

Nouvelles perspectives dans le traitement de l'EI

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Mortality rates of IE in the XXth century Dramatic progress... until 1950

Period	Mortality rate	Reference
1900	100%	Osler 1899
1950	30%	Hunter 1951
2000	26%	Hasbun, 2003 Wallace, 2002 Cabell, 2002 Hoen, 2002
	27%	
	35%	
	17%	

IE: an evolving disease

- More valvular prostheses and PV IE
- More intravascular devices and device-related IE
- More patients with major comorbidities
 - Diabetes, hemodialysis
 - IVUDU, HIV infection
- More nosocomial and nosohusial IE
- More staphylococcal IE
 - More antibiotic-resistant organisms

How to improve the cure rate of IE? Some milestones on a tough pathway

- Refining indications for surgery
- Antiplatelet agents ?
- Newer antibiotics
- Newer strategies

Comparison 1999 vs. 1991

	1991	1999	P
Overall crude incidence	28.6 [25.9-31.6]	25.9 [23.4-28.7]	
Overall standardized incidence	30.9 [27.9-34.1]	26.5 [23.9-29.6]	<0.00001
Standardized incidence by UHD			
- no previously known UHD	10.2 [8.6-12.2]	11.4 [9.7-13.5]	0.78
- previously known UHD	20.6 [18.2-23.4]	15.1 [13.1-17.5]	<10 ⁻⁶
- prosthetic valve	6.9 [5.5-8.6]	4.7 [3.6-6.2]	<0.00001
Standardized incidence by pathogen			
- oral streptococci	7.8 [6.4-9.5]	5.1 [4.0-6.7]	<0.0001
- group D streptococci	5.3 [4.1-6.9]	6.2 [5.0-7.9]	0.67
- <i>Staphylococcus aureus</i>	4.9 [3.8-6.3]	5.7 [4.5-7.3]	0.97
Rate of surgical treatment	31.2 %	49.7 %	<2.10 ⁻⁷
Lethality rate	21.6 %	16.6 %	0.08

Indications for surgery in IE state-of-the-art

- Indications for surgery in IE are well defined
 - Congestive heart failure
 - Refractory infection
 - Severe anatomical/functional valve damages
- Benefits of surgery in IE are supported by clinical experience, not evidence-based
 - Absence of randomized trials (unethical & unfeasible)
 - Unavoidable biases of observational studies
 - Overall, sicker patients are selected for surgery
 - The sickest patients are not operated on.

Impact of valve surgery on 6-month mortality in adults with complicated LS NV IE: a propensity analysis

- **Methods**
 - Propensity analyses to control for bias in treatment assignment and prognostic imbalance
 - Observational cohort study (1990 – 2000) of 513 pts:
 - 230 (45%) underwent valve surgery
 - 283 (55%) received medical therapy alone
- **Results: mortality at 6 months (overall mortality: 26%)**
 - Unadjusted: HR 0.43 (CI 0.29-0.63)
 - Adjusted for heterogeneity: HR 0.35 (CI 0.23-0.54)
 - 218 propensity-matched: HR 0.45 (CI 0.23-0.86)
 - Adjusted for confounding: HR 0.40 (CI 0.18-0.91)
 - Moderate to severe CHF: HR 0.22 (CI 0.09-0.53)

Vikram et al., JAMA 2003;290:3207

Should surgery be performed in all IE patients? (1)

- **IE in IVDU and HIV-1 patients** (Miro, Cardiol Clin 2003)

	RS IE	LS IE
Overall mortality:	<5%	20-30%
Operated patients:	<2%	15-25%
- ***S. aureus* PV IE** (Chirouze, Clin Infect Dis 2004)
 - 61 SA-PVIE from the ICE-MD. Overall mortality rate 47.5%
 - Prognosis analysis:
 - Stroke was associated with an increased risk of death
 - Early valve replacement was not associated with a significant survival benefit in the whole population
 - Patients who developed cardiac complications and underwent early valve replacement had the lowest mortality rate (28.6%).

