De battre mon cœur s'est infecté Endocardite en rapport avec une infection de matériel

Mercredi 12 Juin 2013

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Poitiers

Liens d'intérêts 2011 - 2013

Participation à des congrès internationaux : Abbott, MSD, Pfizer

Expert rémunéré : GSK, Novartis, Pfizer,Thermo Fischer

Vice présidente de la SPILF

Données épidémiologiques

(Greenspon AJ et al J Am Coll Cardiol 2011;58:1001-6)

1993 – 2008
de + en + de défibrillateurs
de + en + d'infections (1,5% à 2,3%)
de + en + de facteurs de comorbidité

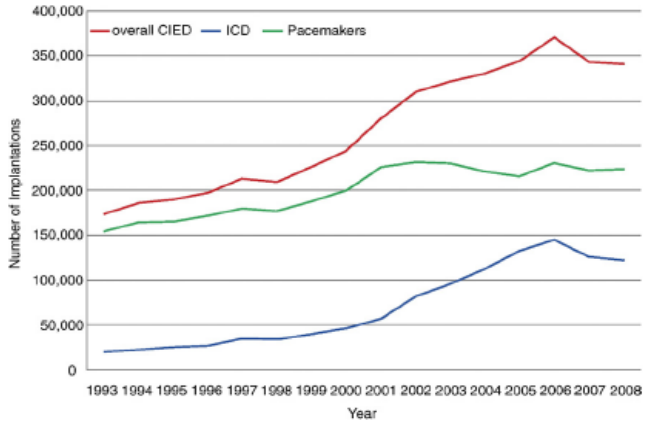

Figure 1 Annual Number of PM and ICD Implantations: 1993 to 2008

Between 1993 and 2008, overall cardiac implantable electrophysiological device (CIED) implantation increased by 96% (an average of 4.7%/year). Pacemaker (PM) implantation increased by 45%, whereas implantable cardioverter-defibrillator (ICD) implantation increased by 504%.

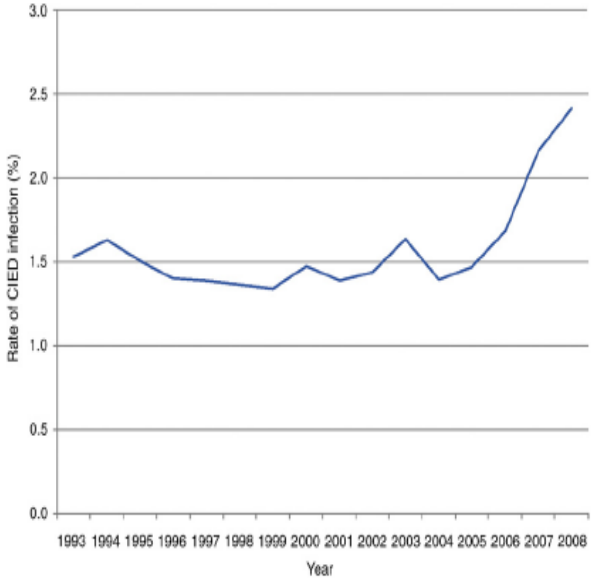

Figure 3 Rate of CIED Infection

The annual rate of cardiac implantable electrophysiological device (CIED) infection remained fairly constant until 2004 when there was a marked increase. The infection rate increased from 1.53% in 2004 to 2.41% in 2008 ($p < 0.001$).

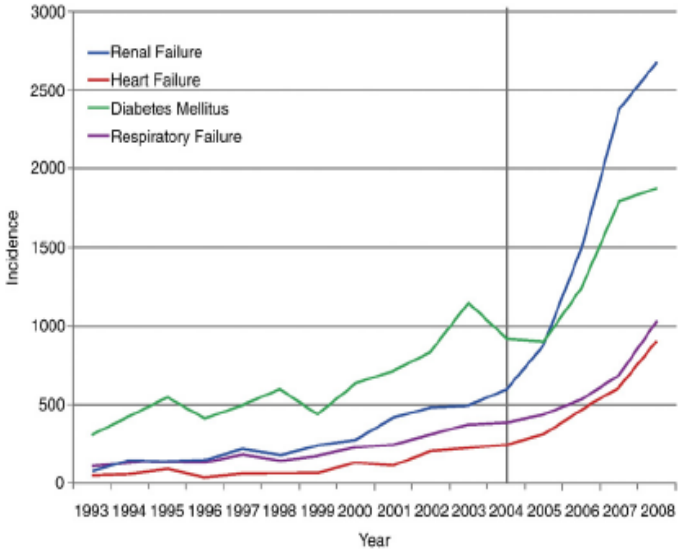

Figure 5 Incidence of Comorbidities in Patients With CIED Infection

The incidence of 4 major comorbidities (renal failure, respiratory failure, heart failure, and diabetes) remained fairly constant until 2004 when a marked increase was observed. This paralleled both the observed increase in implantable cardioverter-defibrillator implantation and the increased infection rate. CIED = cardiac implantable electrophysiological device.

