



Score prédictif d'endocardite infectieuse chez des patients présentant une bactériémie à *Staphylococcus aureus*

Le score VIRSTA un outil pour guider le recours à l'échocardiographie.

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Blood stream infection /Bacteremia

- Growth of a **microorganism** from a **blood** culture obtained from a patient with **clinical signs** of infection
- Major **morbidity** and **mortality** worldwide
 - Incidence: 80-190 cases per 100,000 per year
 - 10th leading cause of death in the US (2002)
- **Uncomplicated/complicated**
 - ≠ deep localizations
 - ≠ treatment guidelines, treatment length

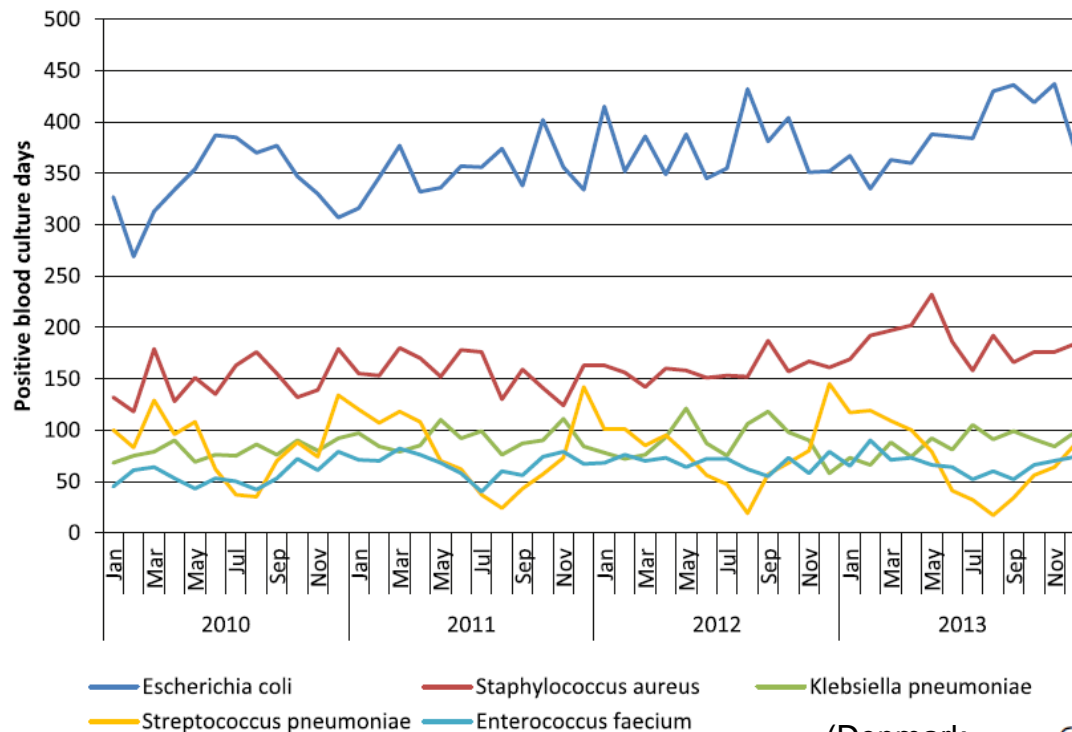
FREQUENT



Microbiologic aetiologies of bact^{er}emia

- Most common aetiologies (Laupland, CMI 2013)

- *Escherichia coli*: 35/100,000/year
- *Staphylococcus aureus*: 25/100,000/year
- *Streptococcus pneumoniae*: 10/100,000/year



of five most common pathogens per blood culture day between 2010 and 2013.

(Denmark

Clin Microbiol Infect 2014; ■: 1.e1–1.e9

Microbiologic aetiologies of endocarditis

- One of the most severe complication in patients with bacteremia

Table 4. Microbiologic Etiology by Region in 2781 Patients With Definite Endocarditis

Cause of Endocarditis	No. (%) of Patients ^a						P Value for the Difference Between Regions
	Total Cohort (N=2781)	Patients Admitted Directly to Study Sites Only ^b (n=1558)	Region				
			North America (n=597)	South America (n=254)	Europe (n=1213)	Other (n=717)	
<i>Staphylococcus aureus</i>	869 (31)	487 (31)	256 (43)	43 (17)	339 (28)	231 (32)	≈40%
Coagulase-negative staphylococcus	304 (11)	161 (10)	69 (12)	18 (7)	156 (13)	61 (9)	
Viridans group streptococci	483 (17)	288 (19)	54 (9)	66 (26)	198 (16)	165 (23)	≈30%
<i>Streptococcus bovis</i>	165 (6)	101 (7)	9 (2)	17 (7)	116 (10)	23 (3)	
Other streptococci	162 (6)	101 (7)	38 (6)	16 (6)	66 (5)	42 (6)	≈10%
<i>Enterococcus</i> species	283 (10)	158 (10)	78 (13)	21 (8)	111 (9)	73 (10)	
HACEK	44 (2)	26 (2)	2 (0.3)	6 (2)	19 (2)	17 (2)	
Fungi/yeast	45 (2)	25 (2)	20 (3)	3 (1)	13 (1)	9 (1)	
Polymicrobial	28 (1)	23 (2)	8 (1)	1 (0.4)	13 (1)	6 (0.8)	
Negative culture findings	277 (10)	122 (8)	41 (7)	51 (20)	123 (10)	62 (9)	
Other	121 (4)	66 (4)	22 (4)	12 (5)	59 (5)	28 (4)	