Should surgery be performed in all IE patients? (2)

- **Conclusion for routine clinical practice**
 - Although patients with clear indications for surgery should undoubtedly undergo early valve replacement, hemodynamically stable patients under careful supervision may be treated safely with antibiotics alone.
- **Some (out of many) pending questions**
 - What is the optimal interval between Ab and surgery?
 - Is earlier better? If yes, how early?
 - Is a large, oscillating vegetation an indication for surgery in itself?

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- **Antiplatelet agents ?**
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Platelets induce/stimulate vegetation growth

1. endocardial lesion, inducing platelet and fibrin deposition at the damaged site
2. adherence of bloodstream pathogens to this site
3. further deposition of platelets and fibrin onto infected endocardium
4. endocardial reseeded, either hematogenously or from intra-endocardial microorganisms

Host defense role for platelets in IE

- Platelets secrete low-molecular-weight cationic antimicrobial peptides (PMPs)
- Thrombin-induced PMP-1 (tPMP-1) is generated from rabbit platelets in vitro upon stimulation with thrombin
- tPMP-1 exerts potent cidal effect and growth inhibition against pathogens such as *S. aureus* and viridans streptococci
- tPMP-1-resistant organisms have an apparent selective survival advantage in experimental IE, in terms of
 - Intravegetation proliferation
 - Extracardiac hematogenous dissemination

Experimental data

- Facts: Low-dose (≤ 10 mg/kg/d) ASA reduces
 - vegetation size
 - bacterial density in vegetations
 - hematogenous dissemination of bacteria
 - frequency of embolic events
- Mechanisms
 - ASA inhibits platelet aggregation
 - Reduces the capacity of microorganisms to adhere to vegetative lesion ?

Questions from a physician

- What can we expect from ASA in IE?
 - improved efficacy of antibiotics
 - abbreviated course of antibiotics
 - reduced incidence of embolic events
- What are the potential risks of ASA in IE?
 - Bleeding (hemorrhagic stroke)
 - increased hemorrhagic risk during cardiac surgery
- If effective and safe, how should aspirin be used?
 - What is the optimal ASA dosage?
 - How long time should ASA be administered?

The CATIE trial

- Double-blind, placebo-controlled, randomized trial
- 14 centers in Canada – 4 years
- ASA dose: 325 mg/d for 4 weeks
- Patients screened: 560 – enrolled 115 (21%)

	Placebo (n=55)	Aspirin (n=60)
In hospital death	6 (11%)	4 (7%)
Embolism	11 (20%)	17 (29%)
Valve surgery	13 (24%)	18 (31%)
Bleeding (all)	8 (15%)	17 (29%)*

p = 0.075

KL Chan et al., JACC 2003;42:775

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Linezolid (Zyvoxid®, Pfizer)

- Linezolid alone or in combination with vancomycin was less effective than vancomycin alone in the Rx of experimental endocarditis due to MRSA.

TABLE 2. Efficacy of 14-day treatment of experimental MRSA acute valve endocarditis.

Treatment Applied	No. of patients with MRSA acute valve endocarditis at 14 days		Mean bacterial count (log ₁₀ CFU/g) at 14 days	
	Vancomycin	Vancomycin + Linezolid	Vancomycin	Vancomycin + Linezolid
Control	1/6	0/6	6.22 ± 0.69	6.86 ± 0.70
Vancomycin	4/6	7/6	6.50 ± 0.64	6.59 ± 0.66
Vancomycin + Linezolid (10 mg/kg, bid, for 14 days)	1/6	7/6	7.80 ± 0.65	6.77 ± 0.62
Vancomycin + Linezolid (20 mg/kg, bid, for 14 days)	0/6	6/6	6.90 ± 0.66	6.64 ± 0.69
Vancomycin + Linezolid (40 mg/kg, bid, for 14 days)	0/6	5/6	6.77 ± 0.61	6.58 ± 0.62

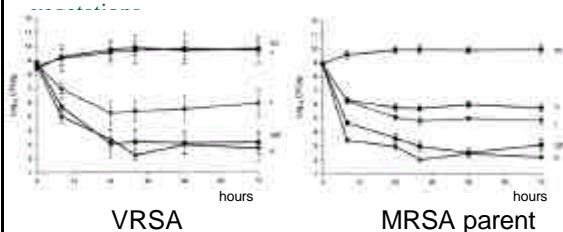
Chiang, AAC 2003;47:3002

- No synergy with rifampin (AAC 2003;47:2655)
- Case reports of clinical failure (CID 2003;37:e29)
- Time- and dose-dependant myelosuppression.