Données épidémiologiques

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Update on Cardiovascular Implantable Electronic Device Infections and Their Management : A Scientific Statement From the American Heart Association

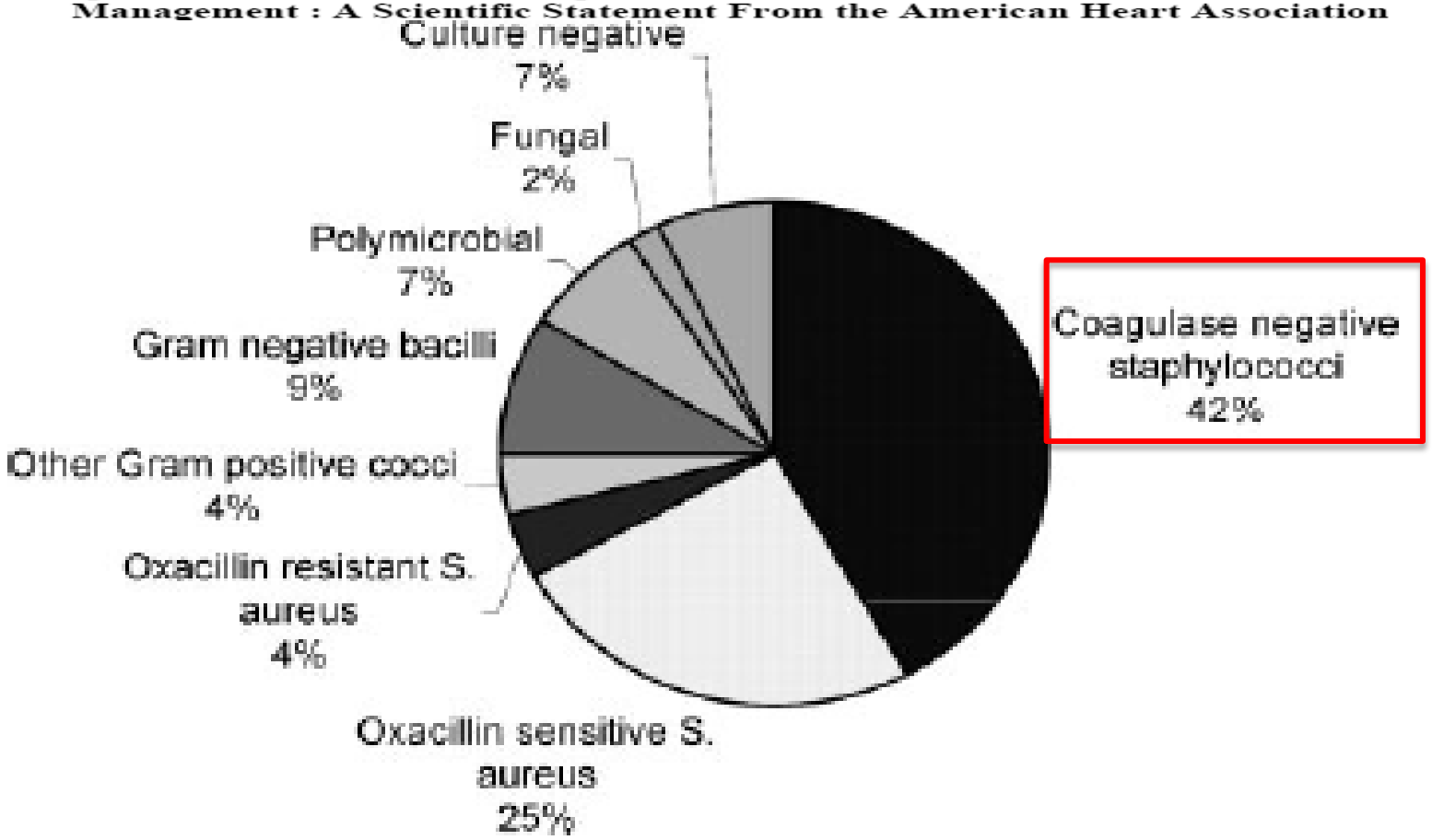

Figure 1. Microbiology of PPM/ICD infections (n=189). From Sohail et al,[38] with permission.

(Baddour LM et al 2010;121:458-77)

Clinical Characteristics and Outcome of Infective Endocarditis Involving Implantable Cardiac Devices

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Pierre Tattevin, MD, PhD
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Enrico Cecchi, MD
Franck Thuny, MD
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Anna Lisa Crowley, MD, MHS
Andrew Wang, MD
for the ICE-PCS Investigators

2000-2006 61 centres, 28 pays, ICE
2760 patients + endocardite certaine
177 (6,4%) endocardites + matériel

Microbiology					
Positive blood cultures	149 (84.2)	126 (83.4)	23 (88.5)	1.74 (0.69-4.38)	.24
Positive lead or vegetation culture	93 (52.5)	79 (52.3)	14 (53.8)	0.62 (0.03-11.83)	.40
Staphylococcus aureus	62 (35.0)	46 (30.5)	16 (61.5)	3.32 (1.95-5.64)	<.001
MRSA	26 (14.7)	18 (11.9)	8 (30.7)	3.54 (1.52-8.28)	.004
Coagulase-negative staphylococci	56 (31.6)	50 (33.1)	6 (23.1)	0.69 (0.33-1.45)	.33
Enterococcus	9 (5.1)	9 (6.0)	0		
Viridans streptococci	5 (2.8)	4 (2.6)	1 (3.8)	1.11 (0.04-27.92)	.95
Gram negative	8 (4.5)	8 (5.3)	0		

(Athan E et al JAMA 2012;16:1727-35)

Madame M…29 ans

- 2008 Cardiomyopathie gravidique
  - défibrillateur
- 2010 Hyperthyroïdie (amiodarone)
  - thyroïdectomie
- Allergies x dont pénicilline

Madame M…29 ans

- 1 mois après la thyroïdectomie
- fébricule (< 38° 5C), asthénie
  - 3 antibiothérapies empiriques (roxythromycine, pristinamycine, TMP-SMZ)
  - hémocultures « en ville »
    - *S. epidermidis* x 2 méti S
    - *S. hominis* x 1 méti S
  - ETT :
    - FEVG 20%
    - valves aortique, pulmonaire, mitrale et tricuspide RAS

