



**XLVIII
CONGRESSO
NAZIONALE
AMCLI**

2019



**9-12 NOVEMBRE 2019
PALACONGRESSI RIMINI**

Percorso Diagnostico

Sessione 6

AMCLI - ESGIAI /ESCMID

**INFEZIONI DA DEVICE
VASCOLARI**

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Disclosure slide for speaker at AMCLI - ESGIAI /ESCMID

“ INFEZIONI DA DEVICE VASCOLARI”

Disclosure of speaker's interests

EFTHYMIA GIANNITSIOTI

(Potential) conflict of interest	None
Potentially relevant company relationships in connection with event ¹	None
<ul style="list-style-type: none">• Sponsorship or research funding²• Fee or other (financial) payment³• Shareholder⁴• Other relationship, i.e. ...⁵	None

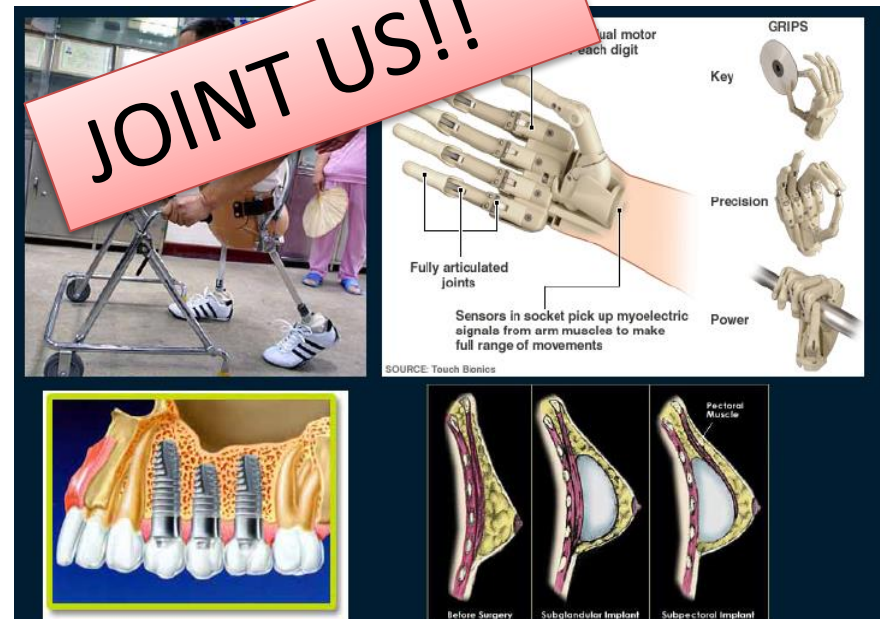
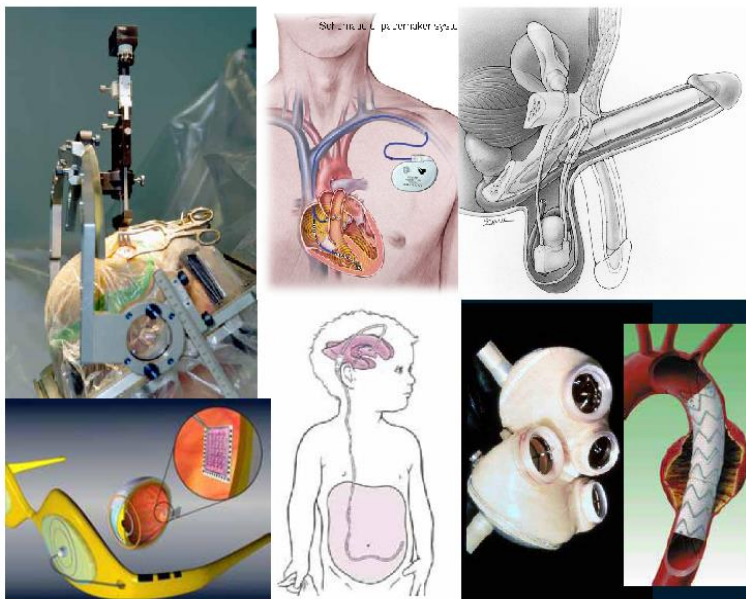
Study Group on Implant-Associated Infections **ESGIAI**



ESCMID

EUROPEAN SOCIETY
OF CLINICAL MICROBIOLOGY
AND INFECTIOUS DISEASES

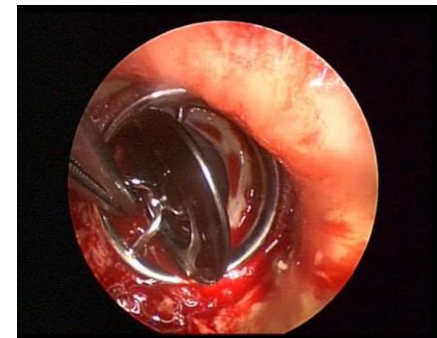
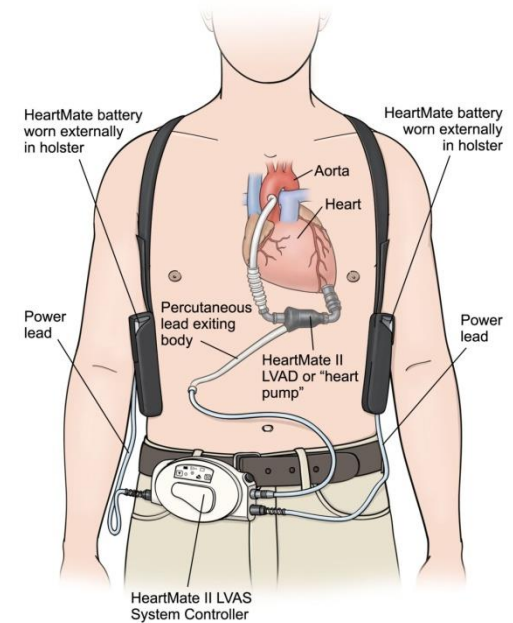
- Increasing challenge of modern medicine (morbidity, mortality, costs)
- Difficult to diagnose and difficult to treat due to presence of biofilm
- Clinical challenges in clinical microbiology and infectious diseases
- An interdisciplinary approach needed



Which implants?



- Prosthetic valves & Transcatheter aortic valve replacement (TAVR)
- Cardiac implantable electronic devices (CIED): pacemakers PPM & cardioverter defibrillators ICD
- Mechanical Circulatory Support (MCS) Device
Ventricular assist devices (VADs)
- Prosthetic Vascular grafts
- (PVG)



