Transparency Declaration

Dr. José M Miró has received honoraria for speaking or participating in Advisory Boards and/or research grants from the following Pharmaceutical Companies:

- Abbvie
- Angelini-Allergan
- Bristol-Myers Squibb
- Contrafect
- Genentech
- Gilead Sciences
- Jansen
- Merck
- Medtronic
- Novartis
- Pfizer
- Roche
- Theravance
- ViiV Healthcare
Infective Endocarditis: Brief Overview of Recent Progresses and Challenges

• Introduction
• Prevention
• Pathogenesis
• Diagnosis & Management
• Antimicrobial therapy
• Surgery
Epidemiological Changes at Hospital Clinic of Barcelona, Spain

1.605 (1979-2018)

Endocarditis Team in 1986

Experimental Endocarditis Model in 1994

IVDA IE NV IE / PVE CIED IE HCA IE TAVI IE

A. Moreno

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The complexity of IE justifies the use of tertiary care. Tertiary hospitals have the following services available: anesthesiology and resuscitation, diagnostic imaging, nuclear medicine (2014), nephrology, neurology (2014), neurosurgery, orthopedics & traumatology, and hemotherapy and blood management.

Mestres, Pare, Miro. REC. 2015; 68:363-8.
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)

3.5.5 Cardiac or vascular interventions ........................................ 3082
3.5.6 Healthcare-associated infective endocarditis ....................... 3082

4. The ‘Endocarditis Team’ ............................................................... 3083
5. Diagnosis ...................................................................................... 3084

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2019 Members of the Hosp. Clinic Cardiovascular Infections & Experimental Endocarditis Working Group

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P. Castro

Anaesthesiology
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I. Rovira

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HCB “IE Team” Improved 1-year Survival

Kaplan-Meier survival estimates (log-rank test p<0.001)

<table>
<thead>
<tr>
<th>Year</th>
<th>1979-1999</th>
<th>2000-2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk</td>
<td>606</td>
<td>960</td>
</tr>
<tr>
<td>Analysis time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>288</td>
<td>613</td>
</tr>
<tr>
<td>3</td>
<td>264</td>
<td>524</td>
</tr>
<tr>
<td>6</td>
<td>246</td>
<td>462</td>
</tr>
<tr>
<td>9</td>
<td>238</td>
<td>410</td>
</tr>
</tbody>
</table>

75.7% (95%CI 74%;77%) 70.2% (95%CI 69%;72%)
74.7% (95%CI 74%;76%) 65.2% (95%CI 63%;67%)
Infective endocarditis incidence*: 3.4 episodes/100,000 habitants/year

- Catalonia: 250 cases/yr.
- Spain: 1,564 cases/yr.
- Europe: 25,260 cases/yr.
- World: 253,296 cases/yr.

### Surgery and Mortality Rates of Infective Endocarditis in the 21st Century

<table>
<thead>
<tr>
<th>Category</th>
<th>Surgery Rate</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IE in i.v. drug users</td>
<td>38%</td>
<td>10%</td>
</tr>
<tr>
<td>IE in general population</td>
<td>48%</td>
<td>17%</td>
</tr>
<tr>
<td>PV IE</td>
<td>49%</td>
<td>23%</td>
</tr>
<tr>
<td>Pacemaker/ICD IE</td>
<td>61%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>≈50%</strong></td>
<td><strong>≈20%</strong></td>
</tr>
</tbody>
</table>

Research in Endocarditis in 2019

88 studies of endocarditis
38 (43%) active studies
- Antimicrobial therapy
- Cardiac surgery
- Diagnosis (Cardiac PET/CT)

Research in Endocarditis in 2019


49 (56%) in Europe
Infective Endocarditis: Brief Overview of Recent Progresses and Challenges

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Research in Prevention

• Oral antimicrobial prophylaxis in invasive procedures: yes or no, that’s the question!
• Prevention of Nosocomial and Non-Nosocomial HCA IE = Zero Bacteremia Protocols!
• Antibiotic prophylaxis in cardiac surgery and intracardiac devices (pacemaker and defibrillator)
• New devices with antibacterial properties
• Immunotherapy & Vaccines (S. aureus)
THE TYRX™ ABSORBABLE ANTIBACTERIAL ENVELOPE
TIME SEQUENCE SIMULATION OF ELUTION & ABSORPTION

