Best of en Infectiologie
Endocardite infectieuse

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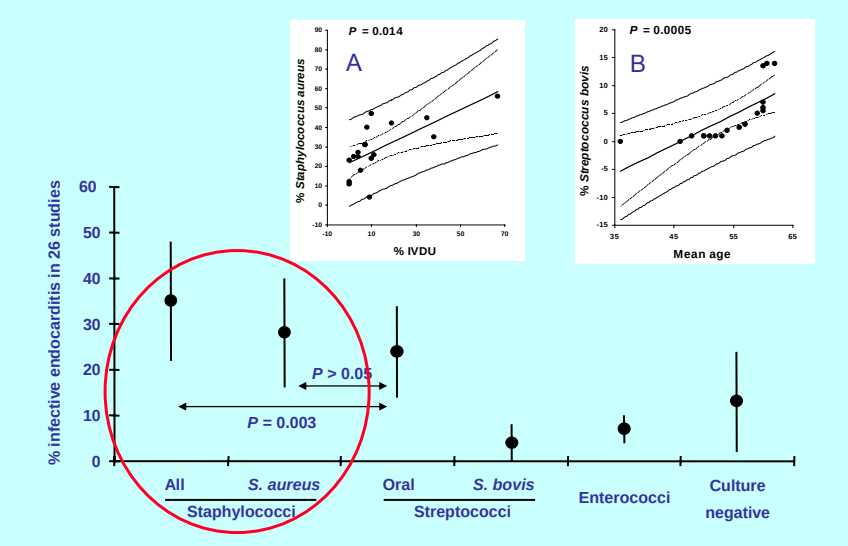
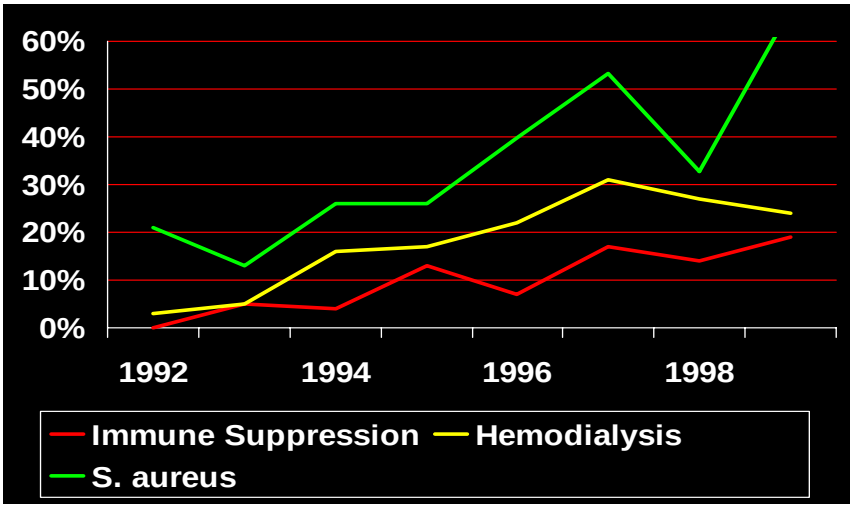
Organism frequency reported in IE in 26 studies between 1993 and 2003



Moreillon P et Que YA Lancet 2004;363:139-149

Major changes in IE



Cabell CH et al, Arch Int Med 2002;162:90-94

Microorganismes des EI en France

◆ *Streptococcaceae*	225	58%
▪ Oral streptococci	*68*	*17%*
▪ Group D streptococci	*98*	*25%*
▪ *S. gallolyticus* (51)		
▪ *S. infantarius* (6)		
▪ *S. bovis* biotype II.2 (4)		
▪ Not further identified (37)		
▪ Pyogenic streptococci	*22*	*6%*
▪ Enterococci	*29*	*7%*
▪ Other *Streptococcaceae*	*8*	*2%*
◆ *Staphylococcaceae*	115	29%
▪ *Staphylococcus aureus*	*90*	*23%*
▪ Coagulase-negative staphylococci	*25*	*6%*
◆ Other microorganisms	18	5%
◆ ≥ 2 microorganisms	13	3%
◆ No microorganism identified	19	5%