Cardiovascular device infections

A. Cardiac device infections:

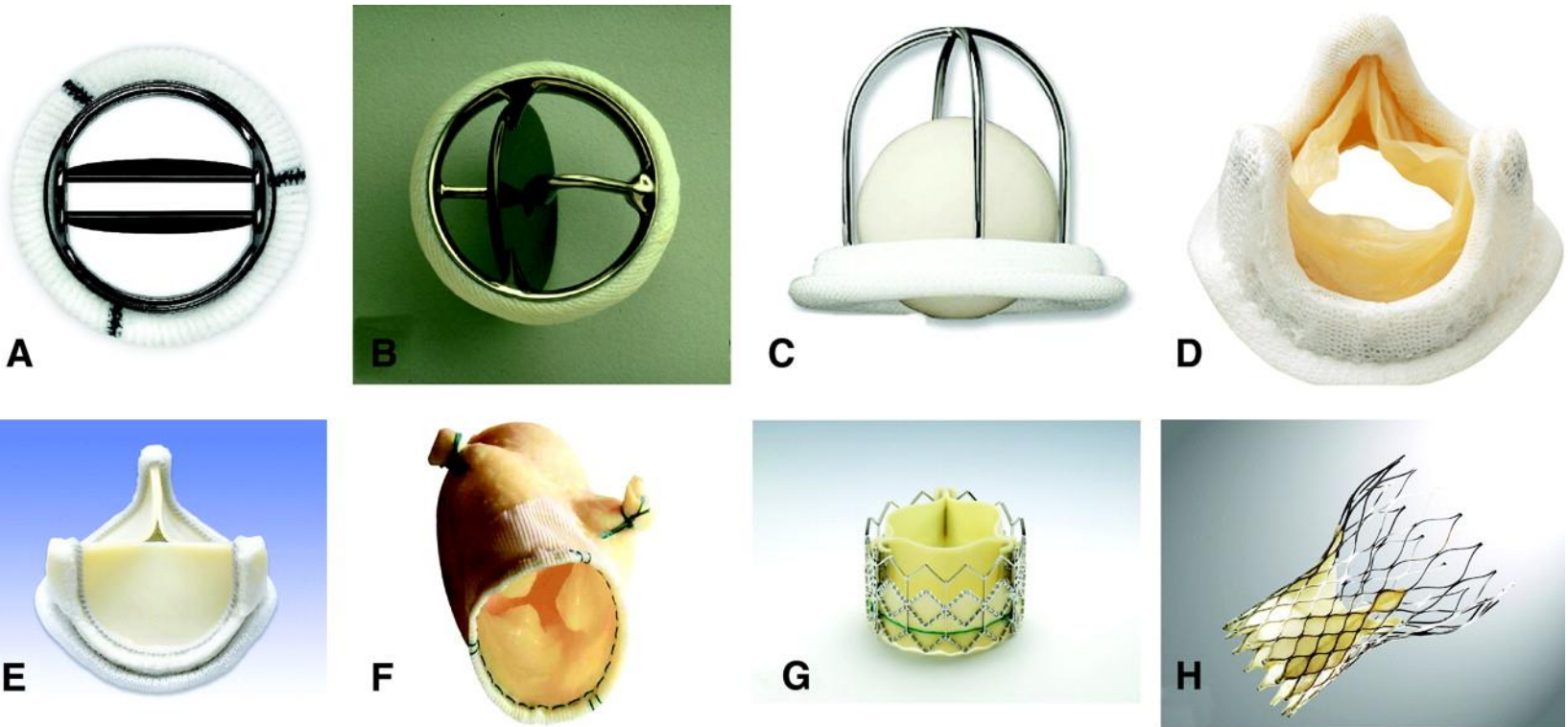
- i) Infective endocarditis (IE) of prosthetic valves-PVE** and TAVR (transcatheter aortic valve replacement)
- ii) Cardiac Implantable Electronic Device Infection (CIEDI) :** Permanent Pacemaker (PPM), Implantable Cardioverter defibrillator (ICD) infections

B. Vascular graft infections (VGI)

C. Central-line associated bloodstream infections (CLABSI)

Different types of prosthetic valves.

Major categories: i. bioprosthetic ii. mechanical
iii. Cryopreservative valvular aortic grafts



Pibarot P , and Dumesnil J G Circulation 2009

Prosthetic valves: are they increasing? What is the risk for endocarditis? (PVE)

Implantation of prosthetic valves

- 280.000/year worldwide
- USA: 90.000/year
- **PVE: 0,5%-1.2% per patient-year.**

Pibarot p & Dumesnil JG Circulation 2009

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)

- **Early prosthetic valve endocarditis (early PVE)**
 - < **1 year** post- implantation. Nosocomial pathogens
40-80% mortality
- **Late prosthetic valve endocarditis (late PVE)**
 - > **1 year** post-implantation. Pathogens as in community-IE
20-40% mortality

The incidence of early PVE declined within decades

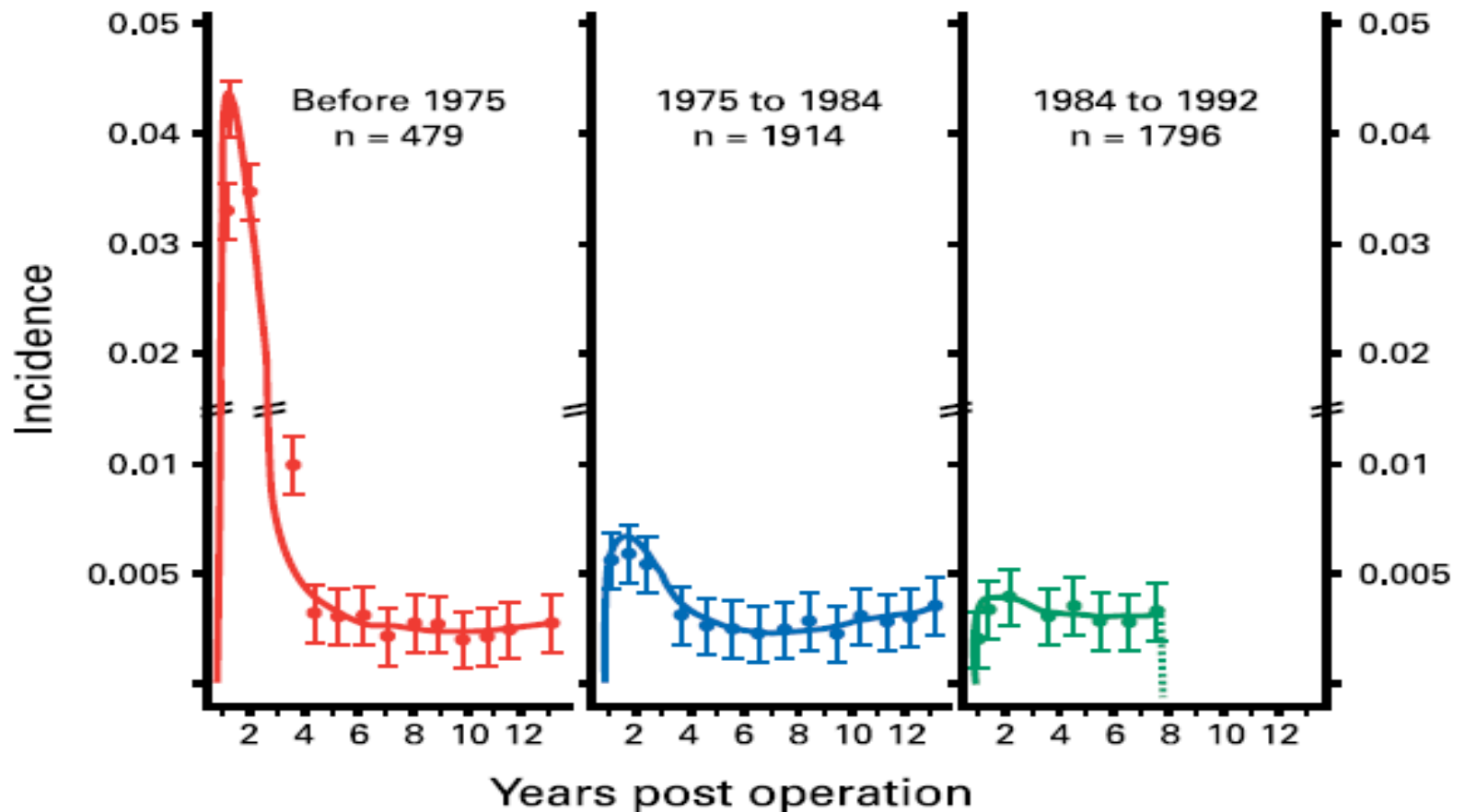


Figure 1. Hazard functions for prosthetic valve endocarditis in 4189 consecutive patients during three successive follow up periods.

Does epidemiology of PVE change?

