Efecto de la gentamicina en la mortalidad de la endocarditis protésica estafilocócica

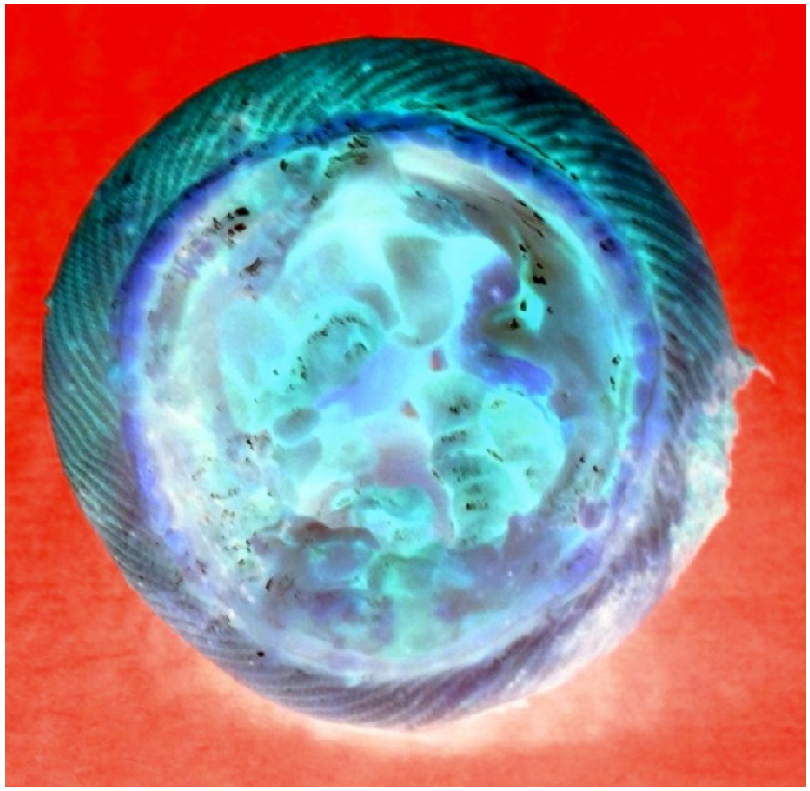
Antonio Ramos Martínez

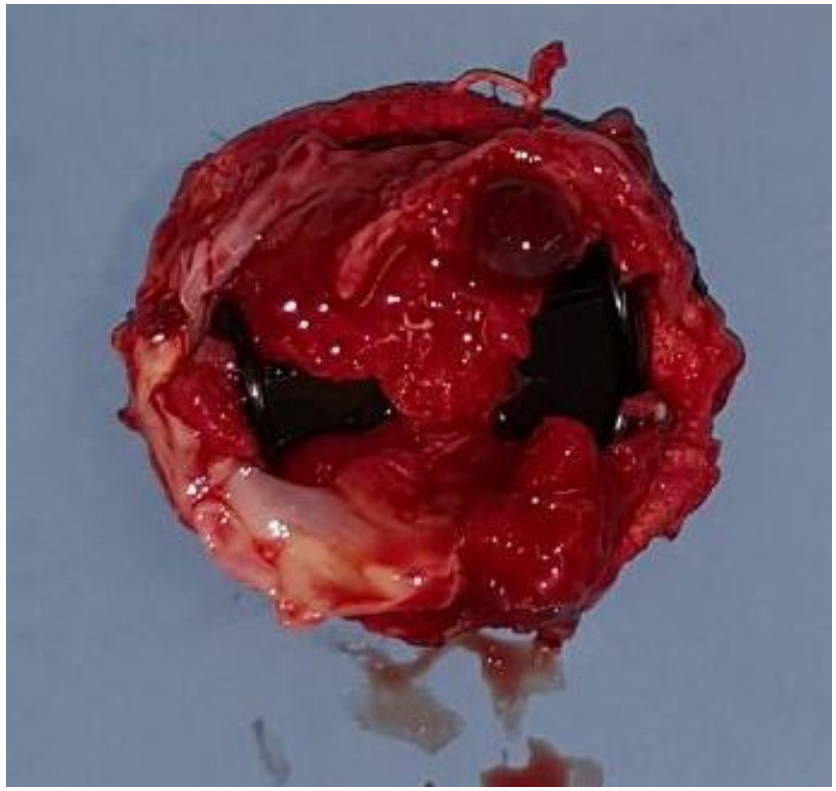
Puerta de Hierro

SEICAV
Sociedad Española de Infecciones Cardiovasculares

SaludMadrid
Hospital Universitario Puerta de Hierro Majadahonda

Endocarditis protésica estafilocócica





Endocarditis protésica estafilocócica

- Incidencia creciente (adquisición nosocomial)
- Complicaciones frecuentes y elevada mortalidad
- Las guías recomiendan añadir gentamicina a vancomicina (o cloxacilina) más rifampicina. Baja tasa de cumplimiento
- Endocarditis nativa no se recomienda gentamicina

Mandell

Tratamiento de la endocarditis sobre válvula protésica causada por estafilococos (sugerido por la American Heart Association)		
RÉGIMEN	**DOSIS Y VÍA DE ADMINISTRACIÓN**	**DURACIÓN**
Estafilococos sensibles a meticilina		
Nafcilina u oxacilina*	2 g i.v./4 horas	≥6 semanas
más		
Rifampicina†	300 mg v.o. o i.v./8 horas	≥6 semanas
más		
Gentamicina‡	3 mg/kg i.v./i.m./24 horas en 2-3 dosis iguales fraccionadas	2 semanas
Estafilococos resistentes a meticilina		
Vancomicina§	15 mg/kg i.v./12 horas	≥6 semanas
más		
Rifampicina†	300 mg v.o. o i.v./8 horas	≥6 semanas
más		
Gentamicina‡	3 mg/kg i.v./i.m. en 2-3 dosis iguales fraccionadas	2 semanas

Guías europeas

Prosthetic valves				
Methicillin-susceptible staphylococci				
(Flu)cloxacillin *or* oxacillin with Rifampin[e] and Gentamicin[f]	12 g/day i.v. in 4–6 doses	≥ 6	I	B
	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I	B
	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B
	Paediatric doses:[g] Oxacillin and (flu)cloxacillin as above Rifampin 20 mg/kg/day i.v. or orally in 3 equally divided doses			
Penicillin-allergic patients[h] and methicillin-resistant staphylococci				
Vancomycin[b] with Rifampin[e] and Gentamicin[f]	30–60 mg/kg/day i.v. in 2–3 doses	≥ 6	I	B
	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I	B
	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B

Habib G, et al. Eur Heart J. 2015; 36: 3075-128

Evidencias tratamiento combinado

Teicoplanin in Endocarditis: A Multicentre, Open European Study

Combination antibiotic therapy in an outbreak of prosthetic endocarditis caused by *Staphylococcus epidermidis*

GREGORY W. HAMMOND, MD, FRCP[C]; H. GRANT STIVER, MD, FRCP[C]

Bacteriological outcome of combination versus single-agent treatment for staphylococcal endocarditis

Dragana Drinković[1], Arthur J. Morris[1]*, Sudha Pottumarthy[1], Donald MacCulloch[1] and Teena West[2]

Departments of [1]Microbiology and [2]Biostatistics, Green Lane Hospital, Auckland, New Zealand

Lewis PJ. Chemotherapy 1995;41: 399-411
Drinković D. J Antimicrob Chemother 2003; 52: 820-5
Hammond GW. Can Med Assoc J 1978; 118: 524-30

Evidencias tratamiento combinado

***Staphylococcus epidermidis* Causing Prosthetic Valve Endocarditis: Microbiologic and Clinical Observations as Guides to Therapy**

ADOLF W. KARCHMER, M.D.; GORDON L. ARCHER, M.D.; and WILLIAM E. DISMUKES, M.D.; Boston, Massachusetts; Richmond, Virginia; and Birmingham, Alabama

Rev Infect Dis. 1983 Jul-Aug;5 Suppl 3:S533-7.

