

## Supplementary material

**Supplementary Table S1.** Definitions of the terms used in the European Society of Cardiology 2015 modified criteria for the diagnosis of infective endocarditis.

### Major criteria

1. Blood cultures positive for IE
  - a. Typical microorganisms consistent with IE from 2 separate blood cultures:
    - Viridans streptococci, *Streptococcus gallolyticus* (*S bovis*), HACEK group, *S. aureus*, or
    - Community-acquired enterococci, in the absence of a primary focus; or
  - b. Microorganisms consistent with IE from persistently positive blood cultures:
    - $\geq 2$  positive blood cultures of blood samples drawn  $> 12$  h apart; or
    - All of 3 or a majority of  $\geq 4$  separate cultures of blood (with first and last samples drawn  $\geq 1$  h apart); or
  - c. Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titre  $> 1:800$
2. Imaging positive for IE
  - a. Echocardiogram positive for IE:
    - Vegetation;
    - Abscess, pseudoaneurysm, intracardiac fistula;
    - Valvular perforation or aneurysm
    - New partial dehiscence of prosthetic valve
  - b. Abnormal activity around the site of prosthetic valve implantation detected by  $^{18}\text{F}$ -FDG PET/CT (only if the prosthesis was implanted for  $> 3$  months) or radiolabelled leukocytes SPECT/CT
  - c. Definite paravalvular lesions by cardiac CT

### Minor criteria

1. Predisposition such as predisposing heart condition, or injection drug use
2. Fever defined as temperature  $> 38^{\circ}\text{C}$
3. Vascular phenomena (including those detected only by imaging): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor

5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE

**Supplementary Table S2.** Clinical presentation of Belgian infective endocarditis patients.

	Total (n = 127)	NVE (n = 75)	PRVE (n = 45)	CDRIE (n = 7)	P-value
<b>Signs and symptoms</b>					
Fever	89/127 (70.1%)	49/75 (65.3%)	35/45 (77.8%)	5/7 (71.4%)	0.390
Cardiac murmur	63/127 (49.6%)	43/75 (57.3%)	19/45 (42.2%)	1/7 (14.3%)	0.047*
Dizziness	26/127 (20.5%)	19/75 (25.3%)	5/45 (11.1%)	2/7 (28.6%)	0.113
Congestive heart failure	23/127 (18.1%)	12/75 (16.0%)	8/45 (17.8%)	3/7 (42.9%)	0.201
Shortness of breath	23/127 (18.1%)	12/75 (16.0%)	9/45 (20.0%)	2/7 (28.6%)	0.515
Cough	12/127 (9.4%)	6/75 (8.0%)	4/45 (8.9%)	2/7 (28.6%)	0.201
Septic shock	12/127 (9.4%)	7/75 (9.3%)	4/45 (8.9%)	1/7 (14.3%)	0.775
Chest pain	7/127 (5.5%)	6/75 (8.0%)	1/45 (2.2%)	0/7 (0.0%)	0.500
Syncope	5/127 (3.9%)	3/75 (4.0%)	2/45 (4.4%)	0/7 (0.0%)	1.000
Janeway lesions	5/127 (3.9%)	2/75 (2.7%)	3/45 (6.7%)	0/7 (0.0%)	0.519
Osler's nodes	4/127 (3.1%)	3/75 (4.0%)	1/45 (2.2%)	0/7 (0.0%)	1.000
Cerebrovascular accident	3/127 (2.4%)	2/75 (2.7%)	1/45 (2.2%)	0/7 (0.0%)	1.000
Cardiogenic shock	2/127 (1.6%)	1/75 (1.3%)	1/45 (2.2%)	0/7 (0.0%)	1.000
Roth spots	2/127 (1.6%)	2/75 (2.7%)	0/45 (0.0%)	0/7 (0.0%)	0.580
<b>Complications at admission</b>					
Embololic events	33/127 (26%)	25/75 (33.3%)	8/45 (17.8%)	0/7 (0.0%)	0.046*
Pulmonary	3/127 (2.4%)	3/75 (4.0%)	0/45 (0.0%)	0/7 (0.0%)	0.404
Cerebral	19/127 (15.0%)	15/75 (20.0%)	4/45 (8.9%)	0/7 (0.0%)	0.169
Splenic	3/127 (2.4%)	2/75 (2.7%)	1/45 (2.2%)	0/7 (0.0%)	1.000
Coronary	1/127 (0.8%)	1/75 (1.3%)	0/45 (0.0%)	0/7 (0.0%)	1.000
Renal	4/127 (3.1%)	4/75 (5.3%)	0/45 (0.0%)	0/7 (0.0%)	0.437
Hepatic	0/127 (0.0%)	0/75 (0.0%)	0/45 (0.0%)	0/7 (0.0%)	1.000
Peripheral	3/127 (2.4%)	2/75 (2.7%)	1/45 (2.2%)	0/7 (0.0%)	1.000

