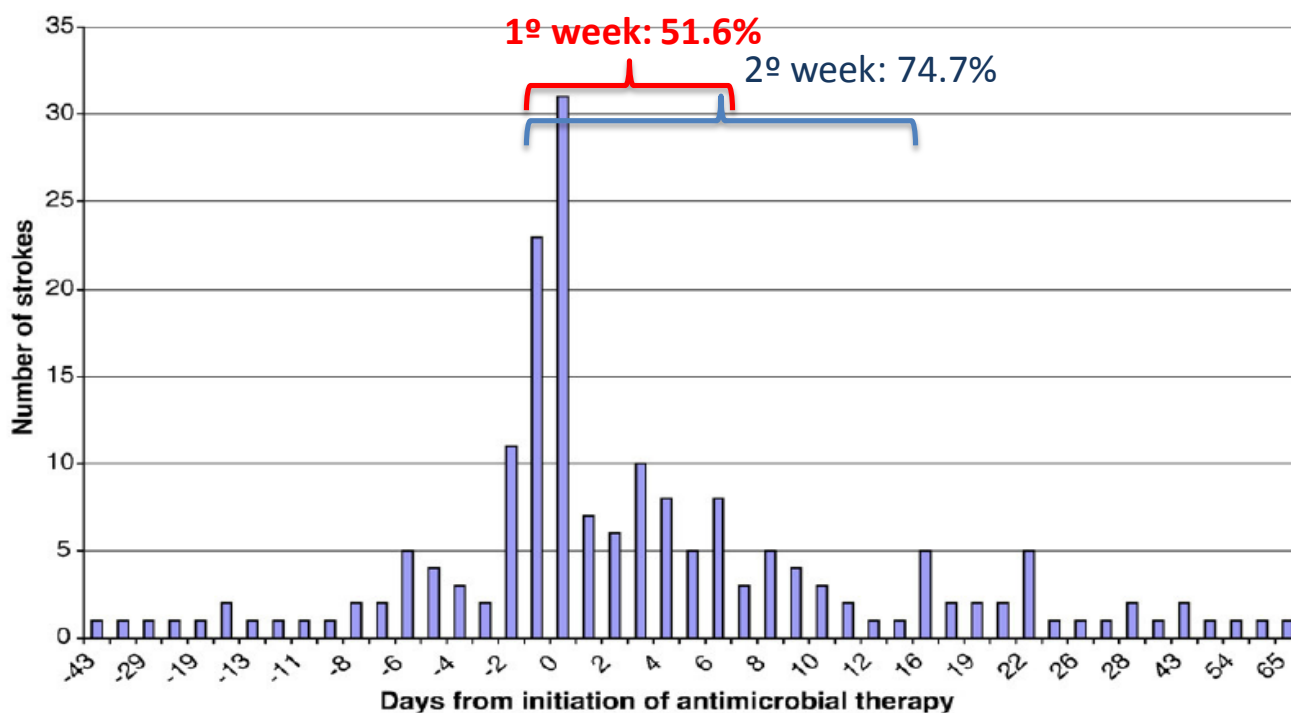
CT: Splenic
Embolism

02-06-16

Neurologic
Complication



RELATION BETWEEN ATB TREATMENT AND THE INCIDENCE OF STROKE IN IE (ICE-PCS)

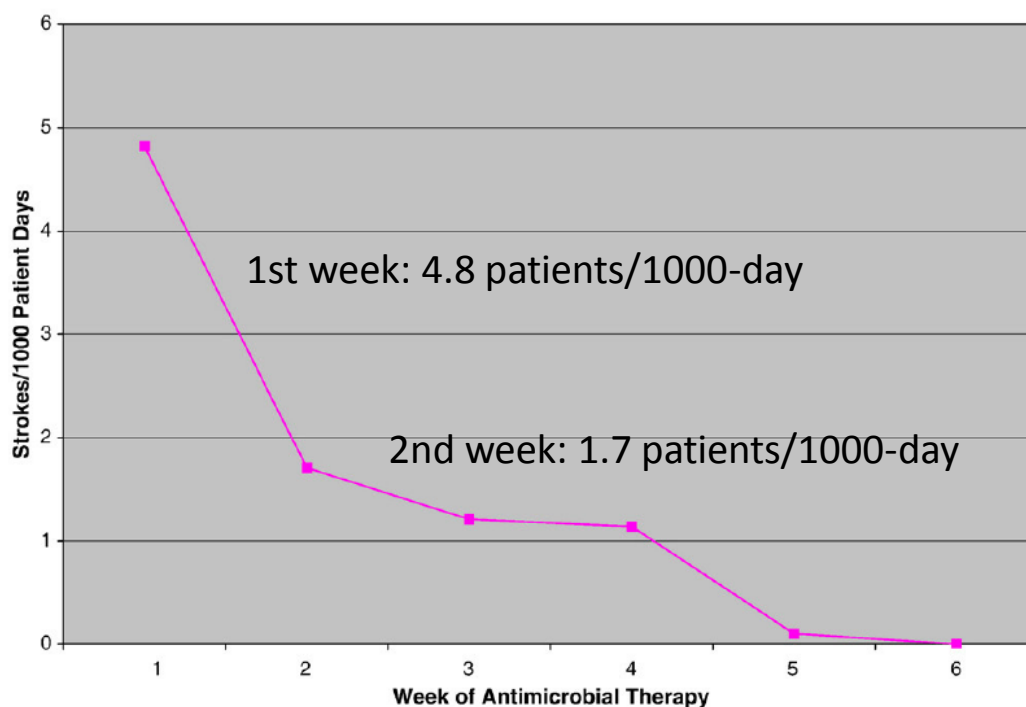


Daily incidence of stroke in ICE cohort.

Embolic events occur mainly during the 1st week



RELATION BETWEEN ATB TREATMENT AND THE INCIDENCE OF STROKE IN IE (ICE-PCS)



Stroke rate after initiation of antimicrobial therapy.

The risk of stroke in IE falls dramatically after the first week of effective antimicrobial therapy to only 3.1% (65% rate reduction in the 2nd week)



THE PATIENT WAS TRANSFERRED
TO A REFERENCE CENTER

EXPERT TEAM UNIT





ON ADMISSION TO THE REFERENCE CENTER

- No fever.
- BP 108/54 mmHg.
- Signs of mild heart failure (bibasal crackles)
- Mitral murmur 3/6
- No clear neurological deficits.