Risk of infective endocarditis and bacteremia

Infective endocarditis (IE) / bacteremia

Bacteremia

Risk of IE

E. coli

Rare

S. aureus (Del Rio, CID, 2009)

5-17%

Letality:30-40%

Enterococci (Bouza, CID, 2015)

3-10%

Letality:38%

Streptococci

S. pyogenes/pneumocoque

Rare

S. viridans*

≈ 13%

S. bovis**

?

* oral cavity commensal micro-organism ; can cause significant infection (IE, meningitis) when the oral mucosa is significantly disrupted and host defense mechanisms are compromised

Echocardiography in patients with bacteremia

- 1) *At what level of suspicion should an echocardiography be obtained?*
- 2) *Should transoesophageal echocardiography be systematically used?*

Echocardiography in patients with bacteremia

- Advantages/disadvantages to **systematically perform** echocardiography

Advantages

Early detection of IE

- Adapt antimicrobial therapy
- Discuss valvular surgery

Disadvantages

Limited access

Costly

Uncomfortable procedures

Echocardiography in patients with bacteremia

- Advantages/disadvantages to **systematically perform** echocardiography

Advantages	Disadvantages
Early detection of IE <ul style="list-style-type: none">- Adapt antimicrobial therapy- Discuss valvular surgery	Limited access Costly Uncomfortable procedures

- **Transthoracic /transesophageal**

TTE	TEE
Sensitivity (40 to 63%) Less costly Less uncomfortable	Higher sensitivity (90 to 100%) More costly More uncomfortable/small risk of death Limited access

What are the current guidelines ?

European guidelines for IE diagnosis

Echocardiography

Transthoracic and transoesophageal echocardiography (TTE/TEE) are now ubiquitous and their fundamental importance in diagnosis, management, and follow-up (Table 8) of IE is clearly recognized.⁷⁰

Echocardiography must be performed rapidly, as soon as IE is suspected. The utility of both modes of investigation is diminished when applied indiscriminately, however, and appropriate application in the context of simple clinical criteria improves diagnostic yield⁷¹ (Figure 1). An exception is the patient with *S. aureus* bacteraemia where routine echocardiography is justified in view of the frequency of IE in this setting and of the virulence of this organism, and its devastating effects once intracardiac infection is established.^{13,72}

Should echocardiography be systematic in all cases of bacteremia?

YES: TTE + TEE for all *S. aureus* bacteremia patients

**What is really done in clinical practice in
S. aureus bacteremia patients ?**



Echocardiography in *S. aureus* b. patients

- **TTE/TEE performed in $\approx 36\%$ of cases** (Holland, JAMA, 2014)
- **Infrequent use of echocardiography** related to :
 - a lack of awareness of the guidelines
 - the low level of scientific evidence supporting them
 - limited access to echocardiography in some settings
 - the desire to avoid uncomfortable procedures
- **The need to rule-out IE remains open to debate:**
 - TEE may be unnecessary in some patients with uncomplicated *S. aureus* bacteremia
 - TEE should be required for all *S. aureus* bacteremia patients



Echocardiography in *S. aureus* b. patients

Source (Study Design)	GRADE Category	Age of Study Population With SAB	No. of Cases	Patients, No./Total (%)		Key Outcomes (KO) Risk Stratification (RS)	Strengths (S) Weaknesses (W)
				TEE or TTE	With IE		
Studies Suggesting TEE Should Be Required for All SAB Cases							
Fowler et al, ¹³ 1997 (prospective cohort)	Low	Mean (SD), 56 (15) y; underwent both TTE and TEE	SAB: 176 (5 PV, 4 CD) IE: 26	TEE: 103/176 (58) TTE: 103/176 (58)	TEE: 26/103 (25) TTE: 7/103 (7)	KO: Positive TEE in 15 of 77 patients (19%) with negative TTE RS: Clinical findings and TTE results did not predict TEE results	S: Physical examination performed by study investigators, blinded repeat reading of all TEEs, 3-mo follow-up W: Single-center
Sullenberger et al, ¹⁷ 2005 (retrospective cohort)	Very low	Mean (SD), 56.5 (19.1) y; underwent TEE	SAB: 176 (1 PV, 0 CD) IE: 11	TEE: 64/176 (36) TTE: 48/176 (27)	TEE: 9/64 TTE: 1/48	YES TEE performed in 59%	
Incani et al, ¹⁴ 2013 (prospective cohort)	Low	Median (IQR), 68 (53-76) y; underwent TEE	SAB: 175 (9 PV, 7 CD) IE: 41	TEE: 144/175 (82) TTE: 144/175 (82)	TEE: 41/144 (28) TTE: 22/144 (15)	KO: Nineteen IE cases (46%) not suspected clinically; 22 of 144 cases (15%) reclassified as definite or possible IE after TEE RS: Clinical findings did not predict TEE results	S: High inclusion rate of 83%, 3-mo follow-up W: Single-center study
Holden et al, ¹⁸ 2014 (prospective cohort)	Very low	Median (IQR), 62 (19-100) y	SAB: 98 (1 PV, 4 CD) IE: 13	TEE: 58/98 (59) TTE: 32/98 (33)	TEE: 9/58 (16) TTE: 3/32 (9)	KO: Six of 13 IE cases (46%) had no risk factors; 1 of 10 patients (10%) who underwent both modalities had negative TTE and positive TEE RS: Clinical findings did not predict TEE findings	S: Follow-up of 3 mo W: Single-center study, small sample size, only 10 patients underwent both imaging modalities

