VI Congreso SEICAV

Endocarditis por *Enterococcus faecalis*: del NOVA score al cáncer de colon

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2 preguntas

1. ¿Con qué herramientas contamos para decidir cuándo realizar una ETE en los pacientes con bacteremia por *E. faecalis*?
2. ¿Qué papel juega el colon, y concretamente el cáncer de colon, en la etiopatogenia de la endocarditis por *E. faecalis* (EFIE)?
3. ¿Qué pasos hay que dar para mejorar el conocimiento de que disponemos con respecto a las dos anteriores preguntas?

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1. Scores diagnósticos

Factores de riesgo de EI en la bacteremia enterocócica

- *E. faecalis*
- Bacteriemia monomicrobiana
- Edad
- Sexo masculino
- Antecedente de EI
- Prótesis valvular
- Otra patología valvular
- Foco desconocido
- Adquisición comunitaria
- Número de HC positivos
- Duración de los síntomas
- Soplo cardíaco
- Embolismos

Maki et al, Medicine 1988; Patterson et al, Medicine 1995; Fernández-Guerrero et al, J Int Med 2002; Anderson et al, Infection 2004; Pinholt et al, CMI 2014; Bouza, CID 2015; Dahl, CID 2016

Recomendaciones en las guías vigentes para la realización de ETT/ETE en bacteriemia enterocócica

Table 10 Role of echocardiography in infective endocarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
A. Diagnosis			
• TTE is recommended as the first-line imaging modality in suspected IE.	I	B	64,65
• TOE is recommended in all patients with clinical suspicion of IE and a negative or non-diagnostic TTE.	I	B	64, 68–71
• TOE is recommended in patients with clinical suspicion of IE, when a prosthetic heart valve or an intracardiac device is present.	I	B	64,71
• Repeat TTE and /or TOE within 5–7 days is recommended in case of initially negative examination when clinical suspicion of IE remains high.	I	C	
• Echocardiography should be considered in *Staphylococcus aureus* bacteraemia.	IIa	B	66,67

Table 3. Definition of Terms Used in the Modified Duke Criteria for the Diagnosis of IE*

Major criteria

Blood culture positive for IE

Typical microorganisms consistent with IE from 2 separate blood cultures: Viridans streptococci, *Streptococcus bovis*, HACEK group, ***Staphylococcus aureus***; or community-acquired enterococci in the absence of a primary focus, or microorganisms consistent with IE from persistently positive blood cultures defined as follows: at least 2 positive cultures of blood samples drawn >12 h apart or all 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart)

Single positive blood culture for *Coxiella burnetii* or anti–phase 1 IgG antibody titer ≥1:800

Evidence of endocardial involvement

Echocardiogram positive for IE **(TEE recommended for patients with prosthetic valves, rated at least possible IE by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients)** defined as follows: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; abscess; or new partial dehiscence of prosthetic valve or new valvular regurgitation (worsening or changing or pre-existing murmur not sufficient)

Etiología EI en la cohorte GAMES 2008-2012

Muñoz et al. Medicine 2015

	Total N = 1804	Native Non-IVDU N = 1079	Native IVDU N = 52	Prosthetic N = 504	Device N = 169	*P*
Definite IE	1498 (83.0)	919 (85.6)	48 (92.3)	409 (81.3)	122 (72.2)	<0.01
Possible IE	300 (16.6)	155 (14.4)	4 (7.7)	94 (18.7)	47 (27.8)	<0.01
Etiology						
Staphylococcus spp.	728 (40.3)	382 (35.3)	30 (55.8)	218 (43.2)	98 (58.0)	<0.01
S. aureus	426 (23.6)	278 (25.8)	26 (50.0)	77 (15.3)	45 (26.6)	<0.01
MSSA	360 (84.5)	235 (84.5)	24 (92.3)	64 (83.2)	37 (82.3)	0.46
MRSA	66 (15.5)	43 (15.5)	2 (7.7)	13 (16.8)	8 (17.7)	
CoNS	302 (16.7)	104 (9.7)	4 (7.7)	141 (28.0)	53 (31.5)	<0.01
Streptococcus spp.	440 (24.4)	329 (30.5)	8 (15.4)	86 (17.1)	17 (10.1)	<0.01
S. bovis	117 (6.4)	80 (7.4)	0	32 (6.5)	5 (3.0)	0.036
S. viridans group	223 (12.3)	171 (16.0)	7 (13.5)	38 (7.5)	7 (4.1)	<0.01
Others	100 (5.5)	79 (7.3)	1 (1.9)	15 (3.0)	5 (5.3)	0.001
Enterococcus spp.	230 (12.7)	142 (13.2)	5 (9.6)	77 (15.3)	6 (3.6)	0.001
Other Gram-positives*	26 (1.4)	14 (1.3)	2 (3.8)	8 (1.5)	2 (1.1)	0.48
Gram-negatives**	93 (5.2)	53 (4.9)	–	25 (5.0)	15 (8.9)	0.05
Fungi***	44 (2.4)	21 (1.9)	2 (3.8)	15 (3.0)	6 (3.6)	0.38
Negative BC	264 (14.7)	152 (14.0)	5 (9.6)	75 (14.8)	32 (18.9)	0.67

NOVA Score for Enterococcal Bacteremia

Bouza et al. *CID* 2015

- 2 objetivos:
  - Identificar los factores que permiten una identificación precoz del subgrupo de pacientes con E-BSI y muy bajo riesgo de E-IE en los que la ETE puede evitarse (cohorte prospectiva 2003-12)
  - Comparar las características de los pacientes con E-BSI con y sin E-IE para valorar las potenciales consecuencias de omitir el diagnóstico de EI (caso-control).

NOVA Score for Enterococcal Bacteremia

Bouza et al. *CID* 2015

Year	E-BSI Episodes	E-BSI/1000 Admissions	EE Episodes	EE/E-BSI (%)	EE/1000 Admissions
2003	109				0.04
2004	114				0.13
2005	129				0.05
2006	149				0.08
2007	178				0.12
2008	177				0.12
2009	170				0.15
2010	149				0.05
2011	181	3.4	14	7.7	0.26
2012	159	3.2	8	5.0	0.14
	1515		65		

