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Staphylococcal and Streptococcal Prosthetic Joint Infection: the Spanish Experience

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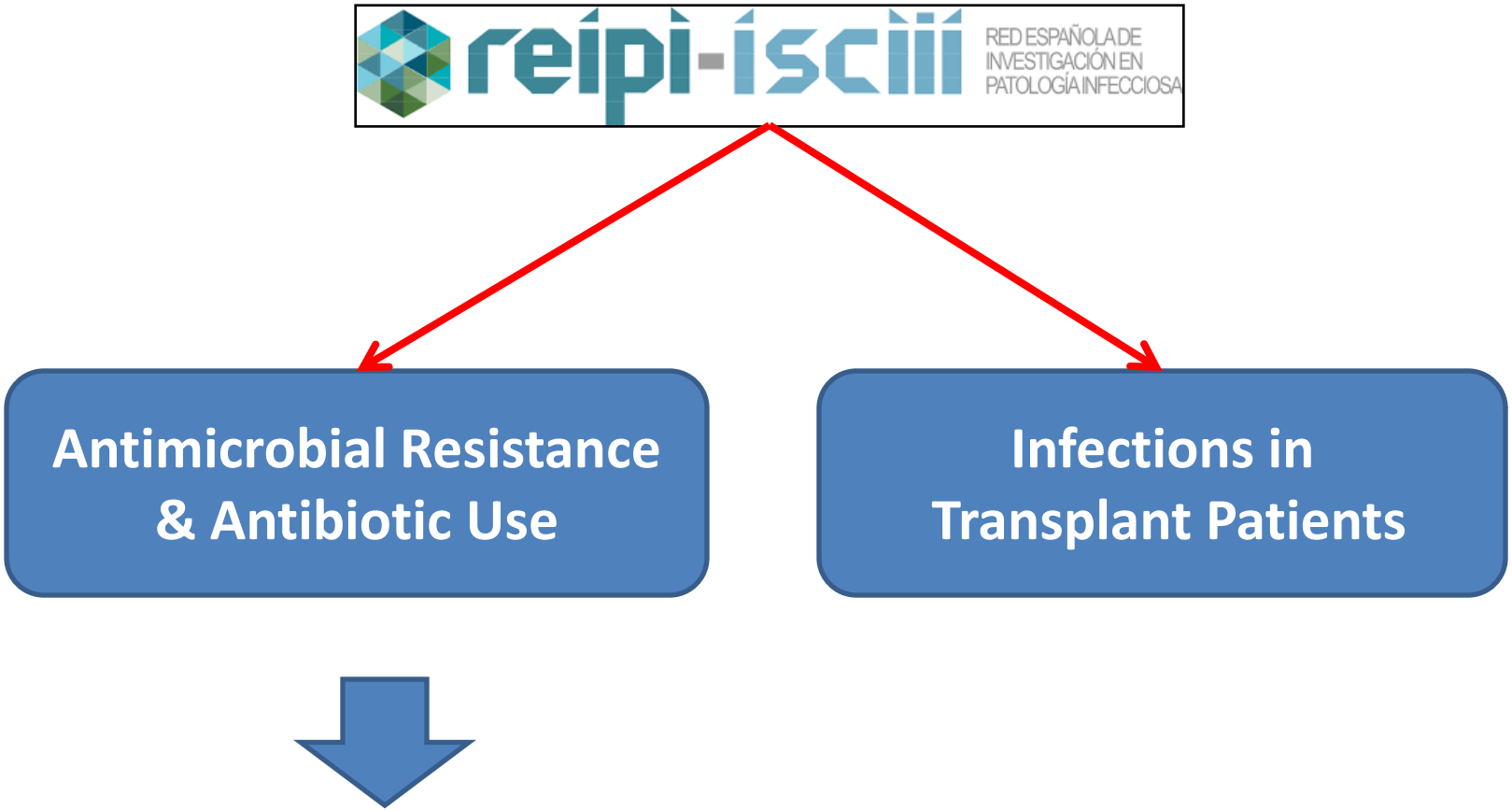
Conflict of interest

None to disclose

Outline

- Spanish platforms for colaborative research in ID
- The aims of our recent studies on staph. and strepto PJI
- Staphylococcal PJI – 2 observational studies and 1 RCT
- Streptococcal PJI – 1 large observational study
- Final thoughts

Bone & Joint Infection – the need for multicenter studies



Work Package 8 - To optimize the management of prosthetic joint infections

Bone & Joint Infection – the need for multicenter studies

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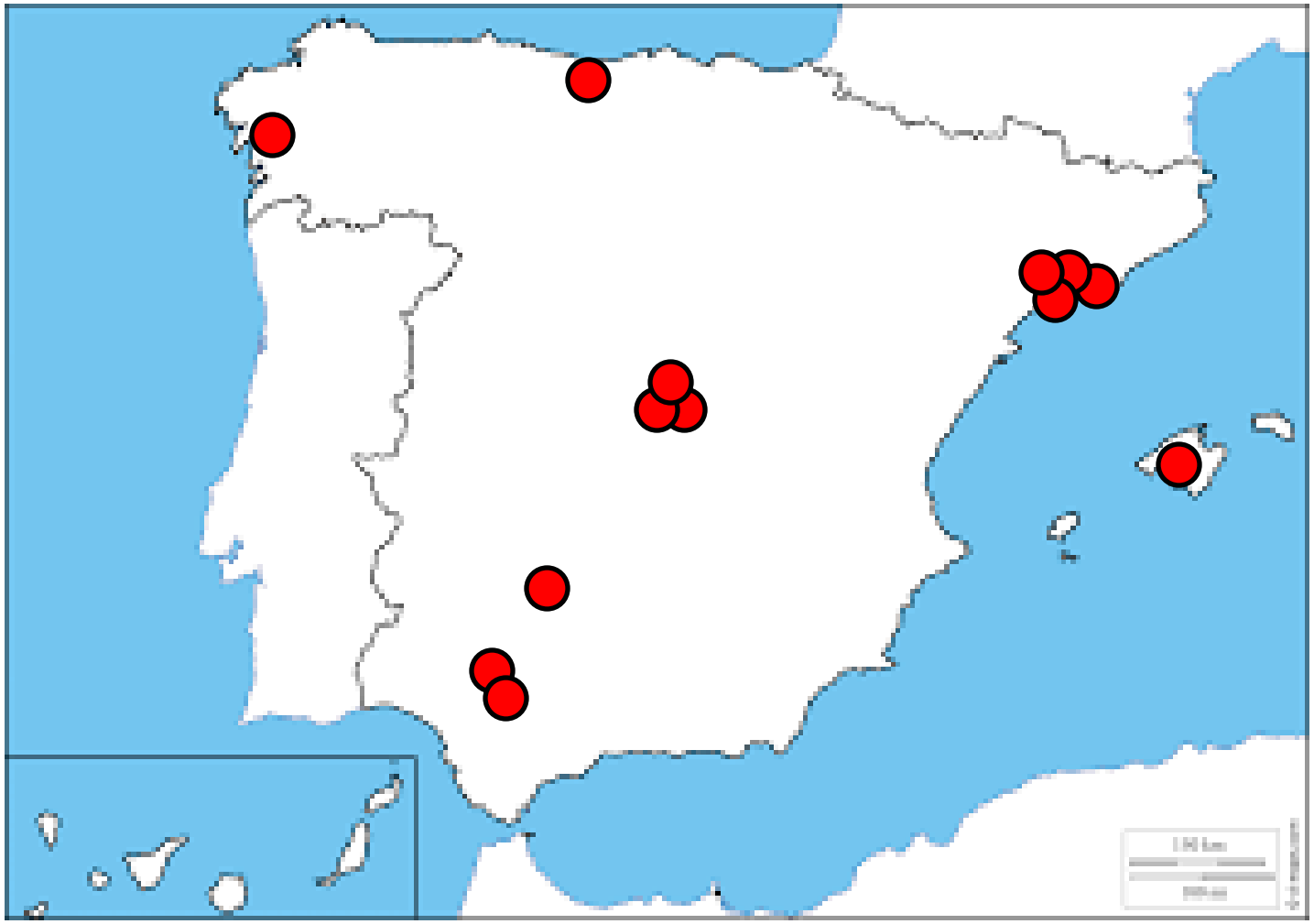
RED ESPAÑOLA DE INVESTIGACIÓN EN PATOLOGÍA INFECCIOSA



Sociedad de Enfermedades Infecciosas y Microbiología Clínica

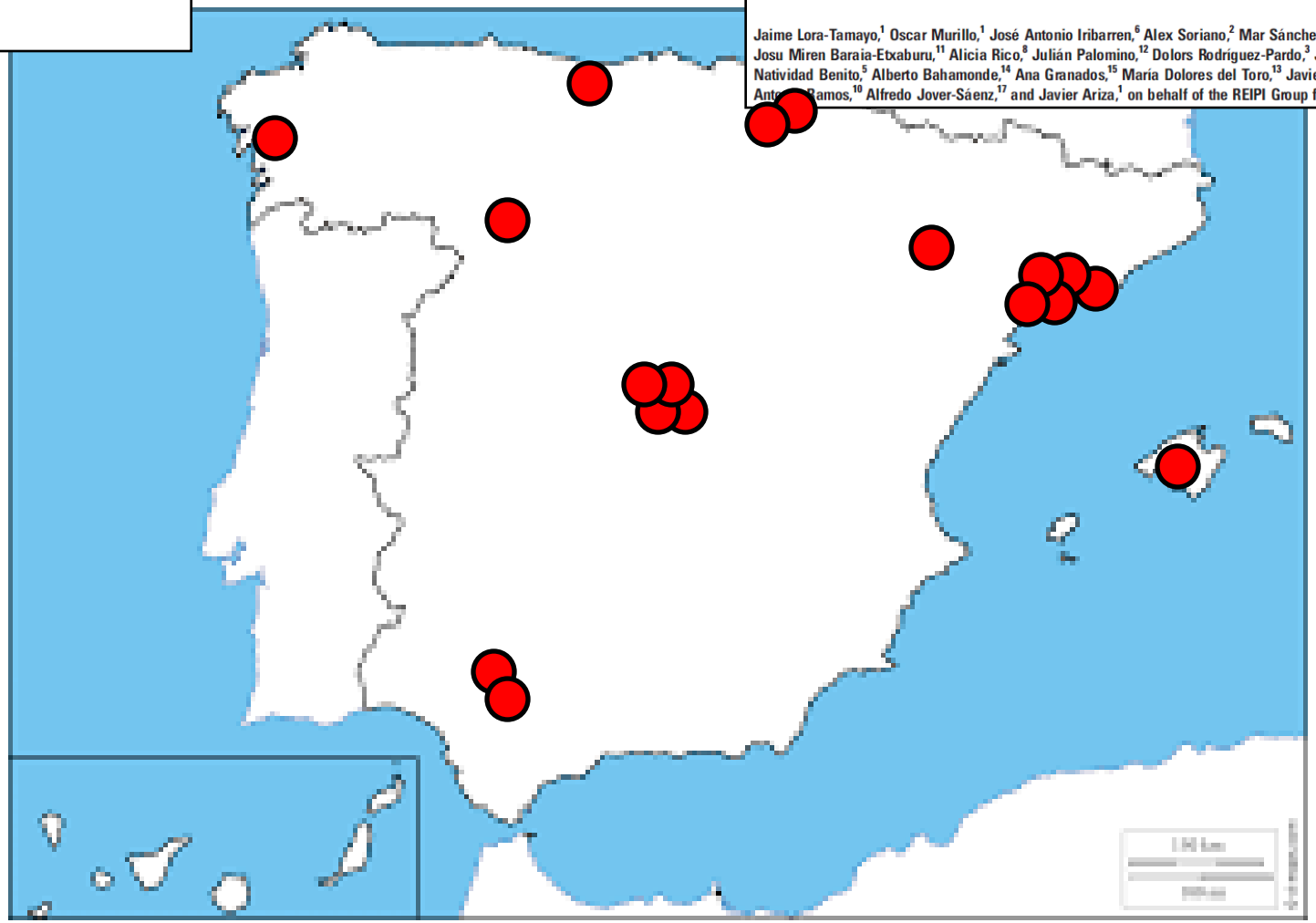
www.seimc.org

Group d'Étude des Infections Osteo-articulaires

Bone & Joint Infection – the need for multicenter studies

A Large Multicenter Study of Methicillin–Susceptible and Methicillin–Resistant *Staphylococcus aureus* Prosthetic Joint Infections Managed With Implant Retention