Daptomycin (Cubicin®, Cubist)

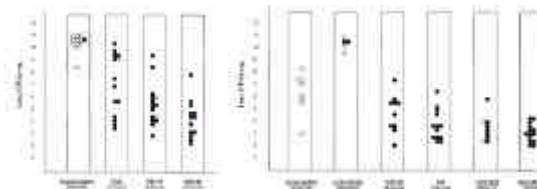
- Cyclic lipopeptide with bactericidal activity against Gram-positive pathogens, including MRSA.
- Approved for use in the Rx of complicated skin and soft-tissue infections (CID 2004;38:1673)
- Currently evaluated in *S. aureus* bacteremia and endocarditis (DAP-IE-01-02)
 - A Phase 3, multicenter, randomized, 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 *Staphylococcus aureus*

Bactericidal Activities of Daptomycin, Q/D, and Linezolid against VRSA in an in vitro pharmacodynamic model with simulated endocardial



Cha et al., AAC 2003;47:3960

Efficacy of daptomycin in experimental endocarditis due to MRSA



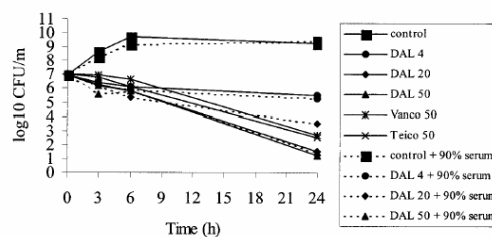
- Daptomycin (at a dose corresponding to a human dose of 4 to 6 mg/kg q24h) was comparable to or better than vancomycin
- The combination of rifampin with daptomycin was superior to daptomycin alone.

Sakoulas et al., AAC 2003;47:1714

Dalbavancin (BI-397, Biosearch Italia)

- Semisynthetic glycopeptide
 - active in vitro and in animal models against gram-positive cocci, including MRSA.
 - elimination half-life of \approx 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).

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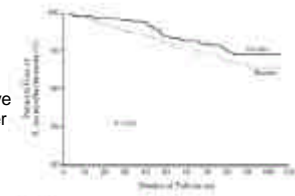
- Refining indications for surgery
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Non-antibiotic antistaphylococcal therapies in bacteremic infections

- Sa-IVIG (Inhibitex)
 - phase III (halted)
- anti-Sa clumping factor A Mab (Aurexis®, Inhibitex)
 - Phase II, multicenter, double-blind, placebo-controlled, evaluating Aurexis® as adjunct therapy in SaB.
- Pooled human Ab against Sa capsule antigens (Altastaph®, Nabi)
 - Phase II, multicenter, double-blind, placebo-controlled, evaluating Aurexis® as adjunct therapy in SaB.

Antistaphylococcal vaccination in high-risk patients

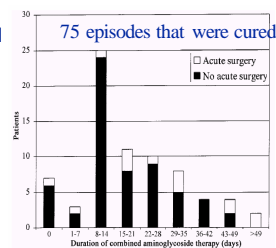
- Methods
 - double-blind trial in HD pts
 - vaccine: *S. aureus* type 5/8 capsular polysaccharides
 - 1804 adult HD patients randomly assigned to receive a single IM injection of either vaccine or saline.
- Results
 - Vaccine conferred partial immunity against *S. aureus* bacteremia for 40 weeks
 - Afterwards protection waned as antibody levels decreased.



Shinefield et al., N Engl J Med 2002;346:491

Enterococcal endocarditis in Sweden, 1995–99: Can shorter Rx with aminoglycosides be used?

- Observational study of 93 cases of enterococcal IE from the Swedish cohort of IE.
- Outcomes
 - Cure: 81%
 - Mortality: 16%
 - Relapse: 3%
- Median length of Rx
 - Total: 42 days
 - Aminoglycosides: 15 days



Olaison & Schaedwitz, CID 2002;34:159