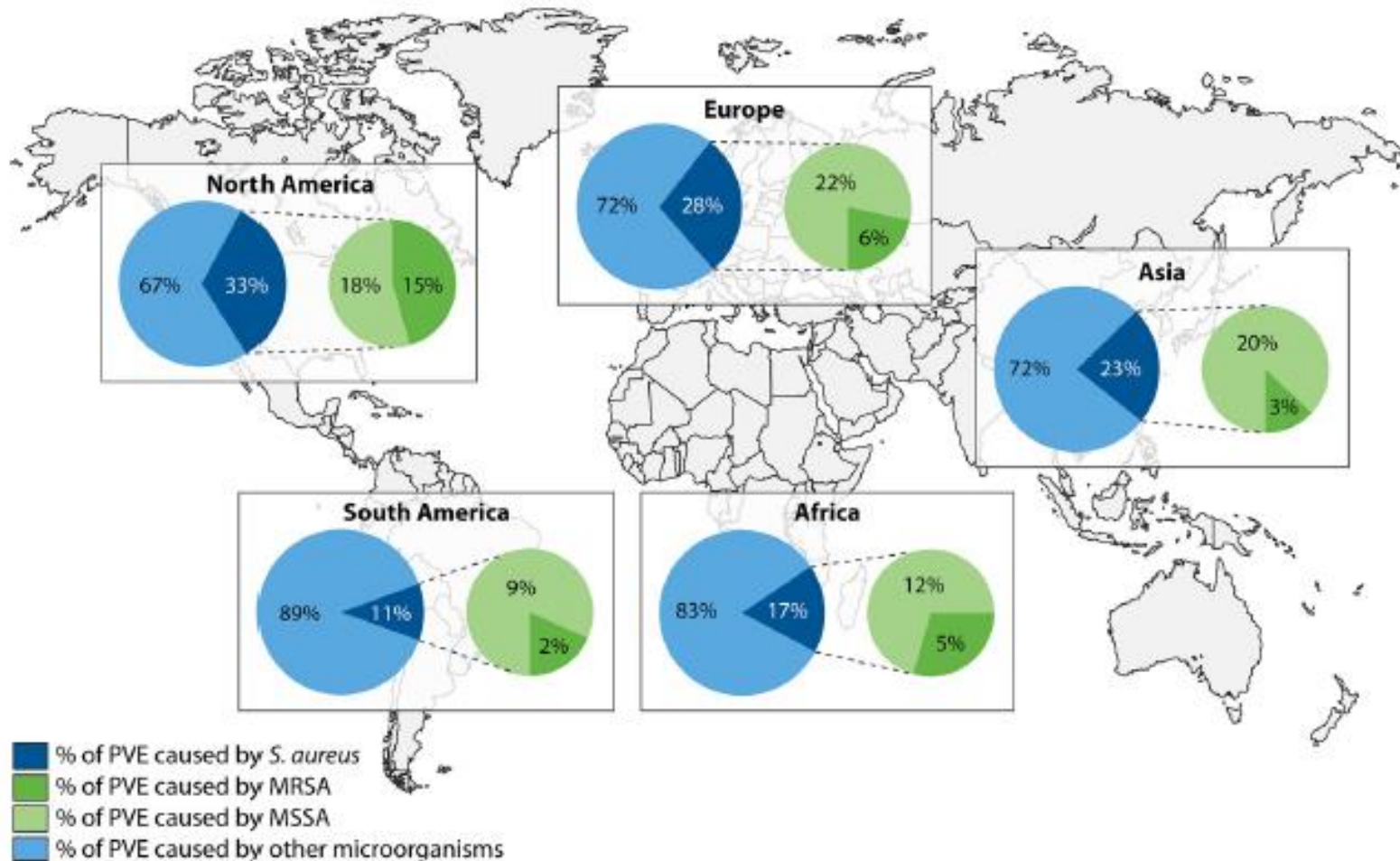
International Collaboration on Endocarditis-ICE 2000-2005

- **2.670** patients with AE
- 28 countries, 61 centers
- 556 patients with PVE (**20%**)
- Elderly
- *S. aureus* 23%, CoNs 17%
- Early PVE 71%
- **Surgery for PVE 49%**
- **Mortality 22.8%**



Data from ICE (International Collaboration on Endocarditis)

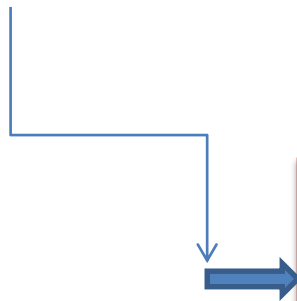
Murdoch et al, Wang et al



Galar et al, CMR 2019

Risk factors of **SAIE** (*S. aureus* IE) in pts with **SAB** (*S. aureus* bacteremia)

Risk factors of SAIE	OR (95%CI)	<i>p</i>
Unknown origin of SAB	4.2 (1.9-9.3)	.001
Valvular prosthesis	9.2 (3.2-26.2)	<.001
Persistent fever	3.1 (1.0-9.2)	.04
Persistent bacteremia	6.8 (2.3-20.2)	.001



6-month mortality
SAB 8% vs **SAIE** 35% ($p < .001$)

S.aureus PVE

- More complications than native valve endocarditis
- Valve peri-annular abscess, pseudoaneurysms, fistula, dehiscence >60%
- Rates of cardiac surgery for PVE decline despite indication
- Frail patients, non-eligible for surgery
- *However....*
- *S.aureus* PVE does not always need surgery.
- Early surgery for SA PVE did not impacted 1 y-mortality.

- *However*
- ***S.aureus* MRSA PVE: difficult to manage**
- **very high mortality! 40%**

Chirouze et al, CID 2015
Tornos et al, Chest 1992

ARTICLE

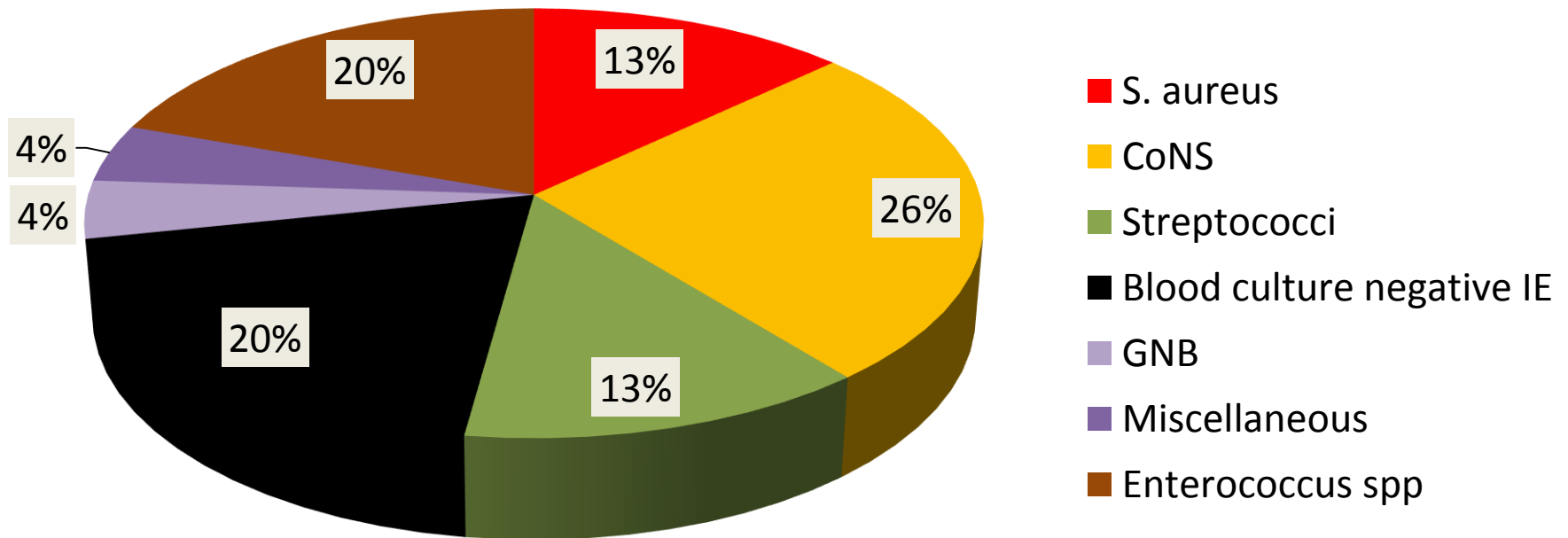
T. Lalani · Z. A. Kanafani · V. H. Chu · L. Moore · G. R. Corey · P. Pappas ·
C. W. Woods · C. H. Cabell · B. Hoen · C. Selton-Suty · T. Doco-Lecompte ·
C. Chirouze · D. Raoult · J. M. Miro · C. A. Mestres · L. Olaison · S. Eykyn ·
E. Abrutyn · V. G. Fowler Jr · The International Collaboration
on Endocarditis Merged Database Study Group