Jaime Lora-Tamayo,[1] Oscar Murillo,[1] José Antonio Iribarren,[6] Alex Soriano,[2] Mar Sánchez-Somolinos,[7] Josu Miren Baraia-Etxaburu,[11] Alicia Rico,[8] Julián Palomino,[12] Dolors Rodríguez-Pardo,[3] Juan Pablo Horcajada,[4] Natividad Benito,[5] Alberto Bahamonde,[14] Ana Granados,[15] María Dolores del Toro,[13] Javier Cobo,[11] Melchor Riera,[16] Ant[illegible] Ramos,[10] Alfredo Jover-Sáenz,[17] and Javier Ariza,[1] on behalf of the REIPI Group for the Study of Prosthetic Infection



Bone & Joint Infection – the need for multicenter studies

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ESGIAI ESCMID STUDY GROUP FOR IMPLANT-ASSOCIATED INFECTIONS

European Society of Clinical Microbiology and Infectious Diseases

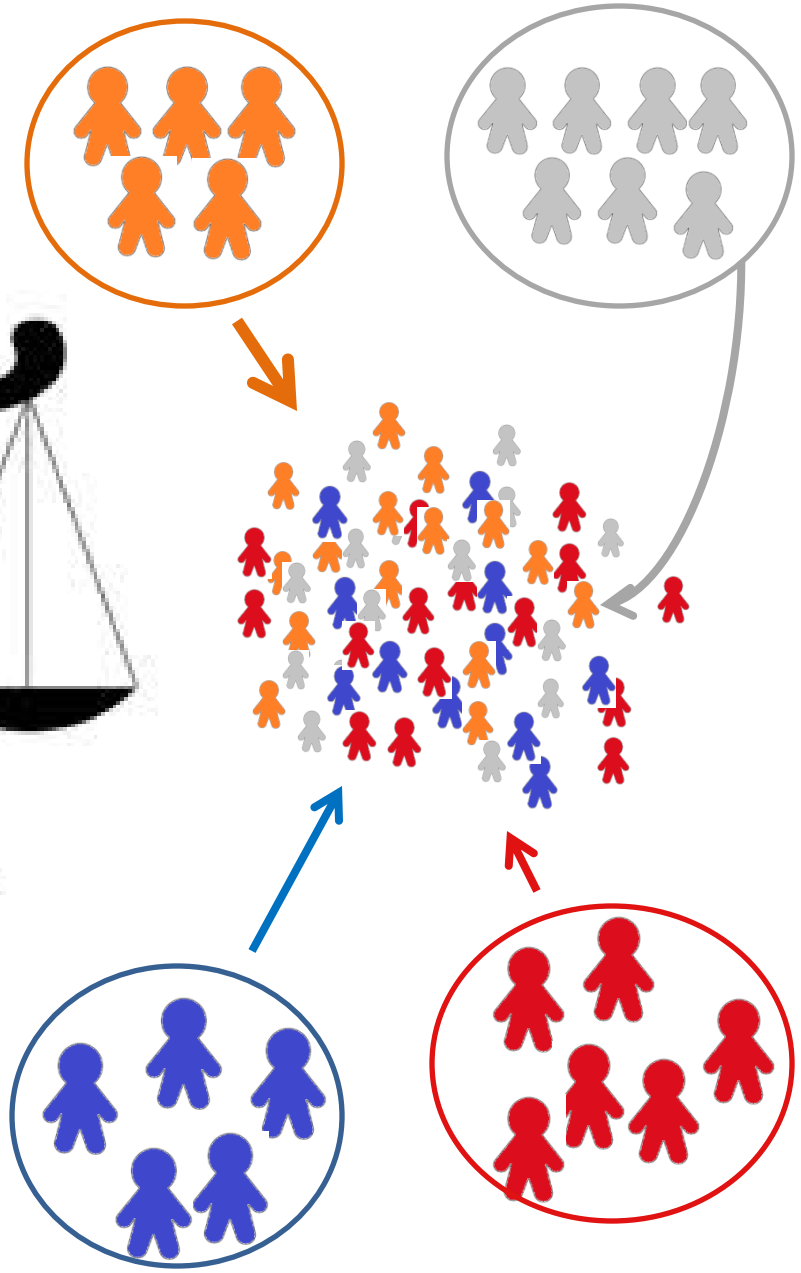
- **52 centres**
- **15 nations**

The Not-So-Good Prognosis of Streptococcal Periprosthetic Joint Infection Managed by Implant Retention: The Results of a Large Multicenter Study

Jaime Lora-Tamayo,[1,2] Éric Senneville,[3] Alba Ribera,[2,4,5] Louis Bernard,[6,7] Michel Dupon,[8] Valérie Zeller,[9] Ho Kwong Li,[5] Cédric Arvieux,[7,10] Martin Clauss,[11] Ilker Uçkay,[12] Dace Vigante,[13] Tristan Ferry,[14] José Antonio Iribarren,[15] Trisha N. Peel,[16] Parham Sendi,[17] Nina Gorišek Miksić,[18] Dolors Rodriguez-Pardo,[2,19] María Dolores del Toro,[2,20] Marta Fernández-Sampedro,[2,21] Ulrike Dapunt,[22] Kaisa Huotari,[23] Joshua S. Davis,[24] Julián Palomino,[2,25] Danielle Neut,[26] Benjamin M. Clark,[26] Thomas Gottlieb,[27] Rihard Trebše,[28] Alex Soriano,[2,29,30] Alberto Bahamonde,[31] Laura Guio,[2,32] Alicia Rico,[33] Mauro J. C. Salles,[34] M. José G. Pais,[35] Natividad Benito,[2,36] Melchor Riera,[2,37] Lucía Gómez,[38] Craig A. Aboltins,[39] Jaime Esteban,[40] Juan Pablo Horcajada,[41] Karina O'Connell,[42] Matteo Ferrari,[43] Gábor Skaliczki,[44] Rafael San Juan,[1,2] Javier Cobo,[2,45] Mar Sánchez-Somolinos,[2,46] Antonio Ramos,[47] Efthymia Giannitsioti,[48] Alfredo Jover-Sáenz,[49] Josu Mirena Baraia-Etxaburu,[50] José María Barbero,[51] Peter F. M. Choong,[52] Nathalie Asseray,[7,53] Séverine Ansart,[7,54] Gwenäel Le Moal,[7,55] Werner Zimmerli,[11] and Javier Ariza[2,4,]; for the Group of Investigators for Streptococcal Prosthetic Joint Infection*

Javier Ariza, Hospital Universitario de Bellvitge, Barcelona

Bone & Joint Infection – the need for multicenter studies



What is the real likelihood of curing a staphylococcal / streptococcal PJI by DAIR?

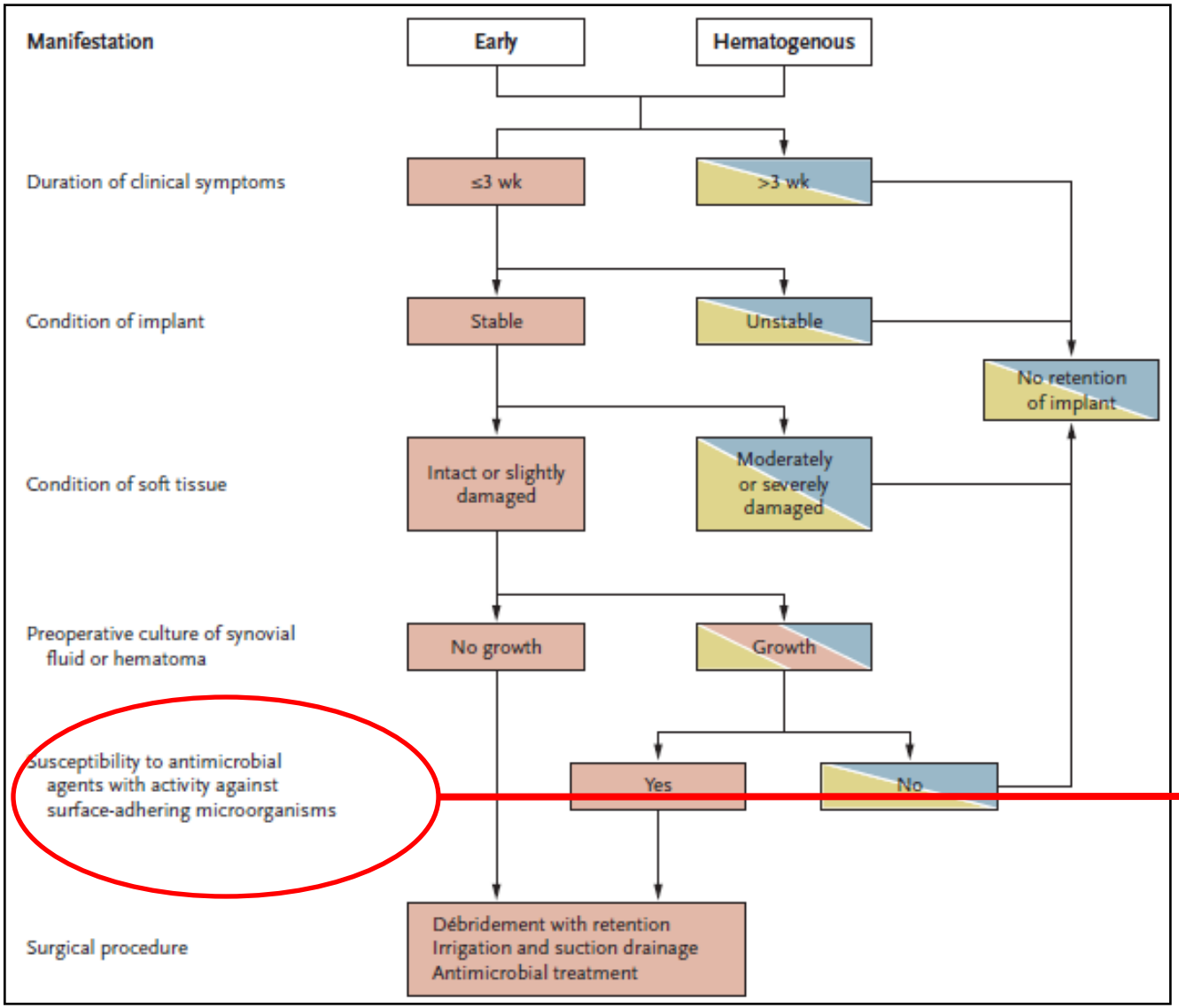
***S. aureus* – 13-90%**

Reference	N (DAIR)	% Success
Brandt 1997	33	36%
Marculescu 2006	32	13%
Barberán 2006	21	62%
Aboltins 2007	19	90%
Byren 2009	48	73%
Vílchez 2011	53	75%
Senneville 2011	41	78%