	Total (n = 127)	NVE (n = 75)	PRVE (n = 45)	CDRIE (n = 7)	<i>P</i> -value
Abscess	17/127 (13.4%)	13/75 (17.3%)	3/45 (6.7%)	1/6 (14.3%)	0.201
Spondylitis	11/127 (8.7%)	7/75 (9.3%)	4/45 (8.9%)	0/7 (0.0%)	1.000
Haemorrhagic Stroke	0/127 (0.0%)	0/75 (0.0%)	0/45 (0.0%)	0/7 (0.0%)	1.000

CDRIE, cardiac device related infective endocarditis; NVE, native valve infective endocarditis; PRVE, prosthetic or repaired valve infective endocarditis. A value of  $P < 0.050$  was considered significant. (\*) denotes significant  $P$ -values.

**Supplementary Table S3.** Microbiology in Belgian infective endocarditis patients.

	Total (n = 110)	NVE (n = 64)	PRVE (n = 39)	CDRIE (n = 7)	<i>P</i> -value
Methi-S <i>S. aureus</i>	37/110 (33.6%)	21/64 (32.8%)	12/39 (32.4%)	4/7 (57.1%)	0.440
Methi-R <i>S. aureus</i>	4/110 (3.6%)	3/64 (4.7%)	0/39 (0%)	1/7 (14.3%)	0.091
Methi-S <i>Staph. coagulase</i>	7/110 (6.4%)	3/64 (4.7%)	4/39 (10.3%)	0/7 (0.0%)	0.638
negative					
Methi-R <i>Staph. coagulase</i>	6/110 (5.5%)	1/64 (1.6%)	5/39 (12.8%)	0/7 (0.0%)	0.083
negative					
<i>S. viridans</i>	17/110 (15.5%)	13/64 (20.3%)	3/39 (7.7%)	1/7 (14.3%)	0.197
<i>Enterococcus</i>	17/110 (15.5%)	6/64 (9.4%)	9/39 (23.1%)	2/7 (28.6%)	0.072
<i>S. gallolyticus</i>	9/110 (8.2%)	6/64 (9.4%)	3/39 (7.7%)	0/7 (0.0%)	1.000
Gram negative bacillus	3/110 (2.7%)	1/64 (1.6%)	2/39 (5.1%)	0/7 (0.0%)	0.637
<i>C. burnetii</i> IgG anti phase I	0/127 (0.0%)	0/75 (0.0%)	0/45 (0.0%)	0/7 (0.0%)	-

Methi-R, methicilline-resistant; Methi-S, methicilline-sensitive. A value of  $P < 0.050$  was considered significant.