Bilan initial

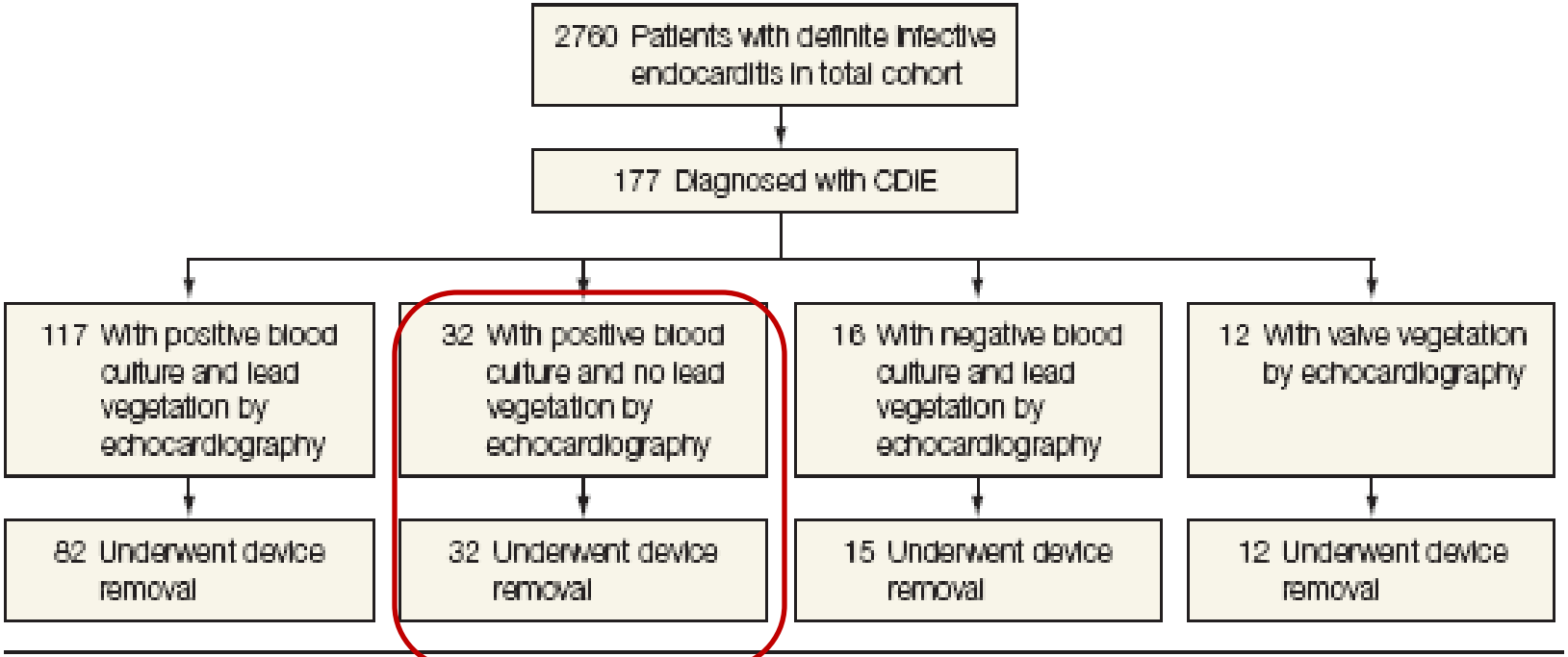
- Leucocytes 8000 / mm3 (68% de PNN)
- Créatinine 77 µmol/l
- CRP 8 mg/l
- NT proBNP 10739 ng/l
- Hémocultures x 4 négatives ….

Antibiothérapie ? …
teicoplanine + gentamicine + rifampicine
et le matériel ?

Clinical Characteristics and Outcome of Infective Endocarditis Involving Implantable Cardiac Devices

2000-2006 61 centres, 28 pays, ICE
177 (6,4%) endocardites + matériel
141 (79.7%) + retrait du matériel, mortalité à 1 an + faible (p=0.02)

Figure 1. Distribution of Patients in Study by Clinical Characteristics and Device Removal Status



Device removal was performed during the index hospitalization.

(*Athan E et al JAMA 2012;16:1727-35*)

Circulation
Arrhythmia and Electrophysiology
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

Outcomes in Patients With Cardiovascular Implantable Electronic Devices and Bacteremia Caused by Gram-Positive Cocci Other Than Staphylococcus AureusClinical Perspective

Malini Madhavan, Muhammad R. Sohail, Paul A. Friedman, David L. Hayes, James M. Steckelberg, Walter R. Wilson, Larry M. Baddour and for the Mayo Cardiovascular Infections Study Group

étude rétrospective
74 bactériémies + matériel
15% de rechutes (3 mois)
maintien possible du matériel si
- pas de signe d'infection
- cocci G+ non *S. aureus*