- Absorbable Envelope is eluting Minocycline & Rifampin
- Absorbable Envelope is dissolving into fragments
- Mesh has no physical presence and is fully absorbed

Antibacterial Envelope to Prevent Cardiac Implantable Device Infection

Khaldoun G. Tarakji, M.D., M.P.H., Suneet Mittal, M.D.,
Charles Kennergren, M.D., Ph.D., Ralph Corey, M.D., Jeanne E. Poole, M.D.,
Edward Schloss, M.D., Jose Gallastegui, M.D., Robert A. Pickett, M.D.,
Rudolph Evonich, M.D., François Philippon, M.D., Janet M. McComb, M.D.,
Steven F. Roark, M.D., Denise Sorrentino, M.D., Darius Sholevar, M.D.,
Edmond Cronin, M.B., B.Ch., B.A.O., Brett Berman, M.D., David Riggio, M.D.,
Mauro Biffl, M.D., Hafiza Khan, M.D., Marc T. Silver, M.D., Jack Collier, M.D.,
Zayd Eldadah, M.D., Ph.D., David J. Wright, M.D., Jeff D. Lande, Ph.D.,
Daniel R. Lexcen, Ph.D., Alan Cheng, M.D., and Bruce L. Wilkoff, M.D.,
for the WRAP-IT Investigators*
Adjunctive use of an antibacterial envelope resulted in a 40% reduction of major CIED infections (pocket)

Hazard ratio through 12 mo, 0.60 (95% CI, 0.36–0.98)
P = 0.04

<table>
<thead>
<tr>
<th>End Point</th>
<th>Envelope (N=3495)</th>
<th>Control (N=3488)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point: major CIED infection</td>
<td>25 (0.7)</td>
<td>42 (1.2)</td>
</tr>
<tr>
<td>within 12 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of major CIED infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pocket infection</td>
<td>14 (0.4)</td>
<td>36 (1.0)</td>
</tr>
<tr>
<td>Bacteremia or endocarditis</td>
<td>11 (0.3)</td>
<td>6 (0.2)</td>
</tr>
</tbody>
</table>

No. at Risk
Control 3488 3360 3277 3179 3053
Envelope 3495 3351 3281 3188 3091
Subcutaneous Defibrillators & Micra Pacemakers can be used in patients with previous CEID infections.

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Research in Pathogenesis

- Human genome markers for IE susceptibility
- Microbial markers for persistent bacteremia
- Microbial factors that foster resistance to host defenses and innate immunity
- Molecular basis of initial adhesion of bacteria to intracardiac devices
- Anti-biofilms agents
- Antimicrobial resistance mechanisms (e.g. Dapto-R)
- Impact of virulence genes (e.g. agr) and *S. aureus* antimicrobial resistance on outcome (e.g. Vancomycin MIC)
Mechanism of Action (MoA) of Daptomycin

- **Ca**²⁺ dependent insertion of lipid tail
- Rapid membrane depolarization
- Bactericidal – [DAP] dependent

Distribution of charge on the surface of the structure of daptomycin. **Red region** denotes negative charge, **blue region** as positive and white region as neutral.
Daptomycin Susceptibility in Gram + Bacteria
EUCAST 2018 (mcg/mL)

- *Staphylococcus aureus* ≤ 1 2-4
- *Enterococcus faecalis* ≤ 2 4-16
- *Enterococcus faecium* ≤ 4 8-32
- *Viridans streptococci* ≤ 1 2 - ≥256
Daptomycin-Resistance and Cell Surface Electrostatic Repulsion in *S. aureus*

CAMPs = Cationic antimicrobial peptides

Increased positive surface charge → DAP and CAMPs Repulsion

Genes associated with daptomycin-resistance in *S. aureus*: *MprF, dltABCD, yycFG, cls, pgsA*

Ernst et al., PLoS Pathog 2009; 5:e1000660
Proposed mechanisms of DAP-R in Enterococci

**E. faecium** = Repulsion

**E. faecalis** = Diversion

High-Level Daptomycin Resistance (HLDR) in VGS (S. oralis) Developed upon \textit{In Vitro} Exposure to Daptomycin

S. oralis

Dapto MIC >256 mg/L

HLDR S. *mitis* Investigators Team
CdsA and PgsA Mutations Mediate Antibiotic Resistance in *Streptococcus mitis* through cardiolipin biosynthesis pathway

Phosphatidylycerol (PG), cardiolipin (CL), phosphatidylserine (PS) and phosphatidylethanolamine (PE).