Strepcococci – 40-100%

Reference	N (DAIR)	% Success
Duggan 2001	5	40%
Meehan 2003	19	89%
Everts 2005	16	94%
Zeller 2009	6	67%
Sendi 2011	20	65%
Corverc 2011	7	42%
Bertz 2015	9	100%

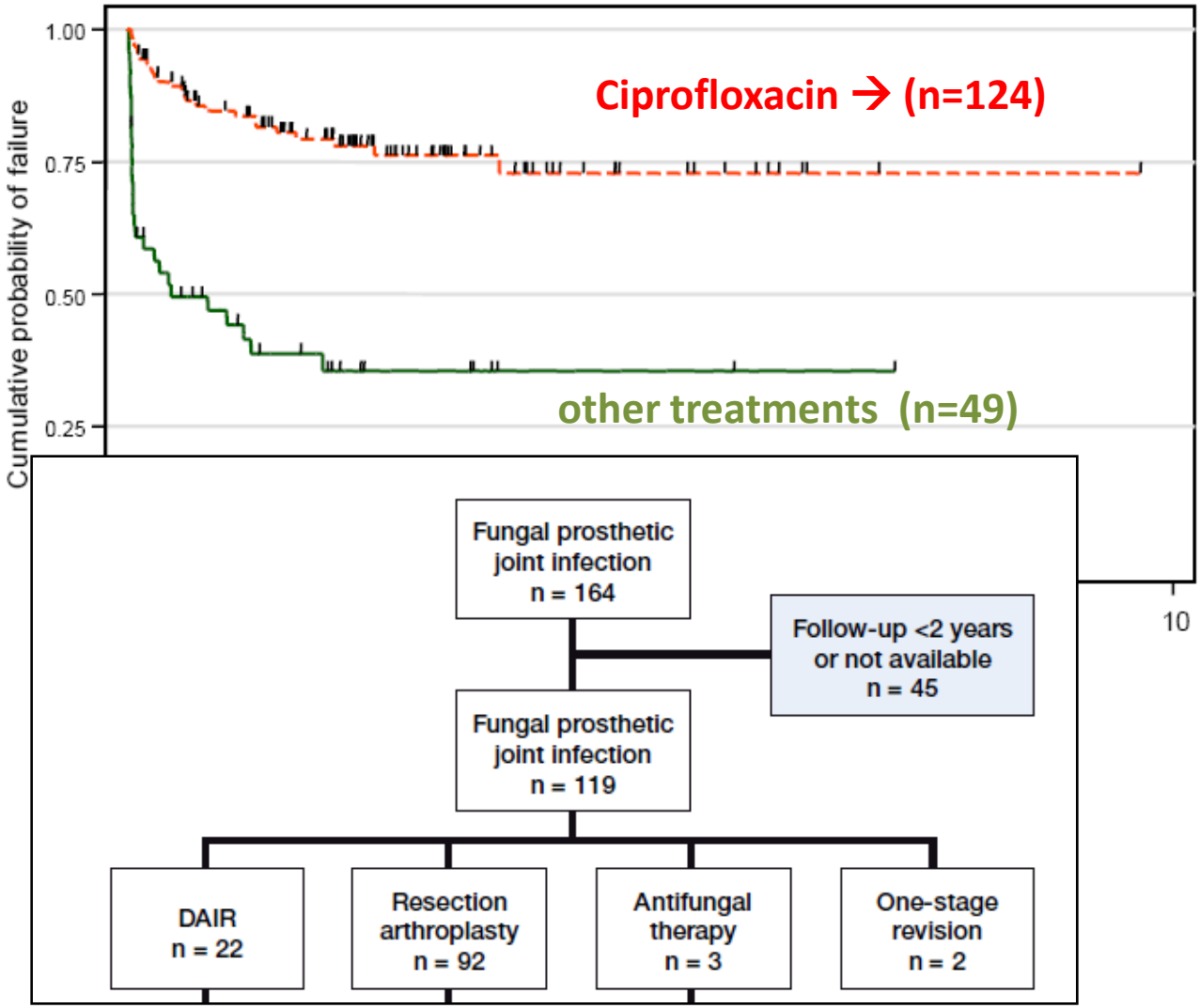
Streptococcal & Staphylococcal PJI – aims



Importance of the etiology & ATB susceptibility profile

Zimmerli, 2004. NEJM

Streptococcal & Staphylococcal PJI – aims



4 (18%) success

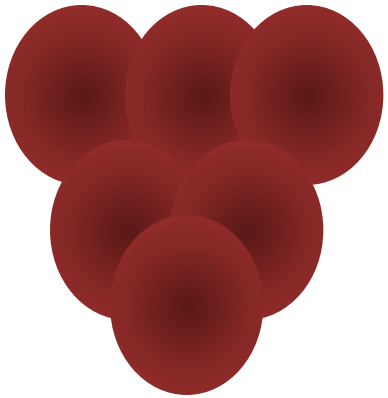
Kuiper et al, 2013. Acta Orthop
Rodríguez, 2014. CMI

Streptococcal & Staphylococcal PJI – aims

Staphylococcus aureus

- Real likelihood of curing
- Outcome of MRSA infection
- Role of rifampin in a large series
- Role of rifampin vs. MRSA
- Role of specific rifampin combinations
- Risk factors for failure

Reference	MSSA + MRSA	% Success
Brandt, et al. 1997	32 + 1	36%
Marculescu, et al. 2006	30 + 2	13%
Barberán, et al. 2006	14 + 7	62%
Aboltins, et al. 2007	8 + 11	90%
Byren, et al. 2009	39 + 9	73%
Vílchez, et al. 2011	49 + 4	75%
Senneville, et al. 2011	35 + 6	78%

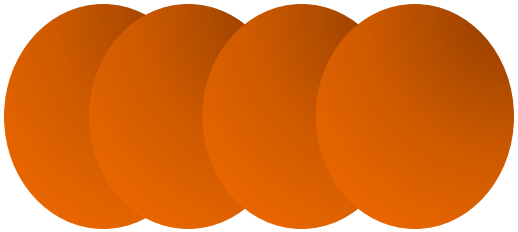


Streptococcal & Staphylococcal PJI – aims

Streptococci

- Real likelihood of curing
- Outcome of specific streptococcal species
- Performance of beta-lactams vs. fluoroquinolones and/or rifampin
- Risk factors for failure

Reference	N (DAIR)	Streptococcal species	% Success
Duggan 2001	5	*S. agalactiae*	40%
Meehan 2003	19	*S. agalactiae*	89%
Everts 2005	16	Various	94%
Zeller 2009	6	*S. agalactiae*	67%
Sendi 2011	20	*S. agalactiae*	65%
Corverc 2011	7	Various	42%
Bertz 2015	9	Various	100%



Analysis of cases managed by DAIR

(regardless of the appropriateness of the indication)

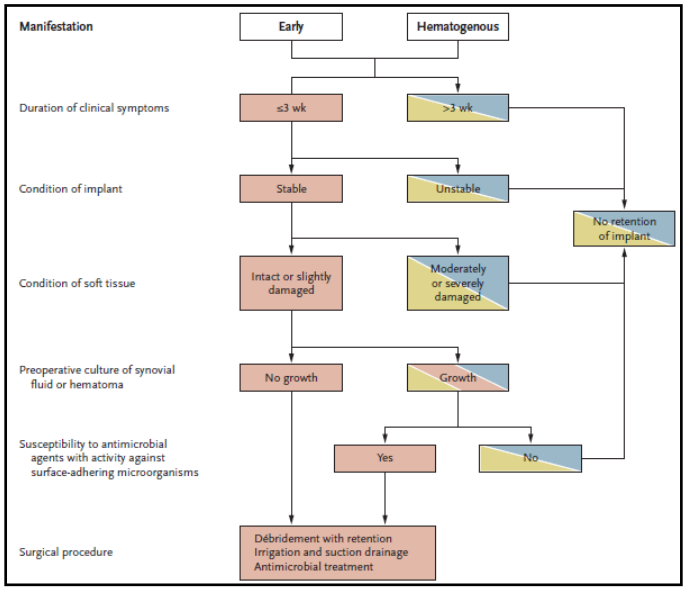
Clinical management of PJI at Spanish hospitals

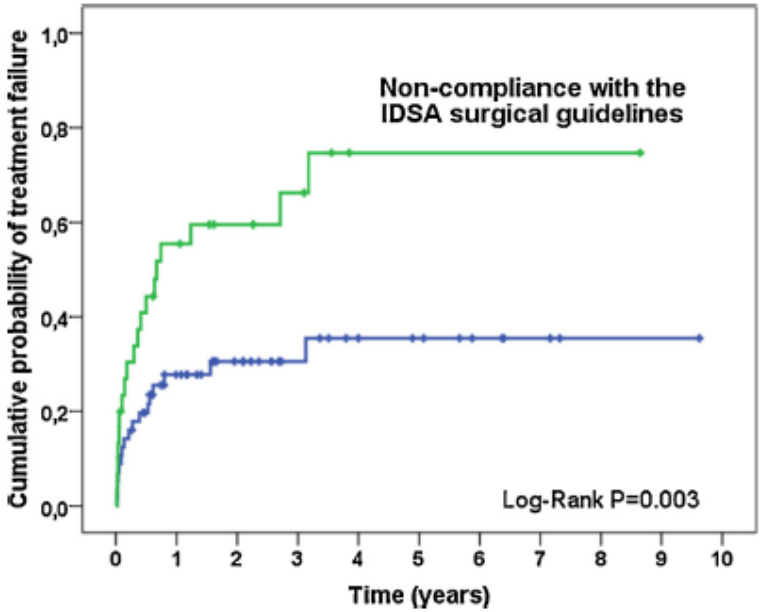
- multi-disciplinar medical teams (orthopedists, IDs, micro, radiologists…)
- Zimmerli's criteria for DAIR
- treatment standards
  - rifampin-based combinations for staphylococci
  - β-lactamas (±rifampin) for streptococci

Streptococcal & Staphylococcal PJI – foreword on methods

Re. criteria for DAIR

- good condition of skin and soft tissues
- soundly fixed prosthesis (surgical criteria)
- young biofilm / acute infection
  - short duration of symptoms (≤21 days)
  - hematogenous or early post-surgical PJI





89 PJI caused by MSSA

Zimmerli, 2004. NEJM

Bouaziz, 2017. Med Mal Infect

Streptococcal & Staphylococcal PJI – foreword on methods

Duration of symptoms

- the sooner, the better… but, when is it too late???

