Nouveaux antibiotiques dans le traitement de l'endocardite infectieuse

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AEPEI

Nouveaux antibiotiques pour le traitement des EI à cocci Gram+ résistants

- Antibiotiques commercialisés
  - Quinupristine-Dalfopristine (Synercid®)
  - Linézolide (Zyvoxid®)
  - Daptomycine (Cubicin®)
- Antibiotiques en développement
  - Telavancine
  - Dalbavancine, oritavancine

Quinupristine-Dalfopristine

- Activité anti-bactérienne
  - activité parfois bactéricide sur certains staphylocoques
  - active sur les souches résistantes d'*Enterococcus faecium*
  - pas d'activité sur *Enterococcus faecalis*.
- Utilisation clinique
  - cathéter veineux central
  - 7,5 mg/kg 3 fois par jour
  - effets indésirables relativement fréquents
    - Arthralgies
    - hyperbilirubinémie
  - efficacité dans le traitement des EI à *S. aureus* résistant à la méticilline ?

Effect of Combinations of Quinupristin-Dalfopristin (Q/D) plus other antibiotics in MRSA or GISA Experimental Endocarditis

Synergy

MRSA

Q/D + gentamicin (Batard, AAC 2002)

Q/D + vancomycin (Pavie, AAC 2002)*

Q/D + β-lactams (Vouillamoz, AAC 2000)

Q/D + rifampin (Zarrouk, AAC 2001)

GISA

Q/D + cefpirome (Vouillamoz, AAC 2000)

* There are several case reports successfully treated with this combination.

Treatment of MRSA infections with Q/D in patients intolerant of or failing prior therapy

	Clinical Success Rates	
	All Treated	Evaluable
Overall	75.6%	74.1%
Bacteremia		
Unknown	3 of 5	-----
Catheter	4 of 6	1 of 1
Endocarditis	6 of 11	0 of 2
	54.4%	

Drew RH et al. J Antimicrob Chemother 2000;46:775.

Linézolide (Zyvoxid®)

- Activité anti-bactérienne (oxazolidinones)
  - inhibition de la synthèse des protéines
  - activité contre les cocci Gram + multi-résistants
    - staphylocoques résistants à la méticilline
    - entérocoques résistants à la vancomycine
- Utilisation clinique
  - 600 mg 2 fois par jour chez l'adulte (IV/PO)
  - Durée maximale d'utilisation : 28 jours
  - myélotoxicité (thrombopénie) temps- et dose-dépendante
  - cytotoxicité mitochondriale
    - neuropathie périphérique, souvent irréversible
    - acidose lactique, d'évolution possiblement fatale

Linezolid et IE expérimentale

- EI à MRSA : le linézolide seul ou en association avec la vancomycine s'est avéré moins efficace que la vancomycine seule.

TABLE 1. Outcome of 5-day treatment of experimental MRSA aortic valve endocarditis

Treatment regimen	No. sterile at the following site/total no. of rabbits		Mean bacterial count (log_{10} CFU/g) ± SD	
	Valve vegetation	Kidney	Valve vegetation	Kidney
Control	0/8	0/8	10.24 ± 0.68	8.66 ± 0.73
Vancomycin	3/8	3/8	$3.31^{a,b}$ ± 3.00	2.23^{a} ± 2.44
Linezolid t.i.d. for 1 day, for 4 days	0/8	7/8	7.80^{a} ± 0.99	0.71^{a} ± 2.02
Linezolid plus vancomycin	0/8	8/8	6.56^{a} ± 1.03	1.00^{a} ± 0.00
Linezolid t.i.d. for 5 days	0/8	3/8	6.27^{a} ± 1.80	1.75^{a} ± 1.47

Chiang, AAC 2003;47:3002

- EI à *Enterococcus faecium* résistant à la vancomycine (phénotype van-A) chez le rat, le linézolide s'est avéré plus efficace que la vancomycine. (Patel AAC 2001)

Linezolid for the Treatment of Multidrug-Resistant, Gram-Positive Infections: Experience from a Compassionate-Use Program

Endocarditis	No.	Clinical Cure*	Bacteriological Cure*
All cases	40	15 (75%)	11 (61%)
- VREF	22	10 (77%)	7 (64%)
- MRSA	8	3 (100%)	4 (100%)

VREF = Vancomycin-resistant *E. faecium*; MRSA = Methicillin-resistant *S. aureus*.
* Outcome = No. of cures / Total No. of courses – Nonevaluable courses

Birminghan MC. Clin Infect Dis. 2003;36:159

Linezolid for the Treatment of IE Due to MRSA with Reduced Susceptibility to Vancomycin

No. Cases**	Duration +BC with Vanco, days	Bacteriological Cure***	Mortality
8	16 (8-32)	4 (50%)	5 (62%)

Linezolid (Lz) alone, 3 cases; in combination, 1case.
Rifampin plus Fusidic acid (R+FA), 1 case.
Sequential Rx (Lz ⇔ R+FA), 3 cases.

*Vanco MIC ranging 2-4 mg/L; **Two cases of PVE; *** Negative BC at 3, 10 and 10 months. The 4th case died of comorbidities. BC were negative after linezolid therapy

Howden BP et al. Clin Infect Dis. 2004; 38:521

Linézolide : observations d'échec

- Ruiz ME, CID 2002; 35:1018–20
  - Cas n°1 : EI à SARM
    - Échec de vancomycine
    - Échec de linézolide
    - Guérison sous cotrimoxazole
  - Cas n°2 : EI à SARM
    - Échec de linézolide
    - Guérison sous vancomycine + rifampicine
- Zimmer SM, CID 2003;37:e29
  - EI à *E. faecalis*, hémodialysé
    - Echec de Linézolide (ATCD d'allergie à ampi et vanco)
    - Guérison sous ampicilline + gentamicine

Linezolid: observations de guérisons

- Archuleta et al. Transpl Infect Dis 2004;6:7
  - EI à VREF, transplanté rénal, infecté par le VIH
    - Linézolide per os. Guérison.
- Babcock et al Clin Infect Dis 2001;32:1373-75
  - EI à VREF, trisomie 21, hémodialysée, cathéter
    - Échecs successifs sous chloramphénicol puis Q/D
    - Linézolide per os. Guérison.
- Rao et al CID 2002;35:902-03
  - EI à *E. faecalis* ampi-S, bioprothèse aortique, diabétique
    - IRA sous ampicilline + gentamicine
    - Linézolide pendant 6 semaines. Guérison.

What Antibiotic Combinations with Linezolid (Lz) Can Improve the *in vivo* activity of Linezolid (Lz) against MRSA Experimental Endocarditis ?