CdsA = Phosphatidate Cytidylyltransferase; PgsA = CDP-diacylglycerol-glycerol-3-phosphate-3-phosphatidytransferase.
Impact of Vancomycin MIC on Outcomes of MSSA Infective Endocarditis

- Cervera C (2014). Van MIC ≥1.5 mcg/mL increased mortality
- Pericas JM (2017). Van MIC ≥1.5 mcg/mL did not increase mortality
- Fernandez-Hidalgo N (2018). Van MIC ≥1.5 mcg/mL did not increase mortality
No Association with Van MIC Phenotype of any Genotypic Characteristics or Clonal Complexes of the 62 MSSA Isolates


- Adhesins
- Toxins
- Virulence genes
- Agr subtypes
- Clonal Complexes (CC5, CC30, CC45)
No Changes in Natural History of MSSA Experimental IE According to the Vancomycin MIC Phenotype

- High Van MIC $\geq 1.5$ mg/L strain
- Low Van MIC $\leq 1.0$ mg/L strain

Day

0

1

2

4

iv MSSA challenge

Micro PET/TC

Animal sacrifice. No differences in qualitative and quantitative cultures of aortic valve vegetations, brain, spleen and kidneys tissues.

Garcia de la Maria C et al. SEIMC. 2018; Manuscript in preparation.
Infective Endocarditis: Brief Overview of Recent Progresses and Challenges

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Research in Diagnosis & Management

• To know the source of the infection (EFIE & Cancer)

• Identify biomarkers: 1) Differentiating bacteremia from IE; 2) Response to therapy; and 3) Inoculum & prognosis

• Very early diagnosis of IE

• Improving microbiological diagnosis of culture-negative IE: Molecular biology

• Role of FDG PET/CT for diagnosis of early PVE (<2 mo.), TAVI-IE, ICED infections and extra-cardiac septic foci

• Role of FDG PET/CT for PVE/ICED management

• Management of embolic strokes (thrombectomy)
Relationship between *Enterococcus faecalis* IE of unclear focus and Colorectal Neoplasms

Pericas JM et al. NEJM; 2016; 375:387-8; Pericas JM et al. Rev Esp Cardiol. 2017;70,451–8
Colonic Lesions in Patients with Enterococcal Endocarditis in the Cleveland Clinic, USA

70% of patients with enterococcal IE who had colonoscopy within a year of admission for IE had at least one significant colonoscopy finding.

5%
EnteroColonus GAMES Project (2020-22)

Multicenter, prospective, matched, interventional cohort

Length of inclusion period: 18 months
Lenght of follow-up: 1 year

Group 1: *E. faecalis* bacteremia/IE with a suspected focus (N≈124)
Group 2: *E. faecalis* bacteremia/IE of unknown origin (N≈124)
Group 3: Healthy subjects undergoing a CRC screening colonoscopy (N≈124)

Note: all subjects should be aged ≥ 50 years.

Tests performed:
Group 1: Same as group 2.
Group 2: Colonoscopy, feces sample for microbiome studies, whole genome analysis & resistance profile studies on *E. faecalis* strains.
Group 3: Colonoscopy and feces sample for microbiome studies.
IV Thrombolysis is not useful in IE

It was not an original exclusion criteria in IE

Intracranial haemorrhage (ICH) in 7/8 cases of i.v. thrombolysis

<table>
<thead>
<tr>
<th></th>
<th>Patients With IE</th>
<th>Patients Without IE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>222</td>
<td>134,048</td>
<td></td>
</tr>
<tr>
<td>Favorable outcome</td>
<td>23 (10)</td>
<td>49,572 (37)</td>
<td>0.01</td>
</tr>
<tr>
<td>Post-thrombolytic ICH</td>
<td>44 (20)</td>
<td>8,730 (6.5)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Asaithambi et al. Stroke. 2013

2016 AHA / ASA Guidelines: NOT Recommended in IE
Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke

Role in IE CNS emboli?

