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% 27% 35% 17%	Hasbun, 2003 Wallace, 2002 Cabell, 2002 Hoen, 2002

IE: an evolving disease

- More valvular prostheses and PV IE
- More intravascular devices and device-related IE
- More patients with major comorbidities
  - Diabetes, hemodialysis
  - IVDU, 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]	$<10^{-8}$
- prosthetic valve	6.9 [5.5-8.6]	4.7 [3.6-6.2]	<0.0001
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
- *Staphylococcus aureus*	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 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 super-vision 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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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 reseeding, 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.

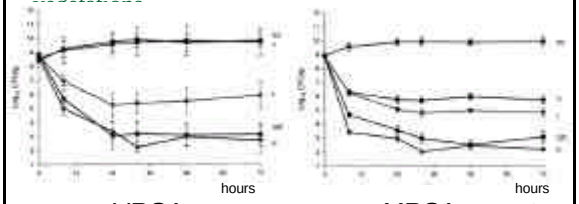
Chiang, AAC 2003;47:3002

- 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 vegetations



VRSA MRSA parent

Cha et al., AAC 2003;47:3960

Efficacy of daptomycin in experimental endocarditis due to MRSA

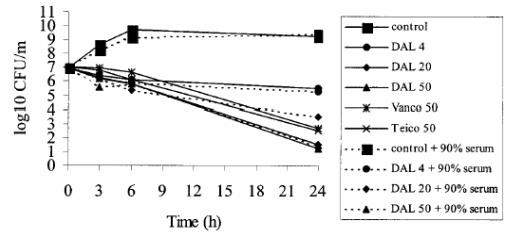
- Daptomycin (at a dose corresponding to a human dose of 4 to 6 mg/kg q24h) was comparable to or better than vancomycin
- The combination of rifampin with daptomycin was superior to daptomycin alone.

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 ≈ 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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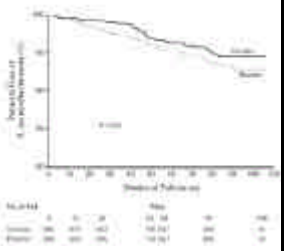
Non-antibiotic antistaphylococcal therapies in bacteremic infections

- 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

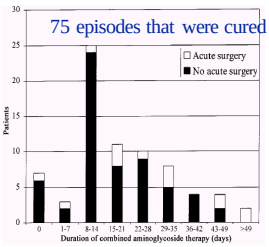
- Methods
  - double-blind trial in HD pts
  - vaccine: *S. aureus* type 5/8 capsular polysaccharides
  - 1804 adult HD patients randomly assigned to receive a single IM injection of either vaccine or saline.
- Results
  - Vaccine conferred partial immunity against *S. aureus* bacteremia for 40 weeks
  - 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 & Schadewitz, CID 2002;34:159