LAB: Hb 9.3 g/dl, Leucocytes 8410, Creatinine 0,84

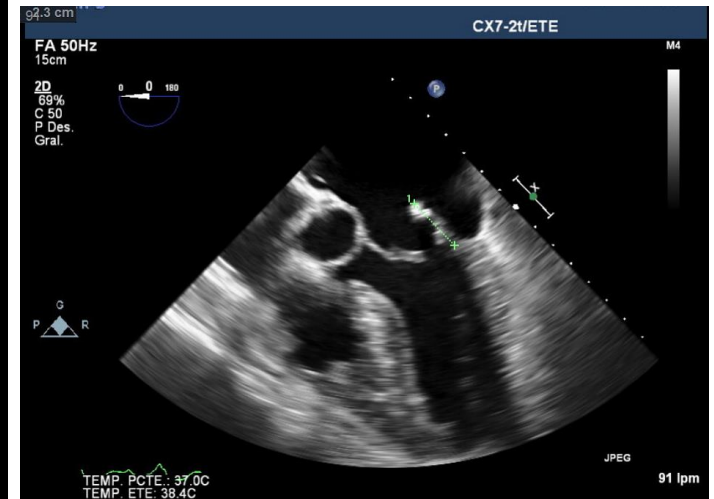
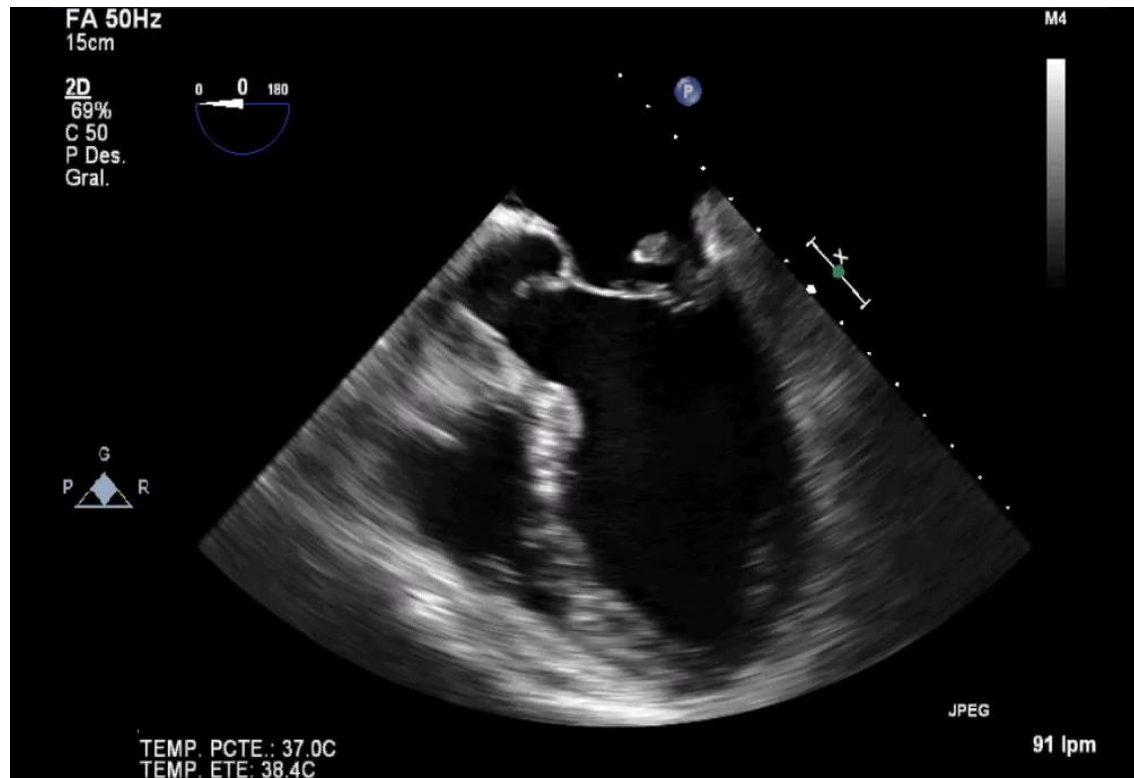
ECG: Sinus rhythm (82 bpm), 1st grade A-V Block (PR 230 msec).

BLOOD CULTURES: Negatives



ON ADMISSION TO THE REFERENCE CENTER

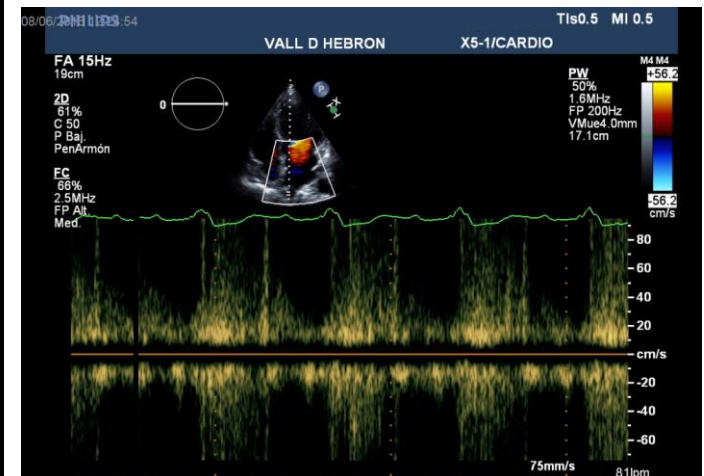
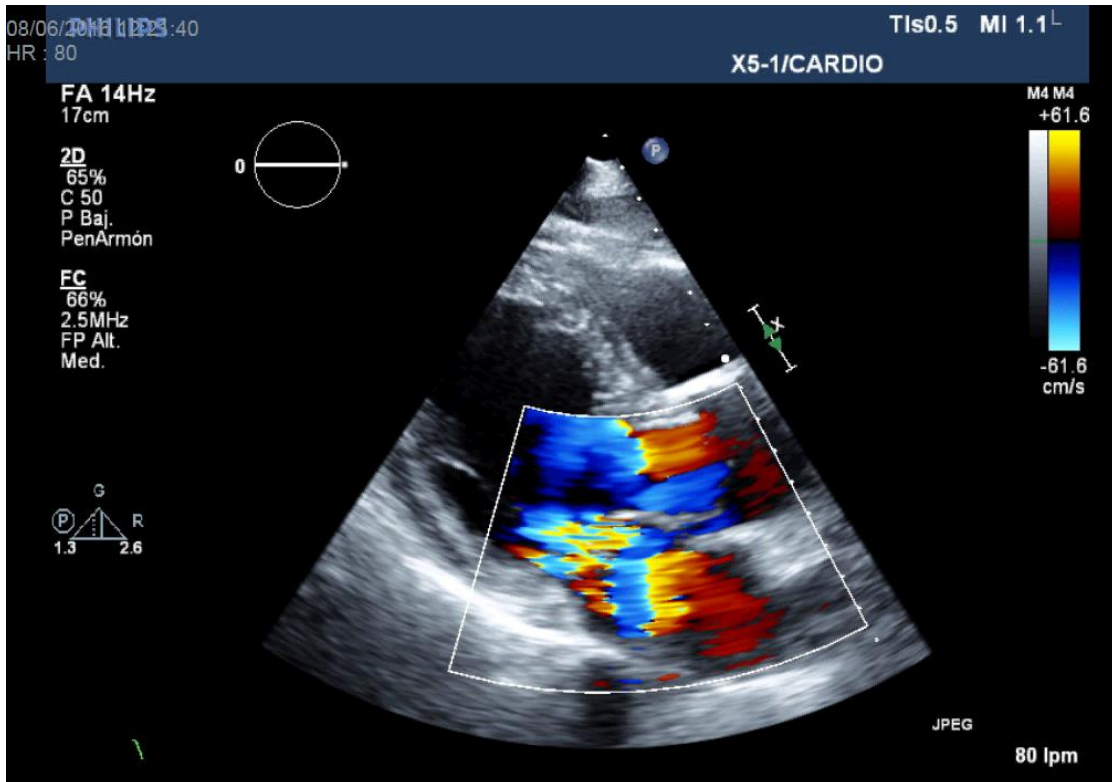
TOE