- **Thrombectomy (N=103)**
  - Score on Modified Rankin Scale:
    - 0: 6.8%
    - 1: 17.5%
    - 2: 18.4%
    - 3: 7.8%
    - 4: 11.7%
    - 5: 18.4%
    - 6: 18.4%
  - Total: **62.1%**

- **Control (N=103)**
  - Score on Modified Rankin Scale:
    - 0: 5.8%
    - 1: 6.8%
    - 2: 1.9%
    - 3: 16.5%
    - 4: 20.4%
    - 5: 15.5%
    - 6: 15.5%
  - Total: **47.5%**

Jovin TG et al. NEJM. 2015.
Experience at the H. Clinic of Barcelona

Patients with ischemic stroke evaluated for acute revascularization
(January 2011– June 2017)

\[ n = 1966 \]

**Treatment modality**

- IV thrombolysis only
  \[ n = 637 \]
- Mechanical Thrombectomy
  \[ n = 494 \]
- None
  \[ n = 835 \]

Infective Endocarditis
\[ n = 6 \ (1.2\%) \]
Male 72 yr, late PVE caused by *Streptococcus dysgalactiae*

**Stroke Code**: aphasia, hemianopsia and right hemiplegia of 4 h.

NIHSS 24

Mechanical Trombectomy at 4 h.
Experience with MT in IE at the H. Clinic of Barcelona

<table>
<thead>
<tr>
<th>Case</th>
<th>Year</th>
<th>Sex</th>
<th>Age</th>
<th>IE</th>
<th>IE Type</th>
<th>Microbiol.</th>
<th>Stroke</th>
<th>Baseline NIHSS</th>
<th>Occlusion site</th>
<th>Time to groin injection</th>
<th>Device</th>
<th>TICI</th>
<th>24 h NIHSS</th>
<th>Intracranial hemorrhage</th>
<th>mRS at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0*</td>
</tr>
<tr>
<td>2</td>
<td>2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2012</td>
<td>F</td>
<td>66</td>
<td>Possible</td>
<td>Native</td>
<td>Negative culture</td>
<td></td>
<td>19</td>
<td>M1</td>
<td>140</td>
<td>retriever (Trevo)</td>
<td>3</td>
<td>2</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0**</td>
</tr>
<tr>
<td>5</td>
<td>2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>2017</td>
<td>M</td>
<td>85</td>
<td>Definite</td>
<td>Prosthetic</td>
<td>epidermidis</td>
<td></td>
<td>8</td>
<td>M1</td>
<td>158</td>
<td>retriever (Trevo)</td>
<td>3</td>
<td>0</td>
<td>No</td>
<td>NA</td>
</tr>
</tbody>
</table>

NIHSS: National Institutes of Health stroke scale
mRS: modified Rankin scale
TICI: thrombolysis in cerebral infarction scale
* Cardiorespiratory arrest during MT and death 2 days after the stroke
** Palliative care only and death 3 days after the stroke
& Also positive molecular biology from the thrombus
NA: not available yet

Intracranial hemorrhage = 0%
Full resolution stroke = 66%
A multicenter study to confirm these results

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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. Badger, MD, FAHA, Chair; Walter R. Wilson, MD; Arnold S. Bauer, 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 E. 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

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)

Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM)
International experts in the antibiotic therapy of IE are not following the Guidelines for SA/CNS IE.
Experimental Endocarditis Model

Day

0
  - Aortic valve lesion - catheter
    (carotid artery)

1
  - I.V. microorganism challenge

2
  - Animal sacrifice. Qualitative & quantitative culture
    of aortic valve vegetations

5
  - Animal sacrifice. Qualitative & quantitative culture
    of aortic valve vegetations

ANTIBIOTIC PROPHYLAXIS

PATHOGENESIS

ANTIBIOTIC TREATMENT

ANTIBIOTIC DIFFUSSION INTO VEGETATIONS

Research in Antimicrobial Therapy

• No gentamicin for MSSA NA IE … but daptomycin?
• Role of rifampin – The ARREST Trial = No role!
• Better therapies for susceptible GP cocci
• Better therapies for MDR GP cocci
• New strategies: IV – Oral De-escalation (several RCT)
• Role of new antibiotics: Dalbavancin for OPAT, Tedizolid for sequential oral therapy.
• Optimal treatment for HACEK, ABI/GRA, Fungal, Whipple, Q fever and Bartonella IE
How to improve the activity of daptomycin in MSSA infective endocarditis

- Daptomycin must be given at high doses (10 mg/kg) and always combined with beta-lactams (cloxacillin, ceftaroline) or fosfomycin.