Therapy for experimental endocarditis due to Staphylococcus epidermidis.

Kobasa WD, Kaye KL, Shapiro T, Kaye D.

Coagulase-negative staphylococcal prosthetic valve endocarditis—a contemporary update based on the International Collaboration on Endocarditis: prospective cohort study

V H Chu,[1,2] J M Miro,[3] B Hoen,[4] C H Cabell,[1,2] P A Pappas,[2] P Jones,[5] M E Stryjewski,[2,6] I Anguera,[7] S Braun,[8] P Muñoz,[9] P Commerford,[10] P Tornos,[11] J Francis,[12] M Oyonarte,[13] C Selton-Suty,[14] A J Morris,[15] G Habib,[16] B Almirante,[11] D J Sexton,[1] G R Corey,[1,2] V G Fowler Jr,[1,2] for the International Collaboration on Endocarditis-Prospective Cohort Study Group

Karchmer AW. Ann Intern Med 1983; 98: 447-55
Kobasa WD. Rev Infect Dis 1983; 5: S533-7
Chu VH, Miro JM. Heart 2009; 95: 570-6


II CONGRESO
SEICAV
VII REUNIÓN
GAMES
BILBAO 2013
Palacio Euskalduna
27/28 de septiembre

Is triple theraphy necessary in staphylococcal prosthetic valve endocarditis?

Dr Antonio Plata (1), Dr. Emilio Garcia-Cabrera (2), Dr. Juan Diego Ruiz-Mesa (1), Dr Jose Maria Reguera (1), Dr Jose M Lomas-Cabeza (3), Dr Francisco Martinez-Marcos (3), Dr Javier de la Torre Lima (4), Dra. Josefa Ruiz (5), Dr Juan Galvez-Acebal (6), Dra. Radka Ivanova (5), Dra. Carmen Hidalgo- Tenorio (7), Dr. Aristides de Alarcon (2)

[1]HRU Carlos Haya (Málaga), [2]H. Virgen del Rocío (Sevilla), [3]H. Juan Ramón Jiménez (Huelva), [4]H. Costa del Sol (Marbella), [5]H. Virgen de la Victoria (Málaga), [6]H. Virgen Macarena (Sevilla), [7]H. Virgen de las Nieves (Granada),

Andalusian Group for the Study of Cardiovascular Infection

MONOTHERAPY / BITHERAPY/ TRIPLE THERAPY

MONOTHERAPY 13 Cases (12%)	Cloxacillin 4 cases Vancomicin 4 cases	MONOTHERAPY	Death 84% (p=0.05) Renal Failure 28%
BITHERAPY 53 Cases (48.6%)	Cloxa + Gentam 14 Cloxa + Rifam 1 Vancom + Genta 27 Vanco + Rifam 9 Others combinat. 2	BITHERAPY	Death 51% (p=n.s.) Renal Failure 37%
TRIPLE THERAPY 43 Cases (39.4%)	Vanco + Genta + Rif 33 Cloxa + Genta + Rif 10	TRIPLE THERAPY	Death 54% (p=n.s.) Renal Failure 38%

Is triple theraphy necessary in staphylococcal prosthetic valve endocarditis?

Dr Antonio Plata (1), Dr. Emilio Garcia-Cabrera (2), Dr. Juan Diego Ruiz-Mesa (1), Dr Jose Maria Reguera (1), Dr Jose M Lomas-Cabeza (3), Dr Francisco Martinez-Marcos (3), Dr Javier de la Torre Lima (4), Dra. Josefa Ruiz (5), Dr Juan Galvez-Acebal (6), Dra. Radka Ivanova (5), Dra. Carmen Hidalgo- Tenorio (7), Dr. Aristides de Alarcon (2)

[1]HRU Carlos Haya (Málaga), [2]H. Virgen del Rocío (Sevilla), [3]H. Juan Ramón Jiménez (Huelva), [4]H. Costa del Sol (Marbella), [5]H. Virgen de la Victoria (Málaga), [6]H. Virgen Macarena (Sevilla), [7]H. Virgen de las Nieves (Granada),

Andalusian Group for the Study of Cardiovascular Infection

MORTALITY ANALYSIS

UNIVARIATE ANALYSIS

Septic shock	p=0.03
Monotherapy	p=0.046
Surgery delayed	p=0.03
Acute renal failure	p=0.05
Charlson age adjusted	p=0.05
Euroscore	P=0.002
Log Euroscore	P=0.0001

MULTIVARIATE ANALYSIS

Monotherapy	p=0.038	6.8 (IC 95% 1.1-41,5)
Log Euroscore	p=0.0001	1.07 (IC 95% 1.04-1.108)

CONCLUSIONS

✓ All the clinical guidelines recommended triple therapy for staphylococcal prosthetic valve endocarditis (vancomicin/cloxacillin + Gentamicin + Rifampicin) but there aren´t studies that respond clearly this question. In this large serie we found that bitherapy was similar to triple therapy in mortality with similar rates of acute renal failure and probably with less drugs interactions.

✓Monotherapy would not be used in staphylococcal prosthetic valve endocarditis because it has more mortality than bitherapy and triple therapy