- Myxomatous mitral valve degeneration with P2 segment prolapse.
- **Large vegetation of 7 x 25 mm on the posterior leaflet.**

ON ADMISSION TO THE REFERENCE CENTER

TOE



- **Severe mitral regurgitation.**
- Mild dilatation of the LV with normal systolic function (EF 72%).
- Systolic PAP 39 mmHg.



EuroValve

January 26-27, 2017
Crowne Plaza Barcelona Fira Center, SPAIN

ON ADMISSION TO THE REFERENCE CENTER

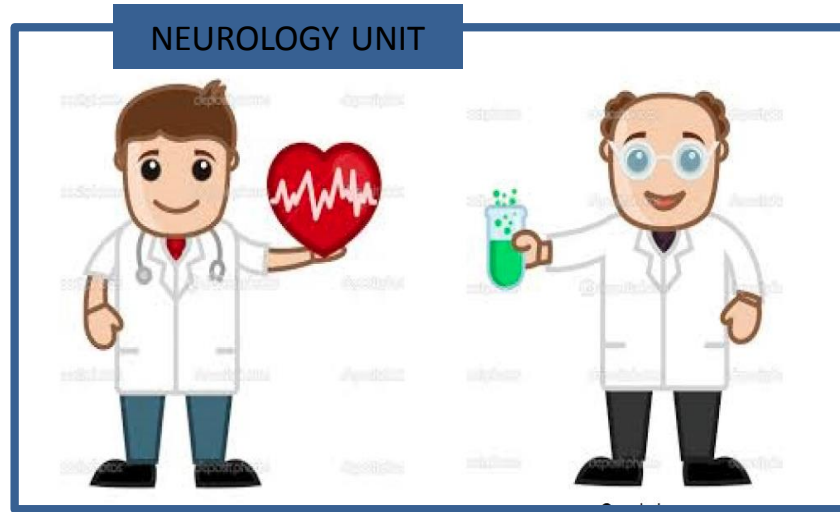


Indications and timing of surgery in left-sided valve infective endocarditis

3. Prevention of embolism			
Aortic or mitral NVE or PVE with persistent vegetations > 10 mm after one or more embolic episode despite appropriate antibiotic therapy	Urgent	I	B
Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk	Urgent	IIa	B
Aortic or mitral NVE or PVE with isolated very large vegetations (>30 mm)	Urgent	IIa	B
Aortic or mitral NVE or PVE with isolated large vegetations (> 15 mm) and no other indication for surgery ^e	Urgent	IIb	C

INDICATION OF SURGERY FOR EMBOLISM PREVENTION

ON ADMISSION TO THE REFERENCE CENTER



PREVIOUS CT: **Haemorrhagic lesions**

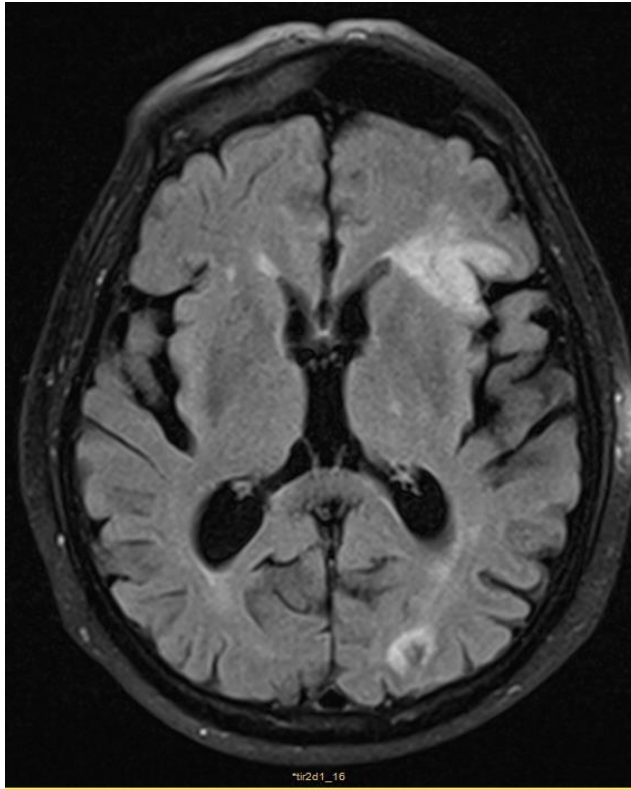
CEREBRAL MRI

- . Better characterization of brain lesions in infective endocarditis.
- . Recommended when surgery is considered after a Neurological complication