Prosthetic valve endocarditis due to coagulase-negative staphylococci: findings from the International Collaboration on Endocarditis Merged Database

PVE	Heart Failure	Valve abscess	Mortality
• 54 CoNs	54%	39%	36%
• 58 <i>S.aureus</i>	33%	22%	47%
• 63 Viridans Str	32%	6%	11%
<i>p</i>	0.03	<0.001	0.02

2019 * submitted PVE n=44 1st cause ***Enterococcus* spp!**

Distribution of pathogens in PVE, Athens GR



GNB= *Pseudomonas aeruginosa*, *Serratia* sp
Miscellaneous = *Brucella* spp, *Coxiella burnetii*
Streptococci= *Viridans*, *S. gallolyticus*, *S. agalactiae*

Infective Endocarditis After Transcatheter Aortic Valve Replacement: The Worst That Can Happen

Gilbert Habib, MD, PhD *J Am Heart Assoc.* 2018;

- Transcatheter aortic valve replacement (TAVR) has emerged as a therapeutic option for patients with aortic stenosis who are at high or prohibited surgical risk.
- Infective endocarditis post-TAVR 0.5-3.1%

Amat-Santos IJ, et al. Circulation 2015
Olsen NT, et al. Circ Cardiovasc Interv 2015

The Infectious Endocarditis after TAVR International Registry (47 centers worldwide)

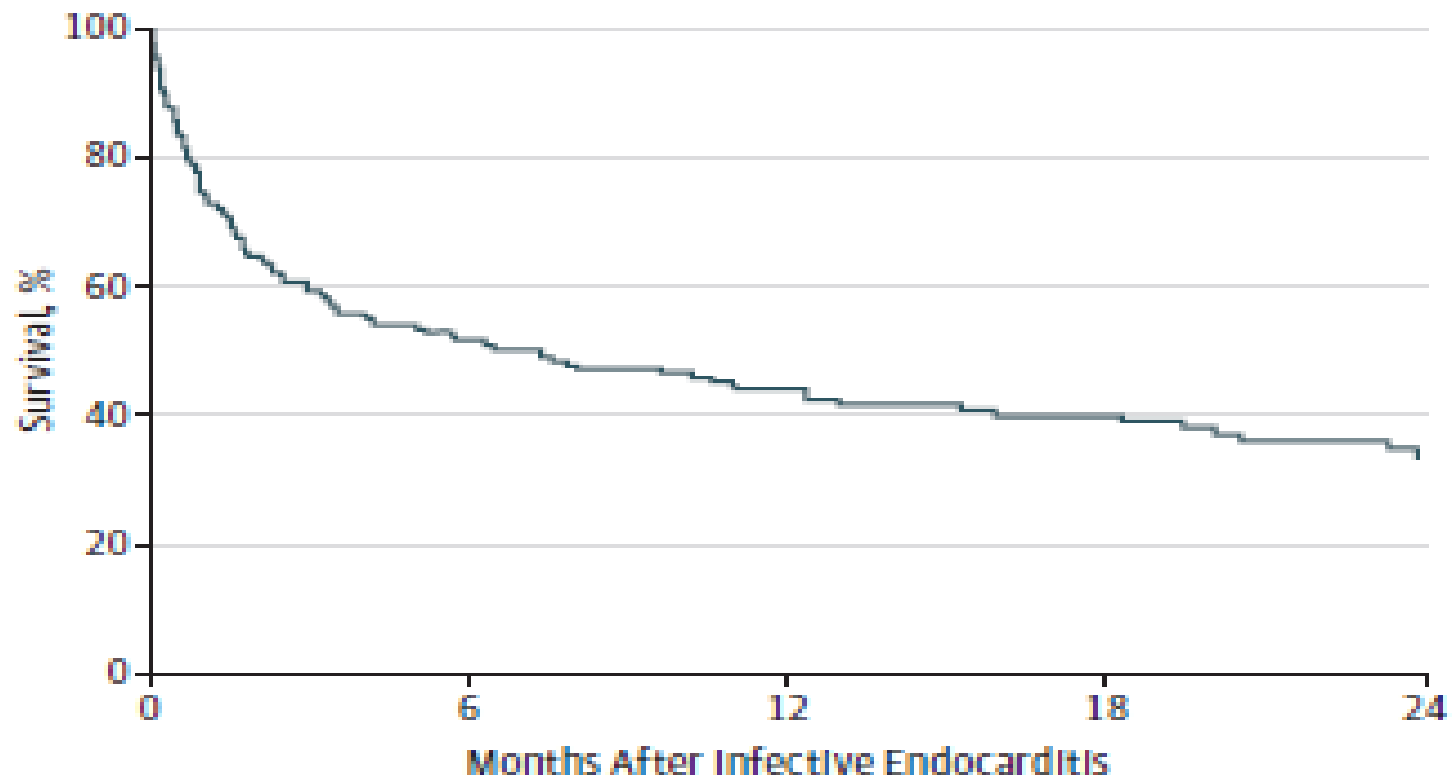
- ❑ **TAVI (n=250) from 20.006 TAVR**
- ❑ **(1.1 infections/patient-year, 95%CI: 1.1%-1.4%**
- ❑ **median age: 80 y; 64%men.**
- ❑ **Fever 80.4%, Acute heart failure 40.0%**
- ❑ **A possible source of bacteremia was identified only in 30.4% of patients (soft tissue infection or intravascular source)**
- ❑ **Health care-associated infective endocarditis 52.8%**

TAVI-International Registry

- **1st cause: *Enterococci* sp (24%)**
- **2nd cause: *Staphylococcus aureus* (23.3%)**
- **3^d cause: Coagulase-negative staphylococci (16.8%).**
- Concomitant mitral valve endocarditis (20.0%) and pacemaker infection (6.0%). Aortic regurgitation= bad prognosis
- **In-hospital mortality 36% (95%CI,30.0%-41.9%)**
- Cardiac surgery for TAVI: 14.8% of patients during the course of endocarditis (95%CI, 10.4%-19.2%).
- It is not clear if surgery affects survival

2-year survival in pts with TAVI

Figure 2. Survival Curve for Patients With Infective Endocarditis After Transcatheter Aortic Valve Replacement in the Global Study Cohort