Studies Suggesting TEE May Be Unnecessary in Some SAB Cases

Van Hal et al, ¹⁹ 2005 (retrospective cohort)	Very low	Median (IQR), 61.4 (22-92) y without IE and 56.3 (28-84) y with IE; without cardiac prostheses; underwent both TTE and TEE	SAB: 808 (0 PV, 0 CD) IE: 22	TEE: 125/808 (15) TTE: 125/808 (15)	TEE: 20/125 (16) TTE: 18/125 (14)	KO: Two IE cases had both negative TTE and TEE; 2 of 125 patients had negative TTE and positive TEE RS: Criteria for proposed low-risk group: (1) no permanent intracardiac device, which was a study exclusion criterion; (2) no embolic phenomena (had NPV of 99/104 [95.2%]); (3) ≤trivial left-sided regurgitation on TTE in the absence of stenosis (had NPV of 55/59 [93%])	S: TTE data assessed by blinded independent observer W: Single-center study, low TEE rate of 15%, only assessed valvular regurgitation
Kaasch et al, ¹⁵ 2011 (2 separate prospective cohorts)	Low	Median (IQR), 67 (21-91) y for INSTINCT cohort and 65 (15-95) y for SAB cohort; hospitalized patients with nosocomial	SABG: 736 (43 PV, 92 CD) IE: 53	TEE: 175/736 (24) TTE: 298/736 (40)	TEE: 31/175 (18) TTE: NA	KO: Low-risk criteria: only 1 of 208 patients (0.5%) had IE in INSTINCT cohort; 52 of 53 patients (98%) with IE fulfilled at least 1 high-risk criteria in SABG cohort RS: Criteria for proposed low-risk group with an NPV of 207/208 (99.5%): (1) no permanent intracardiac device; (2) no prolonged bacteremia (>4 d); (3) no hemodialysis dependency; (4) no spinal infection; (5) no nonvertebral osteomyelitis	S: Multicenter study large sample size, 3-mo follow-up W: Low rate of echocardiography overall (50%)
Rasmussen et al, ¹⁶ 2011 (prospective cohort)	Low	Mean (SD), 65 (16) y with IE and 64 (16) y without IE; underwent echocardiography	SAB: 336 (20 PV, 14 CD) IE: 53	TEE: 152/336 (45) TTE: NA	NA	KO: Forty-seven of 53 IE cases (89%) predicted by high-risk criteria; 6 of 53 IE cases (11%) missed by high-risk criteria: 4 of 6 had both positive TTE and TEE; 2 of 6 had negative TTE and positive TEE RS: Criteria for proposed low-risk group with an NPV of 114/120 (95%): (1) no permanent intracardiac device; (2) no previous IE; (3) no known heart valve disease; (4) no heart murmur; (5) no embolic events; (6) no vascular or immunologic phenomena suggesting IE; (7) known SAB source; (8) not community-acquired infection; (9) no intravenous drug use	S: Multicenter study strict definition of I W: High rate of TTE (38%) without TEE