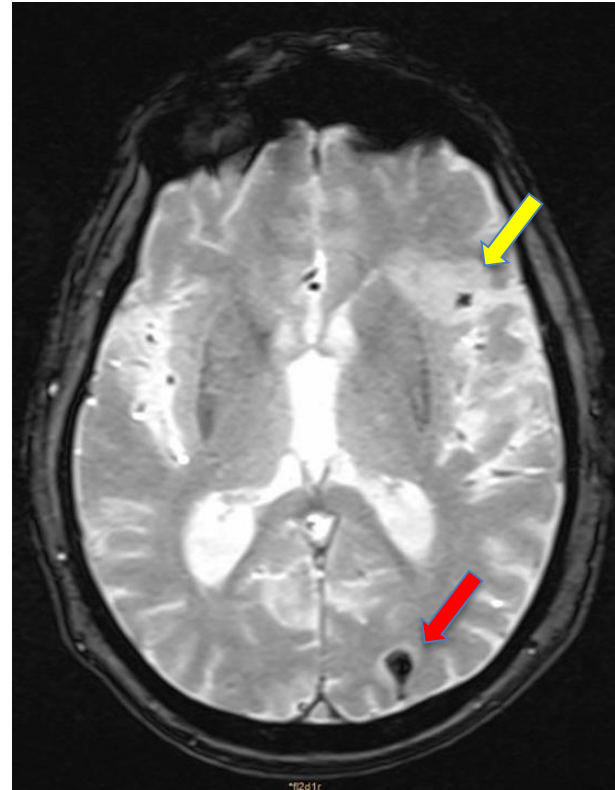
ON ADMISSION TO THE REFERENCE CENTER

CEREBRAL MRI

T2 FLAIR



T2*



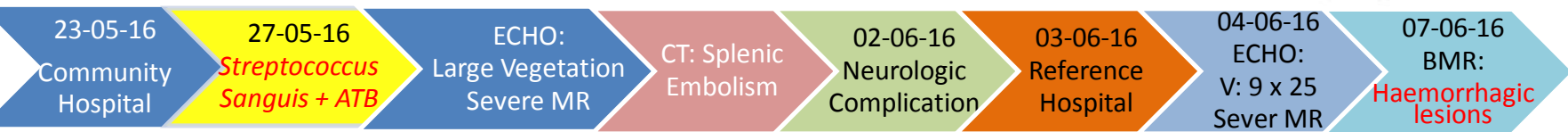
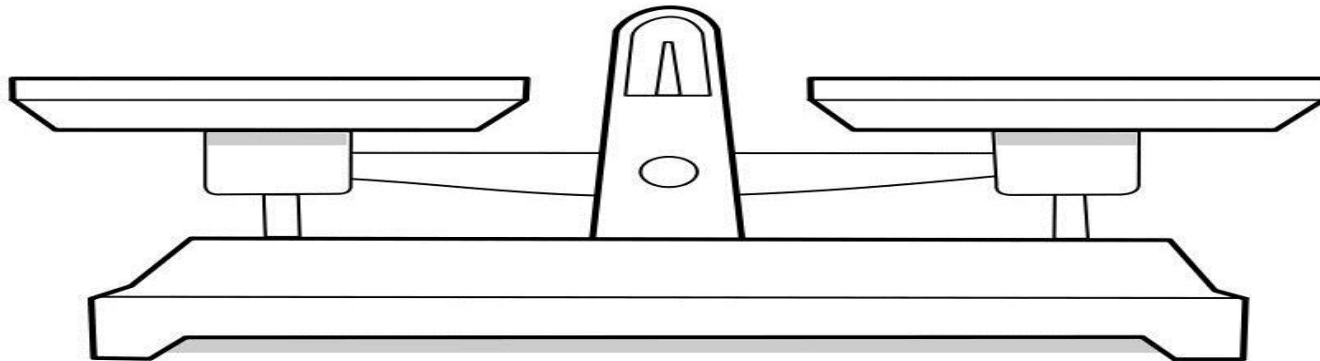
- Acute ischemic lesion in the superficial (cortico-subcortical) territory of the medial left cerebral artery associated with a **petechial bleeding foci**.
- **Haemorrhagic lesions** in the left occipital lobule suggestive of sub-acute septic embolisms.



THERAPEUTIC DESITION

- PERSISTENT LARGE AND MOBIL
SEPTIC VEGETATION (25 mm)
- CEREBRAL EMBOLIC EVENT
DURING ANTIBIOTIC TREATMENT
- SEVERE MITRAL REGURGITATION

**BRAIN
HAEMORRHAGE**

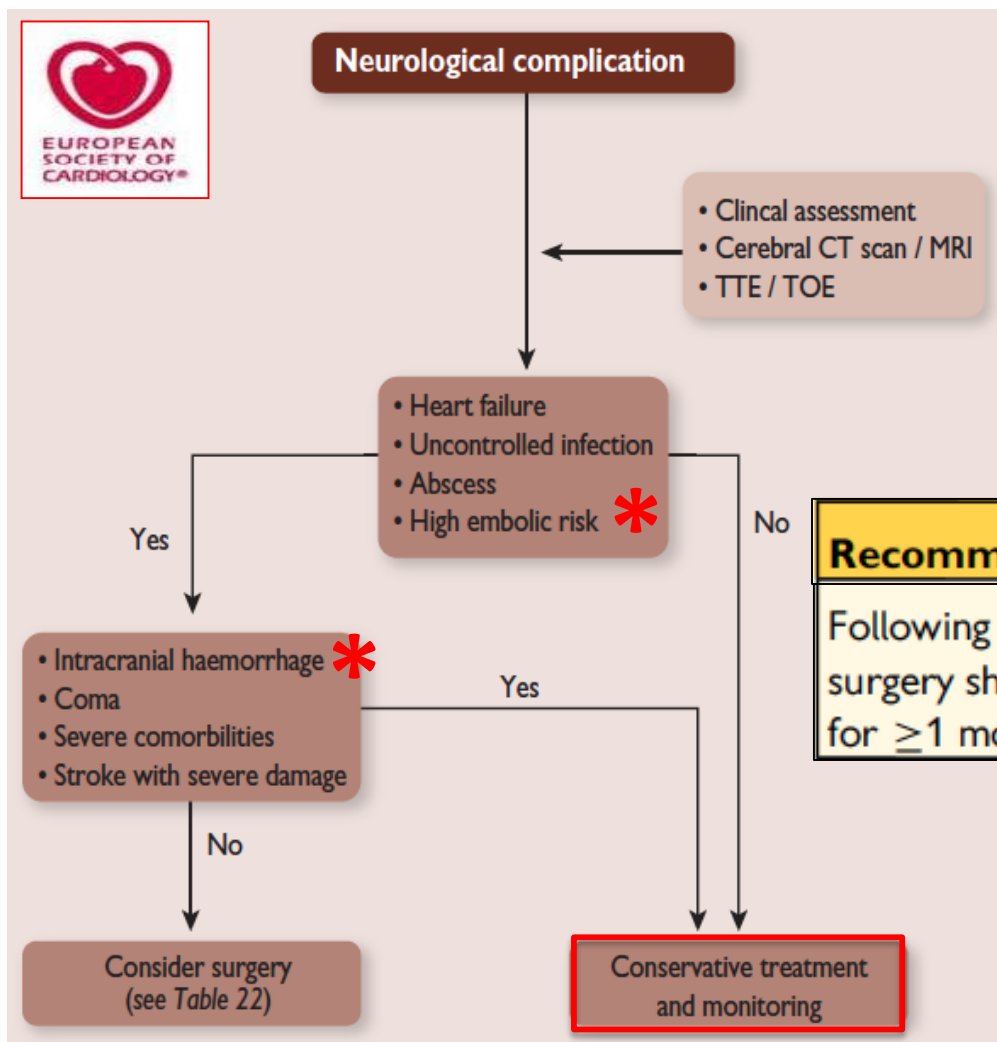




EuroValve

January 26-27, 2017

Crowne Plaza Barcelona Fira Center, SPAIN



Recommendations	Class ^a	Level ^b
Following intracranial haemorrhage, surgery should generally be postponed for ≥ 1 month	IIa	B