Synergy

Lz + imipenem (Jacqueline C, 2005)

No synergy

Lz + Vancomycin (Chiang FY, 2003)

Lz + rifampin (Dailey CF, 2003)

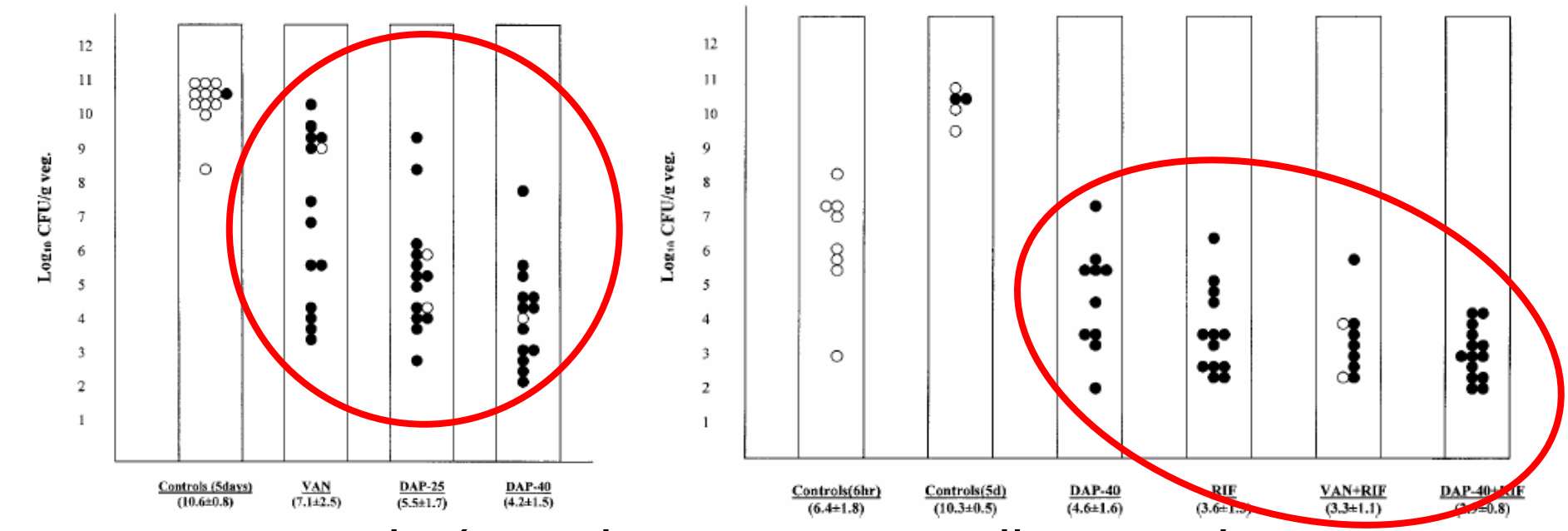
Controversial results

Lz + gentamicin (Jacqueline C, 2004; LaPlante KL, 2004)

Daptomycin (Cubicin®)

- Lipopeptide cyclique bactéricide sur les cocci Gram +, SARM inclus.
- Autorisé aux USA pour le traitement des infections de la peau et des tissus mous. (CID 2004;38:1673)
- Récemment autorisé aux USA pour le traitement des infections bactériémiques à *S. aureus*, incluant les EI du cœur droit (25 Mai 2006)
  - DAP-IE-01-02: a Phase 3, multicenter, randomized, open-label, comparative study to assess the safety and efficacy of daptomycin compared to conventional therapy in the treatment of subjects with infective endocarditis or bacteremia due to *S. aureus.*

Efficacy of daptomycin in experimental endocarditis due to MRSA



- Daptomycin (at a dose corresponding to a human dose of 4 to 6 mg/kg q24h) was comparable to or better than vancomycin
- The combination of rifampin with daptomycin was superior to daptomycin alone.

Sakoulas et al., AAC 2003;47:1714

Efficacy of Daptomycin in MRSA Endocarditis in the Rat Model

Sakoulas G. Antimicrob Agents Chemother. 2003; 47:1714.

Treatment groups	Doses (4-days Rx)	MIC μg/ml	Vegetations* Density (no. rats)
- Control	-	-	6.4 ± 1.8 (8)
- Daptomycin	25 mg/kg/24 h.	1	5.5 ± 1.7 (14)
- Daptomycin	40 mg/kg/24 h.	1	4.2 ± 1.5 (15)[a]
- Vancomycin	150 mg/kg/24 h.	0.5	7.1 ± 2.5 (14)[a]

Daptomycin was given at 25 mg or 40 mg/kg/24 h by SC route in order to simulate human doses of 4 and 6 mg/kg q24 h, respectively; * Mean ± SD $\log_{10}$ cfu/g veg (no. treated animals); a $p<0.05$ for vancomycin versus daptomycin – 40 mg/kg.

Efficacy of Daptomycin in GISA (ATCC 700788) Endocarditis in the Rabbit Model

Treatment groups	Doses* (2-days Rx)	MIC μg/ml	Veg. Density (Sterile veg, %)**
- Control	-	-	9.1 ± 0.9 (0%)
- Daptomycin	iv 6 mg/kg/24 h.	0.5	4.8 ± 3.5 (63%)[a]
- Vancomycin	iv 1 g/12 h.	8	6.0 ± 2.4 (20%)[a]

* Human-like pharmacokinetic profile; ** Mean ± SD $\log_{10}$ cfu/g veg (% of sterile vegetations); a $p<0.05$.

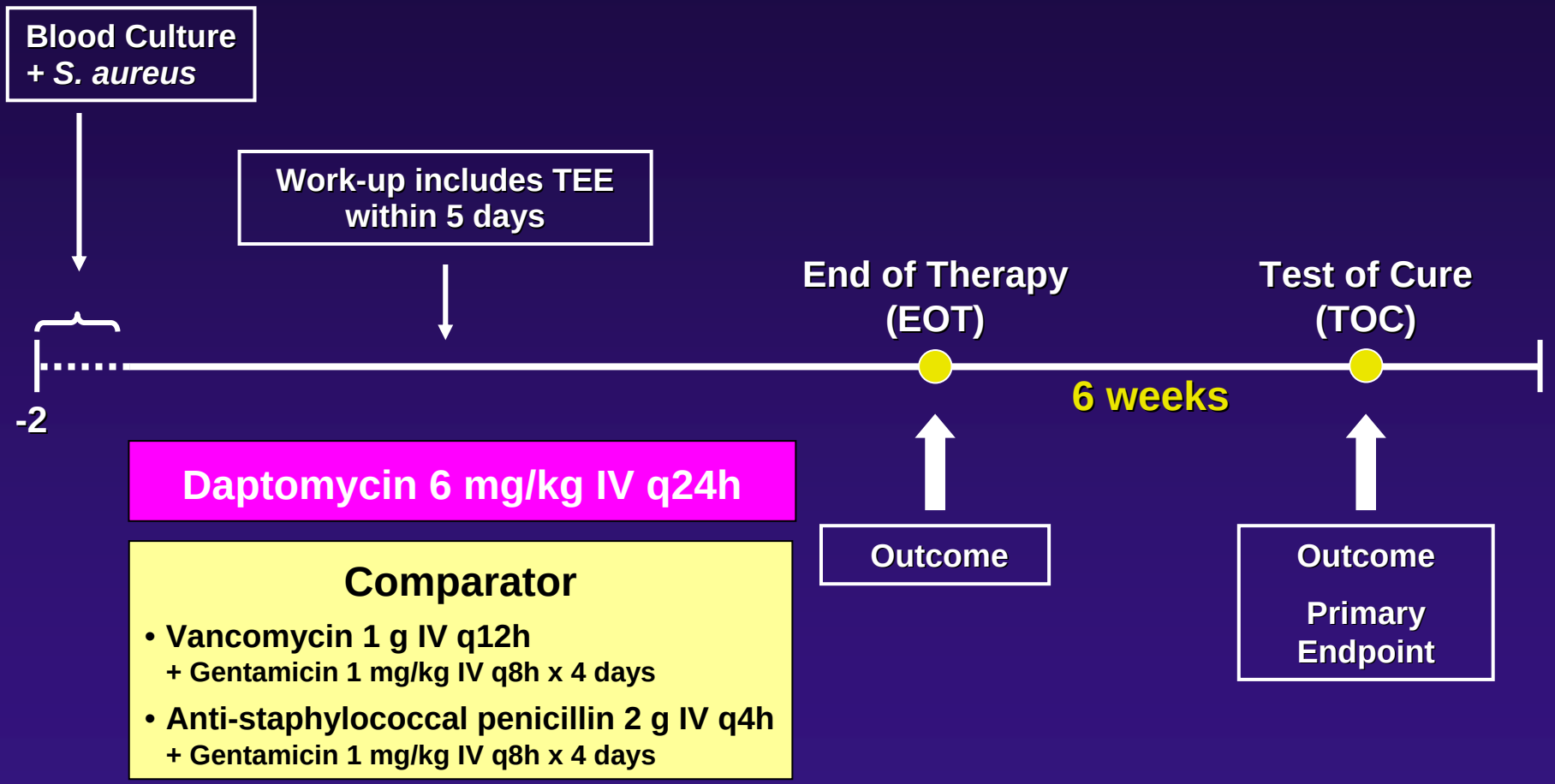
García de la María C et al. 45th ICAAC. 2005