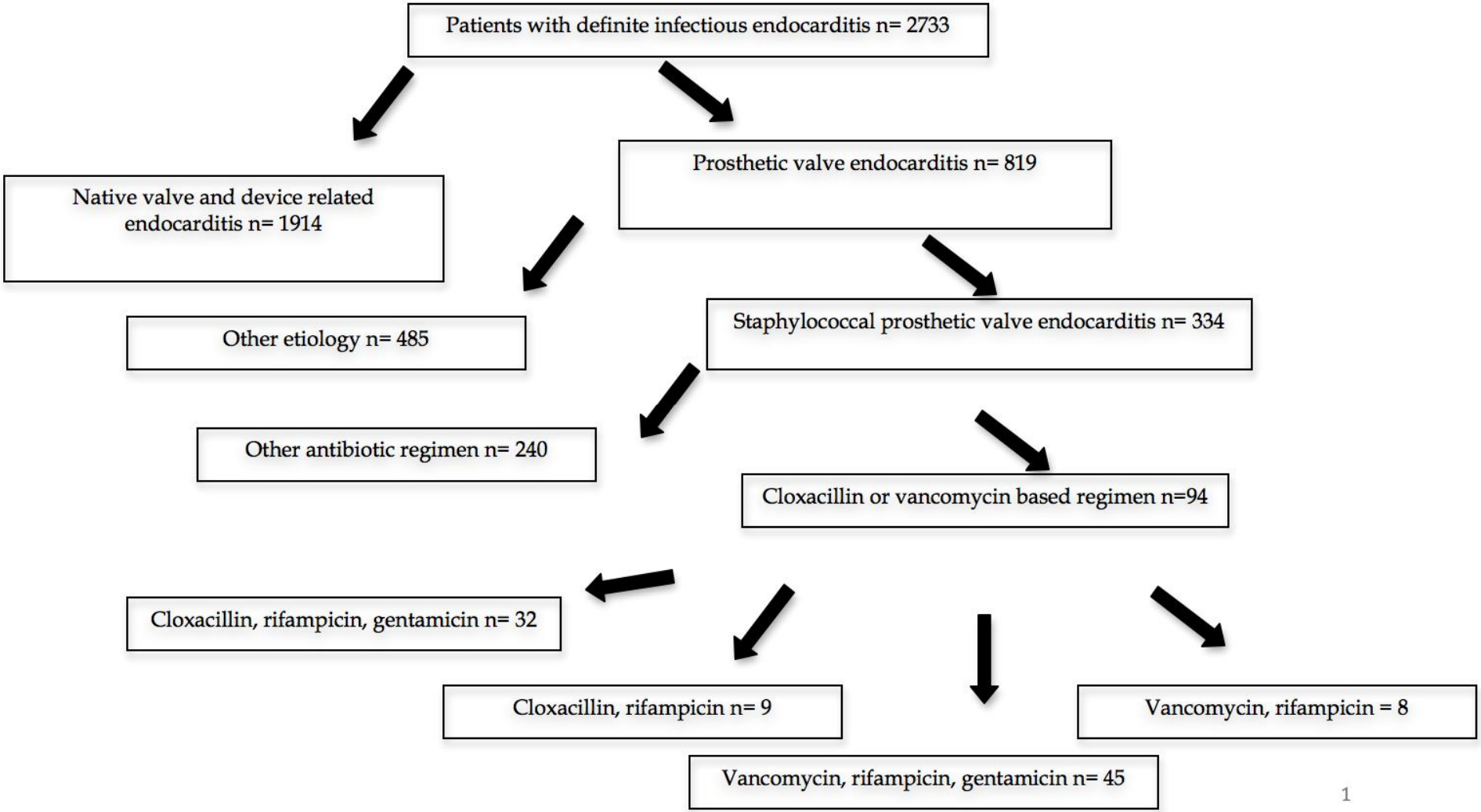
Hipótesis y objetivo

- Hipótesis
  - Los pacientes con EPE tratados sin gentamicina no presentan mayor mortalidad
- Objetivo
  - Impacto de gentamicina en la mortalidad hospitalaria
  - Diferencias entre *S. aureus* y SCN

Métodos

- Registro GAMES con 2733 casos de endocarditis definida. Criterios Duke modificados (2008- 2016)
- Seguimiento: mediana 3,4 años (0,3 - 6,25 años)
- Tto cloxacilina o vancomicina + rifampicina ± gentamicina (> 48 h)
- No otros antibióticos durante > 48h

Distribución de pacientes



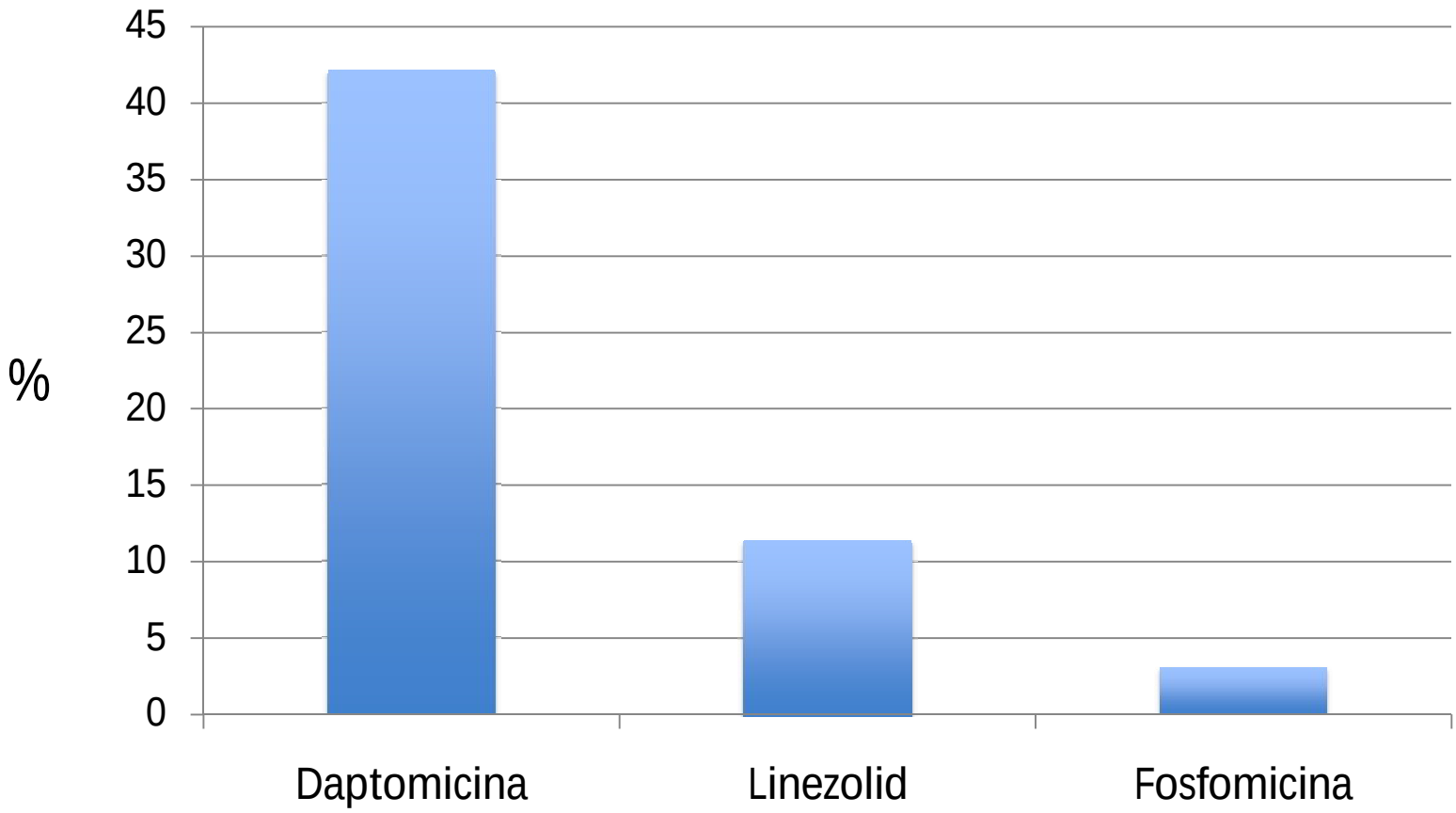
Endocarditis protésica estafilocócica

- 819 pacientes presentaron PVE definida
- 334 pacientes, estafilocócica

- 94 pacientes (28%) cloxa o vanco (+ rifam)
  - 77 pacientes (82%) recibieron gentamicina
  - 17 pacientes (18%) no recibieron gentamicina