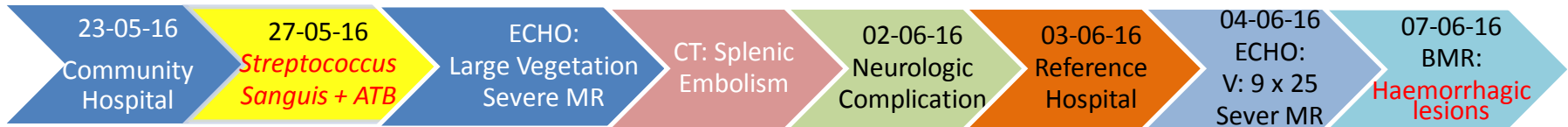
EuroValve

January 26-27, 2017
Crowne Plaza Barcelona Fira Center, SPAIN

CLINICAL COURSE

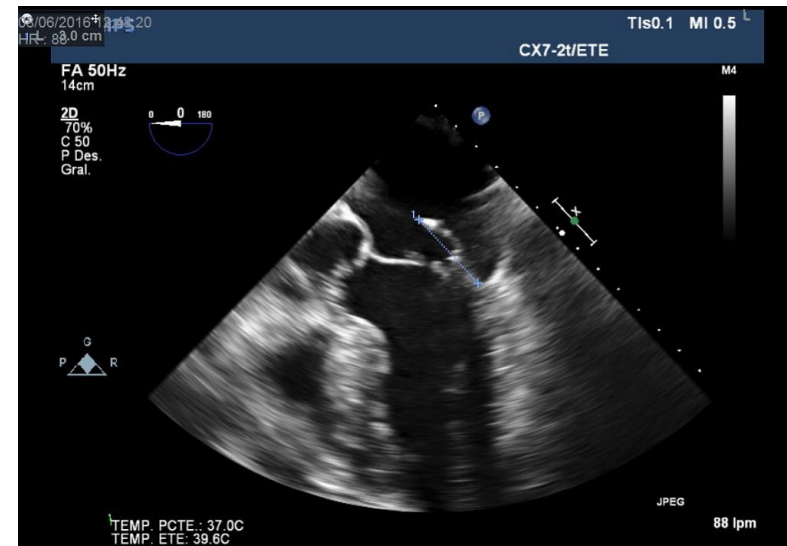
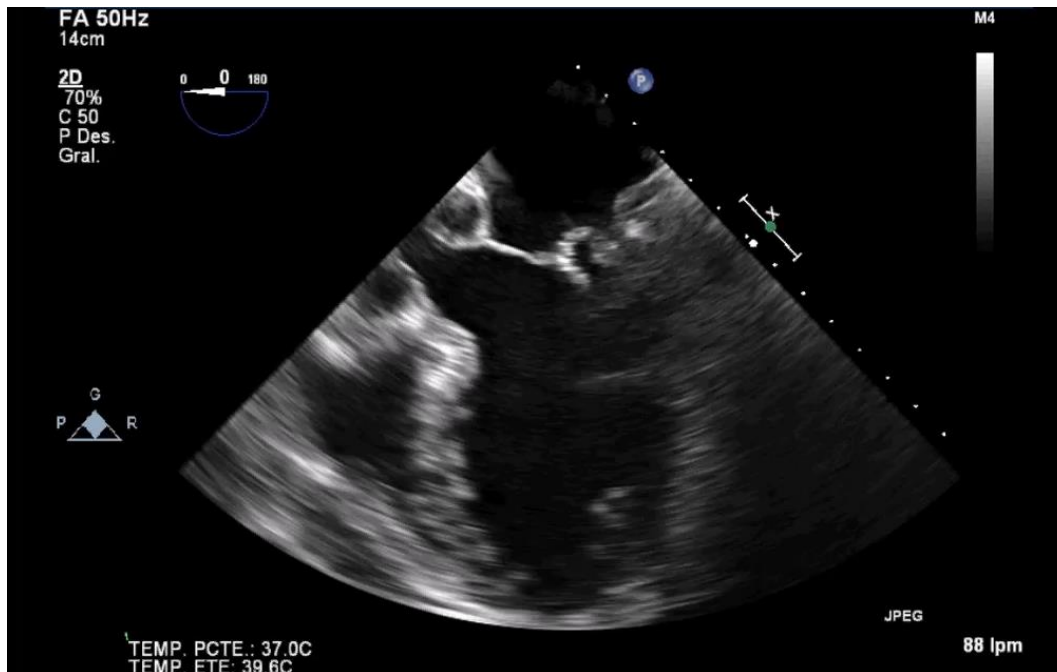
- No fever.
- No signs of heart failure
- No clear neurological deficits.

CONTROL BLOOD CULTURES : Negatives



CLINICAL COURSE

CONTROL TOE 1 WEEK LATER



- Persistent large vegetation of 6 x 32 mm on the posterior leaflet.
- Severe mitral regurgitation.
- Mild dilatation of the LV. EF 72%.
- Systolic PAP 39 mmHg.