DAP-IE-01-02: Key Eligibility Criteria

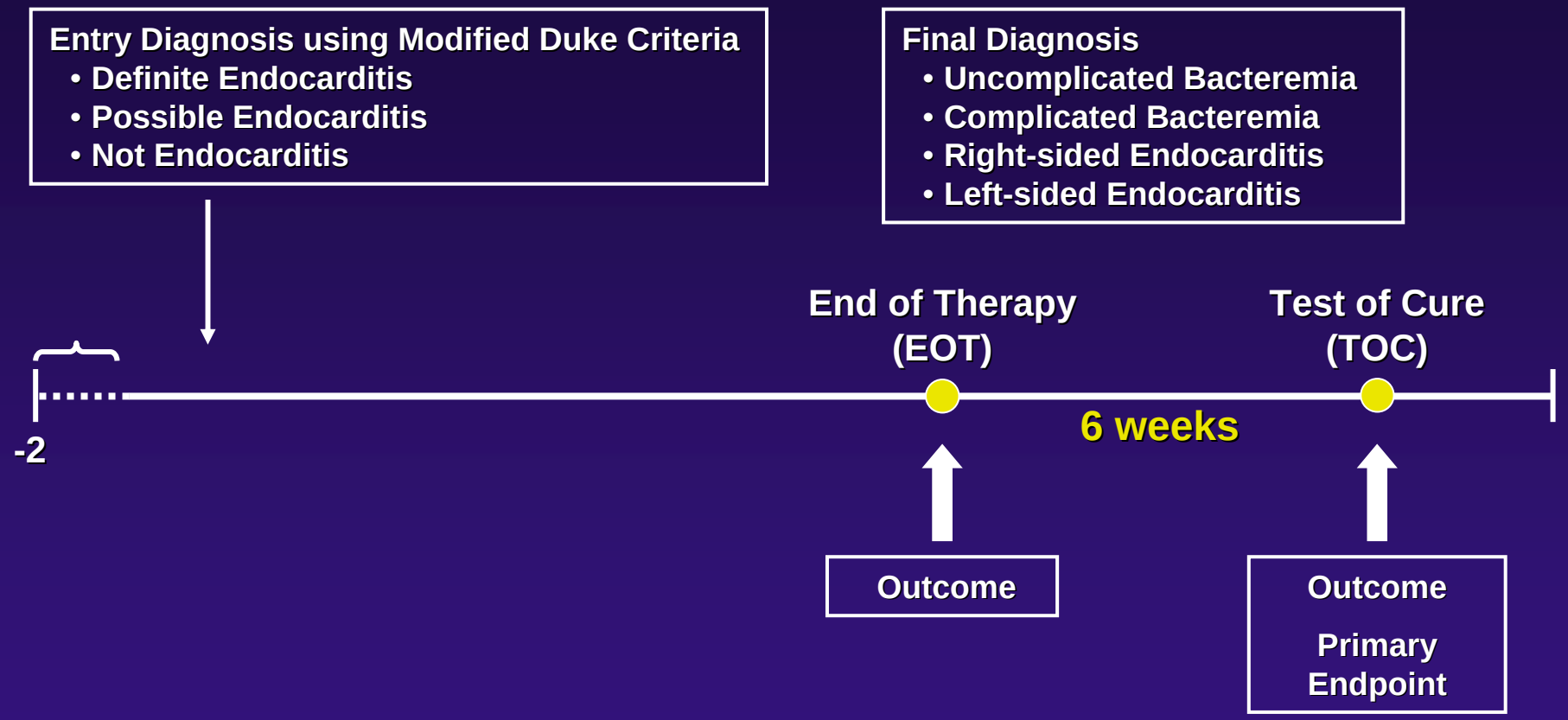
- **Inclusion criteria**
  - **Written informed consent**
  - **≥ 18 years of age**
  - **Documented *S. aureus* bacteremia**
- **Exclusion criteria**
  - **Intravascular foreign material**
  - **Prosthetic heart valve**
  - **Creatinine clearance < 30 mL/minute**
  - **Known pneumonia, osteomyelitis**
  - **Polymicrobial bacteremia**
  - **Moribund**