Hoen B et al. JAMA 2002;288:75-81

De 1991 à 1999: tendances

•Pas de valvulopathir connue	33%	47%
•Microorganisme identifié	92%	95%
•*Streptococcus bovis*	13%	25%
•Staphylocoques	23%	29%
•Trt chirurgical	30%	49%
•Mortalité hospitalière	21%	17%

Hoen B et al. JAMA 2002;288:75-81

Procalcitonin vs. C-Reactive Protein

- 67 consecutive patients admitted for suspected IE

	IE (n=21)	No IE (n=46)	p
CRP, mg/l	146	77	0.04
PCT, ng/ml	6.56	0.44	<0.001
BC+, n(%)	21 (100)	29 (63)	0.001

- AUC_{ROC}: CRP 0.657 PCT 0.856
- Best cutoff value for PCT: 2.3 ng/ml
  - Se: 81% Sp 85%
  - NPV 92% PPV 72%

Muller C et al. Circulation 2004;109:1707-1710

Procalcitonin vs. C-Reactive Protein (2)

- 50 patients with definite IE vs. 40 patients with bacteremia but no IE

	IE (n=50)	No IE (n=40)	p
CRP, mg/l	95	106	NS
PCT, ng/ml	3.48	4.15	NS
BC+, n(%)	46 (92)	40 (100)	NS

	Se	Sp	PPV	NPV
CRP	100	72	78	100
PCT	84	88	87	84

Kocazeybec et al. Chemotherapy 2003

Etiologic diagnosis of IE by universal PCR: a 3-year experience

- 49 patients (42M/7F) with valvular heart disease:
  - 22 definite IE, 13 possible IE, 14 no IE (rejected)
  - 18 patients with prosthetic valves
  - 39 patients had a mean of 6.9 (1-25) blood cultures drawn within prior 6 months
- 63 specimens
  - 52 valves: 38 aortic, 14 mitral
  - 11 other samples:
    - aorta 7,
    - valve swabs 3,
    - pacemaker vegetation 1

Bosshard PP et al. Clin Infect Dis 2003;37:167-172

Results of broad-range PCR compared to culture and microscopy of endocardial specimens (n=63)

Specimen status	Results of broad-range PCR, no. of specimens: Positive (n = 25)	Negative (n = 38)
Culture-positive, microscopy-negative	3[a]	3[b]
Culture-negative, microscopy-positive	7[c]	1[d]
Culture-positive, microscopy-positive	0	0
Culture-negative, microscopy-negative	15	34

b: true negative PCR

True positive

Bosshard PP et al. Clin Infect Dis 2003;37:167-172

Results of broad-range PCR compared to previous blood cultures (n=49)

Blood culture	Total	Broad-range PCR pos	neg
Positive	22	19	3
Duke major criteria	18	17	1
Duke minor criteria	4	2	2
Negative	17	3	14
Not done	10	1	9

- 3 "false-negative" of PCR
  - 7/7 *S. aureus*, Duke definite IE
  - 3/10 CNS, Duke definite IE
  - 7/21 *P. acnes*, Duke definite IE

Bosshard, Clin Infect Dis 2003

Results of broad-range PCR compared to previous blood cultures (n=49)

Blood culture	Total	Broad-range PCR	
		pos	neg
Positive	22	19	3
Duke major criteria	18	17	1
Duke minor criteria	4	2	2
Negative	17	3	14
Not done	10	1	9

- 3 true-positive PCR
  - 10/10 neg bc, *H. aphrophilus*, Duke possible → Duke definite
  - 3/3 neg bc, *S. bovis*, Duke possible → Duke definite
  - 2/2 neg bc, *T. whipplei*, Duke rejected → Duke definite

Bosshard, CID 2003

Molecular diagnosis of culture-negative IE: clinical validation in a group of surgically-treated patients

- Retrospective case-control study
  - 15 Duke defined cases, 17 valve samples
  - 13 matched controls without IE, 13 valve samples
- Universal PCR amplification
  - Two 16S rRNA primers for bacteria
  - Mixed primers of 25S and 5.8S rRNA for fungi
  - Amplicon identification by BLAST algorithm and comparison with electonic database
  - Specific sequencing in some unclear cases.