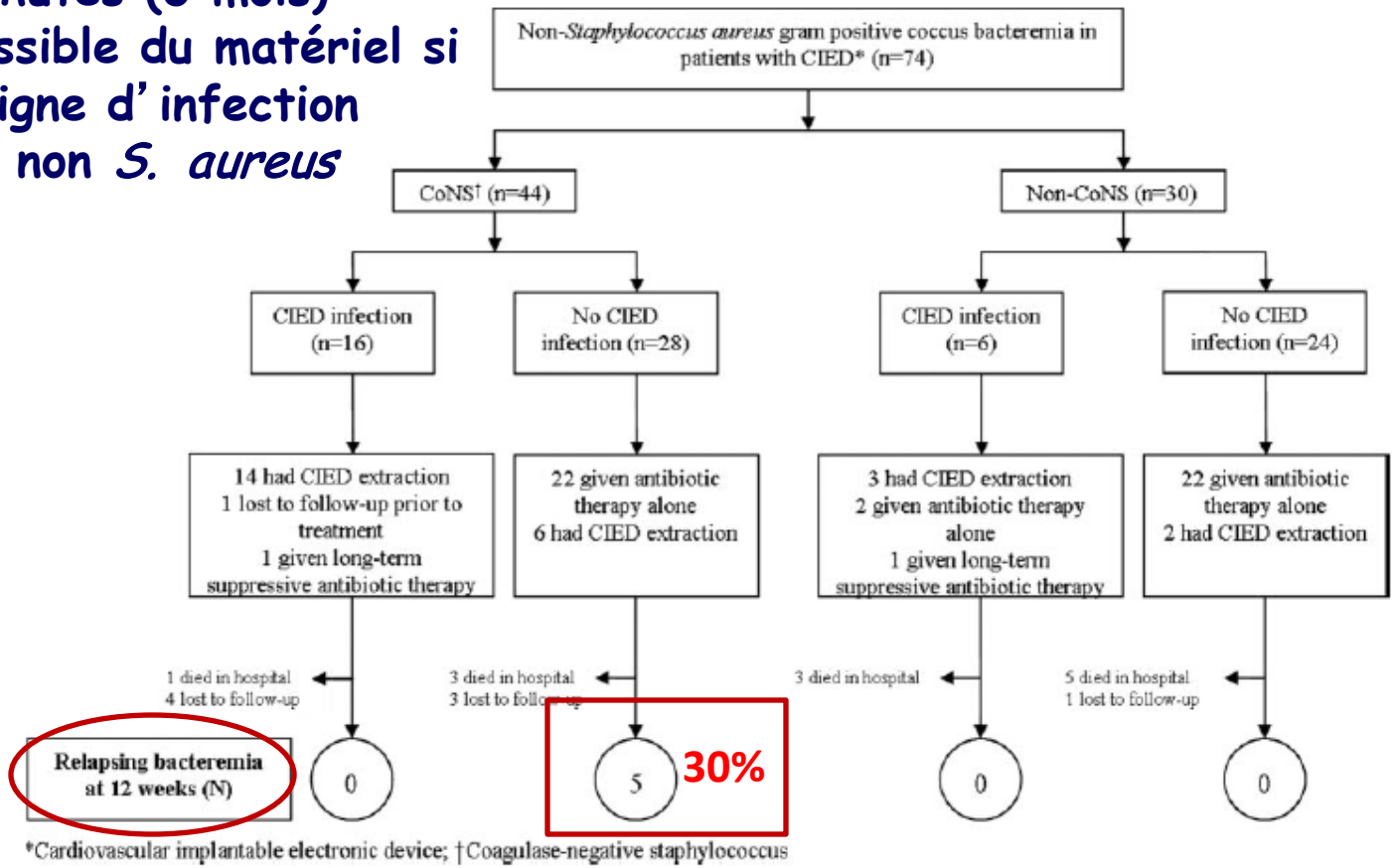


Figure 1. Treatment and outcome of patients with CIED and GPC bacteremia other than *S aureus*.

Circulation
American Heart Association.

Update on Cardiovascular Implantable Electronic Device Infections and Their Management : A Scientific Statement From the American Heart Association

Recommendations for Removal of Infected CIED

Class I

1. Complete device and lead removal is recommended for all patients with definite CIED infection, as evidenced by valvular and/or lead endocarditis or sepsis. (*Level of Evidence: A*)
2. Complete device and lead removal is recommended for all patients with CIED pocket infection as evidenced by abscess formation, device erosion, skin adherence, or chronic draining sinus without clinically evident involvement of the transvenous portion of the lead system. (*Level of Evidence: B*)
3. Complete device and lead removal is recommended for all patients with valvular endocarditis without definite involvement of the lead(s) and/or device. (*Level of Evidence: B*)
4. Complete device and lead removal is recommended for patients with occult staphylococcal bacteremia. (*Level of Evidence: B*)

Class IIa

1. Complete device and lead removal is reasonable in patients with persistent occult Gram-negative bacteremia despite appropriate antibiotic therapy. (*Level of Evidence: B*)

Class III

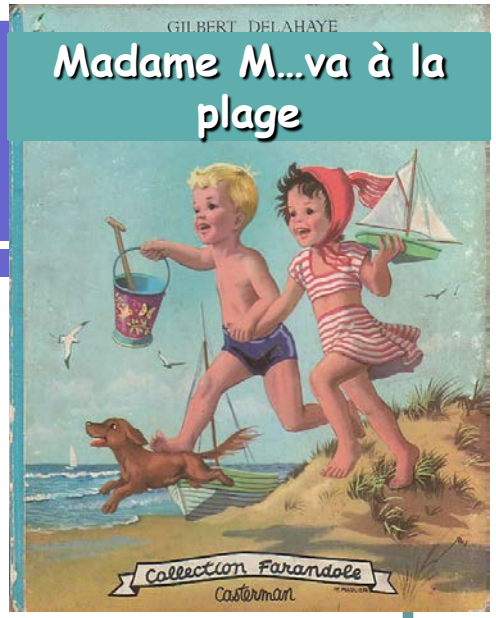
1. CIED removal is not indicated for a superficial or incisional infection without involvement of the device and/or leads. (*Level of Evidence: C*)
2. CIED removal is not indicated for relapsing bloodstream infection due to a source other than a CIED and for which long-term suppressive antimicrobials are required. (*Level of Evidence: C*)

(Baddour LM et al 2010;121:458-77)

Madame M…29 ans

- TTT1 : teicoplanine + gentamicine (X 5 j) + rifampicine
- J 5 : nausées + vomissements
  - créatinine 146 µmol/l
  - teicoplaninémie 62 mg/l
- CAT
  - arrêt des antibiotiques
  - arrêt des autres « néphrotoxiques »
- TTT2 :
  - teicoplanine + ofloxacine dés que concentration sérique ≤ 25 mg/l
  - durée totale 6 semaines

Madame M…29 ans



- arrêt de teicoplanine à J25
- relais par ofloxacine + acide fusidique
- tendinopathie à J45
- arrêt de tout traitement
- 8 jours après arrêt des antibiotiques : récidive de fièvre
  - paracétamol …

Madame M…le retour

- Bilan « systématique » 1 mois après arrêt ttt
  - pas de récidive de la fièvre, pas de signe de décompensation cardiaque
  - CRP 60 mg/l, créatinine 82 µmol/l
  - hémocs x 3 *S. epidermidis*
    - méti S
    - rifampicine R
    - acide fusidique R
    - ofloxacine R
    - teicoplanine S (CMI < 0,5 mg/l)
  - ETT : cardiomyopathie dilatée, valves RAS et sondes ??
- Décision d' ablation du matériel

Madame M…suite et fin ???