Fowler VG, ICAAC 2005

DAP-IE-01-02: Study Design



DAP-IE-01-02: Blinded Independent External Adjudication Committee



DAP-IE-01-02: Outcome Definitions

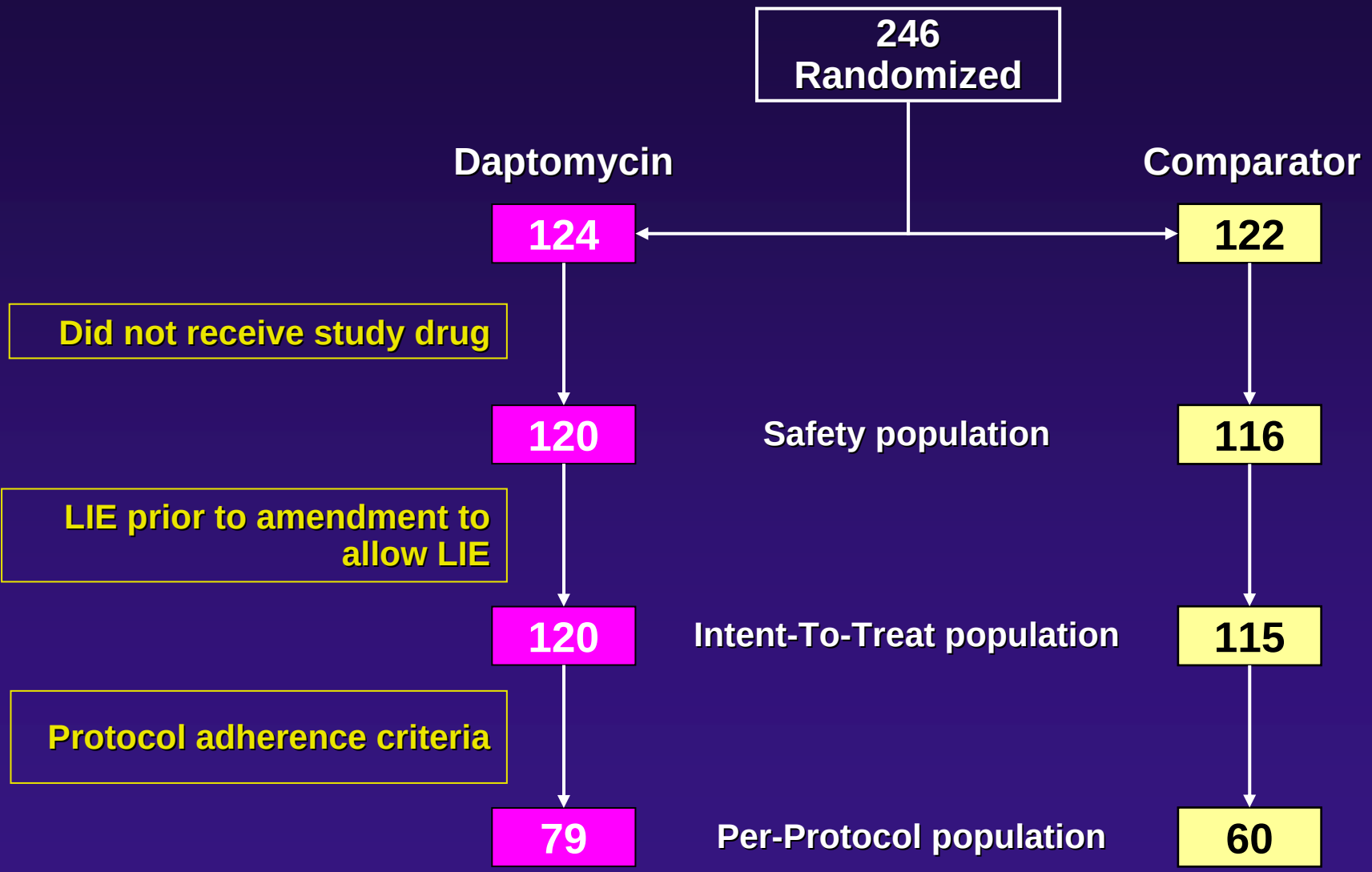
Success (all of the following required)

- Clinically cured or improved
- Negative blood culture
- Did not receive a potentially effective non-study antibiotic
- Received minimum amount of study medication per Investigator

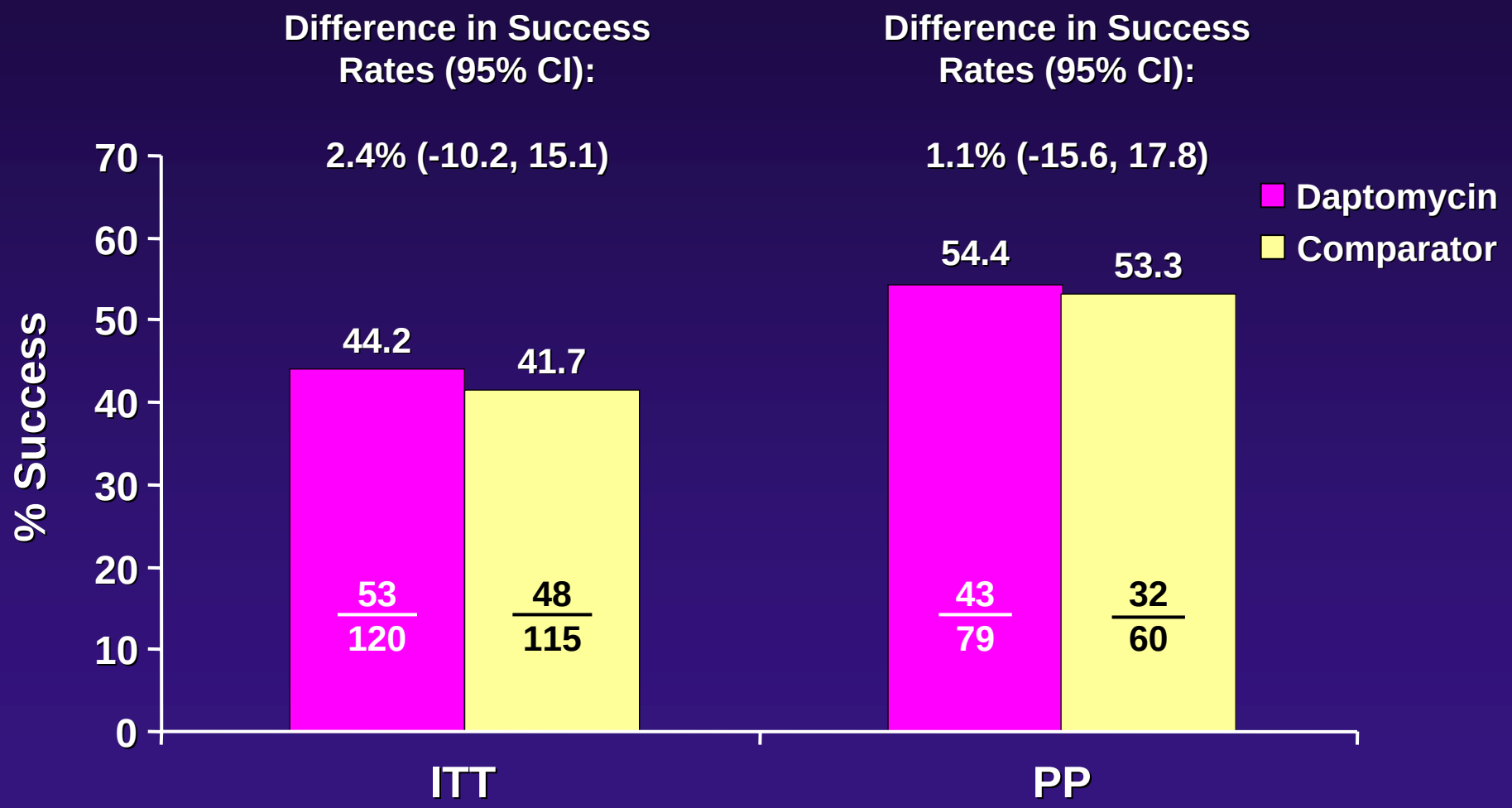
Failure (any of the following)

- Persisting or relapsing *S. aureus*
- Death
- Clinical failure
- Received a potentially effective non-study antibiotic
- Discontinued study medication prematurely due to either:
  - Adverse event
  - Microbiological failure
  - Clinical failure
- No blood culture at Test of Cure