176 ETE (12.1%)

4,29% EI/BSI

16,7% ETT (18); S 32%

35,5% ETE (47); S 95%

100 ETT (14,7%)

288 ETT (34,4%)

NOVA Score for Enterococcal Bacteremia

Bouza et al. *CID* 2015

- *E. faec*
- Bacter
- Adquis
- Adquis
- Foco d
- Foco C

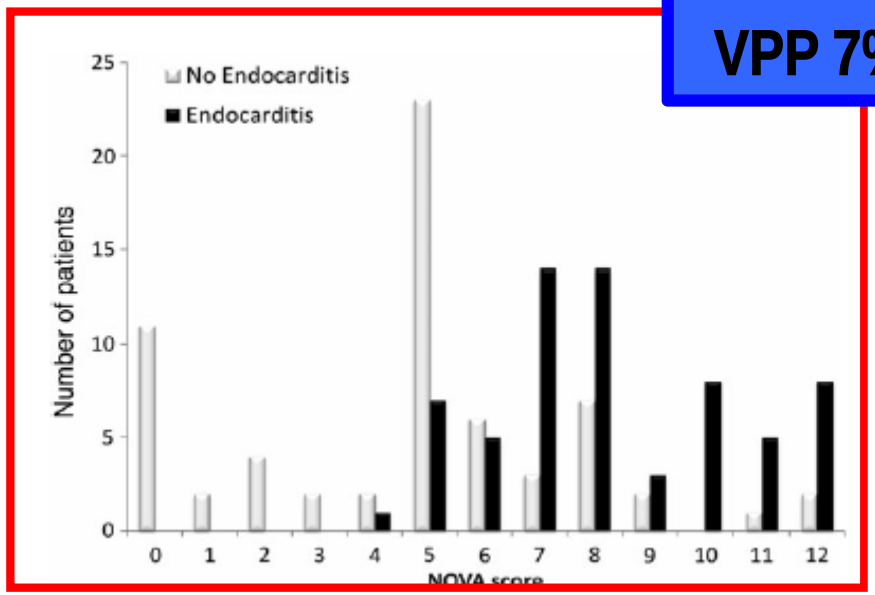
Outcome	Endocarditis N = 65 (%)	No Endocarditis N = 65 (%)	*P* Value
Complications			
Cardiac failure	23 (35.9)	6 (9.2)	<.01
Persistent bloodstream infection	13 (21.7)	9 (13.8)	.09
Central nervous system vascular event	5 (7.9)	0	.02
Other than central nervous system embolic event	10 (15.9)	2 (3.1)	.007
Treatment			
Empiric adequate treatment	54 (96.4)	13 (20.0)	<.01
Mean days of overall treatment (SD)	34 (17.1)	15 (8.2)	<.01
Death	25 (38.4)	10 (15.4)	<.01
Mean days of hospital stay (SD)	47.3 (29.7)	36.2 (33.0)	.04

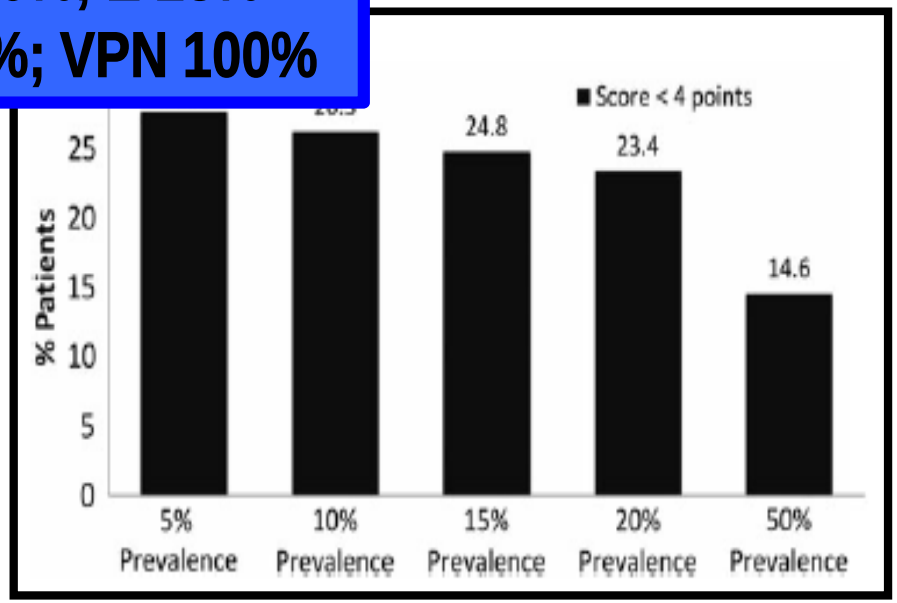
NOVA Score for Enterococcal Bacteremia

Bouza et al. *CID* 2015

Variable	Points	Odds Ratio (95% Confidence Interval)
Number of positive blood cultures (N)	5	9.9 (2.2–40.6)
Unknown origin of bacteremia (O)	4	7.7 (2.5–23.8)
Prior valve disease (V)	2	3.7 (1.6–8.7)
Auscultation of a heart murmur (A)	1	1.8 (.77–4.3)
Total		