- 240 pacientes (72%) tratados con otros regímenes

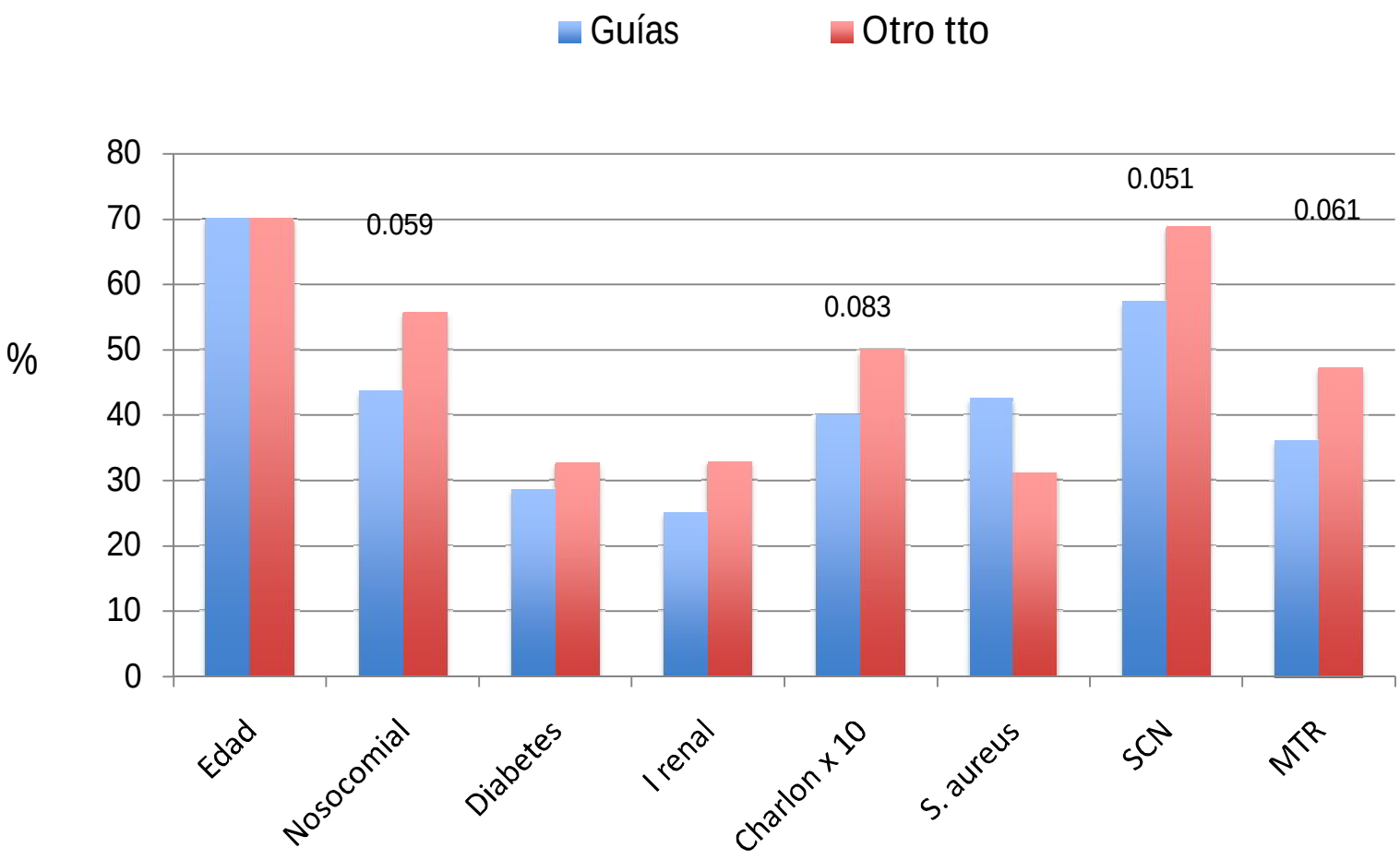
Antibióticos concomitantes en pacientes inicialmente tratados según las guías



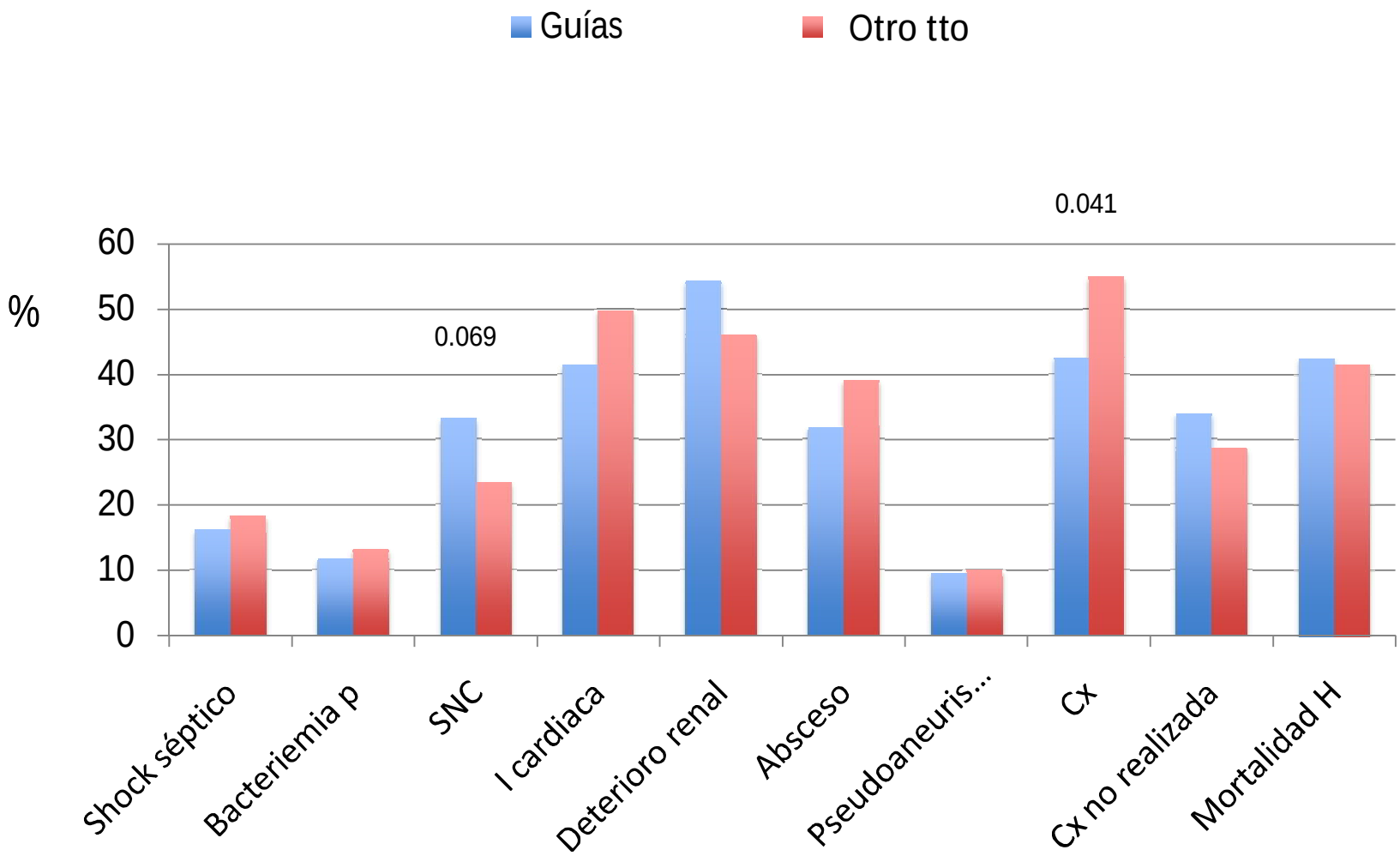
Características de EPE según tratamiento