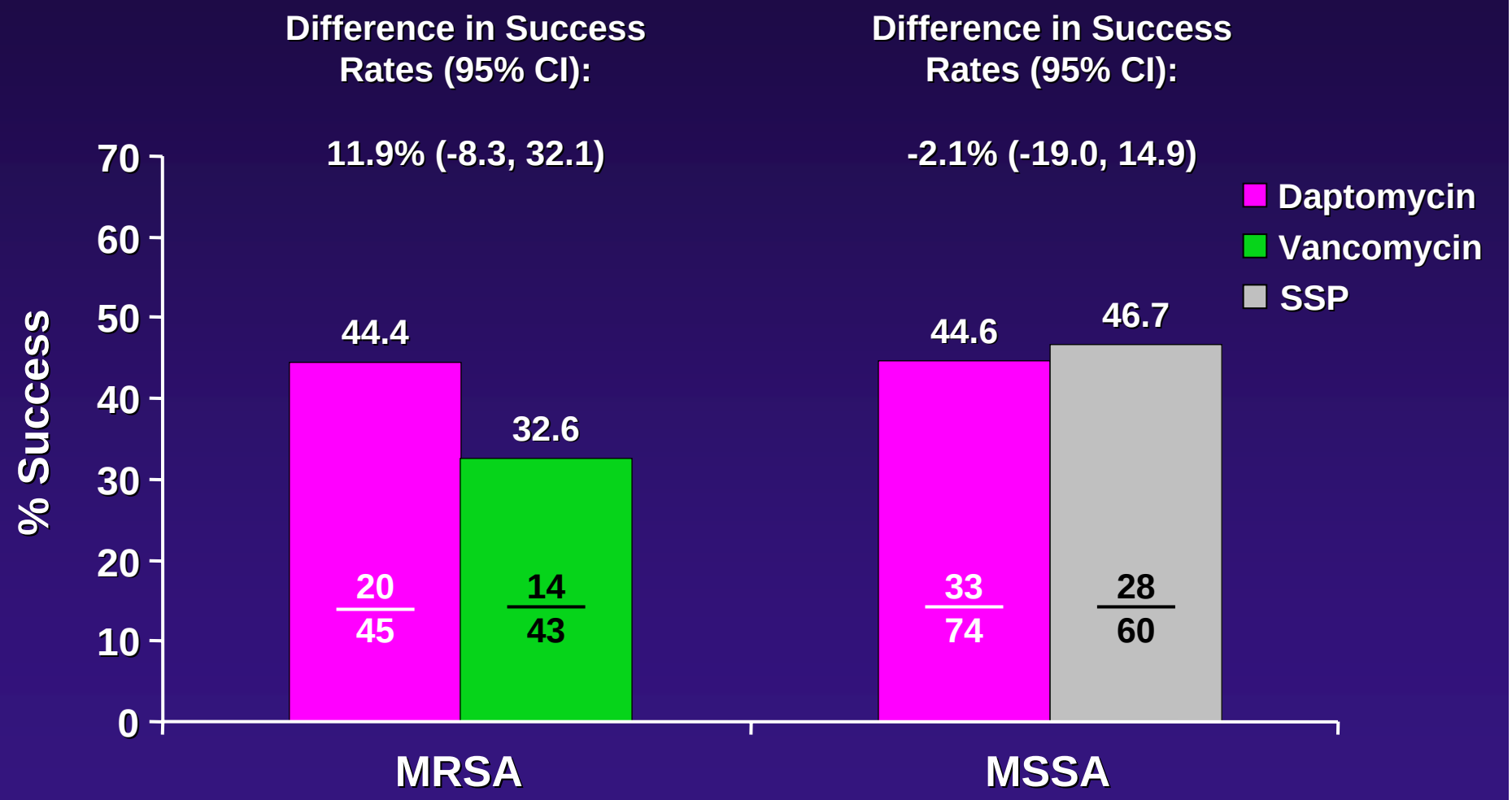
DAP-IE-01-02: Patient Disposition



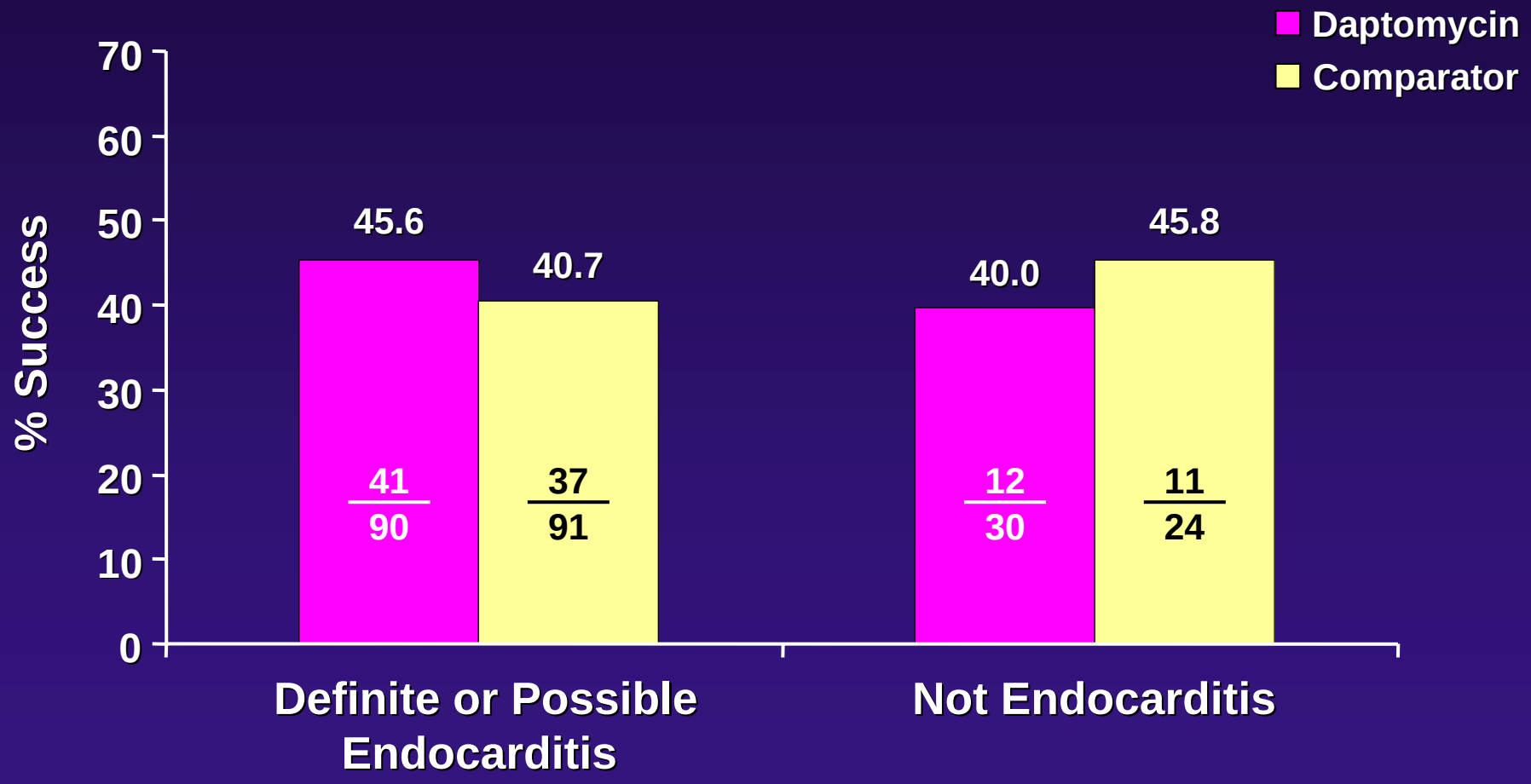
Primary Endpoint: Success at Test of Cure per Adjudication Committee (ITT/PP)