S 100%; E 28%
VPP 7%; VPN 100%

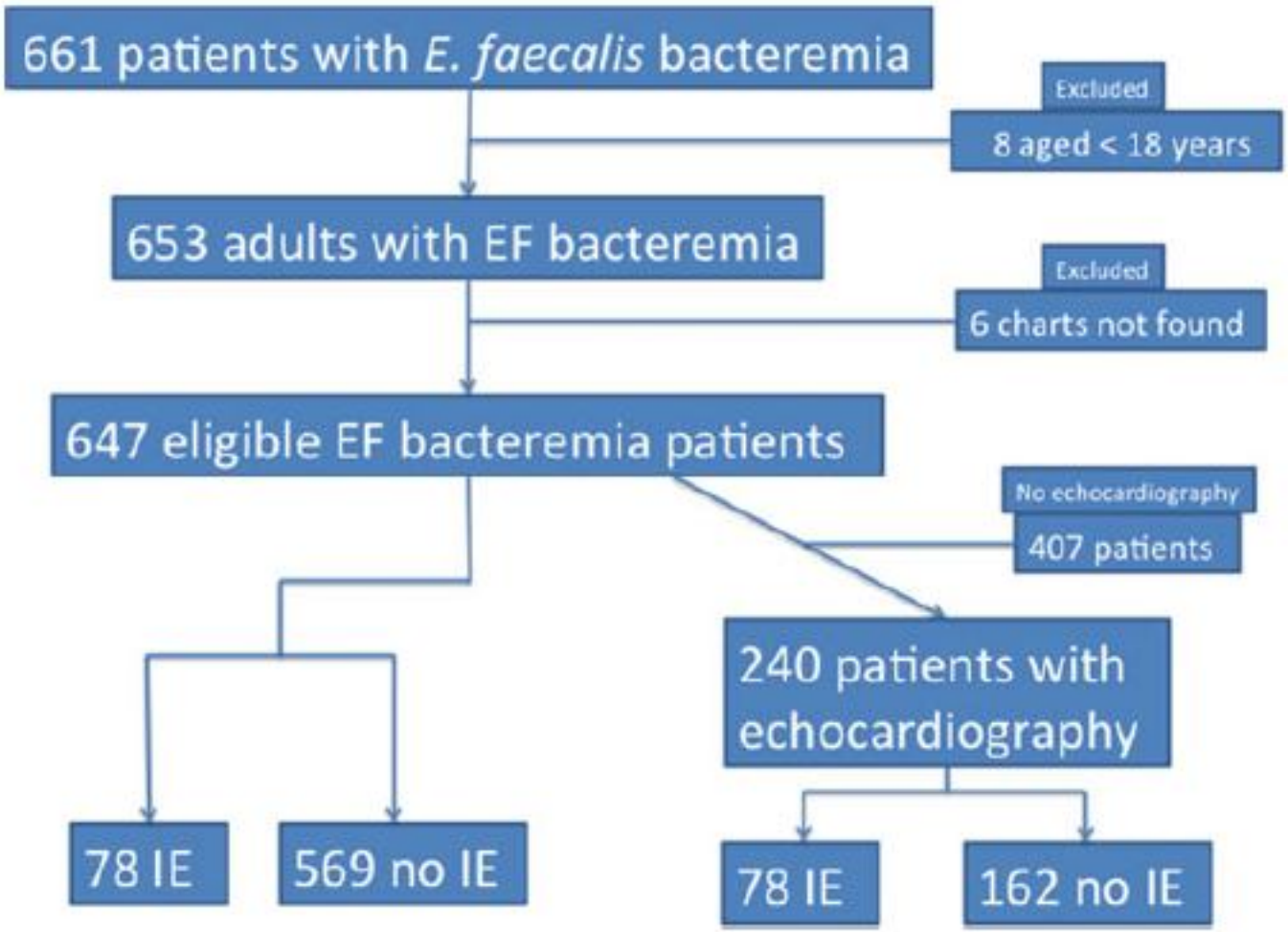




External validation of the NOVA Score

Dahl et al. *CID* 2016

10 hospitales daneses
2010-2013



External validation of the NOVA Score

Dahl et al. *CID* 2016

Variable	Endocarditis n = 78 (%)	No Endocarditis n = 569 (%)	*P* Value
Mean age, years (standard deviation)	74.0 (11.7)	72.7 (13.1)	.400
Sex (male)	67 (85.9)	415 (72.9)	.014
Predisposing conditions			
Cardiac device	13 (16.7)	51 (9.0)	.033
Prosthetic valve	30 (38.5)	20 (3.5)	<.001
Other valve disease	12 (15.4)	39 (6.9)	.009
Previous infective endocarditis	5 (6.4)	2 (0.4)	<.001
Mode of acquisition			
Community	28 (36)	94 (16)	<.001
Healthcare associated	41 (53)	288 (51)	.747
In-hospital	9 (11)	187 (33)	<.001
Port of entry			
Urinary tract	30 (39)	286 (50)	.051
Unknown origin	34 (44)	136 (24)	<.001
Gastrointestinal tract	4 (5)	85 (15)	.018
Intravenous catheter	4 (5)	21 (4)	.355
Wounds	2 (3)	32 (6)	.198
Others	4 (5)	9 (2)	.060
Echocardiography			
Transthoracic echocardiogram	77 (98.7)	158 (27.8)	<.001
Transesophageal echocardiogram	65 (83.3)	51 (9.0)	<.001
Monobacterial	73 (91.0)	342 (60.1)	<.001

External validation of the NOVA Score

Dahl et al. *CID* 2016

Variable	Points
Number of positive blood cultures (N)	5
Unknown origin of bacteremia (O)	4
Prior valve disease (V)	2
Auscultation of a heart murmur (A)	1
Total	12

2/2 BC or > 50%

External validation of the NOVA Score

Dahl et al. *CID* 2016

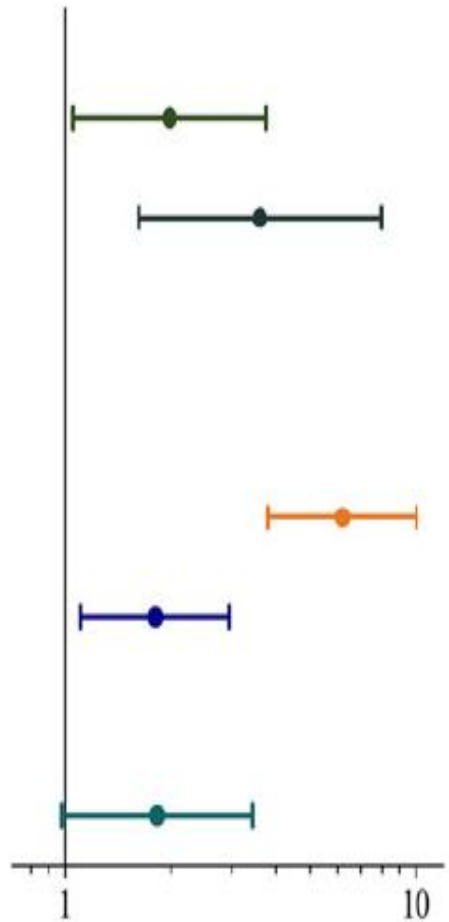
Variable	Endocarditis n = 78 (%)	No Endocarditis n = 162 (%)	*P* Value
Cardiac device	13 (16.7)	25 (15.4)	.806
Prosthetic valve	30 (38.5)	16 (9.9)	<.001
Other valve disease	12 (15.4)	17 (10.5)	.276
Previous infective endocarditis	5 (6.4)	1 (0.6)	.015
In-hospital mortality	12 (15.4)	22 (13.6)	.707
1-year mortality	27 (34.6)	67 (41.4)	.316

External validation of the NOVA Score

Dahl et al. *CID* 2016

Variable associated with IE	Univariable HR (95% CI)	Univariable *P* value	Multivariable HR (95% CI)	Multivariable *P* value
Age	1.01 (0.99–1.03)	.260		
Male sex	2.10 (1.11–3.96)	**.023**	1.99 (1.05–3.76)	**.035**
Monomicrobial EF bacteremia	5.62 (2.58–12.2)	**<.001**	3.60 (1.62–7.97)	**.002**
Previous endocarditis	8.63 (3.48–21.4)	**<.001**		
Cardiac device	1.91 (1.05–3.47)	**.033**		
Prosthetic heart valve	9.94 (6.27–15.8)	**<.001**	6.19 (3.81–10.1)	**<.001**
Community acquisition	2.58 (1.62–4.10)	**<.001**	1.81 (1.11–2.93)	**.017**
Infection of unknown origin	2.61 (1.67–4.08)	**<.001**		
Other valvular disease	2.29 (1.24–4.23)	**.009**	1.82 (0.98–3.42)	.059.