Grijalva M et al. Heart 2003;89:263-268

Molecular diagnosis of culture-negative IE: clinical validation in a group of surgically-treated patients

- Results of PCR in cases
  - PCR positive in 14/15 cases (3 definite, 12 possible).
  - Organisms detected
    - streptococci (3), staphylococci (2), enterobacter (1), *Tropheryma whippelii* (1), *Borrelia burgdorferi* (1), *Candida albicans* (1), and *Aspergillus* species (2)
    - 3 positive PCR without further identification
- Results of PCR in controls
  - PCR positive in 0/13 cases
- Sensitivity 93%, specificity 100%
- 8 hours if PCR only, 48 hours if sequencing

Grijalva M et al. Heart 2003;89:263-268

When to use PCR in IE diagnosis: tentative recommendations

- 16S-rRNA PCR on resected valves:
  - blood culture-negative IE
  - possible IE
  - blood culture = only minor Duke criterion
- Broad-range PCR for fungi on resected valves
  - blood culture-negative PV IE
  - Blood culture and 16S-rRNA PCR-negative NV IE
- Specific PCR on serum
  - High pre-test probability of *Bartonella* IE
  - High pre-test probability of *C. burnetii* IE

Bedside prognostication in IE (complicated left-sided IE)

- Retrospective observational cohort of 513 patients with complicated left-sided IE
  - Derivation cohort: 250 patients
  - Validation cohort: 254 patients
- Predictors of 6-month mortality: RR
  - Altered mental status 1.98
  - Comorbidity 1.76
  - Heart failure 1.91
  - Pathogen ≠ viridans strep 4.87
  - No surgery 2.45

Hasbun R et al. JAMA 2003;289:1933-1940

Bedside prognostication in IE (complicated left-sided IE)

	Prognostic Group				*P* Value for Linear Trend
	1	2	3	4	
Points	≤6	7-11	12-15	>15	
Total cohort (N = 513)					
No. of patients	150	147	124	92	
6-Month mortality, No. (%)	9 (6)	25 (17)	39 (31)	58 (63)	<.001
Derivation cohort (n = 259)					
No. of patients	67	68	71	53	
6-Month mortality, No. (%)	3 (5)	10 (15)	22 (31)	31 (59)	<.001
Validation cohort (n = 254)					
No. of patients	83	79	53	39	
6-Month mortality, No. (%)	6 (7)	15 (19)	17 (32)	27 (69)	<.001
P value†	.73	.49	.90	.29	

Hasbun R et al. JAMA 2003;289:1933-1940

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 HR et al. JAMA 2003;290:3207-3214

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

- 61 SA-PVIE. Overall mortality rate 47.5%
- Stroke is associated with an increased risk of death
- In the whole population early valve replacement was not associated with a significant survival benefit

Cardiac complication*	Early Valve Replacement	Mortality rate n (%)	p value
yes	yes	4/14 (28.6)	.09
yes	no	8/15 (53.3)	
no	no	11/25 (44)	
no	yes	6/7 (85.7)	

Chirouze et al. Clin Infect Dis 2004;38:1323-1327

Aspirin (ASA) in IE: 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

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

Effect of IE on Blood Coagulation and Platelet Activation

Variables	Embolic Event (+) (n = 13)	Embolic Event (−) (n = 63)	Control (n = 34)
PF 1 + 2 (nmol/L)	3.2 ± 1.3*	1.7 ± 0.7	1.4 ± 0.7
TAT (ng/ml)	7.3 ± 1.5†	2.9 ± 1.2	2.2 ± 1.1
β-TG (ng/ml)	63.3 ± 11‡	33.1 ± 12	19.1 ± 11
PF4 (ng/ml)	106.0 ± 29§	50.3 ± 17	43.0 ± 16
PAI-1 (ng/ml)	14.4 ± 6.4¶	8.6 ± 5.9	5.4 ± 4.3

- IE patients with subsequent thromboembolism have
  - increased systemic coagulation activation
  - enhanced platelet activity
  - damaged and impaired fibrinolysis.
- The resulting hypercoagulable state may contribute to the increased risk of thromboembolic events

Ileri M et al. Am J Cardiol 2003;91:689-692

The Multicenter Aspirin Study in IE

- 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

Chan KL et al., J Am Coll Cardiol 2003;42:775-780