	Cloxa o vanco (N=94)	Otros ttos (N=240)	p
Edad, mediana (IQR)	70 (57 - 77)	70 (63 - 76)	0.547
Nosocomial	41 (43.6)	134 (55.8)	0.059
I. renal (Cr>1,4)	24 (25.1)	79 (32.9)	0.189
Charlson x edad (SD)	4 (3-6)	5 (3-6)	0.083
Staph coag neg	54 (57.4)	165 (68.8)	0.051
MTR	34 (36.2)	114 (47.5)	0.061
Bacteriemia persistente	11 (11.7)	32 (13.3)	0.551
Clínica SNC	31 (33.3)	56 (23.5)	0.069
Deterioro renal	51 (54.3)	110 (46.0)	0.176
Cx realizada	40 (42.6)	132 (55.0)	0.041
Cx indicada no realizada	32 (34.0)	69 (28.7)	0.415
Mortalidad hospitalaria	40 (42.6)	100 (41.7)	0.883

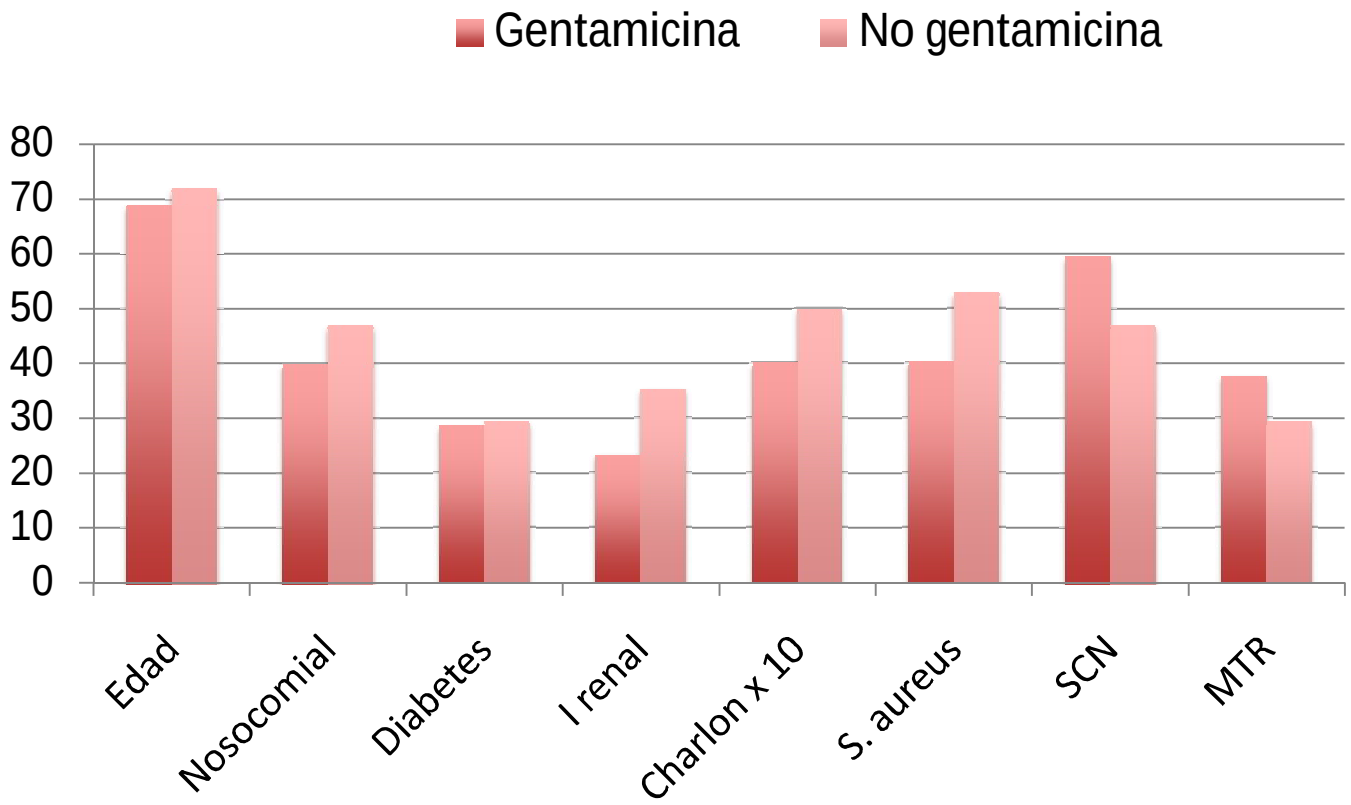
Características de EPE según tratamiento



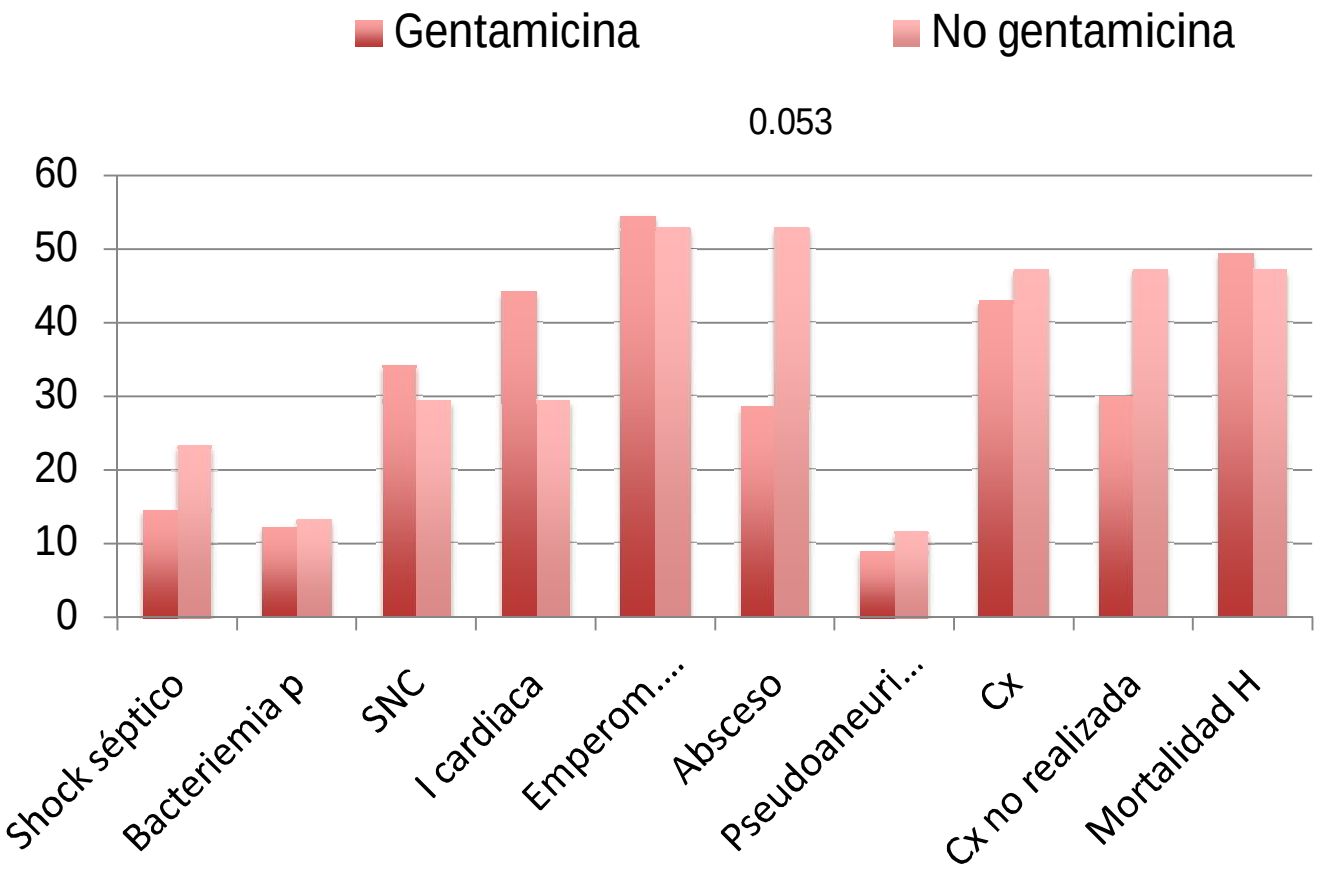
Características de EPE según tratamiento