- ablation de l' ensemble du matériel (1 mois)
- culture des sondes + *S. epidermidis*
- CMI daptomycine 0,75 mg/l

daptomycine
posologie, durée
association ??

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children: Executive Summary

Catherine Liu,[1] Arnold Bayer,[3,5] Sara E. Cosgrove,[6] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[4,5] and Henry F. Chambers[1,2]

III. What is the management of MRSA bacteremia and infective endocarditis?

Bacteremia and Infective Endocarditis, Native Valve

19. For adults with uncomplicated bacteremia (defined as patients with positive blood culture results and the following: exclusion of endocarditis; no implanted prostheses; follow-up blood cultures performed on specimens obtained 2–4 days after the initial set that do not grow MRSA; defervescence within 72 h of initiating effective therapy; and no evidence of metastatic sites of infection), vancomycin (**A-II**) or daptomycin 6 mg/kg/dose IV once daily (**AI**) for at least 2 weeks. For complicated bacteremia (defined as patients with positive blood culture results who do not meet criteria for uncomplicated bacteremia), 4–6 weeks of therapy is recommended, depending on the extent of infection. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (**B-III**).

20. For adults with infective endocarditis, IV vancomycin (**A-II**) or daptomycin 6 mg/kg/dose IV once daily (**A-I**) for 6 weeks is recommended. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (**B-III**).

2- Quelle dose de daptomycine ?

- 4 mg / kg ?
- 6 mg / kg ?
- 8 mg / kg ?
- 10 mg / kg ?

Posologie de daptomycine ?

- Augmentation de CMI en cours de traitement ?
  (Fowler VG et al NEJM 2006;355:653-65)
  - daptomycine 6 mg/kg 120 patients vs 115 traitement conventionnel
  - 19 échecs / bactériémie persistante ou récidivante
  - augmentation de CMI de daptomycine / 7 patients
- Cas cliniques ++
  - ostéomyélites
  - infections profondes, inoculum élevé
  - concentrations faibles

High-Dose Daptomycin for Cardiac Implantable Electronic Device–Related Infective Endocarditis

Emanuele Durante-Mangoni, Roberta Casillo, Mariano Bernardo, Cristina Caianiello, Irene Mattucci, Daniela Pinto, Federica Agrusta, Roberta Caprioli, Rosina Albisinni, Enrico Ragone, and Riccardo Utili

- 25 patients, 68 ans (25-87), endocardite certaine
- *S. epidermidis* (56%), autre SCN (16%), *S. aureus* (28%)
- daptomycine
  - dose médiane 8,3 mg/kg (6,4 – 10,7)
  - durée médiane 20 j (8-52)
- + retrait du matériel 22 patients (88%), délai médian 15 j (3-79), culture + 20 (80%)
- évolution :
  - favorable 20 cas (80%)
  - bactériémie initiale : 21 patients
    - hémocultures négatives J4 19 patients,
    - bactériémie persistante : 2 patients (j8 et j21), pas d'augmentation CMI

(Clin Infect Dis 2012;54:347-54)

Intérêt d'une dose élevée

- **SCV :** *(Tumbarello M et al Clin Infect Dis 2012;54:1516-7)*
  - 6 patients + endocardite liée à du matériel
  - SCN (4), *S. aureus* (2)
  - daptomycine (8,1 à 9,1 mg/kg) : durée médiane 24 j (8-56)
  - retrait du matériel 9 j après début ttt (3 – 16)
  - 5 succès cliniques

Intérêt d'une dose élevée

- **Données pharmacocinétiques : valves et végétations**
  - 2 patients, *S. oralis* et *S. epidermidis*

TABLE 1 Main clinical, microbiological, and PK/PD data from two cases of endocarditis treated with daptomycin[a]

Patient	Endocarditis	Organism in blood culture	Daptomycin MIC (mg/liter), basal	Body wt (kg)	Daptomycin						Tissue culture	Daptomycin MIC (mg/liter)
					Dose (mg/day)	C_{max} (mg/liter)	C_{min} (mg/liter)	C_{max}/MIC	Concn (μg/g) in: Valve tissue	Concn (μg/g) in: Vegetation		
61-year-old male	Mitro-aortic native valve	*Streptococcus oralis*	0.094	72	500 (6.9 mg/kg)	36.6 (day 5)	8.5 (day 5)	389				
					700 (9.7 mg/kg)	81.8 (day 15)	14.8 (day 15)	870	Mitral, 30.8 Aortic, 8.6	Mitral, 26	*S. oralis* (day 18)	0.38 (4-fold increase)
69-year-old male	Aortic, porcine prosthetic valve (Carpentier-Edwards)	*Staphylococcus epidermidis*	0.38	70	500 (7.1 mg/kg)	45.3 (day 5)	9.9 (day 5)	119	Valve, 53.1 Perivalvular,18.1		Negative (day 37)	

[a] Target values for C_{max}, C_{min}, and C_{max}/MIC were >60 mg/liter, <24 mg/liter, and >100, respectively.

(Tascini C et al AAC 2013;57:601-2)

3- Faut il prescrire une association ?

- Gentamicine ?
- FQ ?
- Rifampicine ?
- Oxacilline ?
- Autre ?

Synergie
Limiter le risque de résistance

Quelle association pour les endocardites ?

Review Article

Antibiotic Combinations with Daptomycin for Treatment of *Staphylococcus aureus* Infections

Kristina Nadrah and Franc Strle

TABLE 2: Information on *in vivo* synergy of antibiotic combinations.