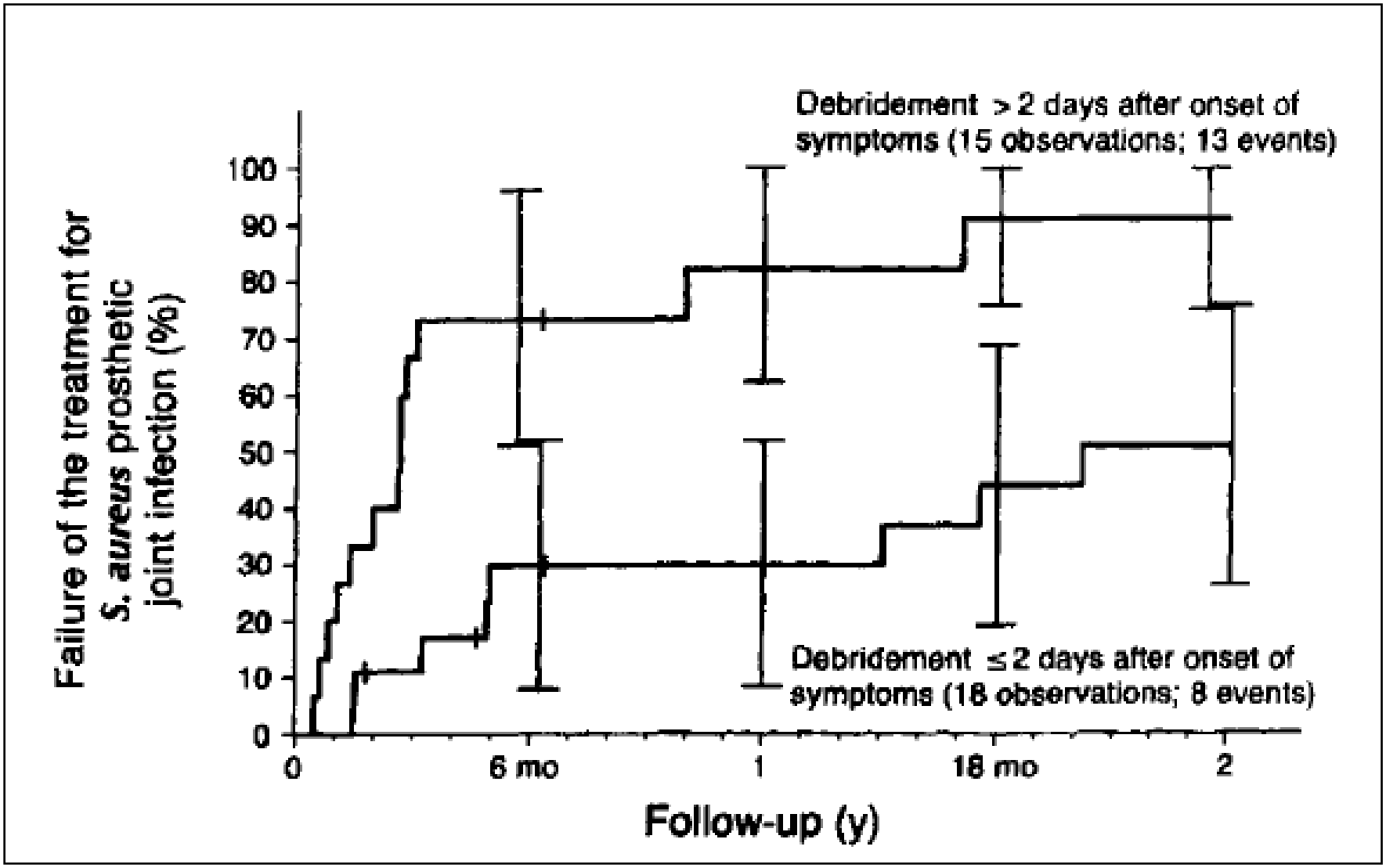
Table 1.—Study Population

Characteristic	Rifampin Combination (n=18)	Placebo Combination (n=15)
Mean (SD) age, y	66 (15)	67 (15)
Sex, male:female	9:9	5:10
Implant		
Hip prosthesis	5	3
Knee prosthesis	3	4
Osteosynthesis	10	8
Microbiology		
Staphylococcus aureus (0/26 methicillin resistant)	15	11
Staphylococcus epidermidis (2/7 methicillin resistant)	3	4
Initial intravenous treatment		
Flucloxacillin	13	13
Vancomycin	5†	2‡
Median duration of infection,* d (range)	5 (0-19)	4 (0-21)

*Duration of signs and symptoms of infection prior to enrollment in the study.
†One patient had methicillin-resistant *S epidermidis;* 4 patients had methicillin-sensitive *S aureus* and allergy.
‡One patient had methicillin-resistant *S epidermidis*; 1 had methicillin-sensitive *S aureus* and allergy.

Zimmerli, 1998. JAMA

Streptococcal & Staphylococcal PJI – foreword on methods



Brandt, 1998. CID

Streptococcal & Staphylococcal PJI – foreword on methods

Reference	N DAIR	Type of prosthesis	Etiology	Symptom duration
Schoifet, 1990 JBJS	31	Knee	Various	21 days vs. 30 days
Burger, 1991 CORR	60	Knee	Various	≤ 21 days
Brandt, 1997 CID	33	Knee & Hip	*S. aureus*	≤ 2 days
Tattevin, 1999 CID	34	Knee & Hip	Various	5 days vs. 54 days
Barberán, 2006 AJM	60	Knee & Hip	Staph.	2.7 days vs. 7.4 days
Marculescu, 2006 CID	99	Knee & Hip	Various	≤ 7 days
Hsieh, 2009 CID	154	Knee & Hip	Various	GN: ≤ 11 days; GP: ≤ 5 days
Cobo, 2011 CMI	117	Knee & Hip	Various	10.2 days vs. 15.7 days
Lora-T, 2013 CID	345	Knee & Hip	*S. aureus*	≤10 days
Lora-T, 2017 CID	462	Knee & Hip	Strepto.	≤ 7 days

The sooner, the better, but…
…when is it too late?

- Microorganism, treatment, surgery
- Overlap with post-surgical symptoms
- Bias: ill patients are debrided earlier

Streptococcal & Staphylococcal PJI – foreword on methods

Prosthesis age as a more reliable parameter (for post-operative infections)

Time from prosthesis placement to surgery of debridement

IDSA guidelines, 2013 CID
Tsukayama, 1996 JBJS
Others

1 month

Zimmerli, 1998 JAMA

2 month

Zimmerli, 2004, NEJM
Others

3 month

The sooner, the better

Influence of etiology?

Multidisciplinar decision

Streptococcal & Staphylococcal PJI – foreword on methods

Cure = cure of the infection at 1st try while retaining a functional prosthesis

Primary endpoint → Failure (broad definition)

- Death related with the infection (clinical criteria)
- Clinical signs of infection persistence/relapse at last visit → due to staph/strepto and/or **other microorganisms**
- Need for salvage therapy, including
  - need for extra debridements > 30 days after the 1st one
  - need for extra couses of ATB beyond the first plan
    - including suppressive antimicrobial therapy

  → due to staph/strepto and/or **other microorganisms**
  - need for prosthesis removal
    - for any reason (including orthopaedics) during the 1st year
    - due to persistent/relapsing infection at any time → due to staph/strepto and/or **other microorganisms**

Staphylococcal PJI managed by DAIR

MAJOR ARTICLE

17 Spanish hospitals – 345 cases

A Large Multicenter Study of Methicillin–Susceptible and Methicillin–Resistant *Staphylococcus aureus* Prosthetic Joint Infections Managed With Implant Retention

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The REIPI Group for the Study of Prosthetic Joint Infection also includes Gorane Euba, Xavier Cabo and Salvador Pedrero (Hospital Universitario de Bellvitge, Barcelona, Spain); Miguel Ángel Goenaga, Maitane Elola and Enrique Moreno (Hospital Universitario Donostia, San Sebastián, Spain); Sebastián García-Ramiro, Juan Carlos Martínez-Pastor and Eduard Tornero (Hospital Clínic i Provincial, Barcelona, Spain); Juan Manuel García-Lechuz, Mercedes Marín and Manuel Villanueva (Hospital Universitario Gregorio Marañón, Madrid, Spain); Iñigo López, Ramón Cisterna and Juan Miguel Santamaría (Hospital de Basurto, Bilbao, Spain); María-José Gómez, Andrés Puente y Pedro Cano (Hospital Universitario Virgen del Rocío, Sevilla, Spain); Carlos Pigrau, Roger Sordé and Xavier Flores (Hospital Universitario Vall d'Hebron, Barcelona, Spain); Luisa Sorlí, Paula González-Miguez and Lluis Puig (Hospital del Mar, Barcelona, Spain); María Franco, Marcos Jordán and Pere Coll (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain); Juan Amador-Mellado, Carlos Fuster-Foz, Luis García-Paíno (Hospital El Bierzo, Ponferrada, Spain); Isabel Nieto, Miguel Ángel Muniain and Ana Isabel Suárez (Hospital Universitario Virgen Macarena, Sevilla, Spain); María Antonia Maseguer, Eduardo Garagorri and Vicente Pintado (Hospital Universitario Ramón y Cajal, Madrid, Spain); Carmen Marinescu and Antonio Ramírez (Hospital Universitario Son Dureta, Palma de Mallorca, Spain); Elena Múñez, Teresa Álvarez and Rodrigo García (Hospital Universitario Puerta de Hierro, Madrid, Spain); and Fernando Barcenilla, Laura Prat and Ferran Pérez (Hospital Universitario Arnau de Vilanova, Lérida, Spain).