Características basales
Gentamicina / No gentamicina



Evolución
Gentamicina /No gentamicina



Mortalidad hospitalaria

	Fallecidos (n=40)	Supervivientes (n=54)	OR (CI 95%)	P
Edad	74 (64 - 78)	67 (55 - 76)		0.018
Charlson	5.2 (2.4)	3.9 (2.4)		0.008
Cloxacilina	13 (32.5)	28 (51.9)		0.061
Vancomicina	27 (67.5)	26 (48.1)		0.061
Gentamicina	33 (72.5)	44 (81.5)		0.899
Absceso perivalvular	21 (52.5)	10 (18.5)	4.9 (1.9-12.3)	<0.001
Insuficiencia cardiaca	25 (62.5)	14 (25.9)	4.8 (2- 11.5)	<0.01
Deterioro F renal	25 (62.5)	26 (48.1)		0.167
Bact persistente	8 (22.9)	3 (5.7)	4.3 (1.1- 17.2)	0.017
Shock séptico	12 (30.0)	3 (5.6)	7.3 (1.9 - 28)	0.001
Cx no indicada	3 (7.5)	19 (31.2)	0.2 (0.04 - 0.6)	0.002
Cx ind. no realizada	19 (47.5)	12 (22.2)	3.2 (1.3 - 7.7)	0.009

Análisis MV

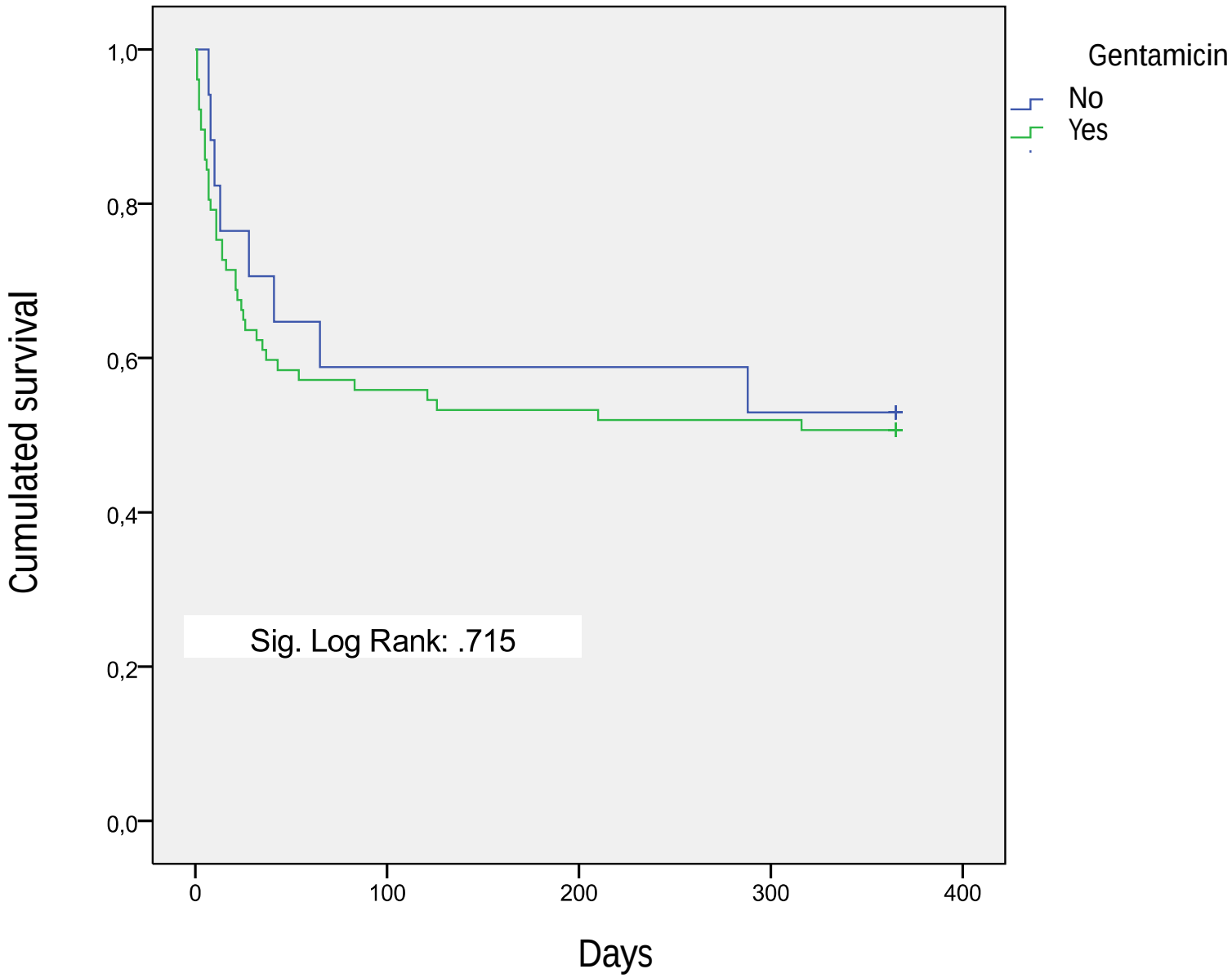
- Variables incluidas: edad> 75 años, aparición de insuficiencia cardiaca, cirugía indicada pero no realizada y régimen antibiótico incluyendo gentamicina

- **Insuficiencia cardíaca** (OR: 4,58; CI 95%: 1,84-11,43)

- **Cirugía indicada, no realizada** (OR: 2,68; IC 95%: 1,03-6,94)

- **Gentamicina** (OR: 1.001; CI 95%: 0.29-3.38).