Model	Strain	Combination	Observation	Ref.
Experimental model of IE	MRSA	Daptomycin 6 mg/kg q24 h + rifampin 300 mg q8 h	Rifampin and gentamicin antagonized/delayed the bactericidal activity of daptomycin	[39]
		Daptomycin 6 mg/kg q24 h + gentamicin 1.3 mg/kg q12 h		
Rabbit model of IE	MRSA	Daptomycin 6 mg/kg q24 h + gentamicin 1 mg/kg q8 h	60% vegetations sterilized	[41]
		Daptomycin 6 mg/kg q24 h + rifampin 300 mg q8 h	20% vegetations sterilized	
Rabbit model of IE	DNS MRSA	Daptomycin 12 mg/kg q24 h + oxacillin 200 mg/kg q8 h	Enhanced bacterial clearance from tissues	[56]
Case report on IE	MRSA with progressive loss of susceptibility during treatment	Treated with vancomycin, then daptomycin 6 mg/kg q24 h, then daptomycin 12 mg/kg q24 h + rifampin 300 mg q8 h	Clinical success	[42]

(Chemother Research and Practice 2011)

Intérêt d'une association ?

- endocardite du lapin *S. aureus* métiR
  - daptomycine vs dapto + genta ou dapto + rifampicine
  - *in vitro :* courbes de bactéricidie (3 souches)
    - dapto + genta (2 X CMI)= synergie
    - dapto + rifampicine = indifférence (2) ou antagonisme (1)
  - *in vivo* :

dapto 6 mg/kg
genta 1 mg/kg x 3
rif 300 mg x 3

D = D+G >> D+R

TABLE 5. Treatment of experimental endocarditis caused by MRSA-572

Treatment group	No. of animals with sterile vegetation/ total (%)[a]	Median (range) IQR (log_{10} CFU/g of vegetation)[b]
Control[a]	0/15 (0)	10 (9.7–10)
Gentamicin	0/12 (0)	8.6 (8.1–9)
Rifampin	0/13 (0)	6.6 (5.2–10)
Daptomycin	10/15 (67)*†	0 (0–2)‡§
Daptomycin + gentamicin	9/15 (60)*¶	0 (0–2)‡‖
Daptomycin + rifampin	3/15 (20)†¶	3 (2–3.5)§‖

[a] The control animals were sacrificed 18 h after the infection was started.
[b] *, $P = 0.70$; †, $P = 0.01$; ‡, $P = 0.83$; §, $P = 0.02$; ¶, $P = 0.02$; ‖, $P = 0.04$. The symbols represent levels of statistical significance between two values with the same symbol.

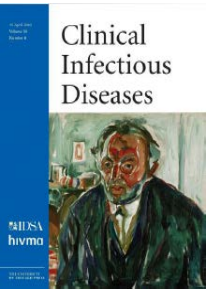
(Miro JM et al AAC 2009;53:4172-7)

+ Oxacilline

- Données expérimentales / SARM

(Garrigos C et al AAC 2012,56:3806-11)

  - *in vitro* : bactéricidie dapto + cloxacilline > daptomycine
  - *in vivo* :
    - bénéfice + cloxacilline (indépendant de posologie de daptomycine)
    - intérêt pour souches SARM rif R ?
- Effet similaire avec autres bétalactamines
  - amo-ac clav, cefotaxime, cefepime, imipenem, ceftaroline …

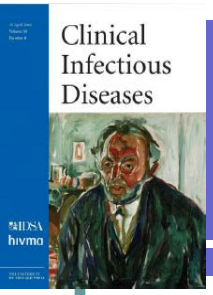


Use of Antistaphylococcal β-Lactams to Increase Daptomycin Activity in Eradicating Persistent Bacteremia Due to Methicillin-Resistant *Staphylococcus aureus*: Role of Enhanced Daptomycin Binding

Abhay Dhand,[1] Arnold S. Bayer,[3,4] Joseph Pogliano,[5] Soo-Jin Yang,[3,4] Michael Bolaris,[3] Victor Nizet,[5] Guiquing Wang,[2] and George Sakoulas[1,5,6]

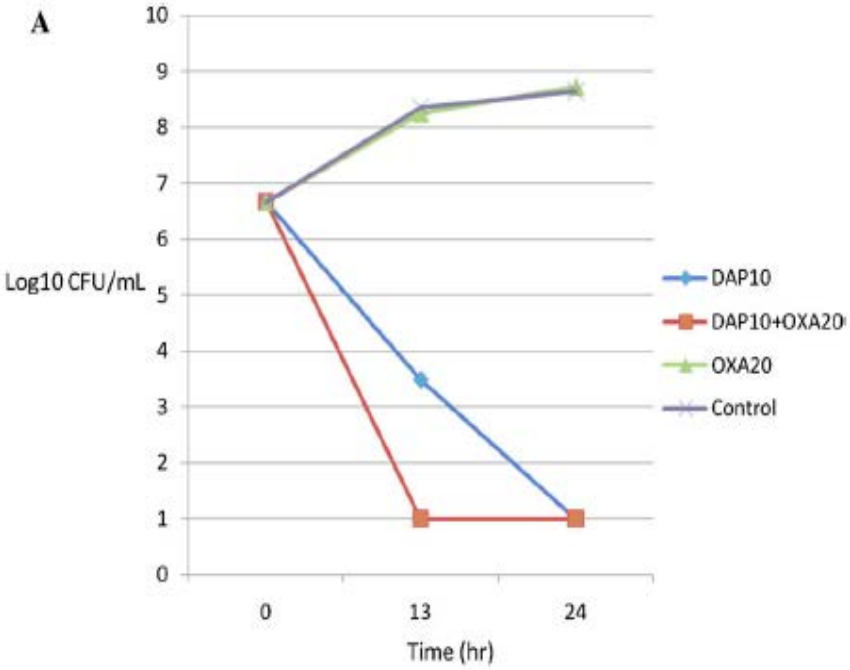
- 7 patients + bactériémie persistante SARM
  - 7 – 22 j, vanco (relais dapto)
  - concentrations sériques de vanco adaptées
  - pas de foyer profond
  - 1 souche VISA (CMI vanco 3mg/l, dapto 2-4 mg/l)
  - dapto (8 – 10 mg/kg) + pénicilline M (2g x 6 /24h) stérilisation des hémocultures, 24h- 48h