- In monotherapy there is a high risk of development of daptomycin resistance (DNS) and the activity in extracardiac metastasis (spleen, kidney) is lower than that of beta-lactams (cloxacillin, ceftaroline)*.

*Garcia de la Maria C et al. ECCMID. Amsterdam, NL, 2019 #00923
<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Animals with sterile vegetations/total (%)</th>
<th>Median log_{10} CFU/g of vegetation (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (No treatment)</td>
<td>0 / 10 (0)</td>
<td>9 (8.1 - 9.3)</td>
</tr>
<tr>
<td>Daptomycin (6mg/kg/24h)</td>
<td>0 / 11 (0)^a,b</td>
<td>2 (2 – 3.3)^c,d</td>
</tr>
<tr>
<td>Cloxacillin (2g/4h)</td>
<td>0 / 10 (0)</td>
<td>3 (2 – 4.5)^e</td>
</tr>
<tr>
<td>Cloxacillin (2g/4h) + Gentamicin (1mg/kg/8h)</td>
<td>3 / 10 (30)^f,g</td>
<td>2 (0.5 – 2)^e,h,i</td>
</tr>
<tr>
<td>Cloxacillin (2g/4h) + Daptomycin (6mg/kg/24h)</td>
<td>8/11 (73)^a,f</td>
<td>0 (0 – 1)^c,h</td>
</tr>
<tr>
<td>Fosfomycin (2g/6h) + Daptomycin (6mg/kg/24h)</td>
<td>10/11 (91)^b,g</td>
<td>0 (0 – 0)^d,i</td>
</tr>
</tbody>
</table>

^aP = .001; ^bP < .001; ^cP = .001; ^dP < .001; ^eP = .026; ^fP = .086; ^gP = .008; ^hP = .080; ^iP = .005
RCT of the Efficacy and Safety of Cloxacillin vs. Cloxacillin plus Daptomycin for the Treatment of MSSA IE

Multicenter, Randomized (1:1) Open-label Clinical Trial

MSSA IE (N=TBD)

Cloxacillin 4-6 wk

Cloxacillin (4-6 wk) + Daptomycin (1 wk)

- Recruitment: 2 yr. Europe
- Only MSSA IE
- End points: TOC 12 weeks after finishing Rx, Toxicity, Relapses, Resistance, Surgery and Mortality.
RCT of the Efficacy and Safety of Cloxacillin vs. Cloxacillin plus Fosfomycin for the Treatment of MSSAB/NVIE

Principal Investigator. Dr. M. Pujol (H. Bellvitge) – SAFO RCT

Multicenter, Randomized (1:1) Open-label Clinical Trial

MSSAB/NVIE (N=386)

- Cloxacillin 2-6 wk
- Cloxacillin (2-6 wk) + Fosfomycin (1 wk)

- Recruitment: 2 yr. Spain
- MSSA Bacteremia or Native Valve IE
- End points: TOC 12 weeks after finishing Rx, Toxicity, Relapses, Resistance, Surgery and Mortality.
Why β-lactams are synergistic with Vancomycin and Daptomycin even though they are not active against *Staphylococcus aureus* (MRSA) or *Enterococcus* spp. (VRE)

- Enhance membrane binding and depolarization and avoid the development of resistance (e.g. DAP in MRSA & EF).
- PBP1-selective beta-lactams enhance the antimicrobial efficiency of daptomycin, resulting in an increased frequency of septation and cell wall abnormalities (DAP induces expression of *pbpA* transcript).
- Attenuate the virulence of resistant strains (e.g. *agr* in MRSA)
- Enhance opsonophagocytic killing by neutrophils (e.g. activation of teichoic acid biosynthesis and complement deposition)
- Enhance the innate immunity (e.g. cationic antimicrobial peptides)

RCT Efficacy and Safety of β-lactam plus Daptomycin vs. Vancomycin for MRSA BSI – CAMERA2
Australasian Society of Infectious Diseases Clinical Research Network

Multicenter, Randomized Open-label Clinical Trial

MRSA BSI (N=440)

- Recruitment: 2016-19; 12 weeks of F/U.
- Drugs adjusted to renal failure
- β-lactams: flucloxacillin, cloxacillin, or cefazolin
- Primary Endpoint (composite outcome at 90-d): Mortality, BC+ 5 days, Relapse, Rx failure.