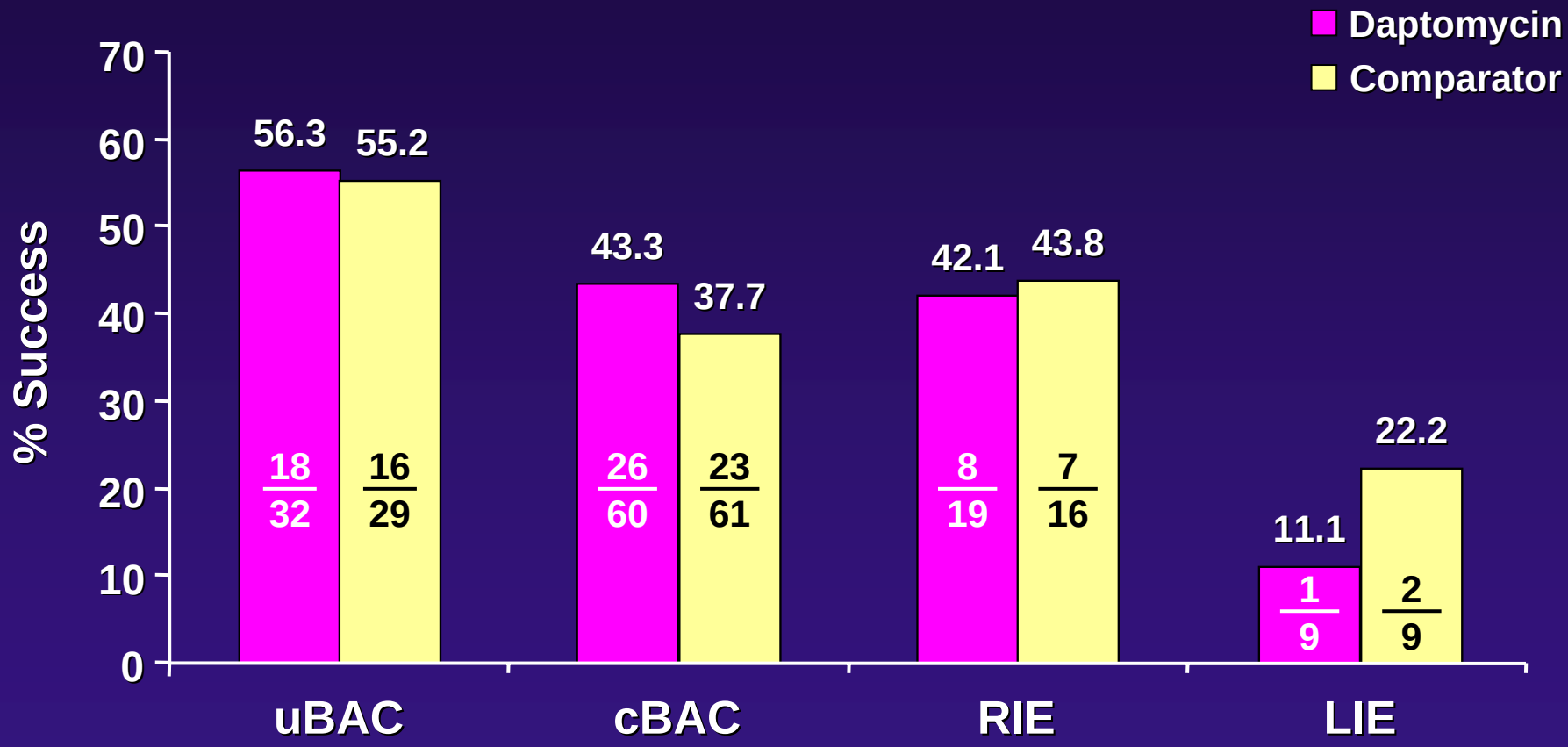
MRSA and MSSA Success at Test of Cure: Pathogen Specific Therapy per Adjudication Committee (ITT)



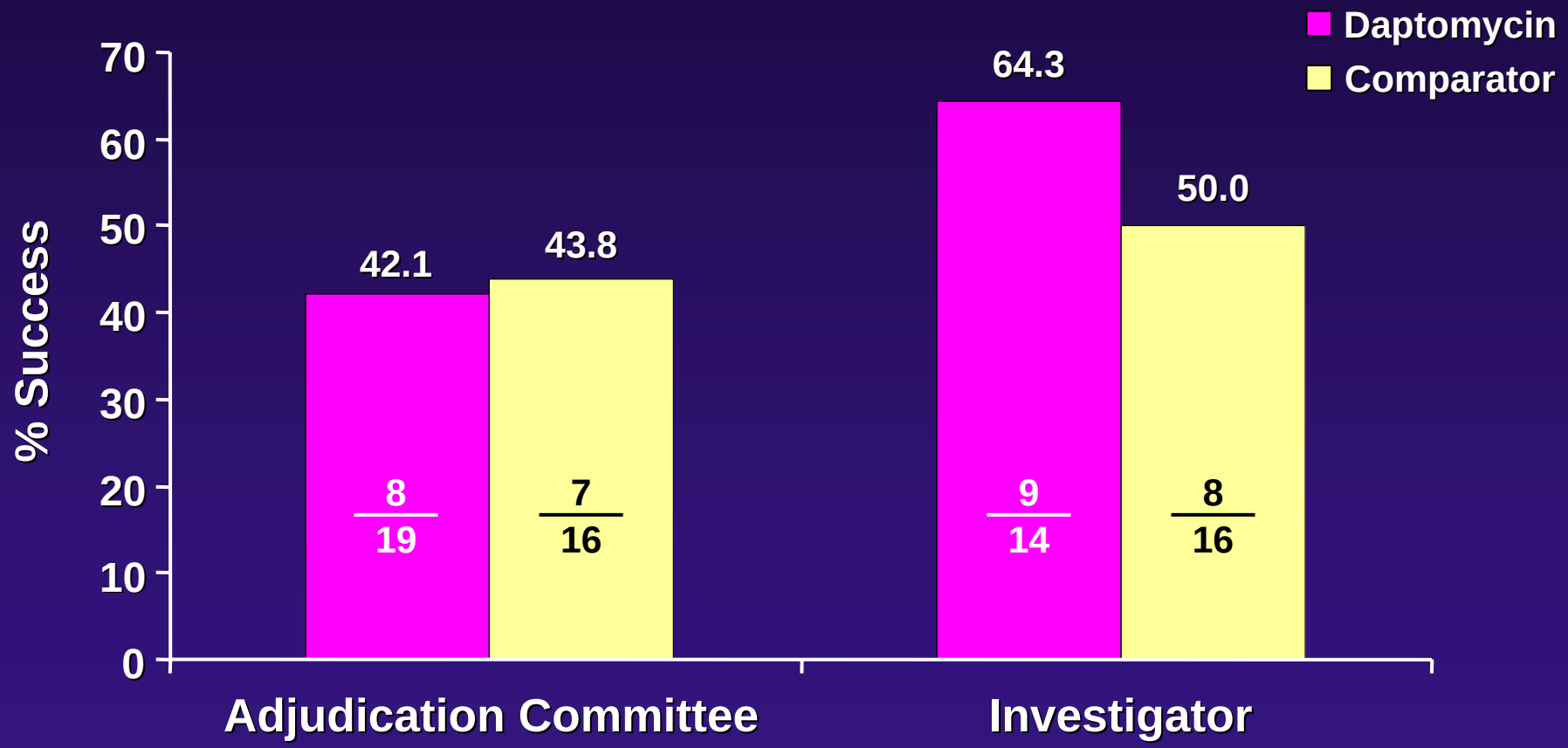
Entry Diagnosis: Success at Test of Cure per Adjudication Committee (ITT)