RISK FACTORS OF EMBOLISM

Table 3. Unadjusted and Adjusted Multivariable Analysis of HR of Risk Factors Associated With Neurological Complications in Patients With Infective Endocarditis

Neurological Complications	Unadjusted HR (95% CI)	P Value	Adjusted HR (95% CI)	P Value
Global neurological complications				
Elderly (age ≥ 70 y)	0.87 (0.68–1.11)	0.22		
Aortic valve	1		1	
Mitral valve	1.16 (0.90–1.48)	0.25	1.29 (1.02–1.61)	0.03
Aortic and mitral valve	0.94 (0.61–1.42)	0.94	1.00 (0.70–1.44)	0.99
<i>Staphylococcus aureus</i>	2.43 (1.94–3.05)	<0.001	2.47 (1.94–3.15)	<0.001
Anticoagulant therapy	1.19 (0.92–1.54)	0.184	1.31 (1.00–1.72)	0.048
Vegetation ≥ 30 mm	2.29 (1.28–4.07)	0.005	1.91 (1.07–3.43)	0.029
Encephalopathy/meningitis				
<i>Staphylococcus aureus</i>	4.50 (2.94–6.88)	<0.001	4.34 (2.84–6.64)	<0.001

VEGETATION SIZE > 3 CM - VERY HIGH RISK



RISK FACTORS OF EMBOLISM

Table 2. Echocardiographic Data: Prognostic Factors of Embolism by Univariate Analysis

	Risk	RR (95% CI)	p Value
Perivalvular complications			0.84
Yes	13.4 (82)	1.06 (0.52–2.16)	
No	12.6 (135)	1	
Vegetation size at follow-up			0.02
Increase	26.7 (15)	2.64 (0.98–7.16)	
No change	10.1 (119)	1	
Decrease	22.6 (31)	2.24 (0.96–5.21)	
Vegetations by TTE			0.84
Yes	13.6 (118)	1.11 (0.56–2.25)	
No	12.1 (99)	1	
Vegetations by TEE			0.58
Yes	13.6 (184)	1.49 (0.48–4.67)	
No	9.1 (33)	1	
Echogenicity by TEE			0.56
Low	20.0 (35)	1	
Intermediate	14.0 (86)	0.70 (0.30–1.62)	
High	10.7 (28)	0.54 (0.15–1.88)	
Mobility by TEE			0.58
Grade I	7.1 (14)	1	
Grade II	12.8 (39)	1.79 (0.23–14.06)	
Grade III	16.3 (98)	2.29 (0.33–15.92)	

VEGETATION SIZE INCREMENT DURING ATB TREATMENT

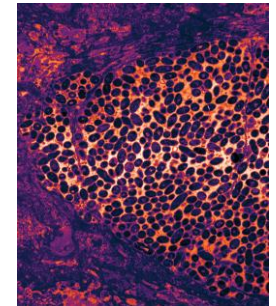
VERY HIGH RISK



EuroValve

January 26-27, 2017
Crowne Plaza Barcelona Fira Center, SPAIN

Cognasse et al. *BMC Immunology* 2014, **15**:15
<http://www.biomedcentral.com/1471-2172/15/15>



RESEARCH ARTICLE

Open Access

Streptococcus sanguinis-induced cytokine and matrix metalloproteinase-1 release from platelets

Fabrice Cognasse^{1,2*}, Hind Hamzeh-Cognasse^{2†}, Adrien Chabert², Elke Jackson^{3,4}, Charles-Antoine Arthaud¹, Olivier Garraud^{1,2} and Archie McNicol^{3,4}

Abstract

Background: *Streptococcus sanguinis* (*S.sanguinis*), a predominant bacterium in the human oral cavity, has been widely associated with the development of infective endocarditis. Platelets play both a haemostatic function and can influence both innate and adaptive immune responses. Previous studies have shown that *S.sanguinis* can interact with, and activate, platelets.

Results: The aim of this study was to determine whether *S.sanguinis* stimulates the release of matrix metalloproteinases (MMPs) 1, 2 and 9 and the pro-inflammatory mediators SDF-1, VEGF and sCD40L, from platelets and to subsequently pharmacologically address the release mechanism (s). *S.sanguinis* stimulated the release of MMP-1, SDF-1, VEGF and sCD40L from platelets and inhibitors of cyclooxygenase and phosphatidylinositol 3-kinase, and antagonists of the $\alpha\text{IIb}\beta\text{3}$ integrin and glycoprotein Ib, each inhibited the secretion of all factors.

Conclusions: Therefore the release of MMP-1, SDF-1, VEGF and sCD40L occurs late in the platelet response to *S.sanguinis* and highlights the complex intracellular signalling pathways stimulated in response to *S.sanguinis* which lead to haemostasis, MMP and pro-inflammatory mediator secretion.

Keywords: Platelets, Cytokines, Signalling, Oral cavity, Inflammation, *Streptococcus sanguinis*

***S. Sanguis* favoures large vegetations formation**



EuroValve

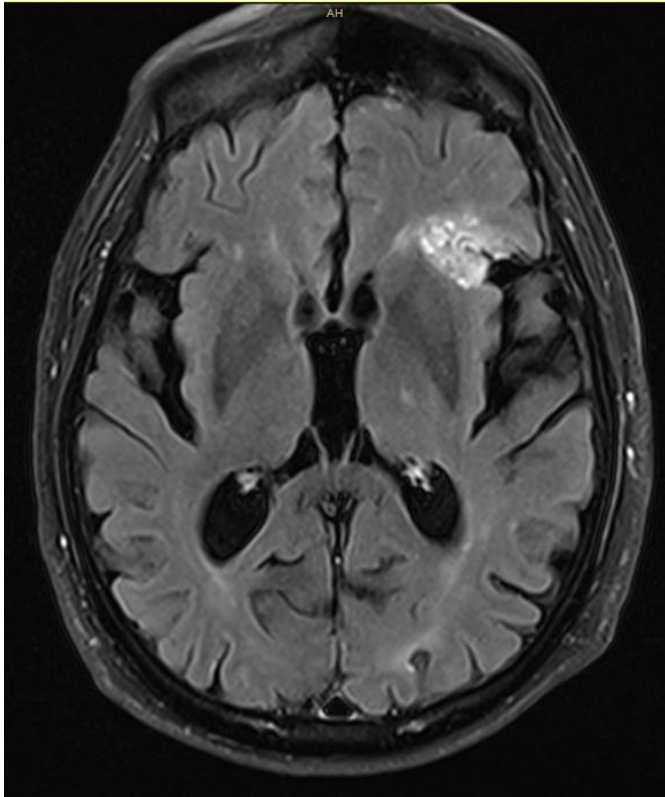
January 26-27, 2017
Crowne Plaza Barcelona Fira Center, SPAIN