No. at risk 247

94

58

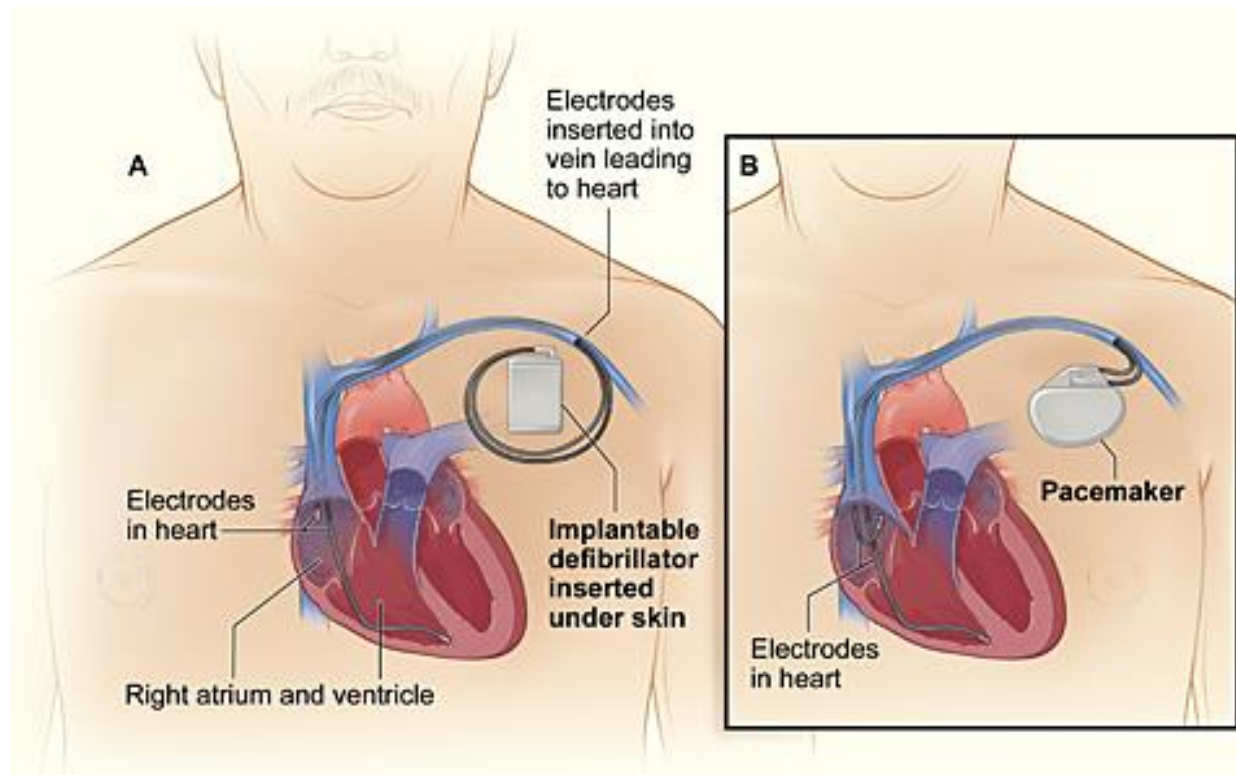
42

24

Regueiro et al JAMA 2016

What is CIEDI?

- **Local or systemic infection on any implantable electronic cardiac device (CIED):**
 1. Permanent Pacemaker (PPM)
 2. Implantable Cardioverter defibrillator (ICD)
 3. Cardiac resynchronization therapy (CRT)



- Different types, most of CIED have:
 - More >1 transvenous leads
 - single or dual chambered
 - a generator subcutaneously at upper thoracic wall (other: abdominal wall)
- novel: subcutaneous ICD, no transvenous leads

Clinical presentation of CIEDI:

Pocket infection: local contamination during implantation/revision

Figure 1: Images of Pocket Infection Over Two Years



Source: Tarakji and Wilkoff, 2013.³⁵

- erythema, warmth, tenderness, purulent discharge, erosion or protrusion of leads through the skin.
- Fever and malaise, but can be absent

True pocket infection?

a

from *Tarakji & Wilkoff, Curr Infect Dis Rep (2014) 16:425*



Frank pocket infection



Reticular telangiectatic erythema
associated with CIED

Definitions of lead associated endocarditis (LAE)

- **CIED infective endocarditis (Duke criteria)**
- Fever
- Bacteremia (>2 BC+)
- Embolization (lungs)
- Lead vegetation on echocardiography
- **LAE is almost ¼ of the total of CIEDI**

*Sohail et al, Am Coll Cardiol. 2007;49:1851–9
Klug, Circulation 1997.;95:2098-107*

Clinical Characteristics of LAE

- **FUO –fever of unknown origin**
- **Delayed infections onset after procedure mean=150days**
- Bacteremia (20-30%)
- Recurrent pneumonia, effusion, lung abscess, pulmonary emboli
- Tricuspid valve regurgitation
- Septic emboli to bones and joints,
- Septic thrombophlebitis
- often both LAE and valve endocarditis



Pathophysiology of LAE:
1) via contiguous
contamination of the lead
by a pocket infection.
In 75% , leads are infected
too (*Klug Heart 2004;90:882-6*).

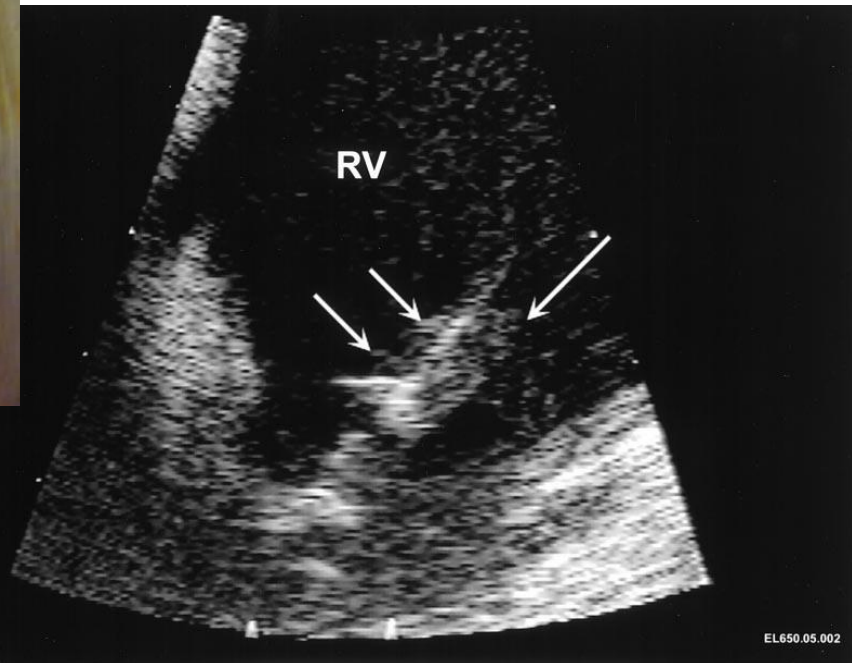


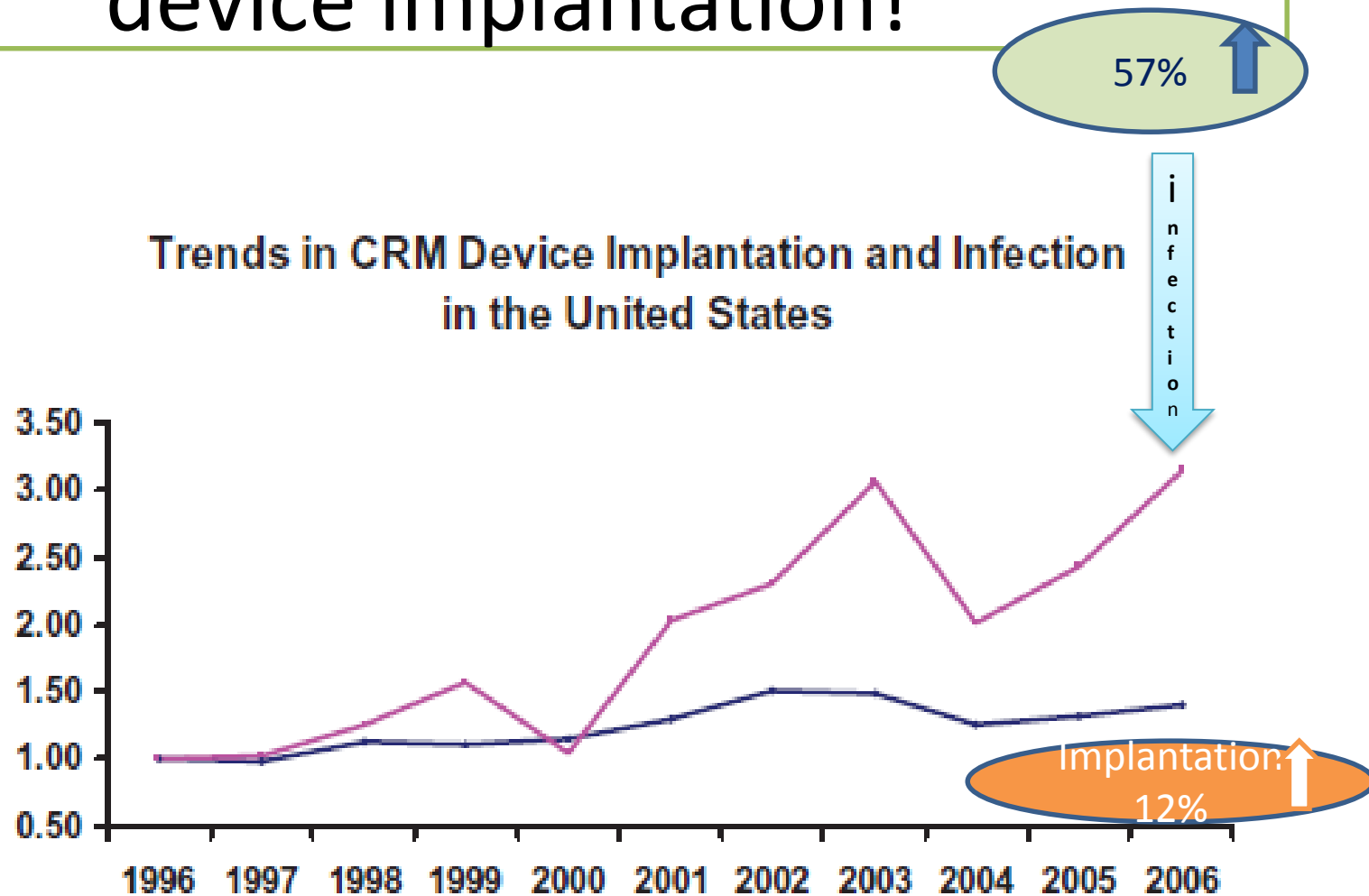
Photo & Echo image
by Kostas Evdoridis
with permission

CIEDI and cost: deleterious event!