Supervivencia al año (modelo de Cox)



Eur J Clin Microbiol Infect Dis (2006) 25: 61–62
DOI 10.1007/s10096-005-0063-1

BRIEF REPORT

O. Ju · M. Woolley · D. Gordon

Emergence and spread of rifampicin-resistant, methicillin-resistant *Staphylococcus aureus* during vancomycin–rifampicin combination therapy in an intensive care unit

- Dosis subóptima de vancomicina en sitio infección
- Escasa penetración de vanco en dispositivos
- La gentamicina (si sensible, podría evitarla?)

Ju O, et al. Eur J Clin Microbiol Infect Dis 2006; 25: 61-62

Resistencia a rifampicina

Treatment of Experimental Foreign Body Infection Caused by Methicillin-Resistant *Staphylococcus aureus*

JEAN-CHRISTOPHE LUCET,† MATHIAS HERRMANN, PETER ROHNER, RAYMOND AUCKENTHALER, FRANCIS A. WALDVOGEL, AND DANIEL P. LEW*

Division of Infectious Diseases, Department of Medicine, Geneva University Hospital, 1211 Geneva 4, Switzerland

	Resistencia a rifampicina cuerpo extraño
Rifampicina	79 %
Rifampicina + vancomicina	16%
Rifampicina + fleroxacino	0%

Lucet JC. Antimicrob Agents Chemother 1990; 34: 2312-7

EMERGENCE OF RIFAMPICIN RESISTANCE DURING RIFAMPICIN-CONTAINING TREATMENT IN ELDERLY PATIENTS WITH PERSISTENT METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* BACTEREMIA

Variable	Emergence of Rifampicin Resistance (n = 7)	No Emergence of Rifampicin Resistance (n = 12)	*P* Value
Age, mean ± standard deviation	82.0 ± 9.3	72.0 ± 7.5	.02
Aged ≥ 80, n (%)	5 (71.4)	1 (8.3)	.02
Female, n (%)	5 (71.4)	6 (50.0)	.63
Diabetes mellitus, n (%)	3 (42.9)	5 (41.7)	> .99
End-stage renal disease, n (%)	2 (28.6)	4 (33.3)	> .99
Stroke, n (%)	2 (28.6)	3 (25.0)	> .99
Malignancy, n (%)	1 (14.3)	6 (50.0)	.17
Hematologic cancer, n (%)	0 (0.0)	3 (25.0)	.43
Solid cancer, n (%)	1 (14.3)	3 (25.0)	.97
Liver cirrhosis, n (%)	1 (14.3)	0 (0.0)	.36
McCabe-Jackson classification, n (%)			
Nonfatal	3 (42.9)	3 (25.0)	.61
Ultimately fatal	4 (57.1)	7 (58.3)	> .99
Rapidly fatal	0 (0.0)	2 (16.7)	.51
Nosocomial infection, n (%)	7 (100)	5 (41.7)	.02
Catheter-related infection, n (%)	4 (57.1)	4 (33.3)	.37
Metastatic infection, n (%)	4 (57.1)	5 (41.7)	.65
Empirical glycopeptides therapy, n (%)	3 (42.9)	3 (25.0)	.61
Vancomycin and rifampicin combination therapy, n (%)	5 (71.4)	10 (83.3)	.97
Teicoplanin and rifampicin combination therapy, n (%)	2 (28.6)	2 (16.7)	.97
Outcome, n (%)			
MRSA-related mortality	3 (42.9)	2 (16.7)	.30
30-day mortality	4 (57.1)	3 (25.0)	.32

Lai CC. Am Geriatr Soc 2010; 58: 1001-3

EI protésica Staph coag neg ICE

Antibiotic regimen	No of patients	In-hospital death (%)
Vancomycin only	15	4 (27)
+ rifampin	12	4 (33)
+ aminoglycoside	15	3 (20)
+ rifampin and aminoglycoside	16	3 (19)
Vancomycin total	58	14 (23)
Penicillinase-resistant penicillin only	5	1 (20)
+ rifampin	1	0
+ aminoglycoside	3	0
+ rifampin and aminoglycoside	6	3 (50)
Penicillinase-resistant penicillin total	15	4 (27)
Both vancomycin and penicillinase-resistant penicillin	4	0
Other*	9	3 (33)

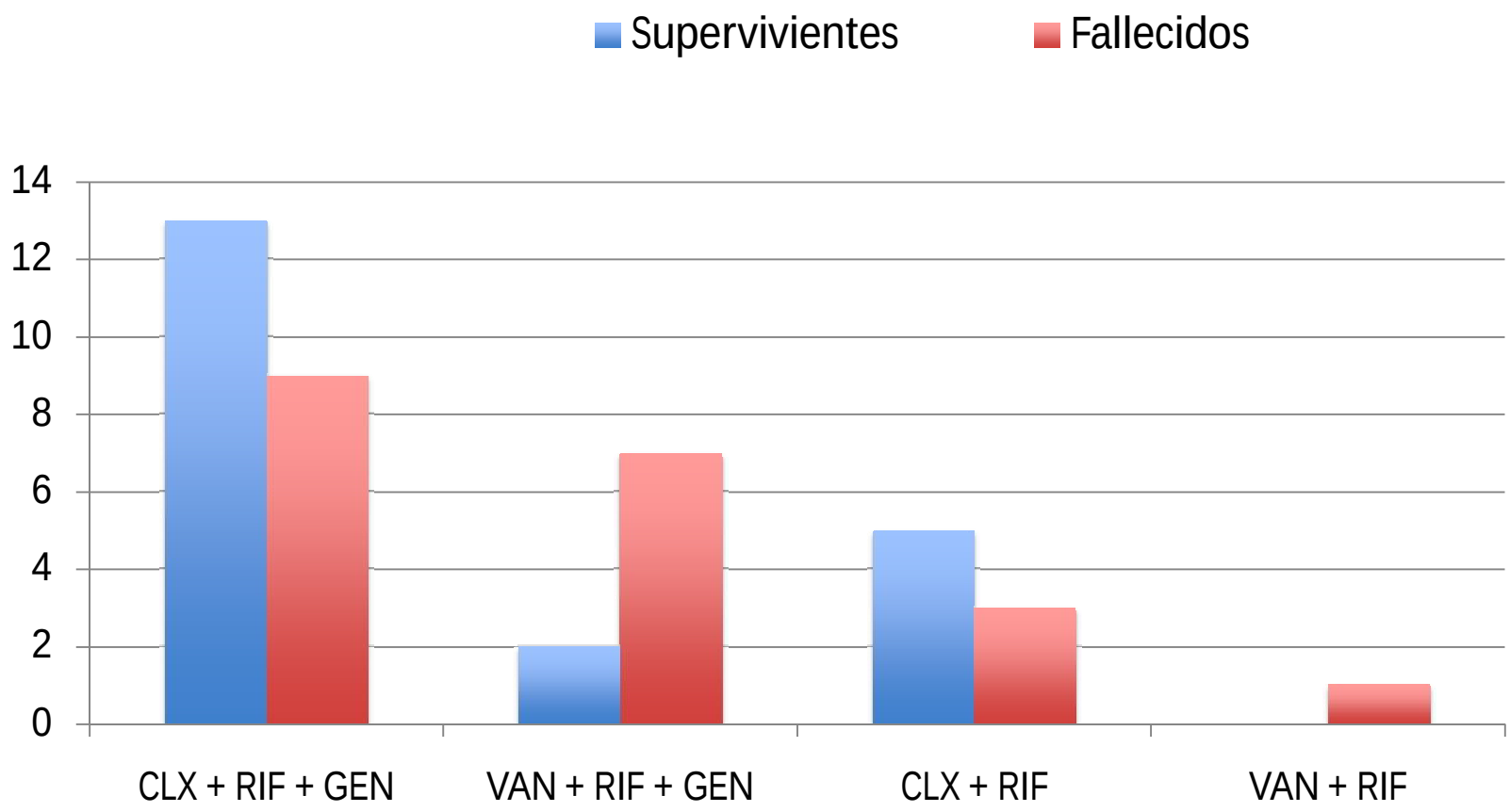
*Other regimens included combinations of the following antibiotics: aminoglycosides, rifampin, daptomycin, teicoplanin, levofloxacin, dicloxacillin and augmentin.