Clin Infect Dis. 2013; 56: 182-94

Staphylococcal PJI managed by DAIR

561 episodes
PJI *S. aureus*

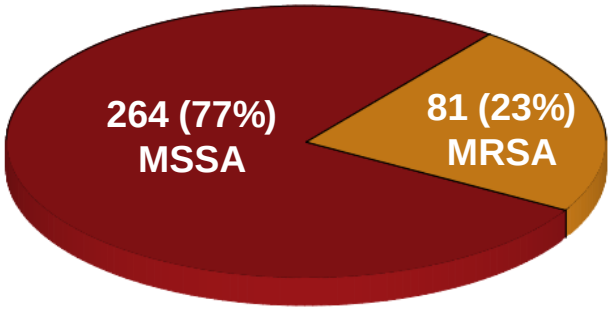
212 no DAIR

4 DAIR
No data

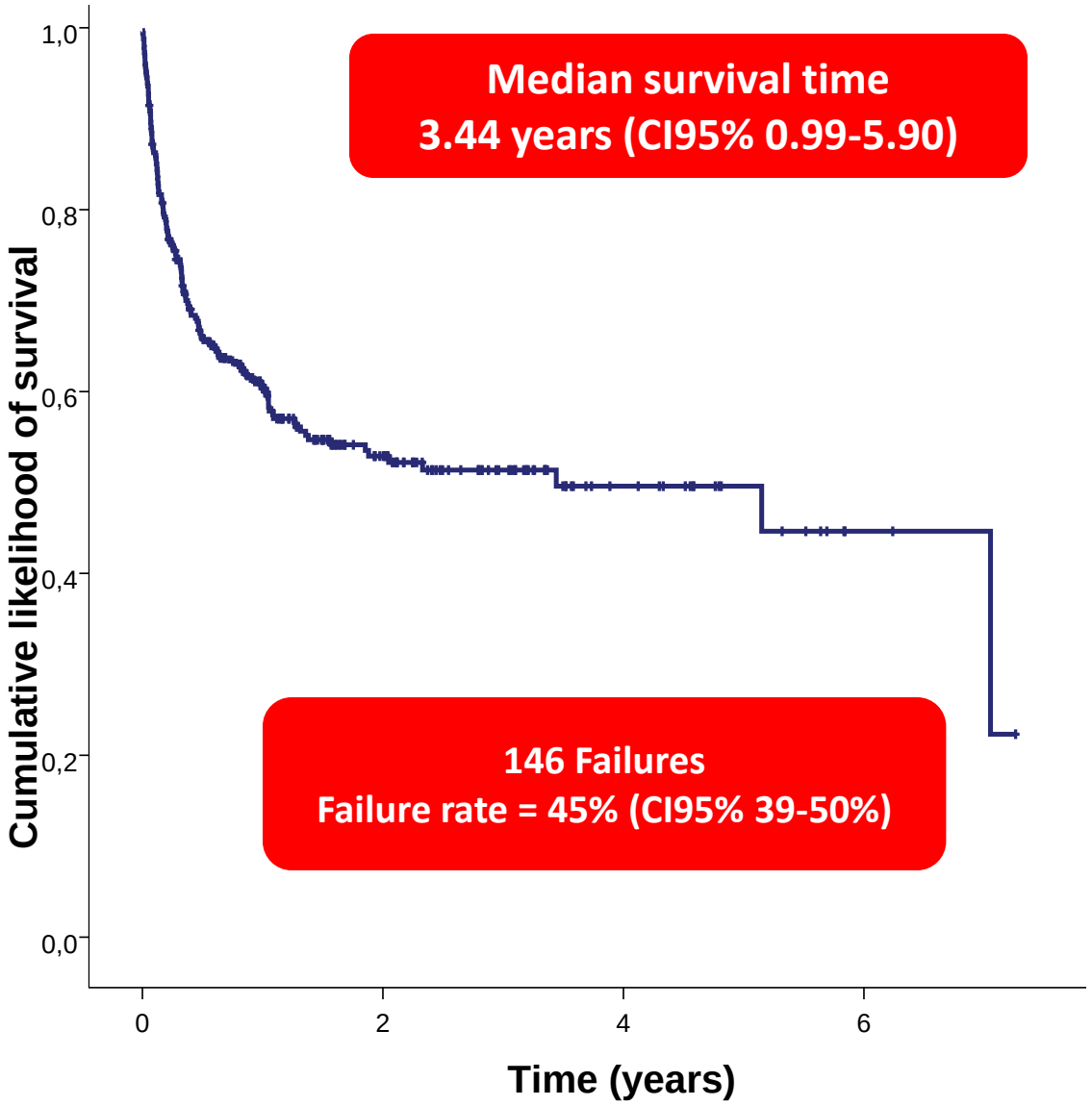
345 (61%)
DAIR

- 195 (57%) Knee
- 146 (42%) Hip (HHA and THA)
- 4 (1%) Other

- 342 patients
- 140 men (41%)
- median age 73 years (range 27 - 95)



Staphylococcal PJI managed by DAIR



Staphylococcal PJI managed by DAIR

Overall failure (146 events)	Unadjusted analysis		Adjusted analysis	
	HR	P	HR	p
Chronic renal impairment	2.03	0.051	-	-
Rheumatoid arthritis	1.84	0.021	-	-
Immunosuppressive ther.	2.31	0.006	2.31	0.013
Revision prosthesis	1.41	0.092	-	-
Infection caused by MRSA	1.19	>0.05		
Haematogenous infection	1.83	0.004	-	-
Bacteremia	2.29	<0.001	1.81	0.015
Polymicrobial infection	1.76	0.005	1.77	0.007
CRP at diagnosis (per 100mg/L)	1.29	<0.001	1.22	0.021
Temperature>37ºC	1.54	0.011	-	-
Abnormal Rx at diagnosis	1.66	0.033	-	-
Debridement delay > 10d	1.39	0.050	-	-
Polyethylene exchange	0.56	0.004	0.65	0.026
Need for ≥ 2 debridements	1.98	0.003	1.63	0.039

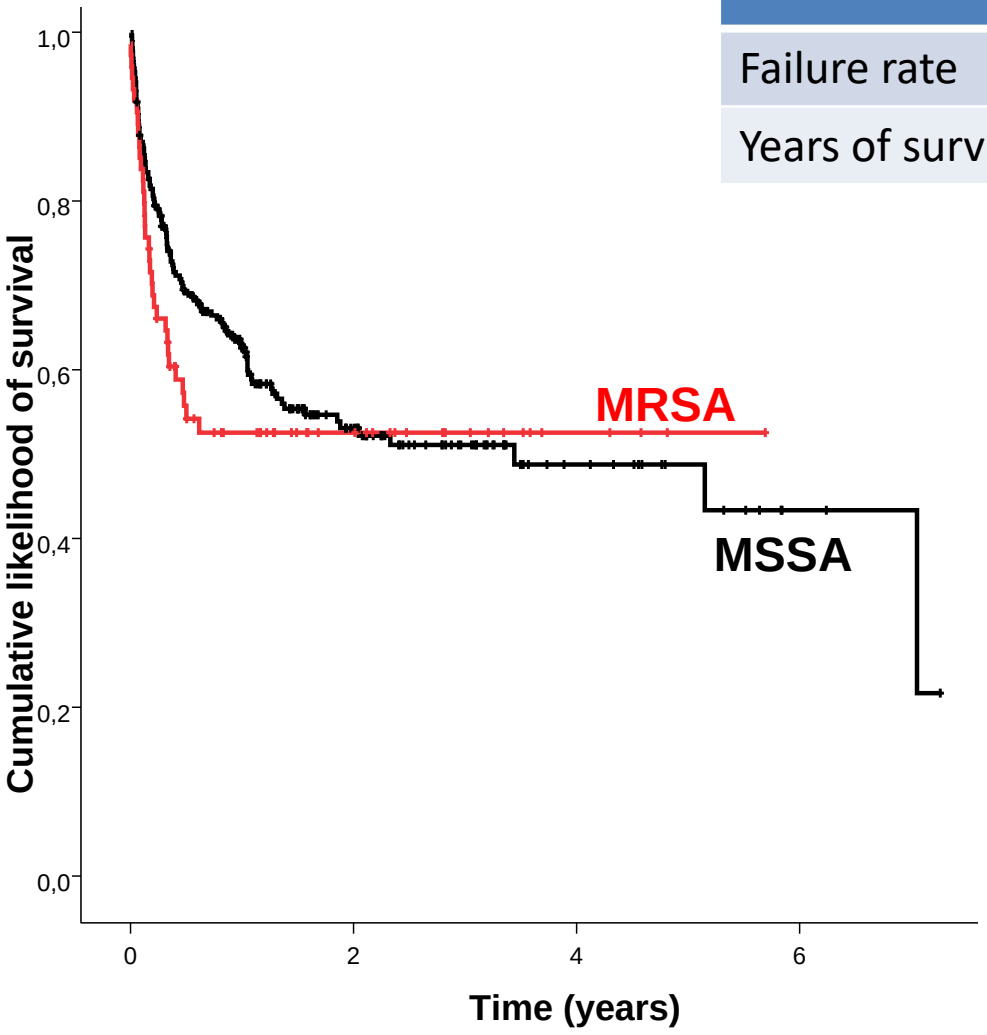
Other parameters with no statistical significance: sex, age, diabetes, prosthesis location, sinus tract

Staphylococcal PJI managed by DAIR

		MSSA (n=264)	MRSA (n=81)	p
Age (years)		71 (63-77)	78 (71-82)	**<0.001**
Diabetes mellitus		47 (18%)	21 (26%)	0.097
Renal chronic impairment		7 (3%)	12 (15%)	**<0.001**
Prosthesis location	**Hip**	97 (37%)	49 (60%)	**<0.001**
	Knee	166 (63%)	29 (36%)	
	Other	1 (0.4%)	3 (3.7%)	
Revision prosthesis		46 (17%)	21 (26%)	0.091
Type of infection	**Hematogenous**	46 (17%)	6 (7%)	**0.057**
	Early post-surg	156 (59%)	58 (72%)	
	Late-chronic	62 (24%)	17 (21%)	
Bacteriemia		44 (17%)	10 (12%)	0.349
Polymicrobial infection		49 (19%)	15 (19%)	0.992
Leukocytes (10E9/L)		9.7 (6.9-13.8)	7.9 (5.1-11.2)	**0.014**

Staphylococcal PJI managed by DAIR

	MSSA	MRSA	*p* value
Failure rate	44%	46%	0.778
Years of survival	3.73 ± 0.26	3.08 ± 0.33	0.374



Similar results when analyzing only post-surgical cases

Staphylococcal PJI managed by DAIR

MSSA & MRSA – similar surgical treatment
MSSA & MRSA – similar use of rifampin

	Whole treatment		
	MSSA	**MRSA**	**p**
Days of Rifampin*	90 ± 90	93 ± 63	NS
>28 days	78%	93%	

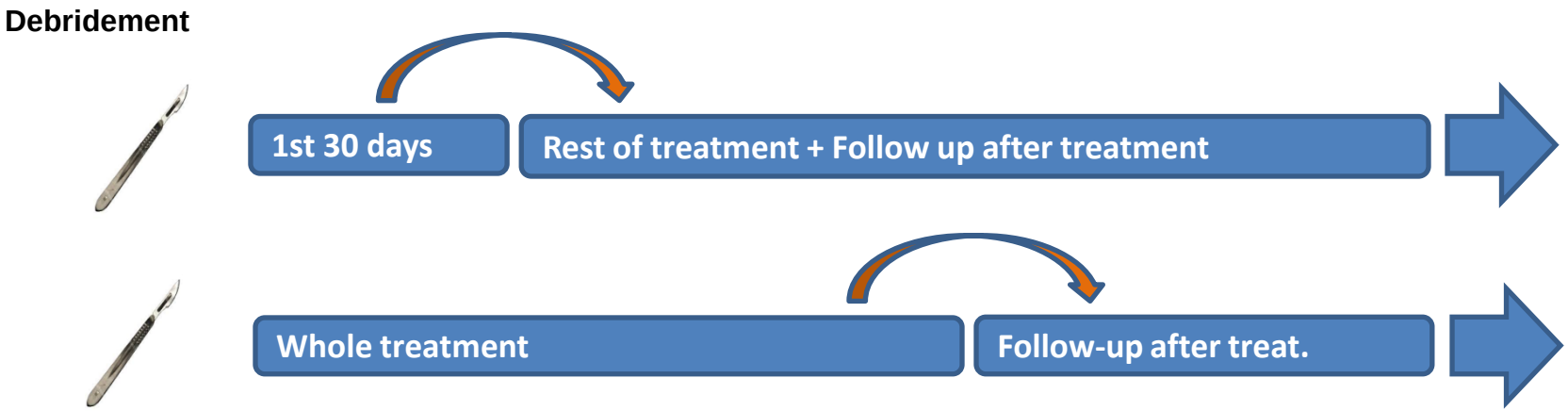
* Mean ± SD

	Treatment in the first 30 days		
	MSSA	**MRSA**	**p**
Days of Rifampin*	21 ± 11	23 ± 11	NS
>14 days	75%	77%	

MSSA
B-lactams
Quinolones (Levo)

MRSA
Vancomycin,
CMX, CLND & LNZ

Staphylococcal PJI managed by DAIR



Risk factors for failure after the 1st 30 days of treatment

n=284; failure = 47	adjusted HR	*p* value
Age (per year)	1.03 (1.00-1.07)	0.052
Immunosuppressive therapy	3.05 (1.30-7.14)	0.010
Infection by MRSA	2.33 (1.25-4.33)	0.008
Sinus tract	1.88 (0.94-3.77)	0.076
Abdnormal Rx at diagnosis	2.28 (1.14-3.54)	0.019
Need for ≥2 debridements	2.25 (1.11-4.56)	0.025
Use of rifampin for >14 days	**0.49 (0.26-0.91)**	**0.024**