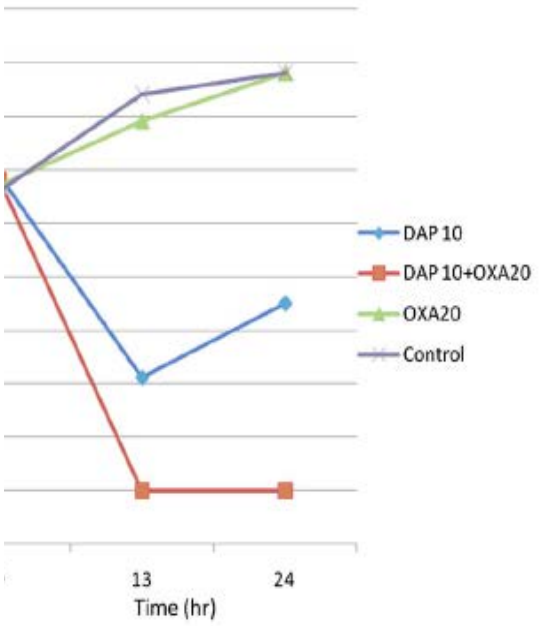
(Dhand A et al Clin Infect Dis 2011;53:158-63)



Courbes de bactéricidie (3 souches)

- Modification de la charge au niveau de la surface bactérienne, fixation de la dapto « renforcée »





(Dhand A et al Clin Infect Dis 2011;53:158-63)

+ Fosfomycine

- Cas cliniques (5)
  - 1 endocardite + défibrillateur
  - 4 endocardites du cœur gauche
    - 3 valves natives
    - 1 bioprothèse
  - ostéomyélite associée 3 cas
- Données microbiologiques
  - SAMS et SAMR
  - synergie
  - apports NaCl ???

+ Autres

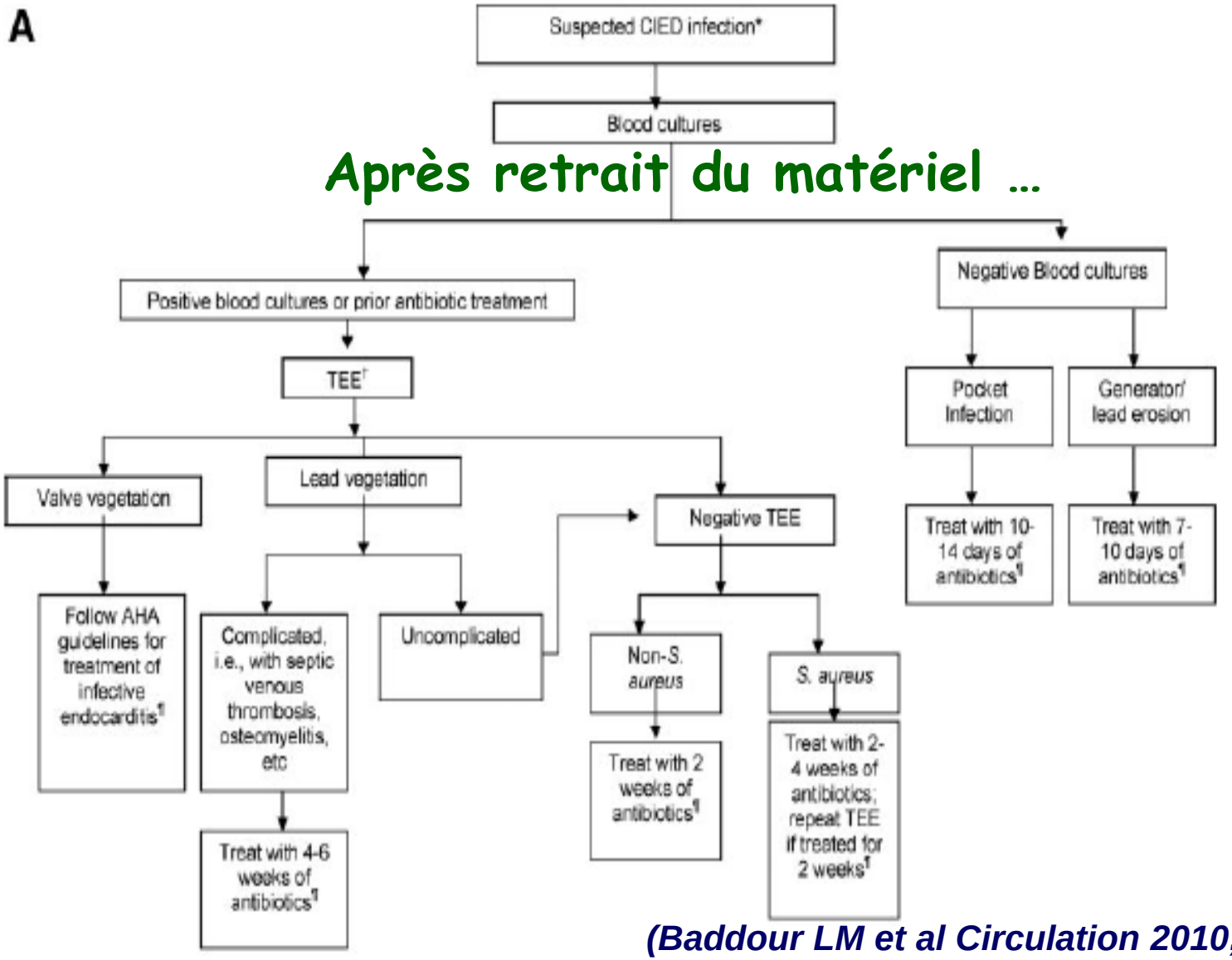
- TMP-SMZ
  - données in vitro : modèle pharmacodynamique d'endocardite + végétations
- Clarithromycine
  - efficacité / biofilm
- Telavancine
  - endocardite du lapin …
- Delafloxacine
  - biofilm…..