Forest plot



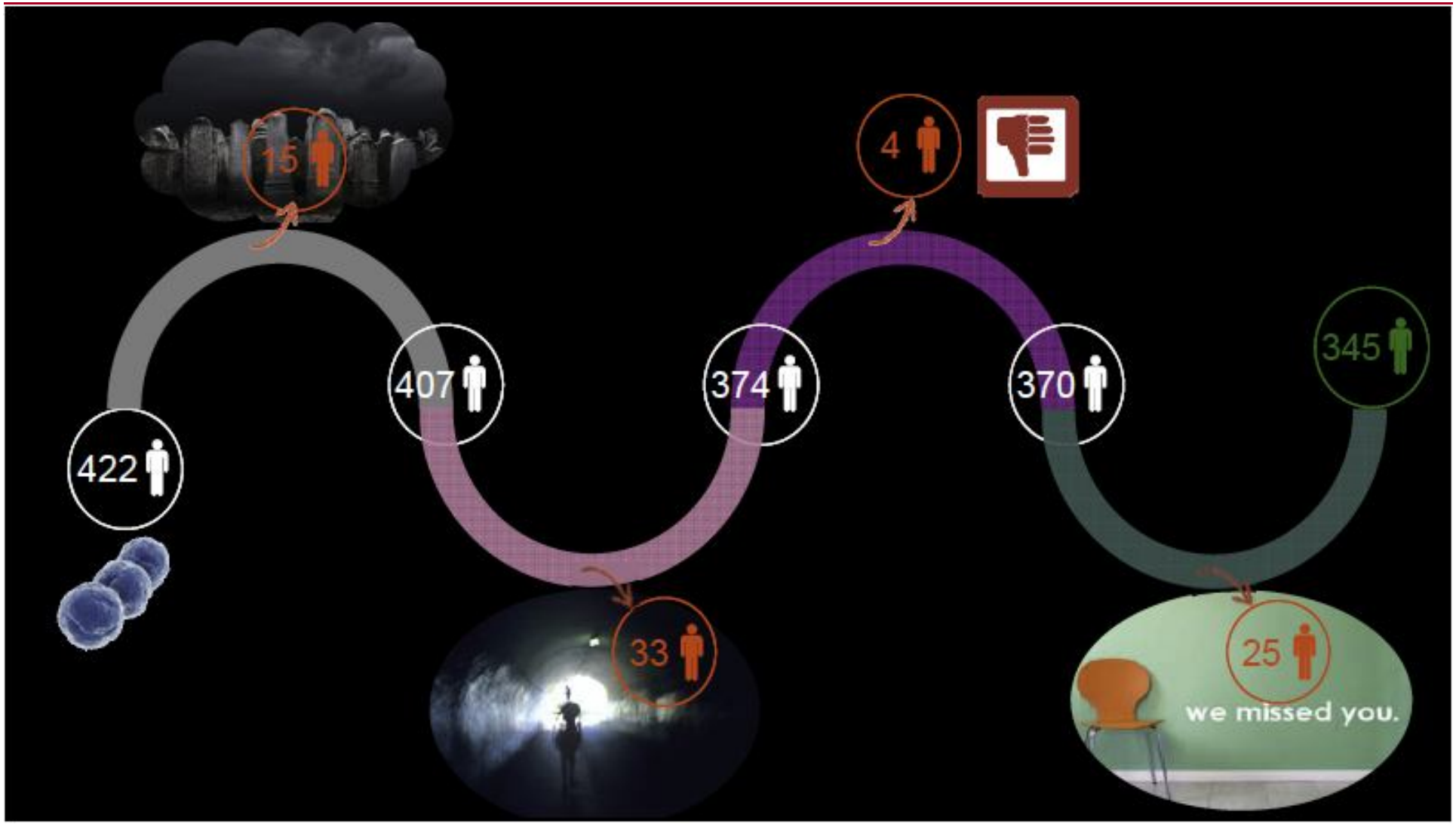
External validation of the NOVA Score

Dahl et al. *CID* 2016

Adapted NOVA Score	Endocarditis (n = 78)	No Endocarditis (n = 162)	Negative and Positive Predictive Value
<4 (TEE not needed)	2	38	95% (negative predictive value)
≥4 (TEE recommended)	76	124	38% (positive predictive value)
Sensitivity	97%		
Specificity	23%		

Prevalence of IE among patients with monomicrobial *E. faecalis* bacteremia

Dahl A. ISCVID 2017, Dublin



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Prevalence of IE among patients with monomicrobial *E. faecalis* bacteremia

Dahl A. ISCVID 2017, Dublin

	Endocarditis (91)	Bacteremia (254)	P value
Age, years, mean (SD)	74.8 (11.5)	74.0 (12.7)	0.621
Sex, women, n (%)	20 (22)	71 (28)	0.267
Diabetes, n (%)	28 (31)	53 (21)	0.056
Heart failure, n (%)	13 (14)	32 (13)	0.682
Nephropathy, n (%)	10 (11)	29 (11)	0.912
Former stroke, n (%)	22 (24)	50 (20)	0.366
Former myocardial infarction, n (%)	**9 (10)**	26 (10)	0.925
Cancer, n (%)	16 (18)	45 (18)	0.977
Disseminated cancer, n (%)	6 (7)	34 (13)	0.082

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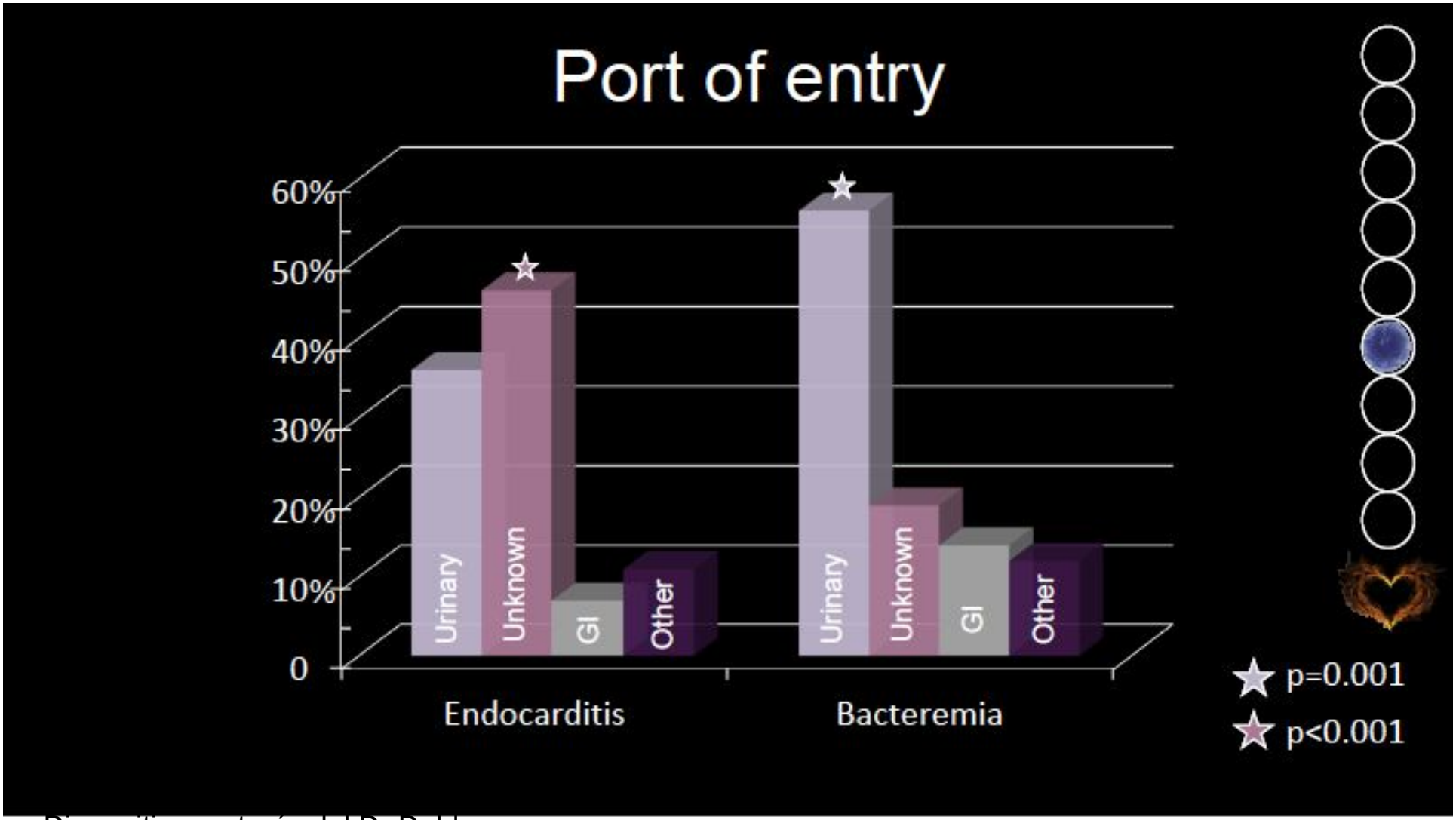
Prevalence of IE among patients with monomicrobial *E. faecalis* bacteremia

Dahl A. ISCVID 2017, Dublin



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Prevalence of IE among patients with monomicrobial *E. faecalis* bacteremia