Staphylococcal PJI managed by DAIR

Debridement

1st 30 days

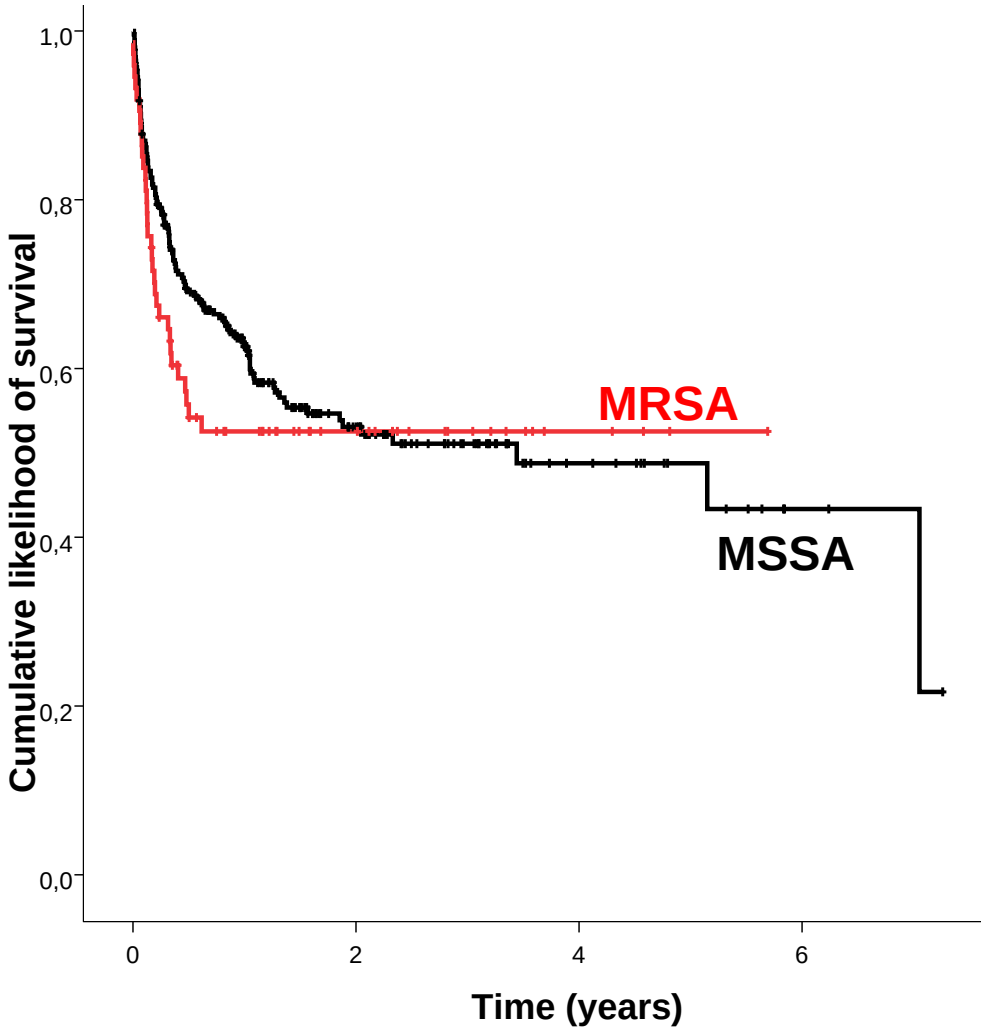
Rest of treatment & follow-up after treat.

Risk factors for failure after the 1st 30 days of treatment in post-surgical cases

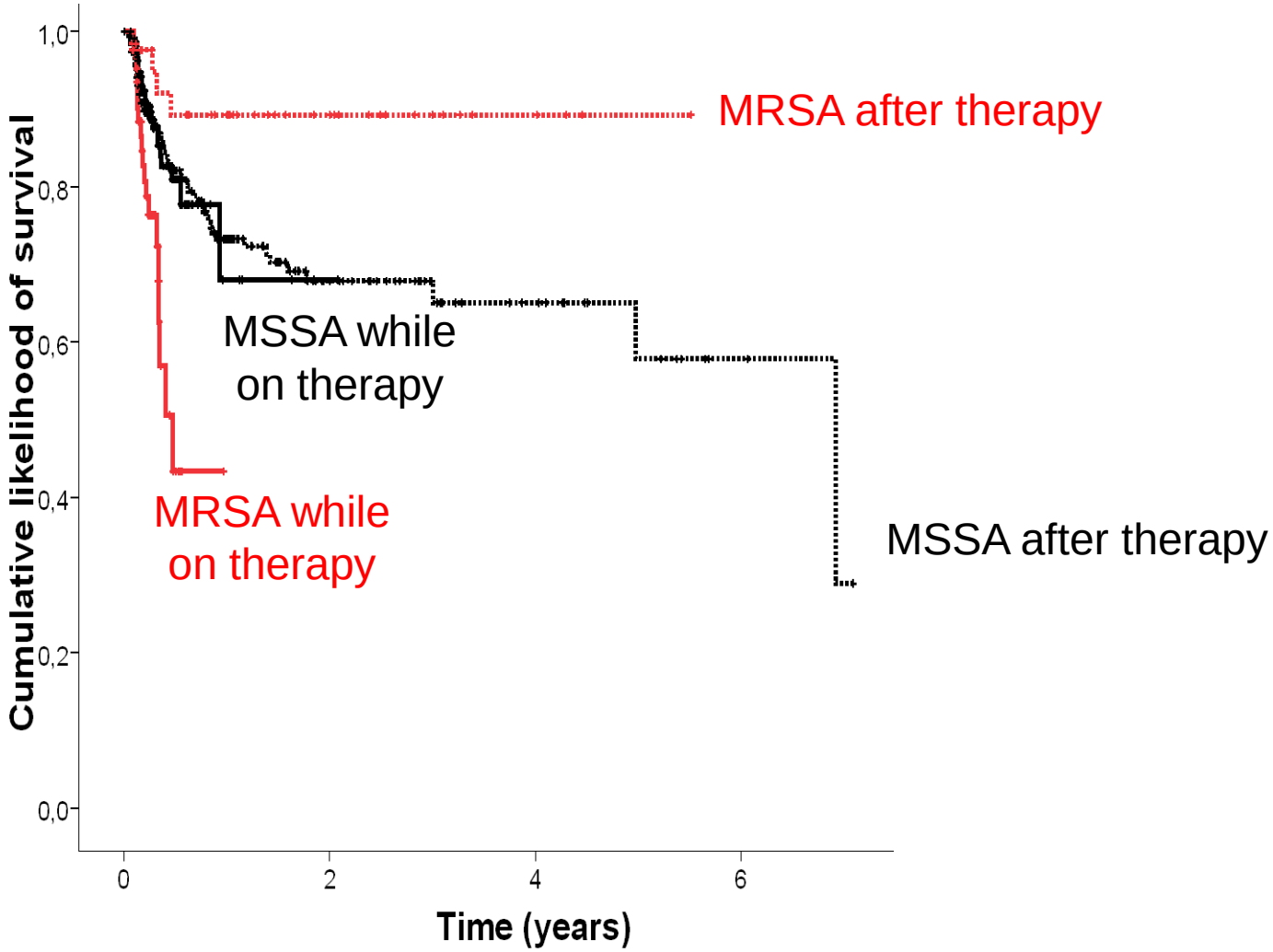
MSSA (n=185, fail=60)	aHR	*p*
Immunosupr. Therapy	3.40 (1.39-8.37)	0.008
Prosthesis age > 3 m	2.18 (1.04-4.56)	0.039
Bacteremia	2.35 (1.04-5.36)	0.040
Need for ≥2 debrid	5.36 (2.88-9.98)	<.001
Levo + Rifampin > 14 d	**0.42 (0.22-0.80)**	**0.008**

MRSA (n=59, fail=21)	aHR	*p*
Abnormal Rx at diagn.	4.49 (1.68-12.0)	0.003
Vanco + Rifamp > 14d	**0.29 (0.10-0.87)**	**0.027**