4- Durée ?

- 2 semaines après ablation du matériel ?
- 4 semaines après ablation du matériel ?
- 6 semaines au total ?
- selon le résultat de culture des sondes / valves ?

Circulation
American Heart Association

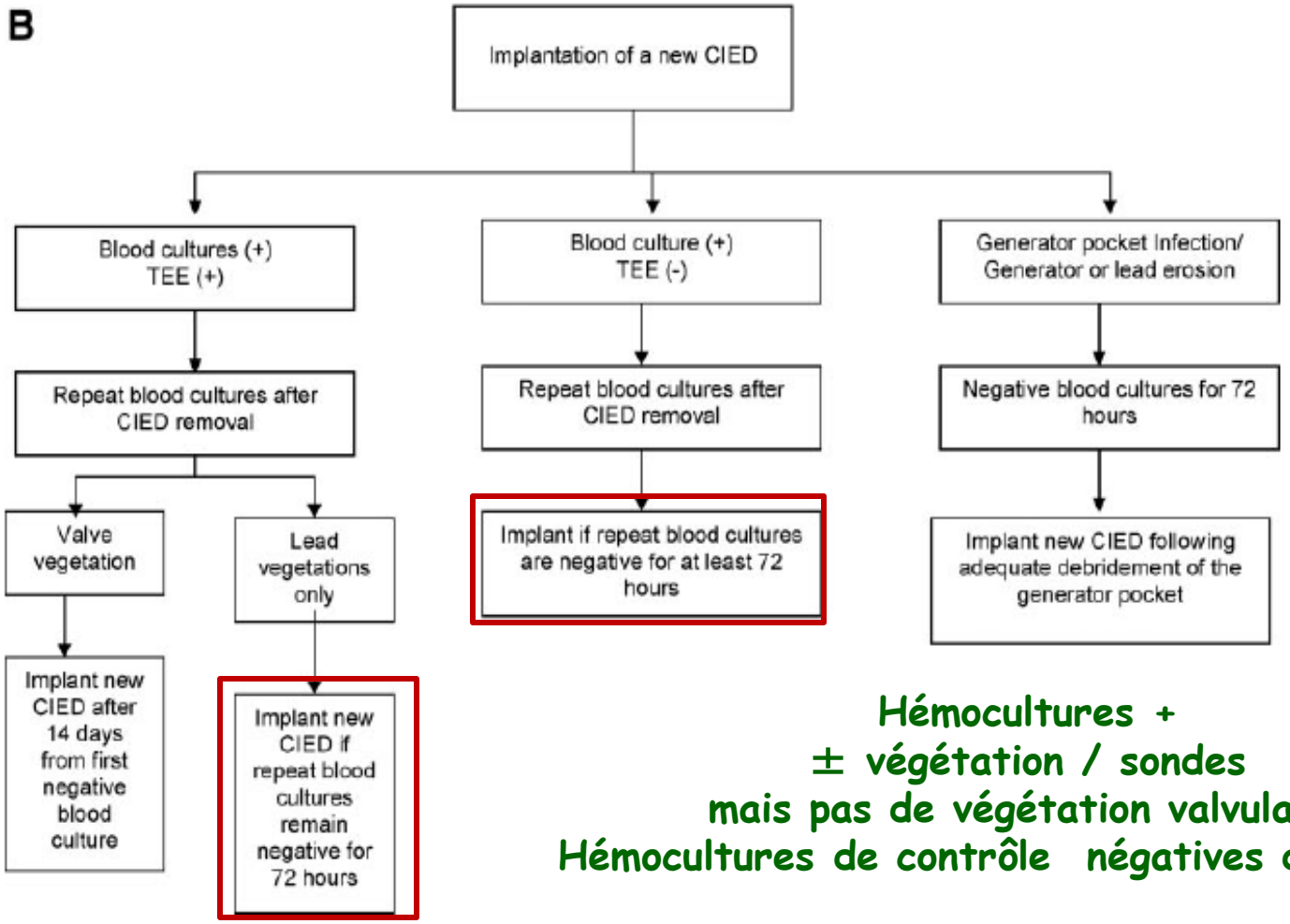
Update on Cardiovascular Implantable Electronic Device Infections and Their Management : A Scientific Statement From the American Heart Association



Après retrait du matériel …

(Baddour LM et al Circulation 2010;121:458-77)

Quand re implanter du matériel ??



Hémocultures +
± végétation / sondes
mais pas de végétation valvulaire
Hémocultures de contrôle négatives depuis 72H

Figure 2. A, Approach to management of adults with CIED infection. AHA indicates American Heart Association. Modified from Sohail et al[38] with permission. *A history, physical examination, chest radiograph, electrocardiogram, and device interrogation are standard baseline procedures before CIED removal. ¶Duration of antibiotics should be counted from the day of device explantation. Treatment can be extended to 4 or more weeks if there are metastatic septic complications (ie, osteomyelitis, organ or deep abscess, etc) or sustained bloodstream infection despite CIED removal. B, Approach to implantation of a new device in patients after removal of an infected CIED. Modified from Sohail et al[38] with permission.

(Baddour LM et al Circulation 2010;121:458-77)

Conclusion

- La dapto pour tous …non
- La dapto à posologie élevée …oui
- La dapto en association …probablement
  - dapto + béta-lactamine …