PERSISTENT LARGE SEPTIC VEGETATION (> 3 CM)
+
SIZE INCREMENT ALTHOUGH ATB TREATMENT

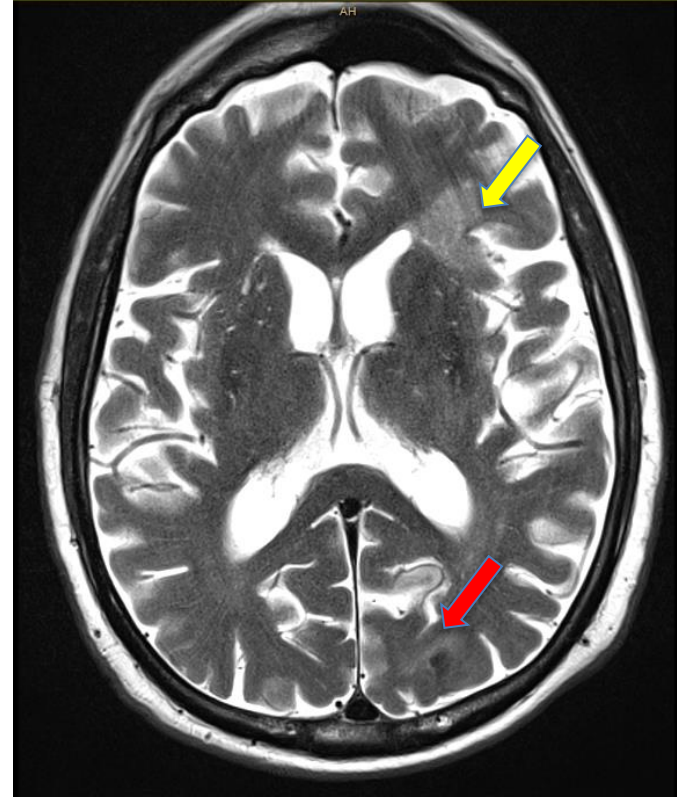
Would you consider surgery 2 weeks after a hemorrhagic neurological complication?



CONTROL CEREBRAL MRI 2 WEEKS AFTER THE NEUROLOGICAL COMPLICATION



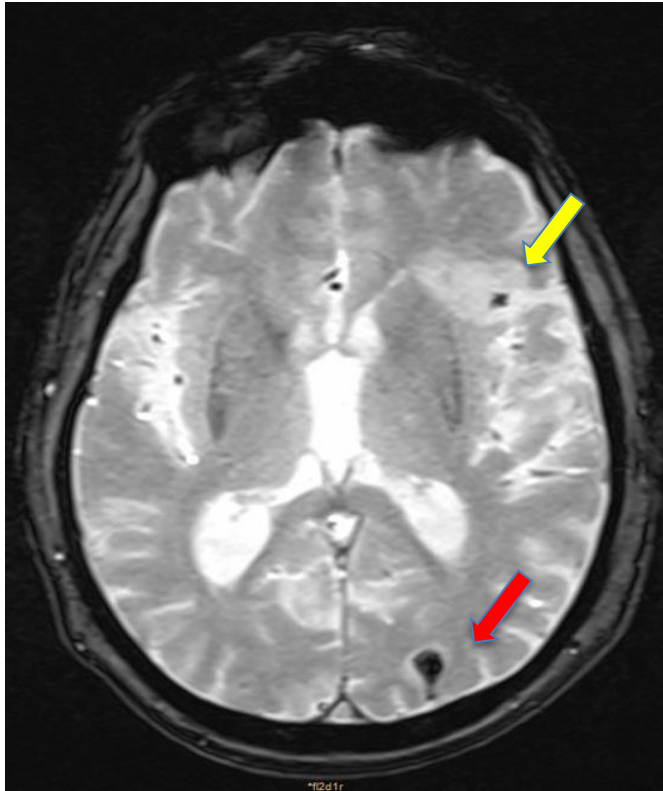
T2 FLAIR



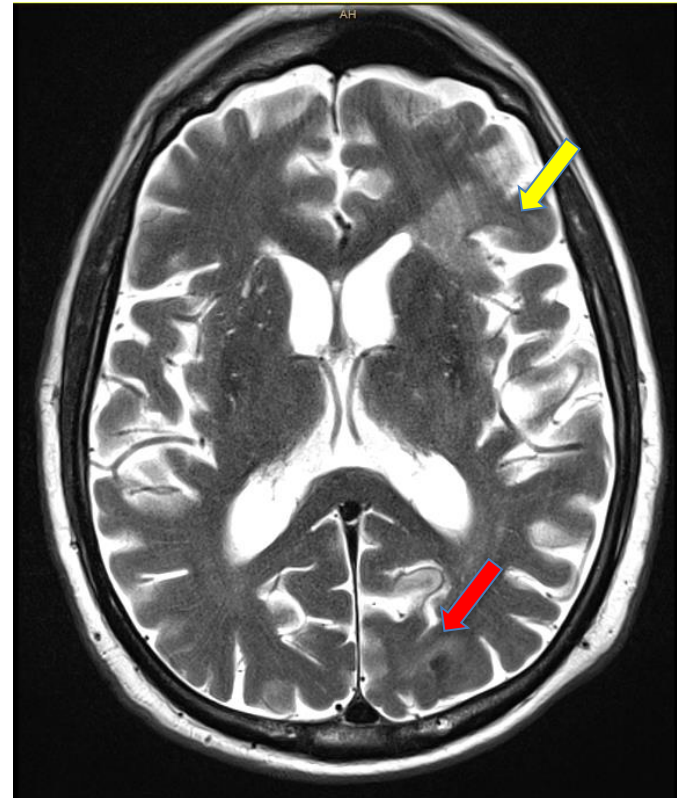
T2*

- Sub-acute ischemic lesion
- Very mild and residual haemorrhagic lesions

CONTROL CEREBRAL MRI 2 WEEKS AFTER THE NEUROLOGICAL COMPLICATION



1st - T2*



2nd T2*

Significant improvement of brain lesions



EuroValve

January 26-27, 2017
Crowne Plaza Barcelona Fira Center, SPAIN

Neurological Outcome of Septic Cardioembolic Stroke After Infective Endocarditis

Elfriede Ruttman, MD; Johann Willeit, MD; Hanno Ulmer, PhD; Orest Chevtchik, MD; Daniel Höfer, MD; Werner Poewe, MD; Günther Laufer, MD; Ludwig C. Müller, MD

Background and Purpose—The aim of this study was to evaluate mortality and neurological outcomes of cardioembolic cerebral stroke in infective endocarditis (IE) patients requiring cardiac surgery.

Methods—A consecutive series of 214 patients undergoing cardiac surgery for IE was followed up for 20 years. In 65 patients (mean age, 52 years), IE was complicated by computed tomography- or magnetic resonance imaging-verified stroke ($n=61$) or transient ischemic attack ($n=4$). Perioperative (30-day) and long-term mortality was assessed with regression models adjusting for age. Complete neurological recovery of IE survivors was defined by a modified Rankin score of ≤ 1 and a Barthel index of 20 points.