NO
TEE performed in 24%

Review

Clinical Management of *Staphylococcus aureus* Bacteremia A Review

Thomas L. Holland, MD; Christopher Arnold, MD; Vance G. Fowler Jr, MD, MHS

Management of *Staphylococcus aureus* Bacteremia

jama.com

Review Clinical Review & Education

Authors' key points

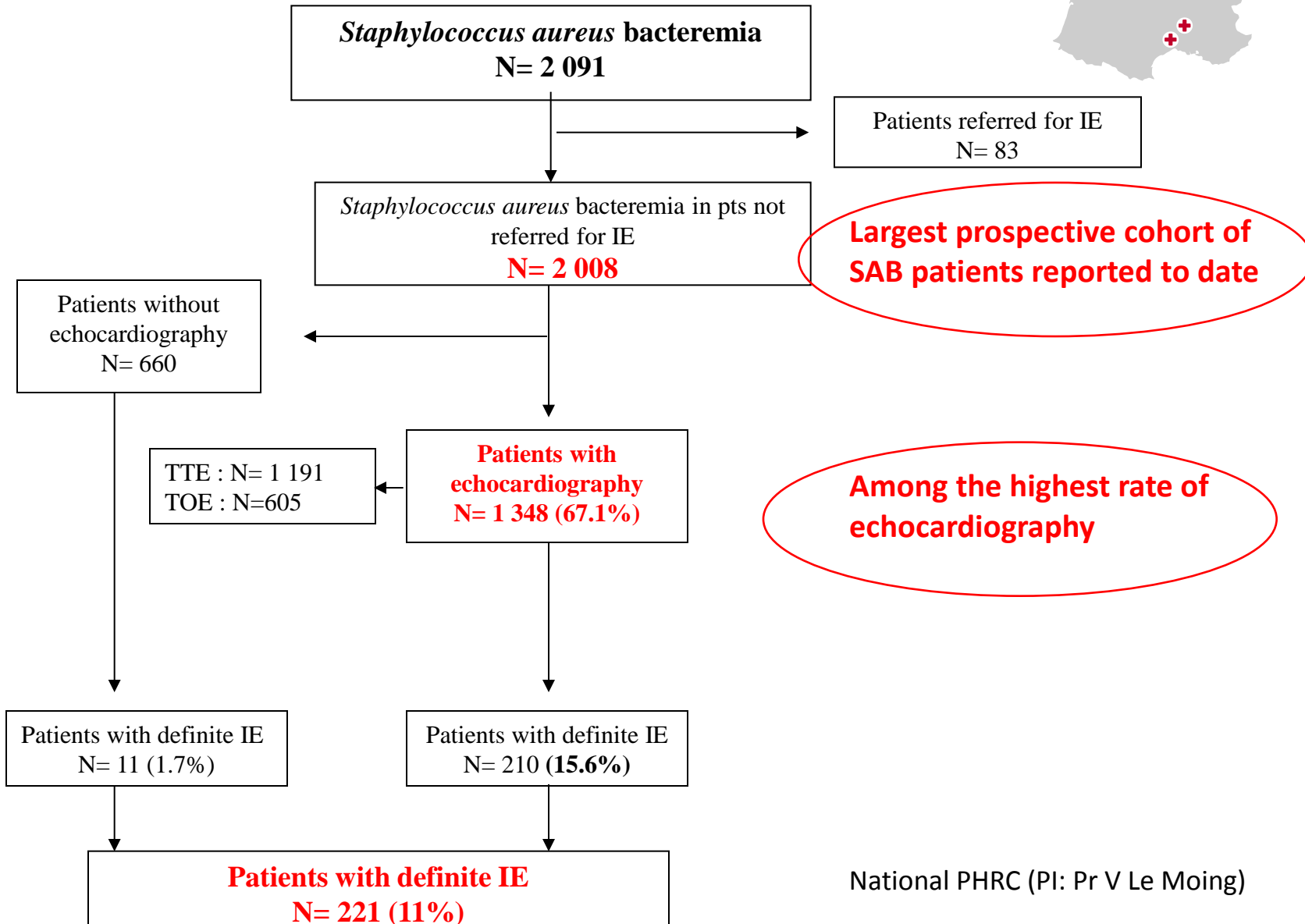
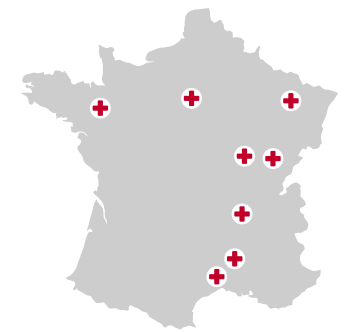
- All patients with *S. aureus* bacteremia should be evaluated with echocardiography, preferably by TEE **UNLESS the patients meets criteria for being at low risk**
- For **low risk patients**, TTE is adequate

How to define « *low-risk* » *S. aureus* b. patients?

- Use of a **criteria** set for guiding **echocardiography** (TEE)

Study	SAB Population	Results	Strengths	Weaknesses
Kaasch, CID, 2011	Nosocomial	TEE dispensable in SAB with 0 criteria (intracardiac device, bacteremia > 4 d, hemodialysis, dependancy, spinal or non-vertebral infection)		Low rate of echocardiography
Khatib, Medicine, 2013	Community-acquired or healthcare-associated	TEE dispensable in uncomplicated SAB (bacteremia < 3d without device, relapse 2ary foci)		Low rate of echocardiography Relapse criteria defined within 100 days

VIRSTA study results



VIRSTA study results

Predictive factors included :

- Background characteristics

Predictive factors	Weight
Cerebral or peripheral emboli*	<u>5</u>
Meningitis*	<u>5</u>
Permanent intracardiac device or previous IE	<u>4</u>
Intravenous drug use	<u>4</u>
Pre-existing native valve disease	<u>3</u>
Persistent bacteremia*	<u>3</u>

VIRSTA study results

Predictive factors included :

- **Background characteristics**

Predictive factors	Weight
Cerebral or peripheral emboli*	<u>5</u>
Meningitis*	<u>5</u>
Permanent intracardiac device or previous IE	<u>4</u>
Intravenous drug use	<u>4</u>
Pre-existing native valve disease	<u>3</u>
Persistent bacteremia*	<u>3</u>

VIRSTA study results

Predictive factors included :