Final Diagnosis: Success at Test of Cure per Adjudication Committee (ITT)



Right Sided Endocarditis: Success at Test of Cure (ITT)

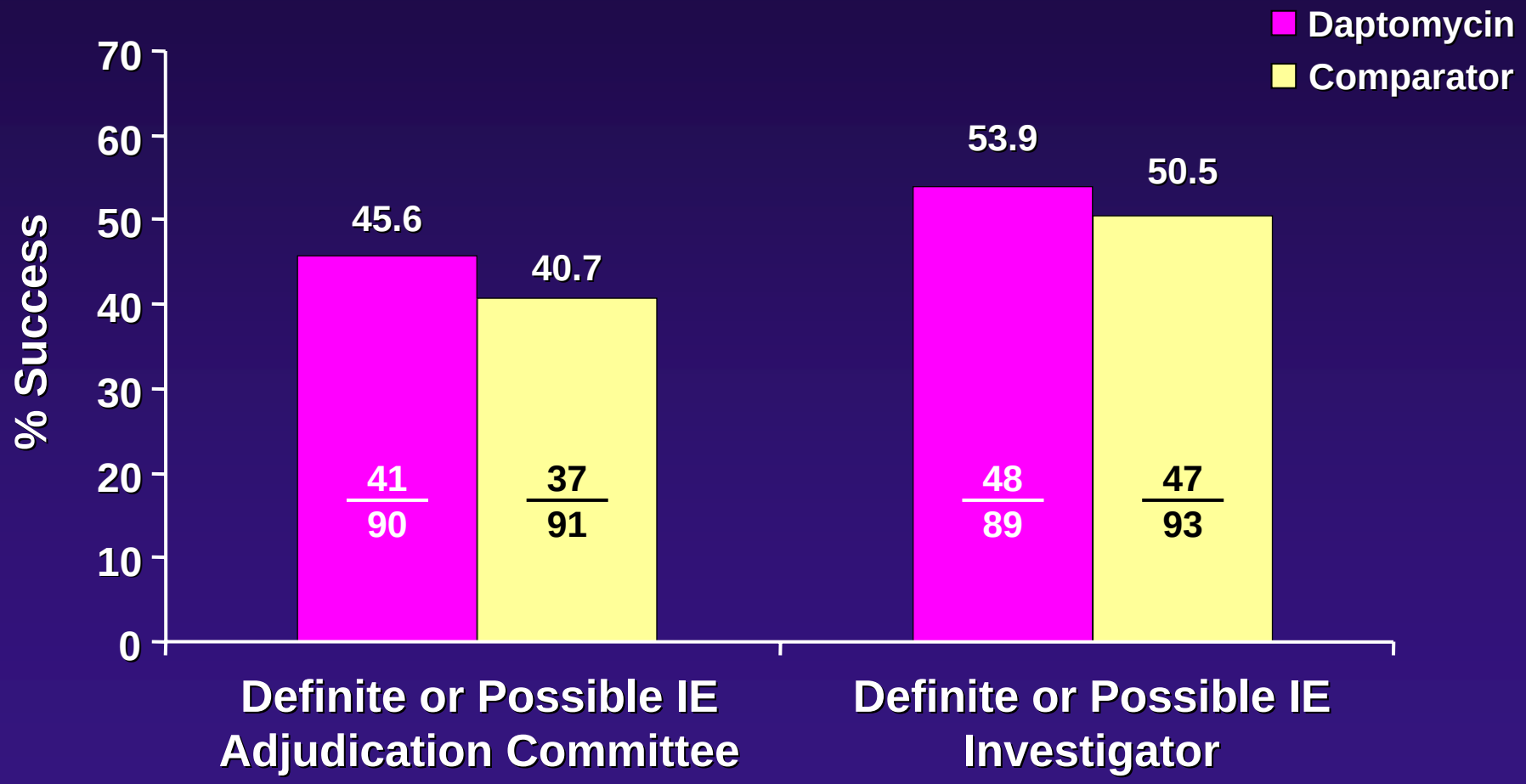


Left Sided Endocarditis (ITT)

	Daptomycin N = 9 n (%)	Comparator N = 9 n (%)
Adjudication Committee Success		
End of Therapy	**4 (44.4)**	**3 (33.3)**
Test of Cure	**1 (11.1)**	**2 (22.2)**
MRSA	**0/5**	**0/4**
MSSA	**1/4 (25.0)**	**2/5 (40.0)**
Survival	**6 (66.7)**	**4 (44.4)**

Comparator patient 001 entered study with LIE prior to LIE amendment
Success at EOT, failed at TOC due to sepsis and death (no valve replacement surgery)

Known or Suspected Endocarditis: Success at Test of Cure (ITT)



DAP-IE-01-02: Efficacy Conclusions

- **Primary efficacy endpoint met in ITT and PP**
- **Daptomycin response higher than vancomycin response in MRSA**
- **Efficacy results robust and consistent**
  - **Across pre-specified subgroups**
  - **Per Adjudication Committee and Investigator**
- **Daptomycin 6 mg/kg IV once daily was efficacious in the treatment of patients with S. aureus bacteremia including those with known or suspected endocarditis.**

Efficacy of daptomycin in the treatment of experimental endocarditis due to susceptible and multidrug-resistant enterococci

Entenza et al. 16th ECCMID. Nice (France) 2006; P-1156.

Strain	Phenotype	Infected rats/total			
		Controls	DAP	VAN	AMX
E. faecalis JH2-2	VAN-S; AMP-S	8/8	1/10	4/9	1/9
E. faecalis JH2-2/pIP819	VAN-R; AMP-S	9/9	2/11*	6/6	1/11
E. faecium D366	VAN-R; AMP-R	10/10	1/10*†	6/6	9/9

* $P < 0.05$ vs VAN † $P < 0.05$ vs AMX

Conclusions: In rats with experimental endocarditis, DAP, at doses simulating human kinetics of 6 mg/kg every 24 h, was significantly superior to VAN against VAN-R *E. faecalis* and *E. faecium*, and to AMX against AMP-R *E. faecium*.