Daptomycin (6-10 mg/kg) ± β-lactam (7 days)

Vancomycin (1.5 g BID) ± β-lactam (7 days)

Tong et al. Trials. 2016; 17:170
Daptomycin plus Fosfomycin vs. Daptomycin plus Cloxacillin for the Treatment of MRSA EE with a Van MIC of 2 mg/L


<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Animals with sterile vegetations/total (%)</th>
<th>Median log10 cfu/g of vegetation (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0/12 (0)</td>
<td>10 (9.8–10)</td>
</tr>
<tr>
<td>Daptomycin (6 mg/kg/24 h)</td>
<td>13/18 (72)(^a)</td>
<td>0 (0–1.5)(^b)</td>
</tr>
<tr>
<td>Daptomycin (6 mg/kg/24 h) + cloxacillin (2 g/4 h)</td>
<td>14/16 (88)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Daptomycin (6 mg/kg/24 h) + fosfomycin (2 g/6 h)</td>
<td>16/16 (100)(^a)</td>
<td>0 (0–0)(^b)</td>
</tr>
<tr>
<td>Daptomycin (10 mg/kg/24 h)</td>
<td>14/15 (93)</td>
<td>0 (0–0)</td>
</tr>
</tbody>
</table>

\(^a\)P = .046
\(^b\)P = .025
Evaluation of the efficacy and safety of Daptomycin ± Fosfomycin for the treatment of MRSA BSI in Spain

PI 12/01907 - Dr. Miquel Pujol (H. Bellvitge) BACSARM RCT

Multicenter, Randomized (1:1) Open-label Clinical Trial

MRSA BSI (N=220)

- Recruitment: 2014-17; 12 weeks of F/U.
- Drugs adjusted to renal failure
- Susceptible to study drugs
- End points: TOC 12 weeks after finishing Rx, Toxicity, Resistance and Mortality.

Daptomycin (DAP)
10 mg/kg/d

DAP (10 mg/kg/d) + Fosfomycin (2 g/6h)
# Table 18 Antibiotic treatment of infective endocarditis due to *Enterococcus* spp.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration, weeks</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-lactam and gentamicin-susceptible strains (for resistant isolates see a,b,c)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin* with Gentamicin</td>
<td>200 mg/kg/day i.v. in 4–6 doses</td>
<td>4–6</td>
<td>1</td>
<td>B</td>
<td>6.8, 129, 135, 136, 186</td>
<td>6-week therapy recommended for patients with &gt;3 months symptoms or PVE</td>
</tr>
<tr>
<td><strong>Paediatric doses:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Gentamicin 3 mg/kg/day i.v. or i.m. in 3 equally divided doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ampicillin with Ceftriaxone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg/kg/day i.v. in 4–6 doses</td>
<td>6</td>
<td>1</td>
<td>B</td>
<td>183–185</td>
<td>This combination is active against <em>Enterococcus faecalis</em> strains with and without HLAR, being the combination of choice in patients with HLAR <em>E. faecalis</em> endocarditis.</td>
<td></td>
</tr>
<tr>
<td>4 g/day i.v. or i.m. in 2 doses</td>
<td>6</td>
<td>1</td>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Paediatric doses:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin as above Ceftriaxone 100 mg/kg/12 h i.v. or i.m.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This combination is not active against <em>E. faecium</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evaluation of the Efficacy and Safety of Ampicillin plus Ceftriaxone vs. Gentamicin for the Treatment of EFIE

Multicenter, Randomized (1:1) Open-label Clinical Trial

- Recruitment: 2 yr. Europe
- Only *E. faecalis* IE without HLAR
- End points: TOC 24 weeks after finishing Rx, Toxicity, Relapses, Surgery and Mortality.

Miro JM et al., Circulation. 2013; 127:1763-6
A paradigm shift in the antibiotic treatment of infective endocarditis has arrived ... 