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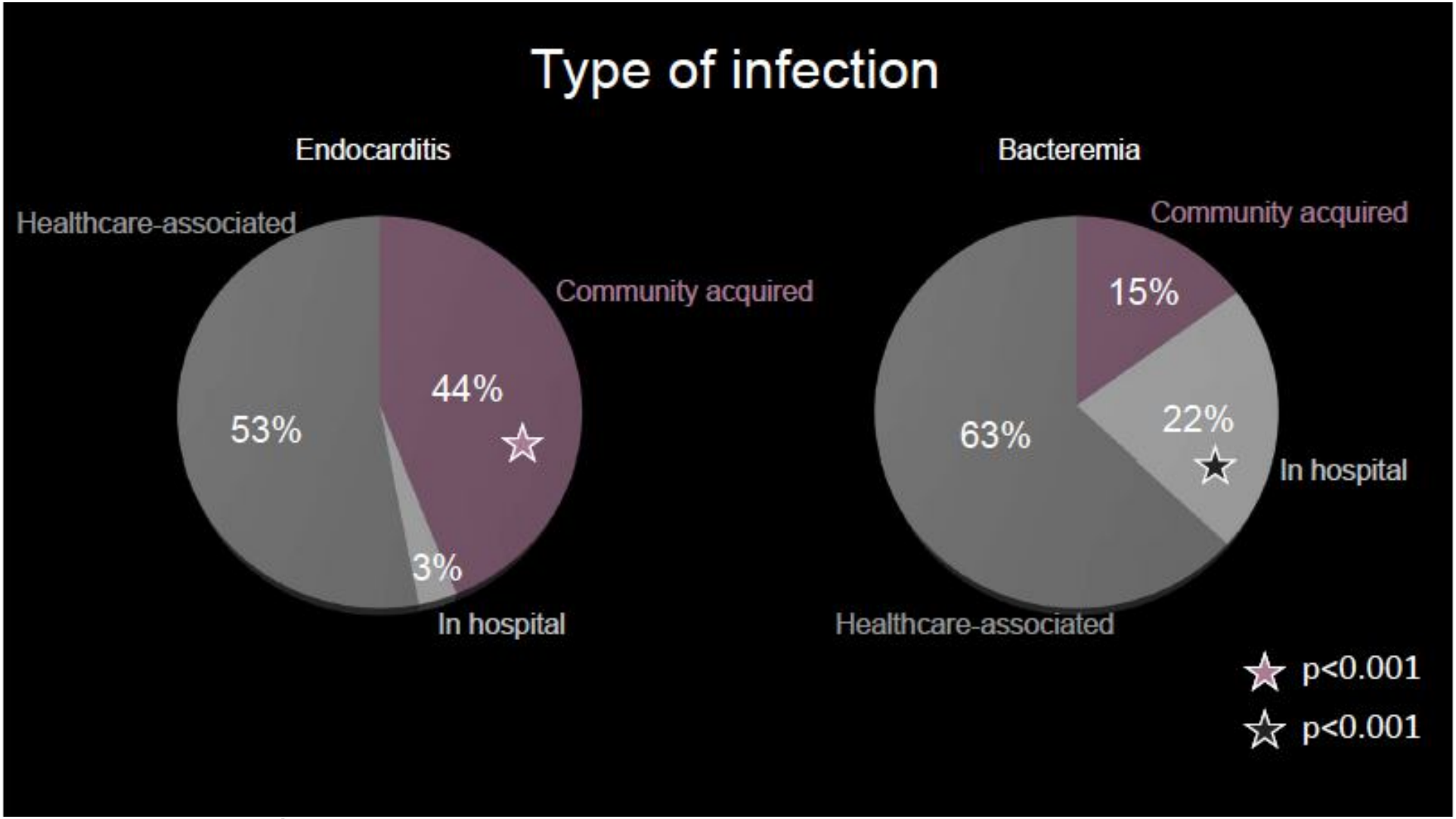

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Prevalence of IE among patients with monomicrobial *E. faecalis* bacteremia

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Predictors of endocarditis

	Univariate analyses		Multivariate analysis		
Predictor for endocarditis	OR (95% CI)	P-value	OR (95% CI)	OR (95% CI)	P-value
Age, years	1.0 (0.9 – 1.0)	0.62			
Sex, male	1.4 (0.8 – 2.4)	0.27			
Community acquired infection	4.3 (2.5 – 7.4)	<0.001		3.7 (1.9 – 7.2)	<0.001
≥ 3 positive blood culture bottles	5.3 (2.8 – 10.0)	<0.001		4.5 (2.2 – 8.9)	<0.001
Unknown origin of infection	3.8 (2.2 – 6.3)	<0.001		3.1 (1.6 – 5.8)	0.001
Known native valve disease	1.3 (0.5 – 3.0)	0.60			
Pacemaker	2.1 (1.2 – 3.9)	0.014			
Prosthetic heart valve	6.9 (3.4 – 13.9)	<0.001		5.2 (2.3 – 11.8)	<0.001
Immunosuppression	1.7 (0.8 – 3.4)	0.155		3.4 (1.5 – 8.1)	0.005
Cerebral embolic event	4.8 (1.5 – 15.1)	<0.001		6.3 (1.7 – 22.8)	0.005

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DENOVA, A revised scoring system for monomicrobial *Enterococcus faecalis* bacteremia

Berge A. ISCVID 2017, Dublin

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Calibration cohort:

689 episodes of *E. faecalis* bacteremia

Excluded: 291 episodes
< 18 years 36 episodes
Lack of med. files 6 episodes
Polymicrobial 249 episodes

398 included episodes of monomicrobial *E. faecalis* bacteremia

354 non-IE

44 definite IE

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DENOVA, A revised scoring system for monomicrobial *Enterococcus faecalis* bacteremia

Berge A. ISCVID 2017, Dublin

Previous IE (%)	7 (16)	5 (1)	12.96 (5.01-33.56)	<0.001
Native valve disease (%)	10 (22.7)	39 (11)	2.25 (1.02-4.98)	0.046
Valve prosthesis (%)	16 (36)	34 (10)	5.17 (2.54-10.51)	<0.001
Intracardiac device (%)	5 (11)	40 (11)	0.99 (0.37-2.65)	0.21
Any predisposing heart condition	26 (59)	65 (18)	6.24 (3.25-11.98)	<0.001
(V in NOVA)*				
Previous bacteremia with E. faecalis (%)	9 (20)	30 (9)	2.68 (1.16-6.21)	0.02
Site of acquisition (%)				
Community	22 (50)	90 (26)	2.91 (1.54-5.48)	0.001
Health care	21 (48)	181 (51)	0.87 (0.47-1.63)	0.66
Nosocomial	1 (2)	81 (23)	0.08 (0.01-0.57)	0.01
Signs at presentation				
Fever (%)	36 (82)	288 (82)	1.03 (0.46-2.34)	0.94
Murmur (%)	36 (82)	49 (14)	28.49 (12.34-65.75)	<0.001
Embolization (%)	8 (18)	1 (0)	75.62 (9.41-607.55)	<0.001
Duration of symptoms >7 days	30 (68)	43 (12)	15.41 (7.59-31.32)	<0.001
Microbiology				
≥2 positive cultures (%)	43 (98)	221 (62)	26.57 (3.38-208.87)	0.002
Focus of infection (%)				
Urinary tract	1 (2)	159 (45)	0.03 (0.003-0.21)	<0.001
Gastrointestinal and bilary	0	52 (15)	N/A	
Other**	2 (5)	40 (11)	0.38 (0.09-1.59)	0.19
Unknown	41 (93)	102 (29)	34.63 (10.51-114.12)	<0.001

DENOVA, A revised scoring system for monomicrobial *Enterococcus faecalis* bacteremia

Berge A. ISCVID 2017, Dublin

	Odds Ratio (95% CI)	p-value
Murmur	13.10 (4.74-36.25)	<0.001
Embolization	49.66 (6.19-398.28)	<0.001
Duration of symptoms ≥7 days	9.65 (3.64-25.59)	<0.001
≥2 positive cultures	6.82 (1.48-31.50)	0.014
Unknown focus of infection	7.27 (2.01-26.33)	0.003