- 78 267 CIED patients (72% de novo) .
- ICD 15% ; PPM 84%
- **The 36-month infection rate: 1.6%.**
- Mean infection-related costs over 24 months were **€20 623 and €23 234 for CIEDs associated with replacement and de novo procedures.** No difference between PPM and ICD .

Clémenty et al, Europace 2018

Raise in CIEDI overcomes rates of device implantation!



Risk factors for CIEDI

- **ICD > PM**
- **Comorbidities:** diabetes mellitus, heart/renal failure
- Steroids
- **Oral anticoagulation**
- Fever prior to implantation
- **Secondary procedures**
- **Multiple leads-epicardial**
- Abdominal site of implantation
- **Early intervention for hematoma**
- **Lack of antibiotic prophylaxis**
- **Physician's experience**
- Staphylococcal bacteremia

Microbiology of CIEDI around the world- Gram (+) 70-90%!

C. Blomström-Lundqvist et al

Table 2 Pathogens isolated in patients undergoing interventions for device infection from three large patient cohorts in North America, Europe, and Asia

Pathogen	Percentage of isolates		
	North America ¹⁶	Europe ¹⁷	Asia ¹⁸
Coagulase-negative staphylococci		69	45.2
Methicillin-resistant	18.8		
Methicillin-sensitive	18.8		
<i>S. aureus</i>		13.8	4.1
Methicillin-sensitive	15.8		
Methicillin-resistant	15.0		
<i>Streptococcus</i> spp.	2.5		
<i>Enterococcus</i> spp.			
Vancomycin-sensitive	2.8		
Vancomycin-resistant	1.4		
<i>Cutibacterium</i> spp. (previously <i>Propionibacterium</i> spp.)		2.5	
<i>Corynebacterium</i>		5	
Gram-negative bacteria	8.9	6.1	9.1
Enterobacteriaceae		3	3.2
Non-fermentative bacilli, incl. <i>Pseudomonas</i> spp.		1.5	5.9
Anaerobes	1.6		
Fungi	0.9	1	0.9
Mycobacteria	0.2		

ERHA position paper Europace 2019

CIEDI: difficult diagnosis

- Bacteremia by CoNs (1/2)
- No pocket infection
- No lead vegetations

.....But

- Persistent FUO
- The CEID is removed



- **Lead (+) culture for the same blood CoNs**
- **Device endocarditis!!**

Long-term mortality from CIED

- **Patients with CIED infection, compared to CIED pts without infection, had increased mortality that persisted for at least 3 years post-admission**
 - PPMs: 53.8% vs 33%
 - ICDs: 47.7% vs 31.6%
 - CRT-D: 50.8% vs 36.5%
- } $p < 0.001$
- Co-existence of CIEDI and valve IE (tricuspid) 37% -increases mortality

Mechanical Circulatory Support (MCS) Device Recipients

- Ventricular Assist Devices (VADs)
- Total Artificial Heart (TAH)
- 1st generation-driveline infections up to 80%
- 2nd generation :continuous-flow rotary pump 27%
- 3d generation: Infections up to 17%
- LVAD bridging to transplantation

Kusne et al, Clin Infect Dis 2017

VADs infections-definitions

ISHLT, Hannan et al, J Heart Lung Transplant 2011

- VAD specific : pump and or cannula, pocket, percutaneous infections;
- VAD related: infective endocarditis, BSI and mediastinitis
- non-VAD related: UTI, pneumonia...

VADs infection-clinical presentation

- **driveline exit site is frequently the portal of entry of pathogens**
- local infection and track deeper to the pocket and the pump itself.
- Bacteremia- often co-existing with PPM/valve endocarditis!!
- Nosocomial MDR pathogens!
- Special pathogens :*Mycobacteria Chimerea* epidemics
- High short and long term mortality

Vascular graft infection- VGI

Classification

```
graph TD; A[Vascular graft infection- VGI] --> B[Extracavitary<br/>(groin, lower extremities)]; A --> C[Intracavitary<br/>(abdomen, thorax)]; B --> D[1.5-2%, groin: 6%]; C --> E[1-5%]; D --> F[Complications : 10-15%<br/>5-year mortality : > 50%<br/>Cost : > 40,000 USD/ episode]; E --> F;
```

- Extracavitary

(groin, lower extremities)

Intracavitary

(abdomen, thorax)

Frequency of VGI

1.5-2%, groin: 6%


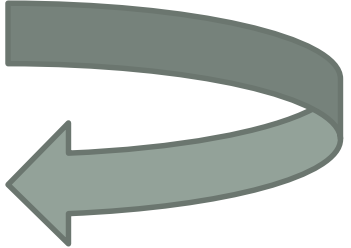
1-5%

Complications : 10-15%

5-year mortality : > 50%

Cost : > 40,000 USD/ episode

Aortic Graft Infection- AGI

- First **population-based cumulative incidence of AGI**
- **Netherlands, 2000-2010**

- Patients old >60y (mean age 69.2), male 85%, with comorbidities
- Elective aortic surgery: 55%
- Among 514 nationally recorded patients who undergo aortic graft surgery, 23 presented **AGI (4.5%)**
-
- **AGI** 2-year post-op risk HR =2.04 (95%CI 1.28-3.25)

- **AGI: 30-d post-op mortality 30%, 1-y mortality 45%**

Risk factors for Aortic graft infection AGI

Risk might increase with

- Age
- Emergency procedures
- Location (aorto-bifemoral)
- Groin incision
- Comorbidities (diabetes, cardiac diseases, COPD)
- Type of grafts (mixed, aortic, extra-cavita..)
- Materials (PTFE, polyester, autologous...)



- **However, due to small sample size none study really confirmed them! Diversity, contradictory results.**

Secondary aortoenteric fistula: **SAEF**

- Definition: **evidence on imaging or/and surgery of a direct communication between the anastomosis (or the peri-anastomotic area) of aortic prosthesis and the GI tract.**
- Rates 0.6-1.3% after aortic graft surgery.
- In 40% of EVAR infected grafts
- **Mortality up to 100% if undiagnosed, untreated.**