Staphylococcal PJI managed by DAIR

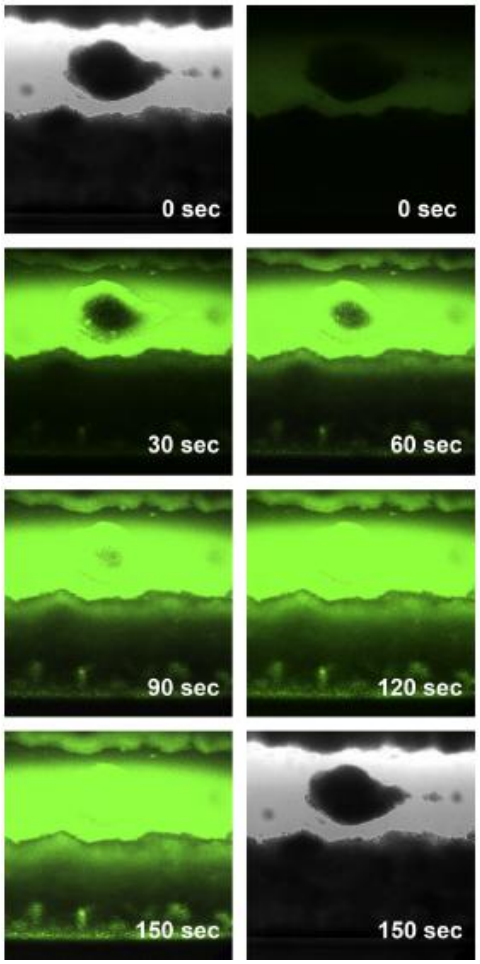


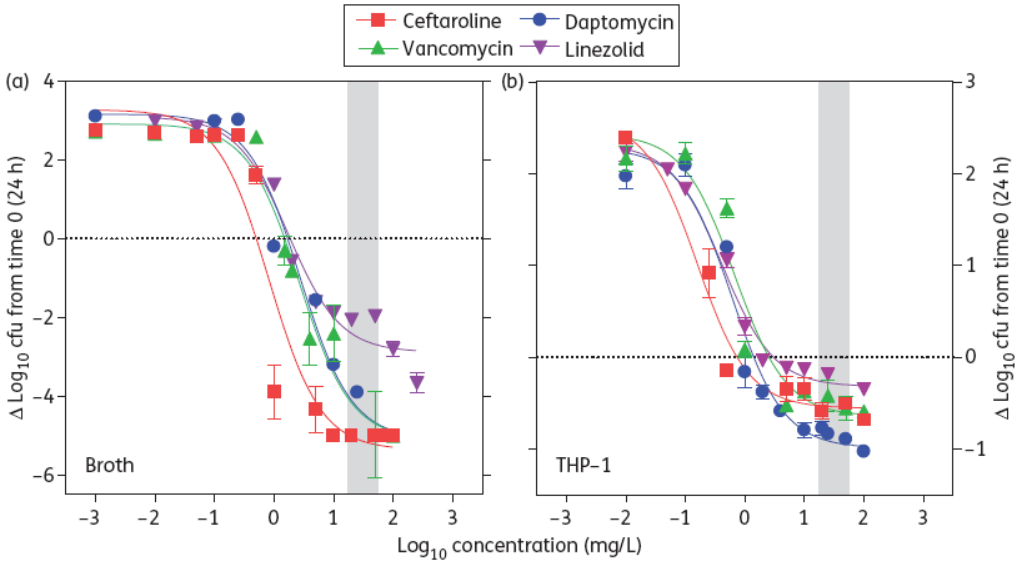
Staphylococcal PJI managed by DAIR

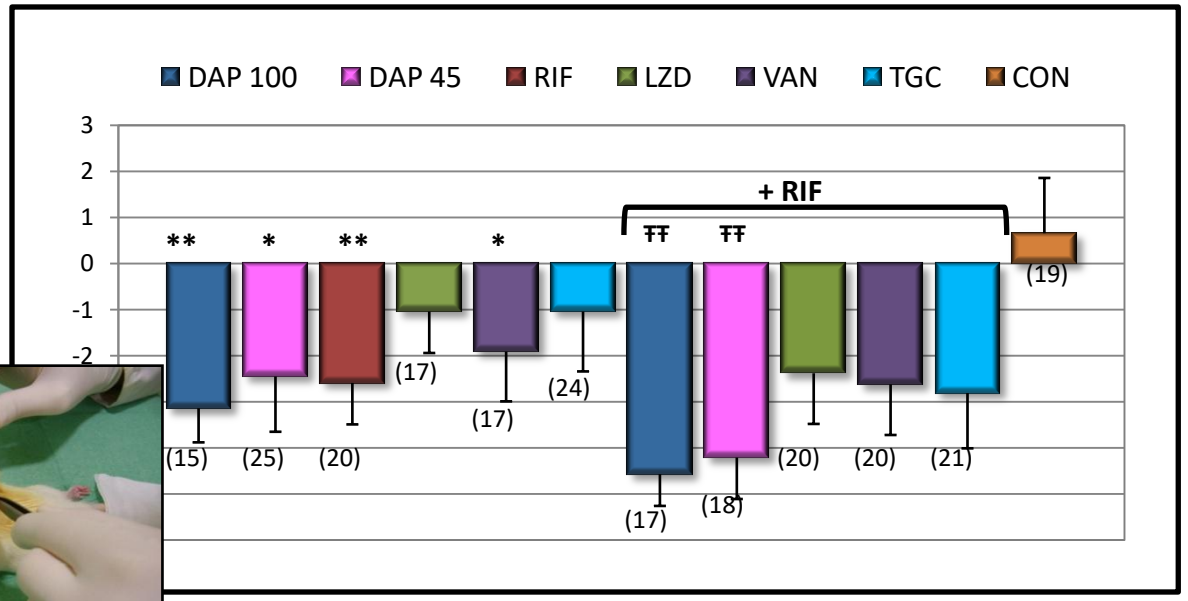


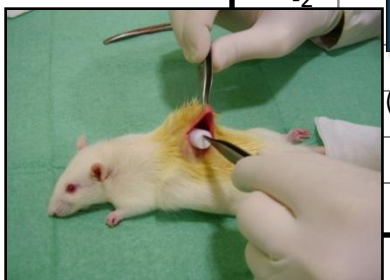
Different ability of Rifampin-based combinations on avoiding relapse

Staphylococcal PJI managed by DAIR









Baltch, 2008. AAC
Stewart, 2009. AAC
Garrigós, 2010. AAC
Mélard, 2013. JAC

Staphylococcal PJI managed by DAIR

High doses of daptomycin (10 mg/kg/d) plus rifampin for the treatment of staphylococcal prosthetic joint infection managed with implant retention: a comparative study

Jaime Lora-Tamayo [a,*], Jorge Parra-Ruiz [b], Dolors Rodríguez-Pardo [c], José Barberán [d], Alba Ribera [a], Eduardo Tornero [e], Carles Pigrau [c], José Mensa [f], Javier Ariza [a], Alex Soriano [f]

N=18

Acute staphylococcal PJI managed by DAIR

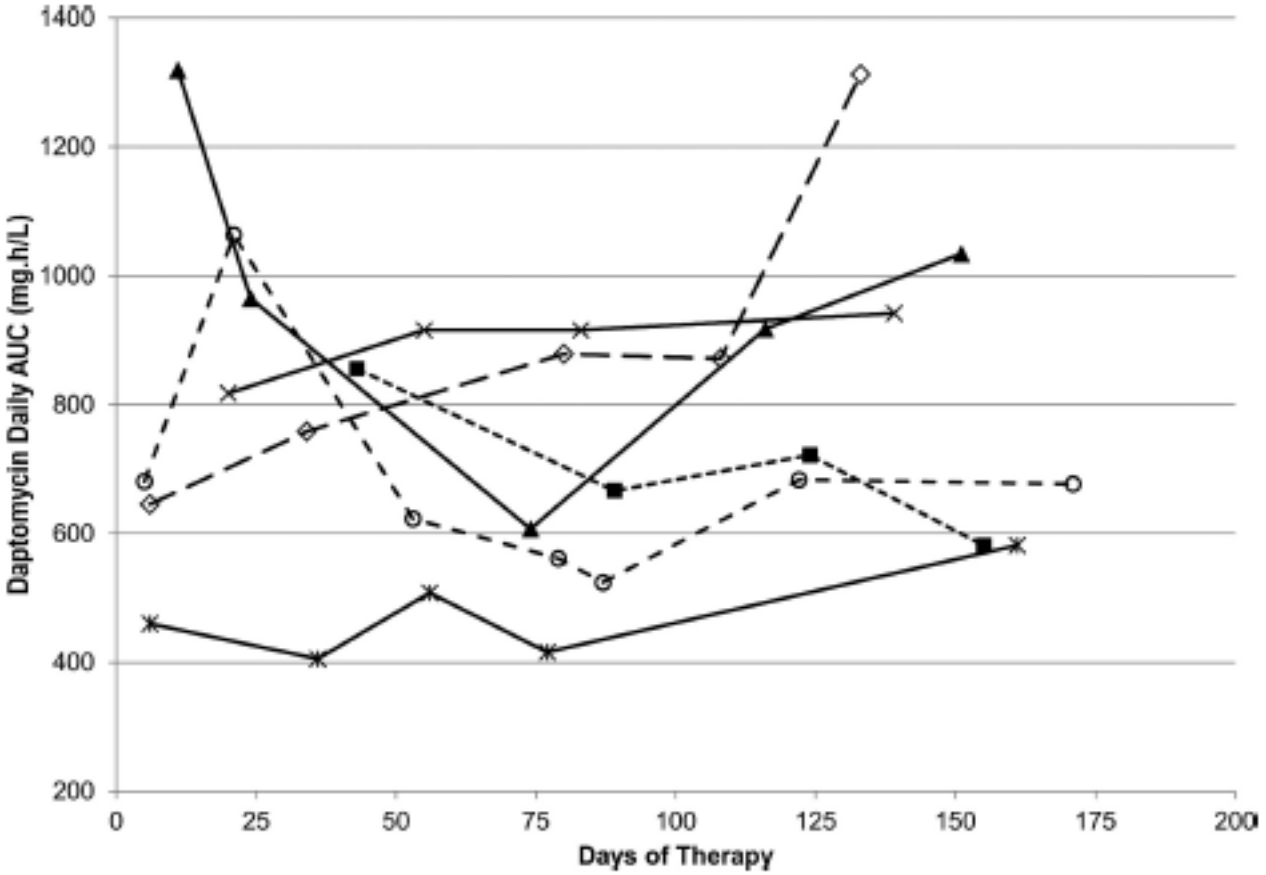
Daptomycin (10 mg/kg/d) + Rifampin x 6 weeks

Outcome	Dapto + Rifa (n=18)	Historical cohort (n=44)	*p*
Clinical failure	9 (50%)	15 (34%)	0.27
Clinical failure while on treatment	2/9 (22%)	11/15 (73%)	0.03
Microbiological failure	5 (29%)	13 (30%)	1.00
Mocribiol fail. while on treatment	1/5 (20%)	9/13 (69%)	0.12

Lora-Tamayo, 2014. Diagn Microbiol Infect Dis

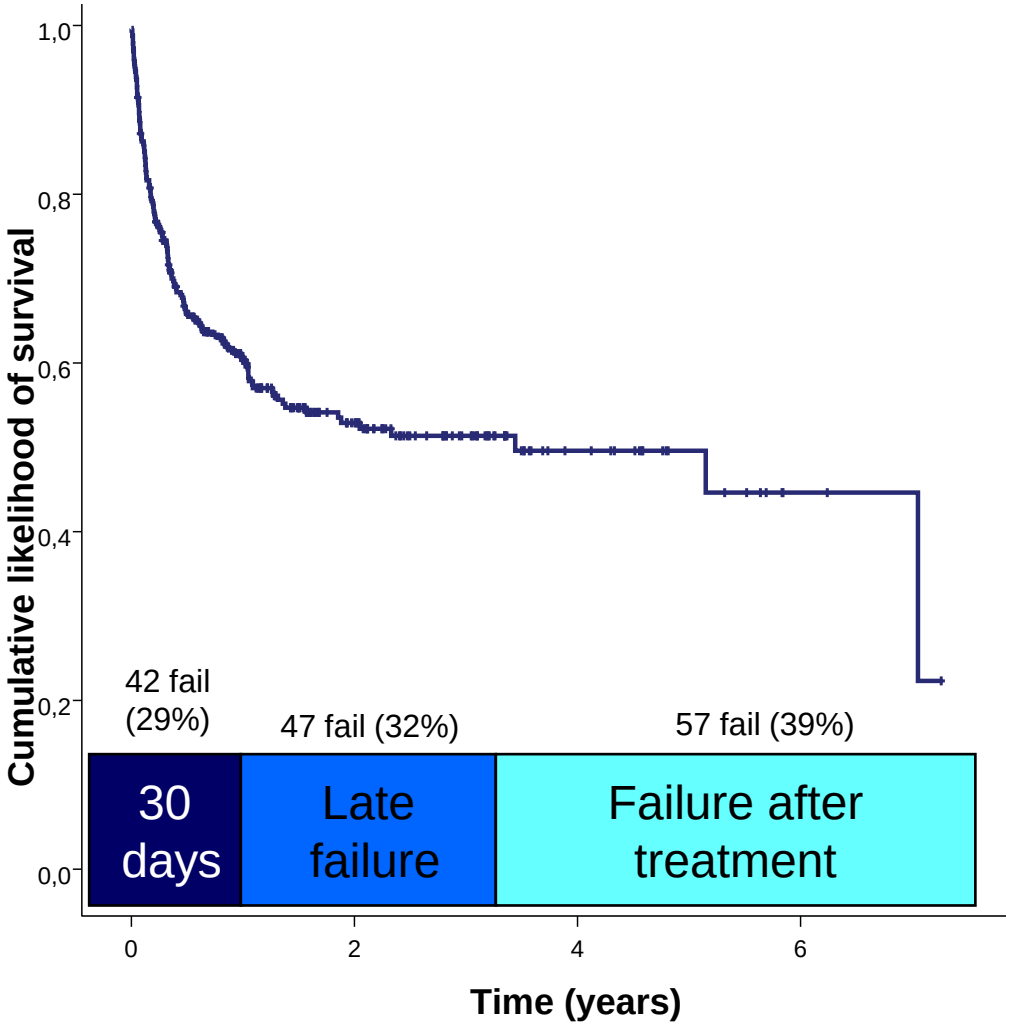
Pharmacokinetic Variability of Daptomycin during Prolonged Therapy for Bone and Joint Infections

Sylvain Goutelle,[a,b,c] Sandrine Roux,[d] Marie-Claude Gagnieu,[g] Florent Valour,[d] Sébastien Lustig,[e] Florence Ader,[d,e,f] Frédéric Laurent,[b,e,f] Christian Chidiac,[d,e,f] Tristan Ferry,[d,e,f] on behalf of the Lyon Bone and Joint Infections Study Group