Diapositiva cortesía del Dr Rasmussen

DENOVA, A revised scoring system for monomicrobial *Enterococcus faecalis* bacteremia

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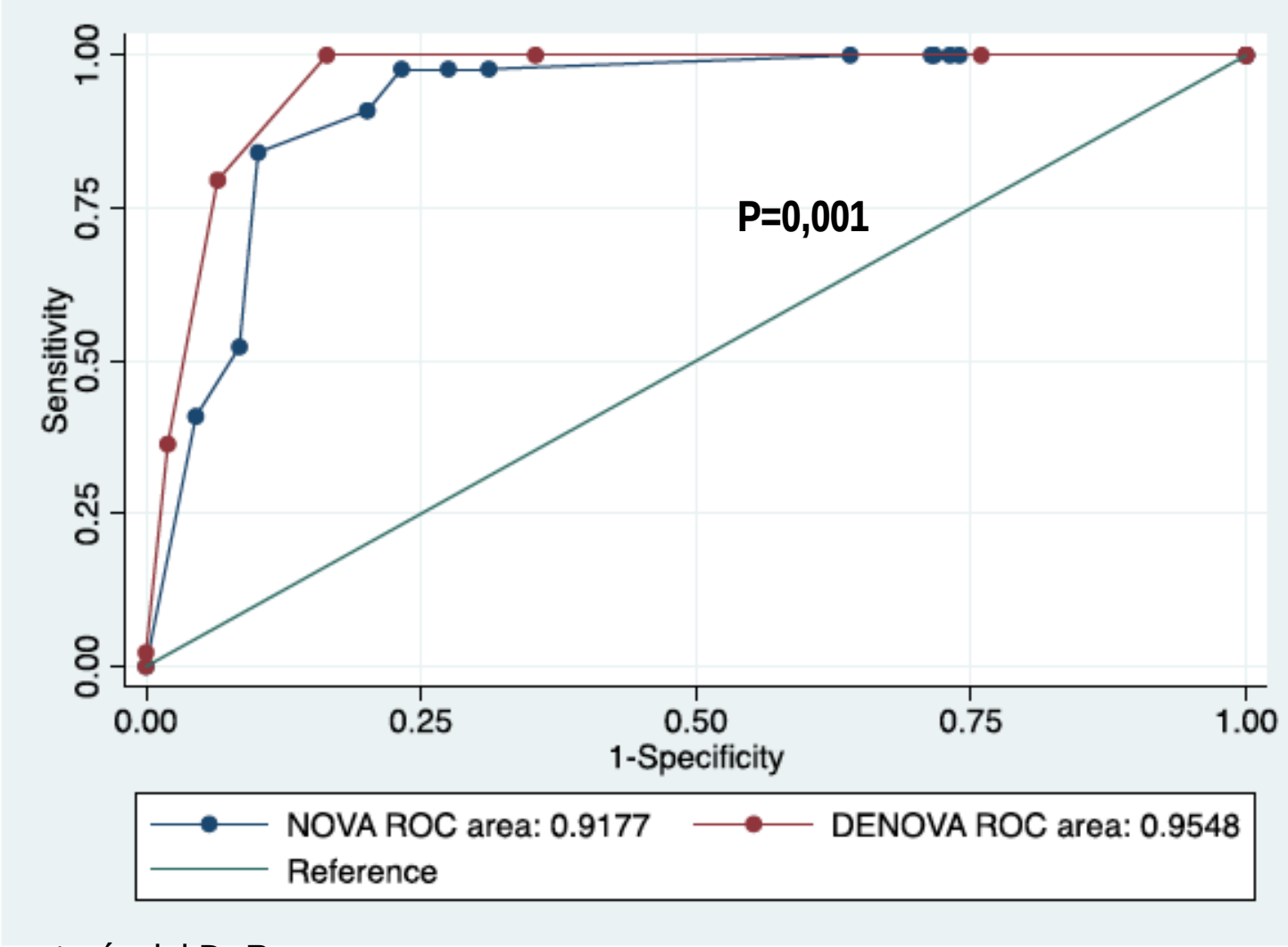

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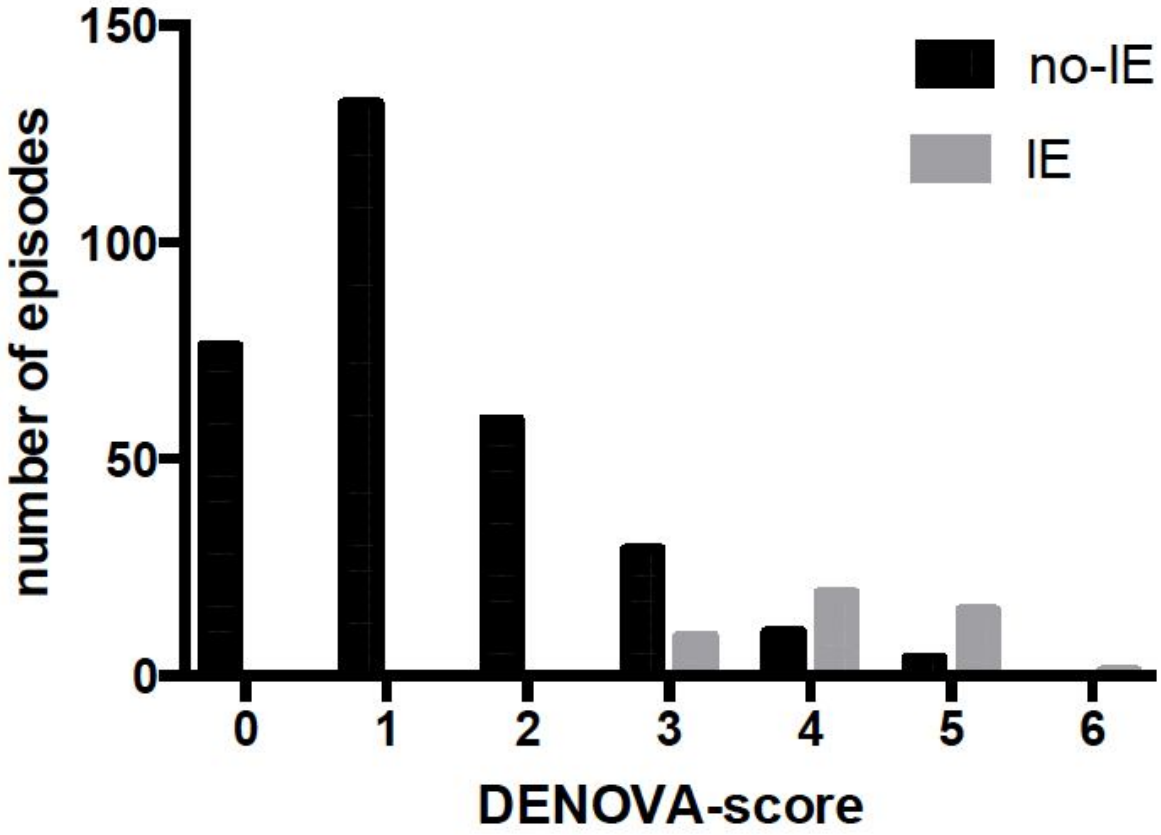

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DENOVA, A revised scoring system for monomicrobial *Enterococcus faecalis* bacteremia

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Validation cohort:

	IE	not IE	
DENOVA ≥ 3	26/26 (100 %)	40/242 (17%)	PPV: 26/62 (**42**%)
DENOVA < 3	0/26 (0 %)	202/242 (**83**%)	NPV: 0/238 (100%)

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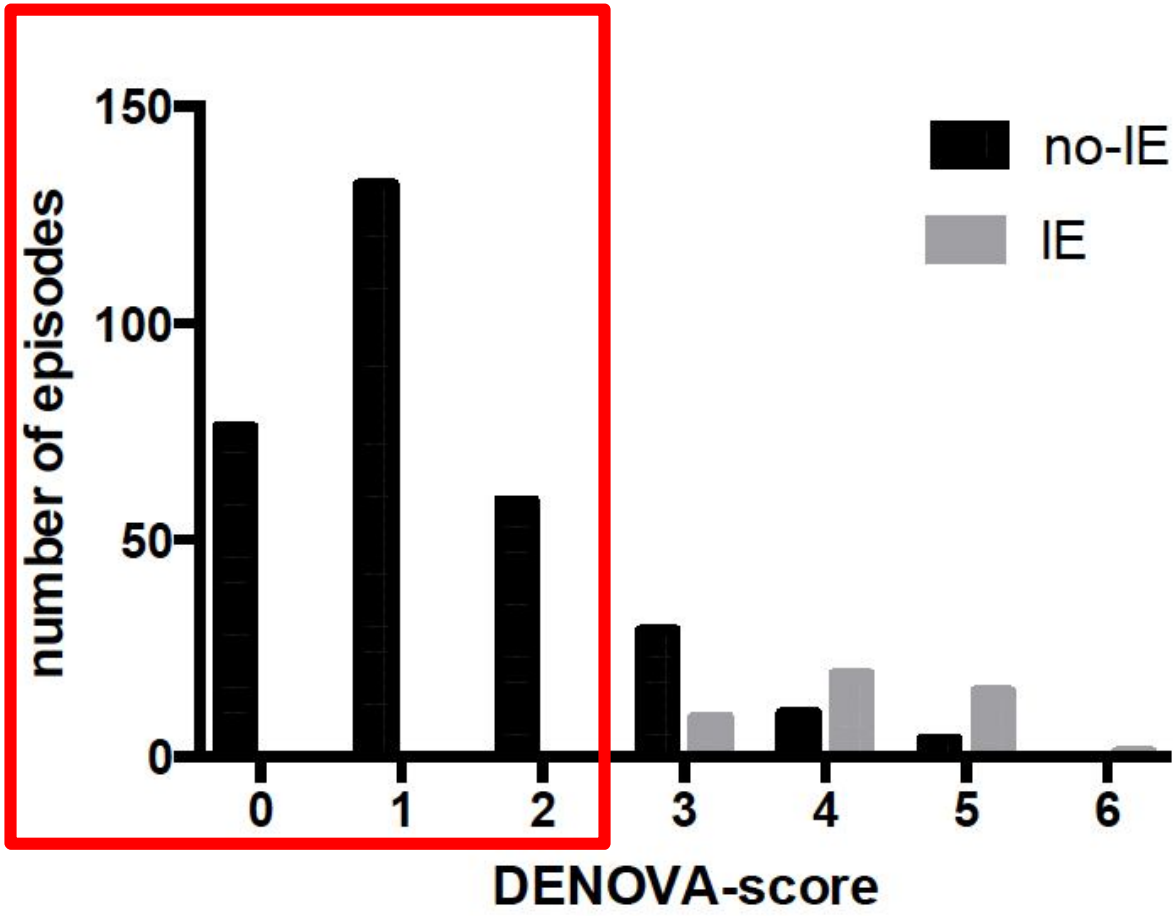
DENOVA, A revised scoring system for monomicrobial *Enterococcus faecalis* bacteremia

Berge A. ISCVID 2017, Dublin



Diapositiva cortesía del Dr Rasmussen

2. EFIE y cáncer de colon

Infective endocarditis in patients with cancer: a consequence of invasive procedures or a harbinger of neoplasm?

Fernández-Cruz et al. Medicine, 2017

Characteristics of infective endocarditis in patients with and without cancer.

Variable (%)	No cancer (N = 2727)	Cancer (N = 161)	P*
Acquisition			
Community-acquired	1610 (61.6)	56 (37.6)	**.01**
Hospital-acquired	782 (29.9)	73 (48.7)	**.01**
Health care-related	220 (8.4)	21 (14.1)	**.02**
Source of endocarditis	1251 (45.9)	108 (67.1)	**.01**
Catheter	169 (6.2)	38 (23.6)	**.01**
Odontogenic	163 (6.0)	5 (3.1)	.13
Respiratory	28 (1.0)	4 (2.5)	.09
Genitourinary	128 (4.7)	17 (10.6)	**.001**
Gastrointestinal	170 (6.2)	24 (14.9)	**.01**
Skin and soft tissue	182 (6.7)	10 (6.2)	.82
Etiology			
Coagulase negative staphylocci	476 (17.5)	26 (16.1)	.67
Staphylococcus aureus	606 (22.3)	38 (23.6)	.68
Enterococcus	378 (13.9)	23 (14.3)	.88
Streptococcus	694 (25.5)	38 (23.6)	.60
Gram-negative bacilli	110 (4.0)	5 (3.1)	.56
Anaerobes	30 (1.1)	1 (0.6)	.57
Candida	43 (1.6)	7 (4.3)	**.009**
Other fungi	10 (0.4)	1 (0.6)	.61
Other etiologies	83 (3.0)	0 (0)	**.03**
Polymicrobial	46 (1.7)	8 (5)	**.003**
Unknown	251 (9.2)	14 (8.7)	.83

Antecedentes relación EFIE y cáncer de colon

Antibiotic Therapy of Bacterial Endocarditis

VI. Subacute Enterococcal Endocarditis: Clinical, Pathologic and Therapeutic Consideration of 33 Cases

By Joseph E. Geraci, M.D., and William J. Martin, M.D.

Arch Intern Med/Vol 125, Feb 1970

While in the majority of cases enterococcal endocarditis is associated with organic heart disease, the infection may be engrafted on normal heart valves. This aspect of enterococcal endocarditis will be commented on later.

Enterococcal endocarditis may complicate urologic instrumentation[29, 30] such as cystoscopy, urethral dilatation or transurethral resection. This infection has been associated with or complicated carcinoma of the sigmoid colon,[28] so-called Blalock-Taussig operation,[31] abortion[32] and normal pregnancy.[33] Periapical dental abscesses have also been implicated.[34]

J Am Osteopath Assoc. 1985 Nov;85(11):751-3.

Enterococcal endocarditis in association with cancer of the colon: report of a case and review of the literature.

Miller PM, Frank EB, Fischer RA.

Differences between IE caused by *S. bovis* and *Enterococcus spp*. and their association with CRC

Corredoira et al. EJCMID, 2015

Endocarditis	*S. bovis*	*Enterococcus* spp.	p-value
Number of cases	109	36 (50% FCS)	
Source of infection			
- Urologic	0	9 (25 %)	0.0000
- Catheter	0	1 (2.8 %)	ns
- Valve surgery	1 (0.9 %)	1 (2.8 %)	ns
- Surgical wound	0	1 (2.8 %)	ns
- Digestive	70 (64.2 %)	9 (25 %)	0.0000
- Unknown	38 (34.9 %)	15 (41.7 %)	ns
Colon tumour	70 (64.2 %)	9 (25 %)	0.0000

Es necesario excluir neoplasia colorrectal en todos los pacientes con EI por *S. Viridans* y *Enterococcus spp*

Kestler et al. SEIMC, Málaga 2015

- 22 pacientes con EI por *Enterococcus spp*
- 17 (77,3%) prueba para descartar CRN (colonoscopia/PET-TAC)
- 10 patología colorrectal (45,4%), 4 CRN (18,2%).
- Mortalidad al año similar a la del grupo sin cáncer.