- Background characteristics
- Initial SAB presentation

Predictive factors	Weight
Cerebral or peripheral emboli*	<u>5</u>
Meningitis*	<u>5</u>
Permanent intracardiac device or previous IE	<u>4</u>
Intravenous drug use	<u>4</u>
Pre-existing native valve disease	<u>3</u>
Persistent bacteremia*	<u>3</u>

VIRSTA study results

Predictive factors included :

- Background characteristics
- Initial SAB presentation

Predictive factors	Weight
Cerebral or peripheral emboli*	5
Meningitis*	5
Permanent intracardiac device or previous IE	4
Intravenous drug use	4
Pre-existing native valve disease	3
Persistent bacteremia*	3
Community or Non-nosocomial Health care associated acquisition	2
C-reactive protein > 190 mg/L	1

VIRSTA study results

Predictive factors included :

- Background characteristics
- Initial SAB presentation
- Early extracardiac events (within the first 48 hours of *S. aureus* bacteremia diagnosis)

Predictive factors	Weight
Cerebral or peripheral emboli*	5
Meningitis*	5
Permanent intracardiac device or previous IE	4
Intravenous drug use	4
Pre-existing native valve disease	3
Persistent bacteremia*	3
Community or Non-nosocomial Health care associated acquisition	2
C-reactive protein > 190 mg/L	1

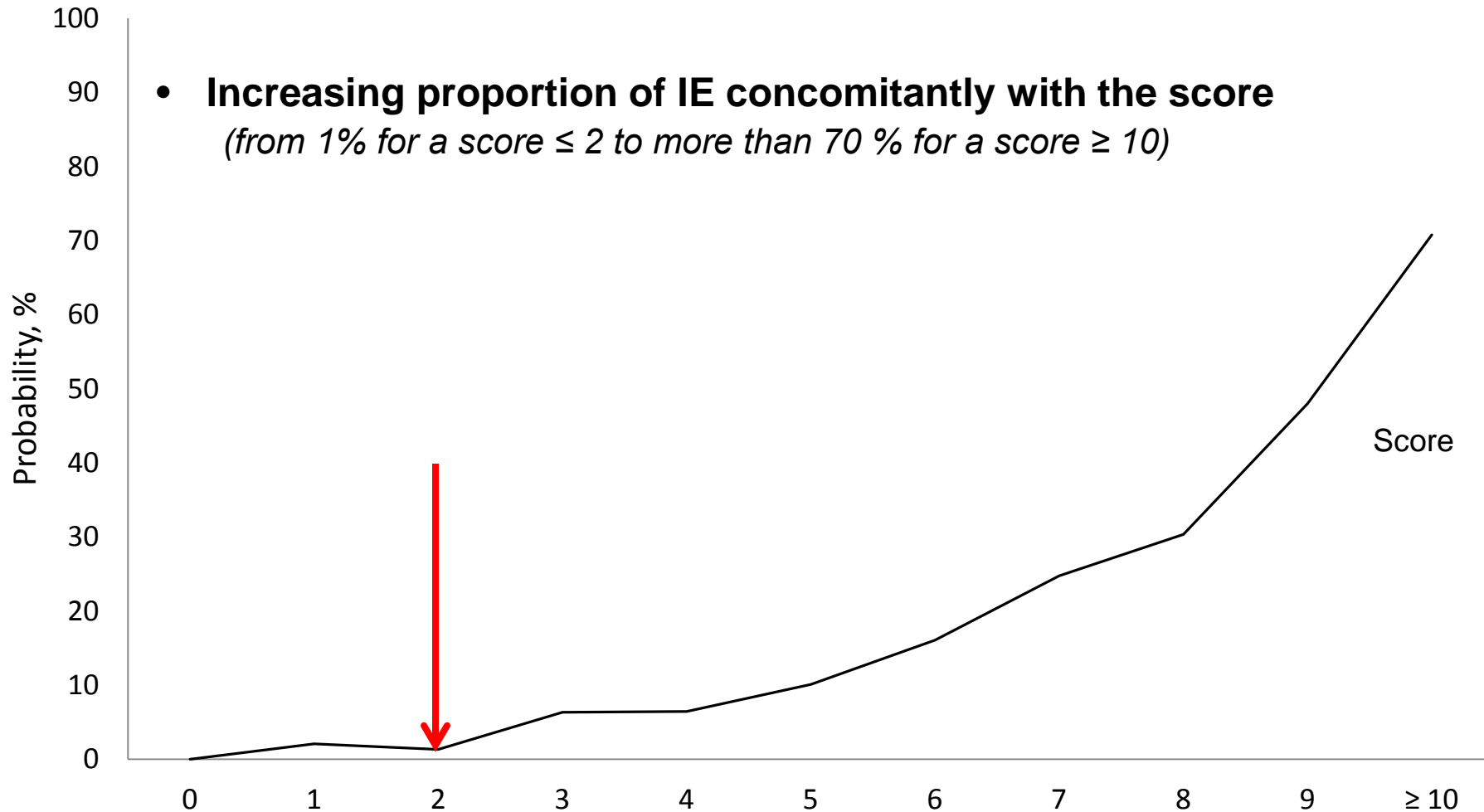
VIRSTA study results

Predictive factors included :