**Supplementary Table S4.** In-hospital complications under therapy in Belgian infective endocarditis patients.

	Total (n = 127)	NVE (n = 75)	PRVE (n = 45)	CDRIE (n = 7)	P-value
<b>Complications under therapy</b>					
Acute renal failure	46/127 (36.2%)	24/75 (32.0%)	19/45 (42.2%)	3/7 (42.9%)	0.459
Embolic events	30/127 (23.6%)	21/75 (28.0%)	9/45 (20.0%)	0/7 (0.0%)	0.211
Pulmonary	4/30 (13.3%)	2/21 (9.5%)	2/9 (22.2%)	-	0.563
Cerebral	14/30 (46.7%)	10/21 (47.6%)	4/9 (44.4%)	-	1.000
TIA	2/25 (8.0%)	2/18 (11.1%)	0/7 (0.0%)	-	1.000
Stroke	8/25 (32.0%)	5/18 (27.8%)	3/7 (42.9%)	-	0.640
Spleen	5/30 (16.7%)	3/21 (14.3%)	2/9 (22.2%)	-	0.622
Coronary	2/30 (6.7%)	1/21 (4.8%)	1/9 (11.1%)	-	0.517
Renal	6/30 (20.0%)	5/21 (23.8%)	1/9 (11.1%)	-	0.637
Hepatic	1/30 (3.3%)	1/21 (4.8%)	0/9 (0.0%)	-	1.000
Peripheral	1/30 (3.3%)	1/21 (4.8%)	0/9 (0.0%)	-	1.000
Positive blood cultures after 48h	26/127 (20.5%)	13/75 (17.3%)	11/45 (24.4%)	2/7 (28.6%)	0.511
Thrombopenia (<100000)	20/127 (15.7%)	13/75 (17.3%)	6/45 (13.3%)	1/7 (14.3%)	0.849
Spondylitis	15/127 (11.8%)	9/75 (12.0%)	6/45 (13.3%)	0/7 (0.0%)	0.909
Septic shock	15/127 (11.8%)	7/75 (9.3%)	6/45 (13.3%)	2/7 (28.6%)	0.216
Increasing vegetation size	12/127 (9.4%)	6/75 (8.0%)	6/45 (13.3%)	0/7 (0.0%)	0.437
CHF	11/127 (8.7%)	8/75 (10.7%)	3/45 (6.7%)	0/7 (0.0%)	0.754
Glomerulonephritis	11/127 (8.7%)	9/75 (12.0%)	2/45 (4.4%)	0/7 (0.0%)	0.338
Persistent fever (>7 days)	9/127 (7.1%)	4/75 (5.3%)	4/45 (8.9%)	1/7 (14.3%)	0.315
Cardiogenic shock	7/127 (5.5%)	4/75 (5.3%)	3/45 (6.7%)	0/7 (0.0%)	1.000
New abscess	7/127 (5.5%)	4/75 (5.3%)	3/45 (6.7%)	0/7 (0.0%)	1.000
AV block	5/127 (3.9%)	3/75 (4.0%)	2/45 (4.4%)	0/7 (0.0%)	1.000
Mycotic aneurysm	4/127 (3.1%)	2/75 (2.7%)	2/45 (4.4%)	0/7 (0.0%)	0.698
Cerebral Haemorrhage	1/127 (0.8%)	0/75 (0.0%)	1/45 (2.2%)	0/7 (0.0%)	0.413

	Total (n = 127)	NVE (n = 75)	PRVE (n = 45)	CDRIE (n = 7)	<i>P</i> -value
Haemorrhagic Stroke	0/127 (0.0%)	0/75 (0.0%)	0/45 (0.0%)	0/7 (0.0%)	1.000

CDRIE, cardiac device related infective endocarditis; CHF, Congestive Heart Failure; NVE, native valve infective endocarditis; PRVE, prosthetic or repaired valve infective endocarditis. A value of  $P < 0.050$  was considered significant.

**Supplementary Table S5.** Univariate Cox regression analysis for all causes of death in hospital in Belgian IE patients.

	Hazard Ratio	95% CI	<i>P</i> -value
Type of endocarditis: prosthesis + repair	2.27	[0.87-5.96]	0.096
Source of infection: community acquired	1.18	[0.14-9.59]	0.880
Age < 65 yo	0.62	[0.24-1.63]	0.806
Age 65 - 79 yo	1.32	[0.53-3.25]	0.335
Age ≥ 80 yo	1.85	[0.40-8.56]	0.553
Gender: male	0.98	[0.37-2.59]	0.964
Charlson index	1.18	[1.04-1.34]	0.011*
Creatinine >2mg/dl	3.49	[1.34-9.08]	0.011*
<i>S. aureus</i>	2.38	[0.88-6.49]	0.089
Congestive heart failure	0.84	[0.28-2.56]	0.757
Vegetation size > 10 mm	2.31	[0.28-19.28]	0.439
Cerebral complication	1.71	[0.28-10.55]	0.564
Abscess	1.13	[0.32-4.00]	0.853
Indication for surgery - not performed	13.72	[1.56-120.61]	0.018*
Indication for surgery - performed	3.34	[0.43-25.93]	0.018*

yo: years old. A value of  $P < 0.050$  was considered significant. (\*) denotes significant  $P$ -values.





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