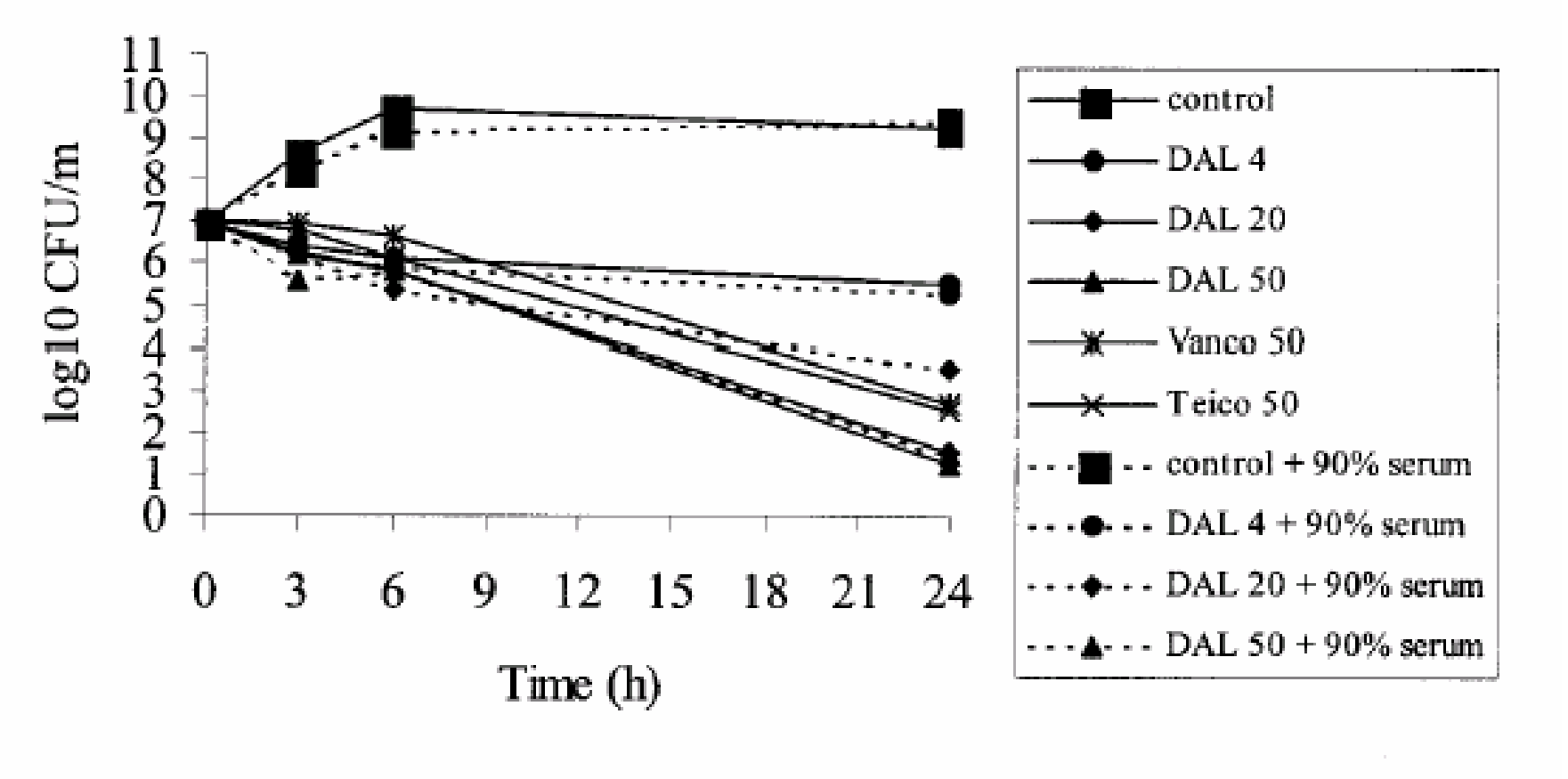
Tentative de synthèse

	SARM	VREF
Q/D	Non	NON
Linézolide	??	Oui
Daptomycine	Cœur D : Oui Cœur G : ?	?

Dalbavancin (BI-397, Biosearch Italia)

- Semisynthetic glycopeptide
  - active in vitro and in animal models against gram-positive cocci, including MRSA.
  - elimination half-life of ≈ 1 week, resulting in high plasma levels sustained in humans for a long time.
- Preliminary studies showed that dalbavancin is at least as potent as vancomycin against MRSA with or without reduced susceptibility to vancomycin.

Activity of dalbavancin in a rabbit model of endocarditis due to GISA



Lefort et al., AAC 2004;48:1061

Telavancin (TD-6424, Theravance)

- Novel glycopeptide, with specific features
  - bactericidal,
  - multiple synergistic mechanisms/sites of action
  - concentration-dependent killing against gram-positive aerobes, including vancomycin-resistant strains
  - postantibiotic effects of up to 6 h against *S. aureus*
- TD-6424 is currently in phase 2 trials for serious gram-positive infections
  - Skin and soft tissue infections
  - Bacteremia and endocarditis (ASSURE trial).

Evaluation of Telavancin in the Rabbit Model of Aortic Endocarditis due to MRSA or VISA.

Madrigal AG et al. Antimicrob Agents Chemother. 2005; 49:3163-5.

Treatment groups	Doses (4-days Rx)	MIC µg/ml	Vegetations* Density (no. sterile)
MRSA strain			
- Control	-	-	7.4 ± 0.2 (0/7)
- Vancomycin	IV 30 mg/kg/12 h.	2	4.0 ± 3.2 (3/10)
- Telavancin	IV 30 mg/kg/12 h.	1	2.7 ± 3.1 (6/11)
VISA strain			
- Control	-	-	6.7 ± 0.5 (0/5)
- Vancomycin	IV 30 mg/kg/12 h.	16	6.8 ± 0.4 (0/6)
- Telavancin	IV 30 mg/kg/12 h.	4	1.2 ± 2.6* (4/6)**

* Mean ± SD $\log_{10}$ cfu/g veg (no. sterile vegetations / treated animals); * $p<0.001$; $p=0.06$.

Susceptibility to Clinafloxacin of GPC isolated from blood cultures of IE patients

Pathogen	N	MIC range (mg/l)
MSSA	33	0.015-0.06
MRSA	5	0.015-0.06
CNS	8	0.015-8
Oral streptococci	28	0.015-0.25
Group B streptococci	8	0.06-0.12
E. faecalis	7	0.12-0.5
E. faecium	2	0.5-8

DP Levine et al, Clin infect Dis 2004;38:620-31

Clinafloxacin for the treatment of IE

- 53 patients with NVE
  - *S. aureus* & oral streptococci most frequent pathogens
  - Overall succes rate: 87%
  - Valve cultures negative in all 12 patients operated on
- 13 patients with PVE
  - *E. faecalis* most frequent pathogen
  - Overall succes rate: 69%

DP Levine et al, Clin infect Dis 2004;38:620-31

Association pour l'Etude et la Prévention de l'Endocardite Infectieuse

Prochaine assemblée générale :
19 septembre 2006, 14 h à 17 heures
Hôtel-Dieu, Paris

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