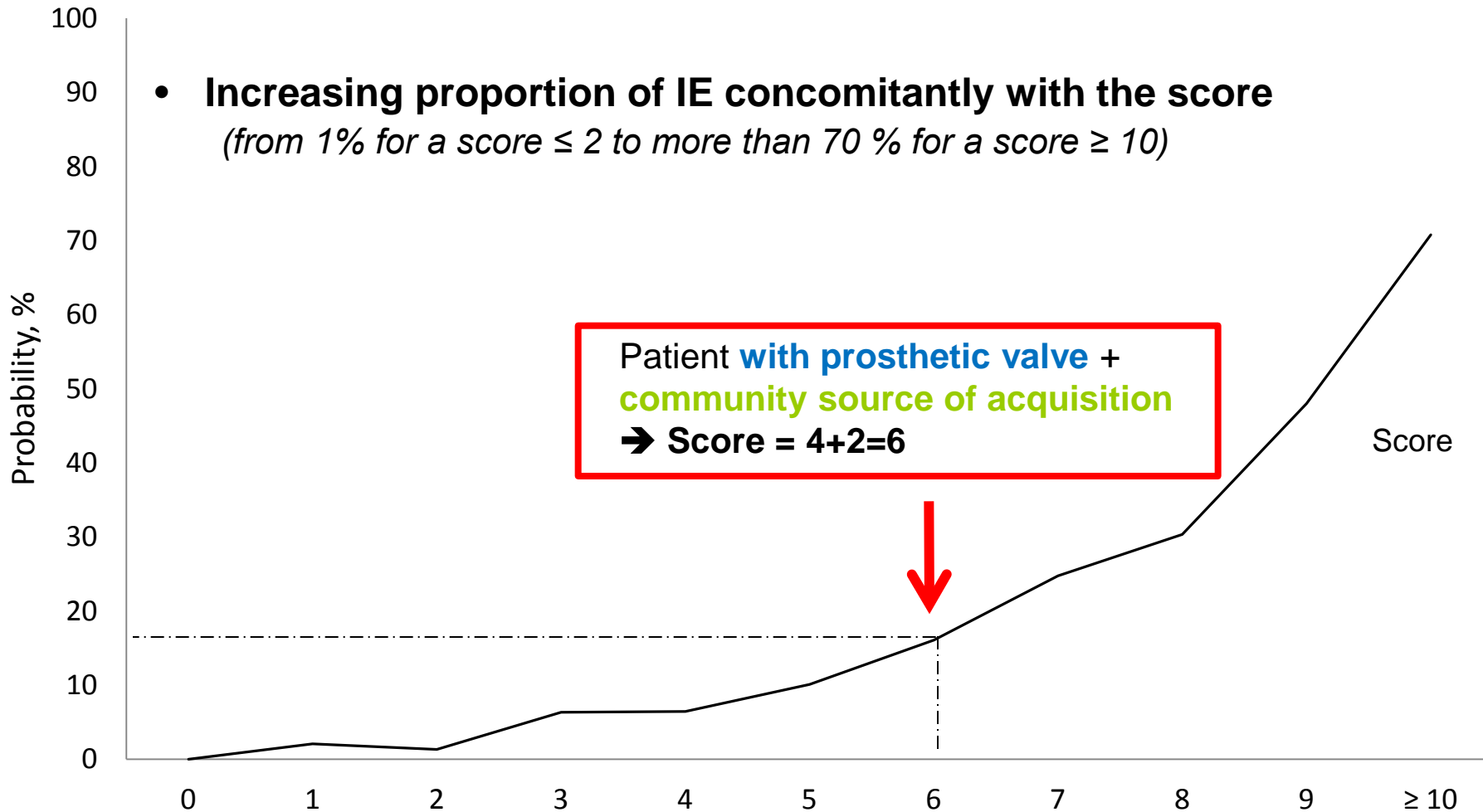
- Background characteristics
- Initial SAB presentation
- Early extracardiac events (within the first 48 hours of *S. aureus* bacteremia diagnosis)

Predictive factors	Weight
Cerebral or peripheral emboli*	<u>5</u>
Meningitis*	<u>5</u>
Permanent intracardiac device or previous IE	<u>4</u>
Intravenous drug use	<u>4</u>
Pre-existing native valve disease	<u>3</u>
Persistent bacteremia*	<u>3</u>
Vertebral osteomyelitis*	2
Community or Non-nosocomial Health care associated acquisition	2
Severe sepsis or shock*	1
C-reactive protein > 190 mg/L	1

