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I have no financial relationships to disclose.
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*)
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.
ON ADMISSION

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

Major criteria
1. Blood cultures positive for IE
   a. 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
   b. 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
   c. Single positive blood culture for Coxiella burnetii or phase I IgG antibody titre >1:800

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

Minor criteria
1. Predisposition such as predisposing heart condition, or injection drug use.
2. Fever defined as temperature >38°C.
3. 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.
4. Immunological phenomena: glomerulonephritis, Osler’s nodes, Roth’s spots, and rheumatoid factor.
5. 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

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.

Vilacosta I, et al. JACC 2002;39:1489-95
### ON ADMISSION

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

<table>
<thead>
<tr>
<th>3. Prevention of embolism</th>
<th>Urgent</th>
<th>I</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic or mitral NVE or PVE with persistent vegetations &gt; 10 mm after one or more embolic episode despite appropriate antibiotic therapy</td>
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<td>I</td>
<td>B</td>
</tr>
<tr>
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<td>Ila</td>
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<td>Ila</td>
<td>B</td>
</tr>
<tr>
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<td></td>
<td>IIb</td>
<td>C</td>
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</table>

**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

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**
  - Perianular complications
  - Severe left-sided valve regurgitation
  - Low left ventricular ejection fraction
  - Pulmonary hypertension
  - Large vegetations
  - Premature mitral valve closure and other signs of elevated diastolic pressures

INDICATIONS FOR **HEART TEAM EVALUATION**

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.
Embolic events occur mainly during the 1st week

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 mseg).

BLOOD CULTURES: Negatives
ON ADMISSION TO THE REFERENCE CENTER

- 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.
ON ADMISSION TO THE REFERENCE CENTER

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

3. Prevention of embolism

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</tr>
</tbody>
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INDICATION OF SURGERY FOR EMBOLISM PREVENTION

ON ADMISSION TO THE REFERENCE CENTER

NEUROLOGY UNIT

PREVIOUS CT: Haemorrhagic lesions

CEREBRAL MRI

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

• 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
Neurological complication

- Clinical assessment
- Cerebral CT scan / MRI
- TTE / TOE

Heart failure
- Uncontrolled infection
- Abscess
- High embolic risk

- Intracranial haemorrhage
- Coma
- Severe comorbidities
- Stroke with severe damage

Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Following intracranial haemorrhage, surgery should generally be postponed for ≥1 month</td>
<td>IIA</td>
<td>B</td>
</tr>
</tbody>
</table>

Consider surgery (see Table 22)

Conservative treatment and monitoring

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**

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

**VEGETATION SIZE > 3 CM - VERY HIGH RISK**

## RISK FACTORS OF EMBOLISM

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

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

**VEGETATION SIZE INCREMENT DURING ATB TREATMENT**

**VERY HIGH RISK**

Vilacosta I, et al. JACC 2002;39:1489-95
Streptococcus sanguinis-induced cytokine and matrix metalloproteinase-1 release from platelets

Fabrice Cognasse\textsuperscript{1,2*}, Hind Hamzeh-Cognasse\textsuperscript{2*}, Adrien Chabert\textsuperscript{2}, Elke Jackson\textsuperscript{3,4}, Charles-Antoine Arthaud\textsuperscript{1}, Olivier Garraud\textsuperscript{1,2} and Archie McNicol\textsuperscript{3,4}

Abstract

\textbf{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.

\textbf{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 αββ3 integrin and glycoprotein Ib, each inhibited the secretion of all factors.

\textbf{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.

\textbf{Keywords:} Platelets, Cytokines, Signalling, Oral cavity, Inflammation, Streptococcus sanguinis

\textit{S. Sanguis} favours large vegetations formation
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

- 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
Neurological Outcome of Septic Cardioembolic Stroke After Infective Endocarditis

Elfriede Ruttmann, MD; Johann Willeit, MD; Hanno Ullmer, PhD; Orest Chevtchik, MD; Daniel Höfer, MD; Werner Pocew, MD; Günther Laufner, 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.]

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 Gariboldi3, Jean-Paul Casalta4, Alberto Riberi2, Roch Giorgi3, Frédérique Gouriet4, Laurence Tafanelli1, Jean-François Avierinos1, Sébastien Renard1, Frédéric Collart2, Didier Raoult4, and Gilbert Habib5*

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%

Thuny F. Et al. Europeann Heart Journal 2011;32:2027-33
Days: 1

27-05-16
Streptococcus Sanguis + ATB
DEFINITIVE DIAGNOSIS

1
ECHO: Large Vegetation Severe MR

2
CT: Splenic Embolism

10
02-06-16
Neurologic Complication

11
03-06-16
Reference Hospital

12
04-06-16
ECHO: V: 9 x 25 Sever MR

15
07-06-16
BMR: Haemorrhagic lesions

19
ECHO 11-06-16: ↑ Vegetation Severe MR

25
17-06-16
BMR: Haemorrhagic lesions

19

EMBOLIC EVENT WITH ATB TREATMENT

20-06-16 Cardiac Surgery
MITRAL VALVE REPLACEMENT
. 28 days after the diagnosis of IE
. 18 days after a Neurological Complication

Bad evolution: tamponade > shock and multiorganic failure
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.