Valentine RJ et al, J Am Coll Surg 2008
Numan F. et al. J Cardiovasc Surg. 2011

Clinical presentation of SAEF

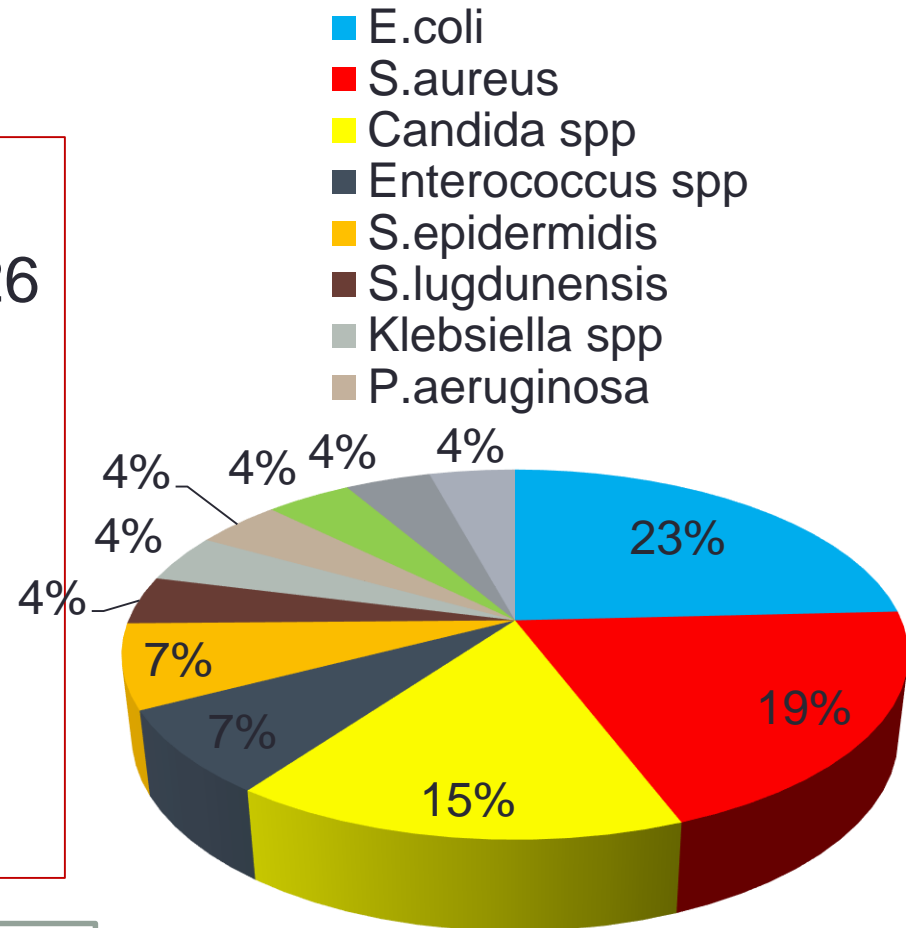
- ❖ More frequently: **bleeding**
- ❖ **From sepsis to Indolent symptoms:** low grade fever, malaise, abdominal/lumbar pain, loss of weight,
- ❖ Delay in diagnosis up to 18months (and more...)

- ❖ **If GI bleeding, or sepsis, or abdominal pain occur in a patient with aortic graft, SAEF should be considered until disproved.**
- ❖ **CT scan and GI endoscopy**

Microbiology of AGI

Nationwide study 2012-, Italy

- 13.000 EVAR after 2002
- Post-EVAR infections, n=26
- Positive intra-operative cultures up to 80%
- Bacteraemia <20%
- Polymicrobial up to 20%



Cappocia et al, Ann Vasc Surg 2015

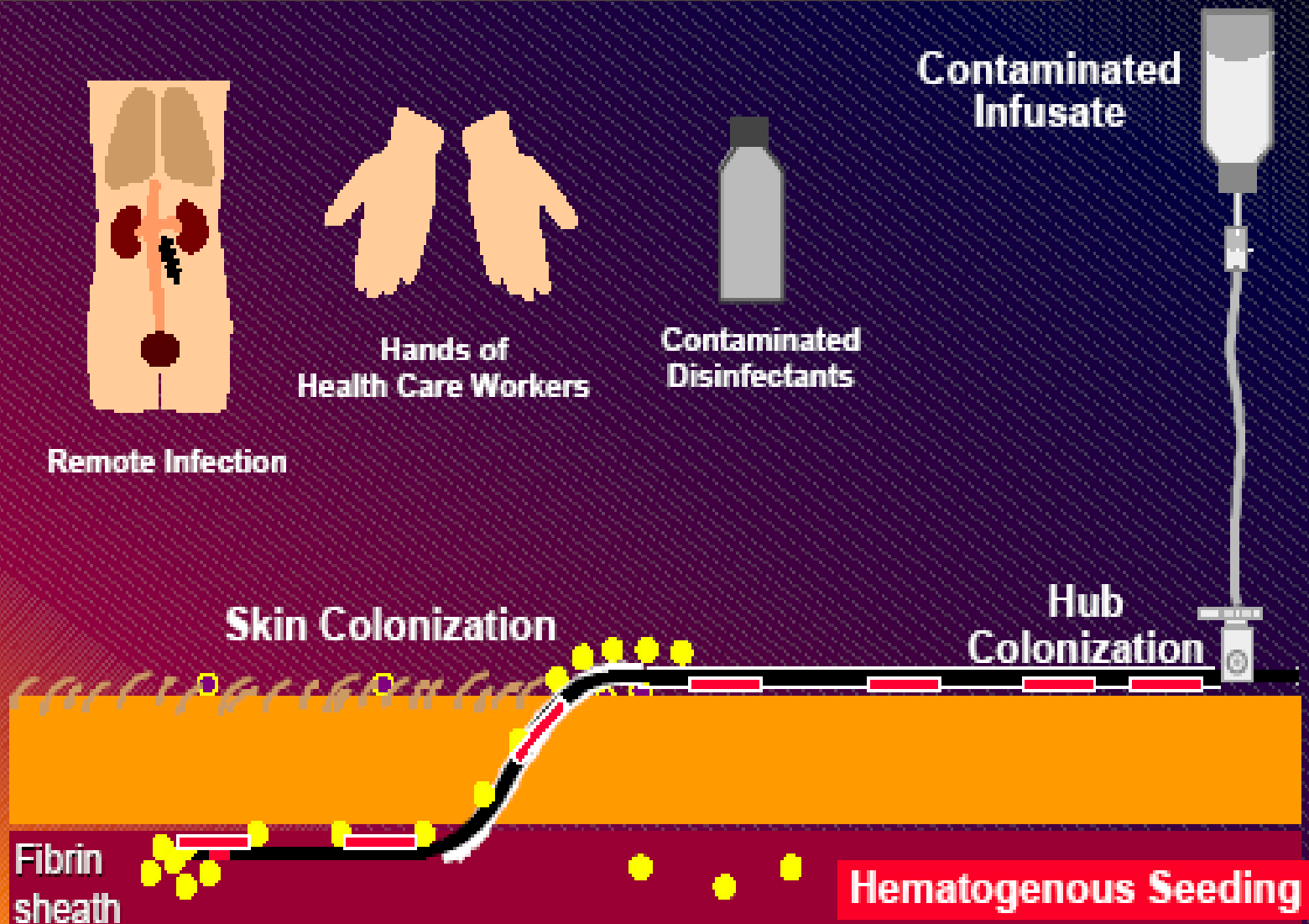
Endovascular aortic replacement EVAR infections