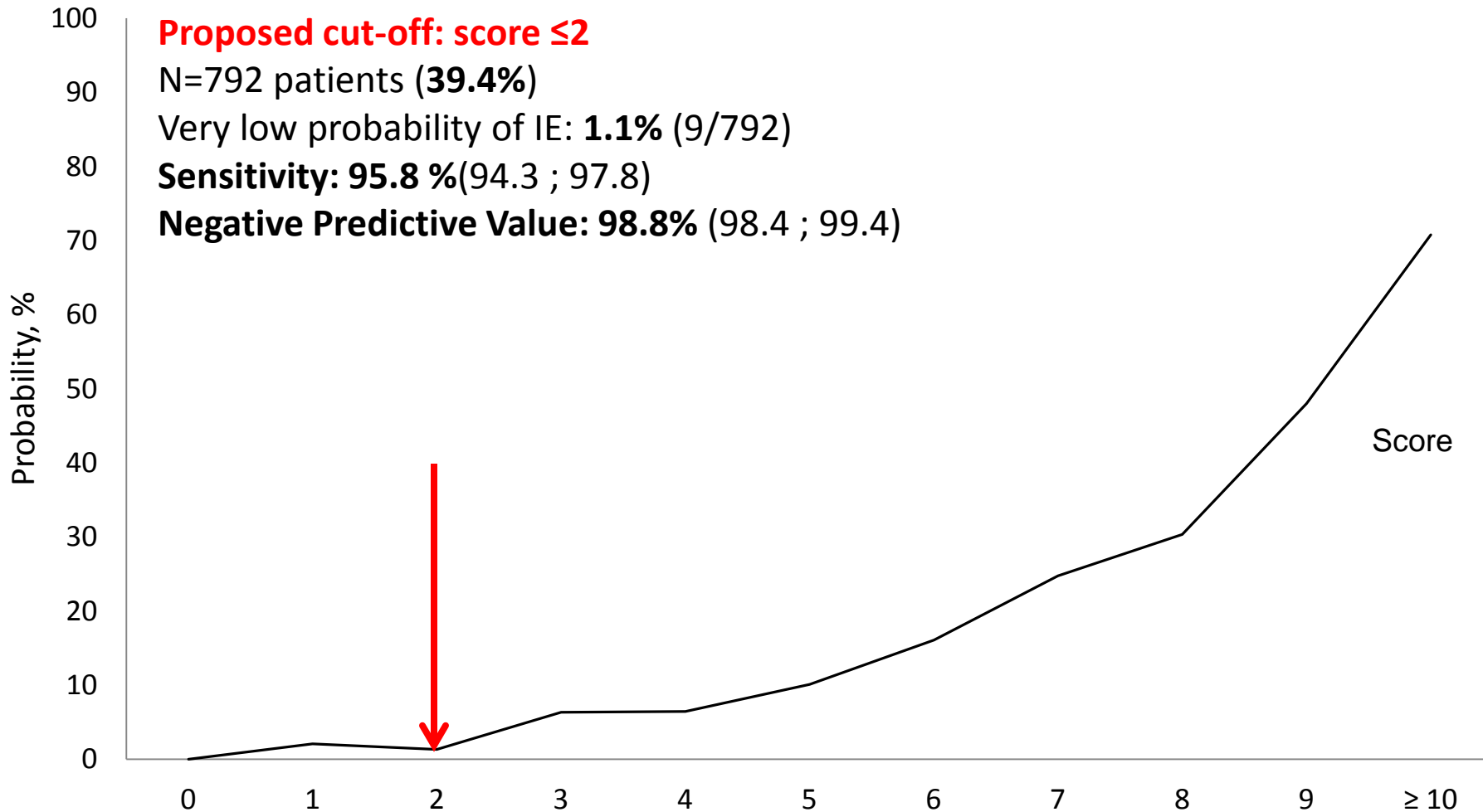
Association between score and IE probability in 2,008 patients with *Staphylococcus aureus* b



Association between score and IE probability in 2,008 patients with *Staphylococcus aureus* b



Association between score and IE probability in 2,008 patients with *Staphylococcus aureus* b



VIRSTA study results

Predictive factors included :

- Background characteristics
- Initial SAB presentation
- Early extracardiac events (within the first 48 hours of *S. aureus* bacteremia diagnosis)

Predictive factors	Weight
Cerebral or peripheral emboli*	<u>5</u>
Meningitis*	<u>5</u>
Permanent intracardiac device or previous IE	<u>4</u>
Intravenous drug use	<u>4</u>
Pre-existing native valve disease	<u>3</u>
Persistent bacteremia*	<u>3</u>
Vertebral osteomyelitis*	2
Community or Non-nosocomial Health care associated acquisition	2
Severe sepsis or shock*	1
C-reactive protein > 190 mg/L	1

Should echocardiography be systematic
in all cases of SAB bacteremia?

Conclusion

SAB guidelines: TTE/TEE systematic

TEE not needed in all patients with bacteremia

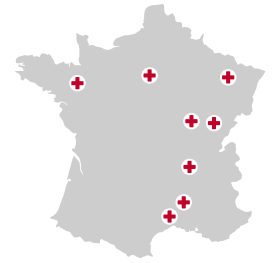
Depending on **clinical judgment + microorganism/patient**

Proposed strategy: TEE if

- **Permanent intracardiac device or previous IE**
- **Native valvulopathy**
- **IVD use**
- **Persistent bacteremia**
- **Cerebral/peripheral emboli or meningitis in the 1st 48H**
- **or if the VIRSTA score >2**