Sequential antimicrobial treatment: from INTRAVENOUS to ORAL
The POET Trial: IV to Oral De-escalation Trial
Iversen K et al. Am Heart J 2013;165:116-22

Multicenter, Randomized (1:1) Open-label Clinical Trial in Denmark

- Recruitment will finished by 2017.
- All cases of streptococcal, staphylococcal, or enterococcal left sided NV/PV IE will be included.
- Susceptible to study drugs & PK studies
- The primary end point is a composition of all-cause mortality, unplanned cardiac surgery, embolic events, and relapse.
Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Kaplan–Meier Plot of the Probability of the Primary Composite Outcome

IV Antibiotic Treatment at Hospital
No OPAT !!!

Outpatient Oral vs. Parenteral Antimicrobial Therapy for IE trial (OraPAT-IE GAMES trial)

Investigator-driven, multicentre, open, non-inferiority randomized clinical trial

IE diagnosis according to modified Duke criteria

N=360

Randomization

> 10 days of IV therapy and/or >7 days of surgery and IV therapy

N=180

OPAT

End of therapy

Month 6

N=180

Oral therapy

Follow-up period

Antibiotic therapy
The RODEO Trial: IV to Oral De-escalation Trial

Multicenter, Randomized (1:1) Open-label Clinical Trial in France

S. aureus & CoNS IE (N=324)

Full course of IV Therapy 6 weeks (2015 ESC)

IV (14 d.) to Oral Therapy LEV+RIF 4 weeks

- Approved in October 2014.
- Recruitment started on March 2016.
- Only staphylococcal left sided NV/PV IE will be included. Susceptible to study drugs (MSSA, MSSE)
- The primary end point is a composition (M3) of all-cause mortality, unplanned cardiac surgery and relapse.
Infective Endocarditis: Brief Overview of Recent Progresses and Challenges

• Introduction
• Prevention
• Pathogenesis
• Diagnosis & Management
• Antimicrobial therapy
• Surgery
To find a more accurate “IE Prognosis Score” (e.g. a new “EuroScore” for IE)

Optimal timing of cardiac surgery in patients with intermediate risk: we need a RCT!

Surgery for big vegetations in non-VGS IE

How and when perform surgery in SAIE. Surgery for uncontrolled infection

Surgery in special patients (e.g. TAVI-IE, cirrhosis)

Optimal timing for reimplantation of PCM & DF
IE Scores and Mortality at the H. Clinic of Barcelona. 130 Consecutive Cardiac Surgeries for IE (2015-18)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obs</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES1EuroSCO</td>
<td>130</td>
<td>34.63082</td>
<td>25.20175</td>
<td>2.38</td>
<td>89.72118</td>
</tr>
<tr>
<td>ES2EuroSC</td>
<td>129</td>
<td>22.34253</td>
<td>21.09654</td>
<td>1.27</td>
<td>85.03457</td>
</tr>
<tr>
<td>PALSUSE</td>
<td>130</td>
<td>2.638462</td>
<td>1.446749</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>RISKE</td>
<td>130</td>
<td>21.60769</td>
<td>12.5182</td>
<td>0</td>
<td>62</td>
</tr>
<tr>
<td>Costa</td>
<td>130</td>
<td>15.03077</td>
<td>7.780854</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td>DeFeo</td>
<td>87</td>
<td>17.18391</td>
<td>10.0192</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>AEPEI</td>
<td>130</td>
<td>1.995385</td>
<td>1.908645</td>
<td>0</td>
<td>6.6</td>
</tr>
<tr>
<td>STSrisk</td>
<td>130</td>
<td>11.18615</td>
<td>14.03079</td>
<td>.28</td>
<td>79.26</td>
</tr>
<tr>
<td>ICEPS</td>
<td>130</td>
<td>9.384615</td>
<td>3.628878</td>
<td>2</td>
<td>18</td>
</tr>
</tbody>
</table>

Score-based mortality 2-35%

In-hospital Mortality = 6.5%
Proposal of a RCT to Test Early Surgery in Intermediate/High Risk Left-Sided IE (Endoval Trial)
Take home messages

- Endocarditis team!
- Prevention: WRAP-IT Pocket Infections
- Pathogenesis: Dapto MoR & Impact Van MIC
- Diagnosis & Management: CRC & EFIE and Thrombectomy
- Antimicrobial therapy: Proposed RCT and role of Oral Therapy
- Surgery: Improving Scores & Timing of Surgery
2019 ISCVID Conference

University of Lausanne
Amphipôle Building
Laussane, Switzerland

June 2nd-4th 2019