Results—Fifty of 61 stroke patients (81.9%) survived surgery. In comparison with nonstroke patients, the age-adjusted perioperative mortality risk was 1.70-fold (95% CI, 0.73 to 3.96, $P=0.22$) higher and long-term mortality risk was 1.23-fold (95% CI, 0.72 to 2.11, $P=0.45$) higher in stroke patients. Patients with complicated stroke (meningitis, hemorrhage, or brain abscess) showed a higher perioperative mortality rate (38.9% vs 8.5%, $P=0.007$) but no higher neurological complication rate than patients with uncomplicated ischemic stroke. Complete neurological recovery was achieved in 35 IE survivors (70%, 95% CI, 55% to 82%). However, in the case of middle cerebral artery stroke, recovery was only 50% and was significantly lower compared with non—middle cerebral artery stroke ($P=0.012$).

Conclusion—Uncomplicated IE-related stroke showed a favorable prognosis with regard to both long-term survival and neurological recovery. The formidable risk of secondary cerebral hemorrhage due to cardiac surgery seems to be much lower than previously thought. (*Stroke*. 2006;37:2094-2099.)



European Heart Journal (2011) 32, 2027–2033
doi:10.1093/eurheartj/ehp089

CLINICAL RESEARCH
Endocarditis

The timing of surgery influences mortality and morbidity in adults with severe complicated infective endocarditis: a propensity analysis

Franck Thuny¹, Sylvain Beurtheret², Julien Mancini³, Vlad Gariboldi², Jean-Paul Casalta⁴, Alberto Riberi², Roch Giorgi³, Frédérique Gouriet⁴, Laurence Tafanelli¹, Jean-François Avierinos¹, Sébastien Renard¹, Frédéric Collart², Didier Raoult⁴, and Gilbert Habib^{1*}

¹Department of Cardiology, La Timone Hospital, Boulevard Jean Moulin, 13005 Marseille, France; ²Department of Cardiothoracic Surgery, La Timone Hospital, Marseille, France; ³Department of Statistics, La Timone Hospital, Marseille, France; and ⁴Department of Microbiology, La Timone Hospital, Marseille, France

PERSISTENT EMBOLIC RISK

NO brain hemorrhage + NO severe neurological damage
Surgery has a low neurological risk of 3-6%

Ruttman E. et al. *Stroke* 2006;37:2094-99

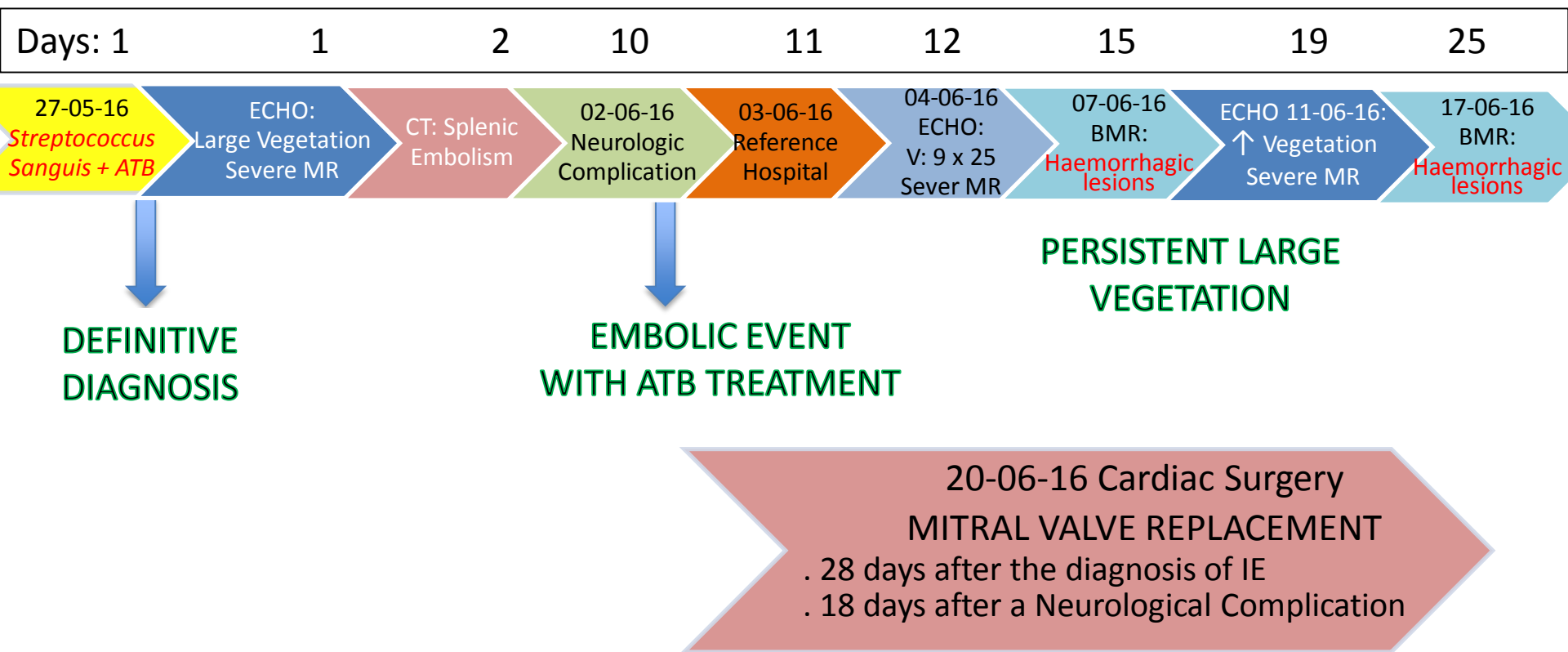
Thuny F. Et al. *European Heart Journal* 2011;32:2027-33

Habib G, et al. *Eur Heart J* 2015;36(44):3075-3128.



EuroValve

January 26-27, 2017
Crowne Plaza Barcelona Fira Center, SPAIN



Bad evolution: tamponade > shock and multiorgan failure



EuroValve

January 26-27, 2017
Crowne Plaza Barcelona Fira Center, SPAIN

HOME MESSAGES

- ***Risk of Embolism*** must always be calculated in patients with large vegetations and ***Early surgery*** for embolism prevention should be considered.
- Patients with high risk of embolism should be evaluated in a Reference Centre with an **IE Heart Team**.
- Once a neurological complication occurs, the extent of the ischemic lesion and the presence of haemorrhage must be assessed using MRI, when available. Haemorrhagic lesions may be a surgical contraindication.
- Patients with uncomplicated stroke and a persistent high risk of embolism can undergo surgery with a relatively low neurological risk.