External validation

Virsta study group



Clinical centres: **Besançon:** Catherine Chirouze, Elodie Curlier, Cécile Descottes-Genon, Bruno Hoen, Isabelle Patry, Lucie Vettoretti. **Dijon:** Pascal Chavanet, Jean-Christophe Eicher, Marie-Christine Greusard, Catherine Neuwirth, André Péchinot, Lionel Piroth. **Lyon:** Marie Célard, Catherine Cornu, François Delahaye, Malika Hadid, Pascale Rausch. **Montpellier:** Audrey Coma, Florencé Galtier, Philippe Géraud, Hélène Jean-Pierre, Vincent Le Moing, Catherine Sportouch, Jacques Reynes. **Nancy:** Nejla Aissa, Thanh Doco-Lecompte, François Goehringer, Nathalie Keil, Lorraine Letranchant, Hephher Malela, Thierry May, Christine Selton-Suty. **Nîmes:** Nathalie Bedos, Jean-Philippe Lavigne, Catherine Lechiche, Albert Sotto. **Paris:** Xavier Duval, Emila Ilic Habensus, Bernard Jung, Catherine Leport, Pascale Longuet, Raymond Ruimy. **Rennes:** Eric Bellissant, Pierre-Yves Donnio, Fabienne Le Gac, Christian Michelet, Matthieu Revest, Pierre Tattevin, Elise Thebault.

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Erasmus University Rotterdam: Alex Van Belkum, Willem Vanwamel.

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Thank you

Demographic and clinical variables present at the time of *Staphylococcus aureus* bacteremia diagnosis in the 2,008 enrolled patients, VIRSTA Study

	N or med	IQR or %	Non IE N=1,787	IE N=221	p-value
Background characteristics					
Age (Yr)	67	(65 ; 78)	67(5;78)	67 (3 ;79)	0.9
Gender (male)	1295	(64.5)	1151 (64.4)	144 (65.2)	0.8
Chronic hemodialysis	211	(10.5)	185 (10.4)	26 (11.8)	0.5
Mac Cabe score					
Ultimately fatal disease	751	(37.4)	674 (37.8)	77 (34.8)	0.4
Rapidly fatal disease	368	(18.3)	332 (18.6)	36 (16.3)	
Predisposing cardiac conditions					
Permanent intracardiac device or previous IE	341	(17.0)	255 (14.3)	86 (38.9)	<0.0001
Pre-existing native valve disease	264	(13.1)	221 (12.4)	43 (19.5)	
None	1403	(69.9)	1311 (73.4)	92 (41.6)	
Initial SAB presentation					
Intravenous drug use	63	(3.1)	39 (2.2)	24 (10.9)	<0.0001
Known source of infection [†]	1602	(79.8)	1441 (80.6)	161 (72.9)	0.01
Presumed setting of acquisition					
Nosocomial	1075	(53.5)	1006 (56.3)	69 (31.2)	<0.0001
Community or non-nosocomial Health care associated	875	(43.6)	726 (40.6)	146 (67.4)	
Unknown setting of acquisition	58	(2.9)	55 (3.1)	3 (1.4)	
C-reactive protein > 190 mg/L ‡					
No	952	(47.4)	880 (49.2)	72 (32.6)	<0.0001
Yes	929	(46.3)	788 (44.1)	141 (63.8)	
Missing value	127	(6.3)	119 (6.7)	8 (3.6)	

Demographic and clinical variables present at the time of *Staphylococcus aureus* bacteremia diagnosis in the 2,008 enrolled patients, VIRSTA Study

	N or med	IQR or %	Non IE N=1,787	IE N=221	p-value
Early extracardiac events (0-48 hours)					
Severe sepsis or septic shock	495	(24.7)	400 (22.4)	95 (43.0)	<0.0001
Cerebral or peripheral emboli	90	(4.5)	38 (2.1)	52 (23.5)	<0.0001
Meningitis	22	(1.1)	9 (0.5)	13 (5.9)	<0.0001
Vertebral osteomyelitis	28	(1.4)	20 (1.1)	8 (3.6)	<0.008
Persistent bacteremia	344	(17.1)	259 (14.5)	85 (38.5)	<0.0001

Final predictive model of infective endocarditis in the 2008 enrolled *Staphylococcus aureus* bacteremia patients (Stepwise backward approach)

	Odds Ratio	(95% CI)	p-value
Cerebral or peripheral emboli	10.4	(6.0 ; 17.9)	<0.0001
Meningitis	9.6	(3.2 ; 29.2)	<0.0001
Permanent intracardiac device or previous IE	7.3	(4.9 ; 10.9)	<0.0001
Pre-existing native valve disease	3.6	(2.3 ; 5.7)	
Intravenous drug use	5.8	(2.8 ; 11.7)	<0.0001
Persistent bacteremia	3.9	(2.8 ; 5.7)	<0.0001
Vertebral osteomyelitis	3.2	(1.2 ; 8.9)	0.03
Community or Non nosocomial Health care associated acquisition	2.6	(1.8; 3.7)	<0.0001
Unknown setting of acquisition	0.5	(0.1;1.9)	
Severe sepsis or shock	2.0	(1.4 ; 2.9)	0.0001
C-reactive protein > 190 mg/L	1.9	(1.3 ; 2.7)	0.0006

Quite similar determinants of IE obtained with the 2 sensitivity analysis

➔ ROBUSTNESS of the model