B. Excised infected EVAR
A. Aortic Cryopreserved allograft

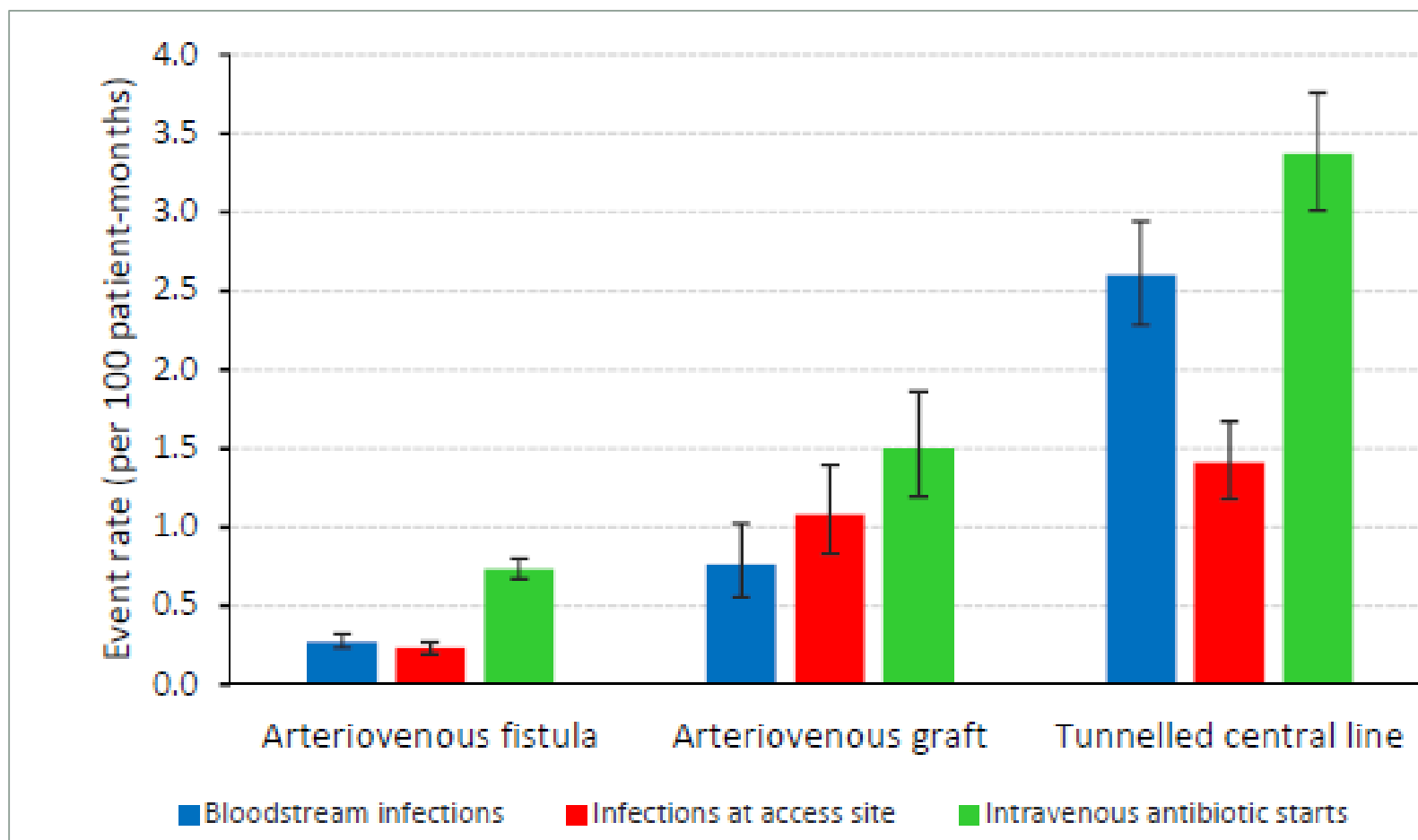
- ❖ Multi-centre nationwide study
- ❖ Infections: 0.3% (n=33)
- ❖ Fever and pain: 64%
- ❖ CTA (+): 94%
- ❖ Aorto-enteric fistula 33%
- ❖ Blood cultures (+): 27%
- ❖ Graft culture (+) 74%
 - Staphylococci, Streptococci, GNB
 - Enterococci, Anaerobes, Fungi
- ❖ **Dual Rx: 67%, triple RX 21%**
- ❖ **All endografts were removed!**
- ❖ Re-infection 5%
- ❖ 1-y survival 44%

Central Line Associated Bloodstream infections- CLABSI



Widmer AF. In: Wenzel RP: Prevention and Control of Nosocomial Infections, 1987

End Stage renal Failure-Haemodialysis ESDR/HD infections, Australia 2008-2015, 48 centers 3449 /79803 pts-mo



Worth et al , J Infect 2017

UK Renal Registry 19th Annual Report: Chapter 10 Epidemiology of Reported Infections in Patients Receiving Dialysis in England between January 2015 and December 2015: a Joint Report from Public Health England and the UK Renal Registry

Nephron 2017;137(suppl1):251-258

Table 10.1. Number of infectious episodes reported to Public Health England (PHE) and validated by renal centres in 2015

	MRSA	MSSA	CDI	<i>E.coli</i>
Total number of episodes after validation process	31	560	245	405

2015: total 1241 cases of infection

1. *S.aureus*
2. *E.coli*
3. *Cl difficile*

Table 10.4. Type of dialysis access in use at the time of infection for HD patients

	Number of episodes (1/01/2015–31/12/2015)				
	AVF	AVG	CVC	PD	No data
Estimated number of patient years at risk	12,938	1,368	7,026*	3,093	
MRSA	7	1	17		6
MSSA	153	20	271	9	107

Catheter removal and outcomes of multidrug-resistant central-line-associated bloodstream infection

Medicine 2018

Jason P. Burnham, MD^{a,*}, Rebecca P. Rojek, MPH^b, Marin H. Kollef, MD^c

A total of 430 patients met inclusion criteria

S. aureus 81 (18.8%)

Enterococcus sp 173 (40.2%) ➡ *E. faecium* 9.8%

Enterobacteriaceae :116 (27.0%)

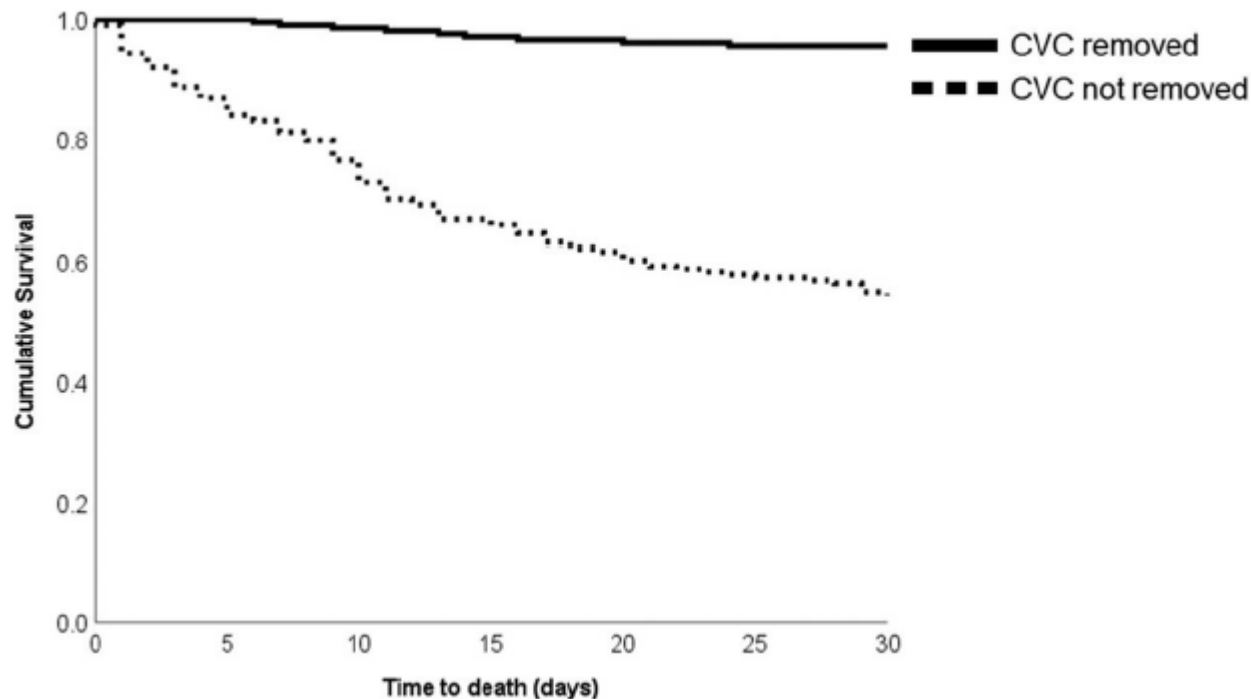
- Enterobacter cloacae* 46%
- E. coli* 29.3%
- K. pneumoniae* (10)
- Citrobacter freundii* (5)
- Proteus mirabilis* (2)

P. aeruginosa: 11 (2.6%)

Acinetobacter spp :5 (1.2%)

Polymicrobial infections:44 (10%).

Among MDRO polymicrobial infections 72% mixed Gram +/- infections.



CVC remained in place, 45.3% of patients died (n=97).

- Time 4.8 4 days till removal was found in non-survivors.
- **Failure to remove a CVC was strongly associated with 30-day all-cause mortality. HR: 13.5 (6.8–26.7)**



RIMINI ITALY

ΕΛΛΗΝΙΣΤΙΚΟ ΚΕΝΤΡΟ ΝΟΣΟΚΟΜΕΙΟ
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