Relationship between EFIE of unclear focus and Colorectal Neoplasms

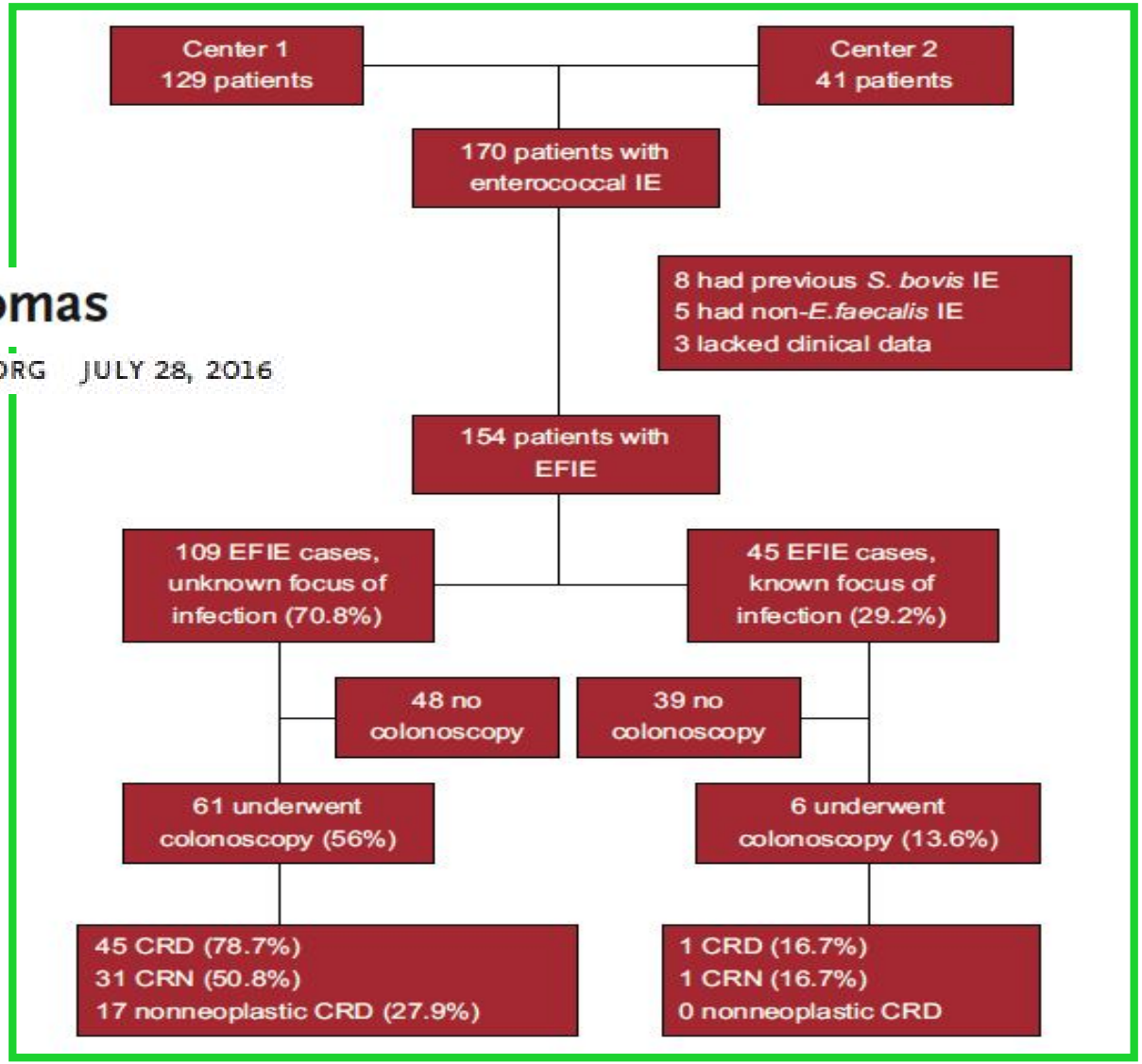
Pericàs et al. REC, 2017

1979-2015

154 pts

Colorectal Adenomas

N ENGL J MED 375;4 NEJM.ORG JULY 28, 2016



Relationship between EFIE of unclear focus and Colorectal Neoplasms

Pericàs et al. REC, 2017

Variable	Unknown origin	Known origin	*P*
Number of cases	109	45	
Patients with colonoscopy during the admission or within the first 90 days after diagnosis	61 (56)	6 (13.6)	<.001
P			4
C			1
			1
			3
Colorectal cancer	4 (3.7)	0 (0.0)	
Nonneoplastic diseases diagnosed using colonoscopy[b]	17 (15.6)	0 (0.0)	.005
New diagnosis of adenocarcinoma during follow-up (after 90 days of admission)[c]	1/56 (1.8)	0/31 (0.0)	.560

diagnosed with CRN. The prevalence of adenomas was slightly higher than that of the Spanish population in the same age range, whereas that of CRC was 17-fold higher.

Conclusions: CRN was found in more than half of patients with EFIE and an unclear focus of infection who underwent colonoscopy. Colonoscopy should be recommended in patients with EFIE and an unclear source of infection.

Case Report

Infectious Endocarditis from *Enterococcus faecalis* Associated with Tubular Adenoma of the Sigmoid Colon

Case Reports in Infectious Diseases
Volume 2017, Article ID 3095031, 4 pages

Emilly Caroline de Freitas Silva, Camila Ronchini Montalvão, and Simone Bonafé

Journal of Infection and Public Health 10 (2017) 681–684

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Short report

Colon cancer and enterococcus bacteremia co-affection: A dangerous alliance

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3. Perspectivas y propuestas de futuro

Scores diagnósticos

- La evidencia acumulada hasta la fecha es notable
- Validación
- Inclusión en guías
- Nuevos estudios
- ¿Cómo puede influir la realización sistemática de una colonoscopia en la O?

Relación EFIE-foco desconocido-colon

- Evidencia insuficiente
- Relación plausible
- Importantes implicaciones clínicas y pronósticas
- Dificultad realización FCS en pacientes graves o muy ancianos
- ¿En el caso de bacteriemia y ETE inicial normal?
- Necesidad de estudios prospectivos

Estudio a nivel europeo

- España, Dinamarca, Suecia, Francia
- FCS en todos los casos de EFIE de foco desconocido
- Duración: 2 años
- Prospectivo, no aleatorizado
- Grupo control con matching 1:1
- Valorar subgrupo con bacteriemia y no EI (con Score en el límite)
- …

1ª Fase: revisar todos los casos de GAMES de EFIE con y sin FCS

4. Conclusiones

1. El desarrollo y utilización de scores para la realización de ETE en la bacteriemia enterocócica ha resultado de gran utilidad.
2. Deben ser contemplados en las guías internacionales mientras se resuelven los “blind spots”
3. La relación del cáncer de colon y la EFIE parece ser significativa
4. Mientras se recoge nueva evidencia debe realizarse una FCS en los casos de EFIE de foco desconocido
5. Un proyecto europeo es factible y oportuno

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