Chu VH, Miro JM. Heart 2009; 95: 570-6

S. aureus

	Cx not indicated (n=11)		Cx performed (n=11)		Cx indicated not performed (n=18)		Total	
	Survivors (n=9)	**non-survivors (n=2)**	**Survivors (n=6)**	**Non-survivors (n=5)**	**Survivors (n=5)**	**Non-survivors (n=13)**	**Survivors (n=20)**	**Non-survivors (n=20)**
CLX + RIF + GEN	9 (90)	1 (10)	2 (67)	1 (33)	2 (22)	7 (78)	13 (59)	9 (41)
VAN + RIF + GEN	0	1 (100)	0	3 (100)	2 (40)	3 (60)	2 (22)	7 (78)
CLX + RIF	0	0	4 (80)	1 (20)	1 (33)	2 (77)	5 (62)	3 (37)
VAN + RIF	0	0	0	0	0	1 (100)	0	1 (100)

S. aureus


Supervivientes
Fallecidos
14
12
10
8
6
4
2
0
CLX + RIF + GEN
VAN + RIF + GEN
CLX + RIF
VAN + RIF

S. aureus

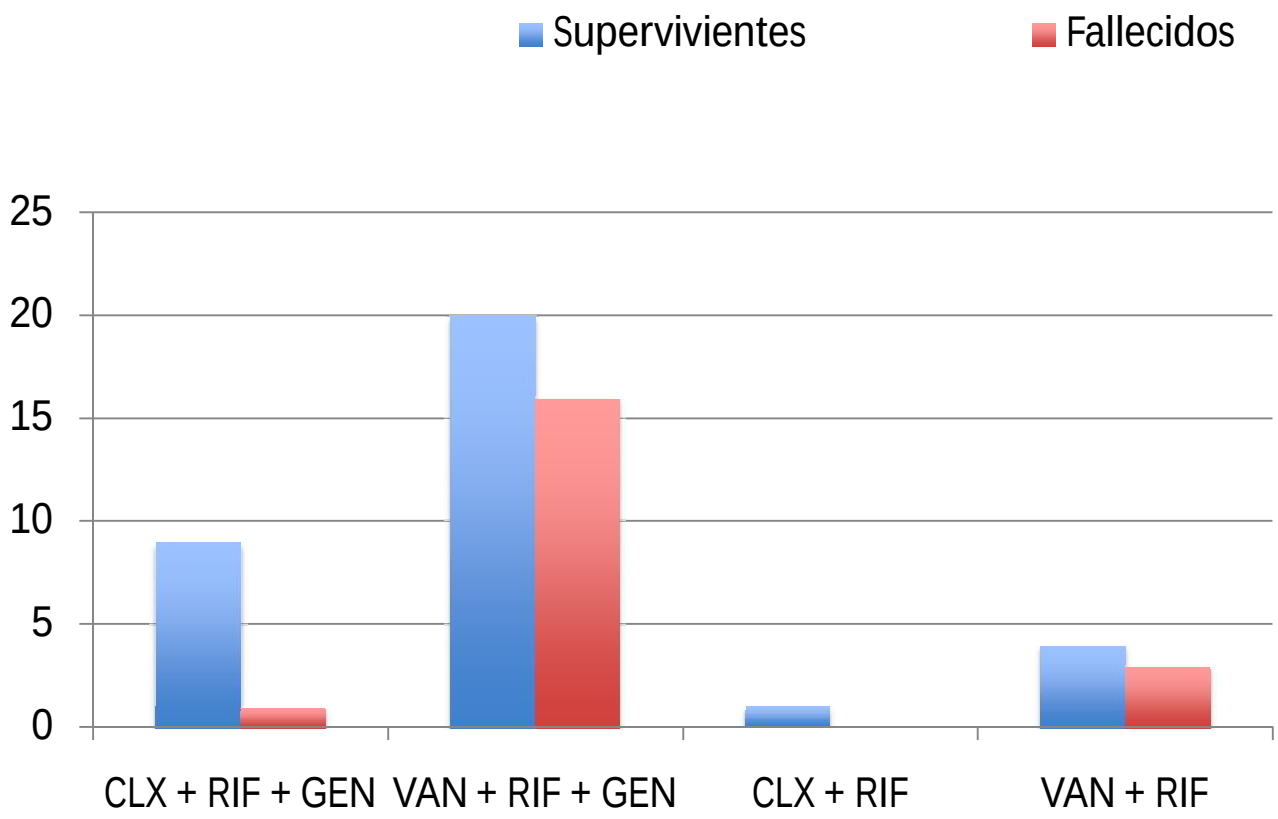
	Supervientes	Fallecidos
Vancomicina	2	8
Cloxacilina	18	12

P=0,03

Staph coagulasa negativo

	Cx not indicated (n=11)		Cx performed (n=30)		Cx indicated not performed (n=13)		Total	
	Survivors (n=9)	Non-survivors (n=2)	Survivors (n=6)	Non-survivors (n=5)	Survivors (n=5)	Non-survivors (n=13)	Survivors (n=20)	Non-survivors (n=20)
CLX + RIF + GEN	1 (100)	0	7 (100)	0	1 (50)	1 (50)	9 (90)	1 (10)
VAN + RIF + GEN	8 (89)	1 (11)	9 (45)	11 (55)	3 (43)	4 (57)	20 (56)	16 (44)
CLX + RIF	0	0	0	0	1 (100)	0	1 (100)	0
VAN + RIF	1 (100)	0	1 (33)	2 (67)	2 (67)	1 (33)	4 (57)	3 (43)

SCN


Supervivientes
Fallecidos
25
20
15
10
5
0
CLX + RIF + GEN
VAN + RIF + GEN
CLX + RIF
VAN + RIF

Staph coagulasa negativo

	Supervientes	Fallecidos
Vancomicina	24	19
Cloxacilina	10	1

P=0,03

Limitaciones

- Estudio no aleatorizado
- Número reducido de casos sin gentamicina (impide obtener conclusiones firmes)
- Estudio conjunto de *S. aureus* y SCN
- Hospitales terciarios. Muchos pacientes referidos de otros centros
- No se puede descartar un posible efecto de agrupamiento.

Conclusiones EPE

- Bajo cumplimiento de las guías (28%)

- Mortalidad EPE elevada
  - Desarrollo de insuficiencia cardiaca
  - Cx indicada pero no realizada

- Mortalidad similar en relación con gentamicina
- Mortalidad superior con vancomicina