Goutell, 2016. Antimicrob Agents Chemother

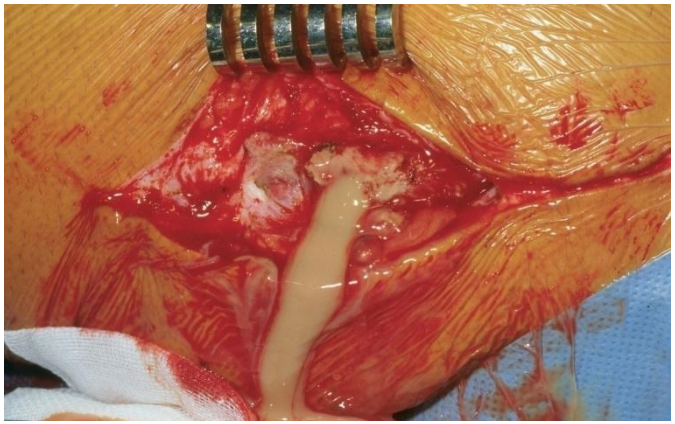
Staphylococcal PJI managed by DAIR



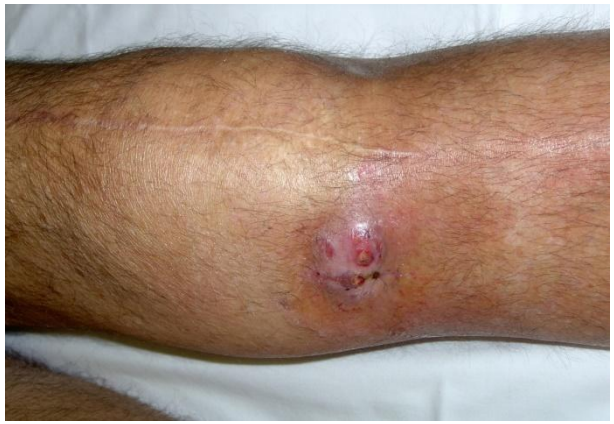
Staphylococcal PJI managed by DAIR

Parameter	Early failure (Odds Ratio)	Late Failure (Hazard Ratio)	Fail. After Ther (Hazard Ratio)
Sex male	2.48 (1.19-5.19)		
Age (per year)		1.03 (1.00-1.07)	
Rheumatoid arthritis	3.88 (1.44-10.4)		
Immunosupr. Therapy		3.05 (1.30-7.14)	
Hematogenous PJI			2.46 (1.35-4.48)
MRSA		2.33 (1.25-4.33)	0.33 (0.12-0.92)
Bacteremia	5.03 (2.11-12.0)		
Polymicr. Infection	7.50 (3.23-17.4)		
CRP (per 100 mg/L)	1.52 (1.11-2.09)		
Sinus tract		1.88 (0.94-3.77)	
Abnormal Rx at diagn		2.28 (1.14-4.54)	
Symptoms duration (per day)			1.00 (1.00-1.01)
Need for ≥2 debridements		2.25 (1.11-4.56)	2.51 (1.27-4.98)
Rifampin		0.49 (0.26-0.91)	

Staphylococcal PJI managed by DAIR



Planctonic bacteria
(early failure)



Biofilm-embedded bacteria
(delayed failure)

Adaptive processes of *Staphylococcus aureus* isolates during the progression from acute to chronic bone and joint infections in patients

Less biofilm
More virulence
Less intracellular infection
…

More biofilm
Less virulence
More intracellular infection
…

Trouillet-Assant, 2016. Cell Microb

Staphylococcal PJI managed by DAIR

Serum Bactericidal Activity of Rifampin in Combination with Other Antimicrobial Agents against *Staphylococcus aureus*

CORINNE J. HACKBARTH, HENRY F. CHAMBERS, AND MERLE A. SANDE*

Department of Medicine, School of Medicine, University of California, San Francisco, and The Medical Service, San Francisco General Hospital, San Francisco, California 94110

Received 19 July 1985/Accepted 3 January 1986

TABLE 3. Comparison of rates of bacterial killing

Drug(s) (concn [μg/ml])	6-h killing rate (log_{10} CFU/ml per h; mean ± SEM
Nafcillin (40)	−0.24 ± 0.05[a]
Nafcillin-rifampin	−0.11 ± 0.04
Vancomycin (30)	−0.23 ± 0.04[a]
Vancomycin-rifampin	−0.11 ± 0.02
Teicoplanin (5)	−0.25 ± 0.05[a]
Teicoplanin-rifampin	−0.08 ± 0.02
Clindamycin (10)	−0.11 ± 0.02[a]
Clindamycin-rifampin	−0.23 ± 0.03
Erythromycin (5)	−0.12 ± 0.03[a]
Erythromycin-rifampin	−0.24 ± 0.04
Trimethoprim (5)	−0.16 ± 0.06
Trimethoprim-rifampin	−0.09 ± 0.02
Ciprofloxacin (5)	−0.44 ± 0.03[a]
Ciprofloxacin-rifampin	−0.07 ± 0.01
Pefloxacin (5)	−0.37 ± 0.05[a]
Pefloxacin-rifampin	−0.03 ± 0.02
Rifampin (5)	−0.13 ± 0.01
Control	+0.32 ± 0.01

[a] $P < 0.02$ compared with the drug in combination with rifampin.

Hackbarth, 1986. AAC

Staphylococcal PJI managed by DAIR

REVIEW 10.1111/1469-0691.12003

Antimicrobial treatment concepts for orthopaedic device-related infection

P. Sendi[1,2,3] and W. Zimmerli[1]

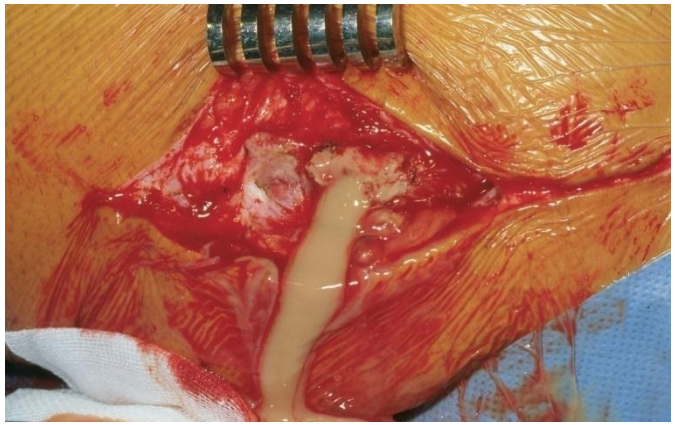
Start and dosage of rifampin therapy

No study has investigated the optimal time for starting rifampin therapy in patients with staphylococcal ODRI. Concerns regarding liver toxicity or drug interactions with compounds

become clinically relevant after several days [18]. However, it is prudent not to use rifampin in the early course of infection, for the following reasons. First, perioperative rifampin therapy increases the risk of superinfection with rifampin-resistant staphylococci by selection pressure on the local flora [19]. Second, emergence of resistance is highest when the bacterial load is high [7]. Thus, there are arguments for

Sendi & Zimmerli, 2012. CMI

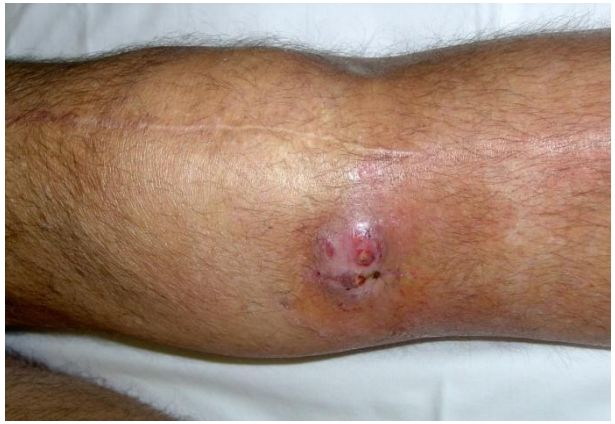
Staphylococcal PJI managed by DAIR



Planctonic bacteria (early failure)

- B-lactams
- Vancomycin
- Daptomycin combination

First 5-10 d after debridement



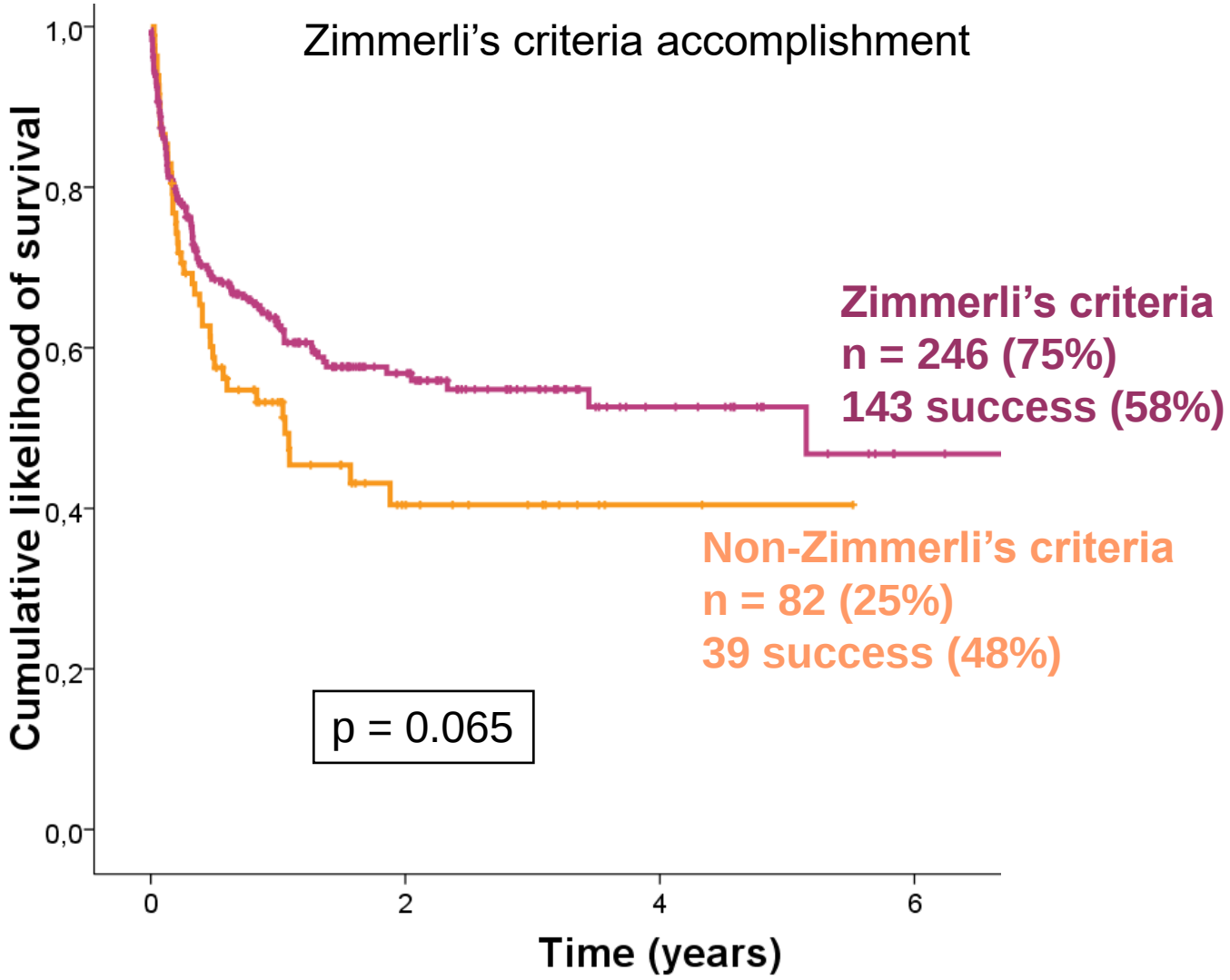
Biofilm-embedded bacteria (delayed failure)

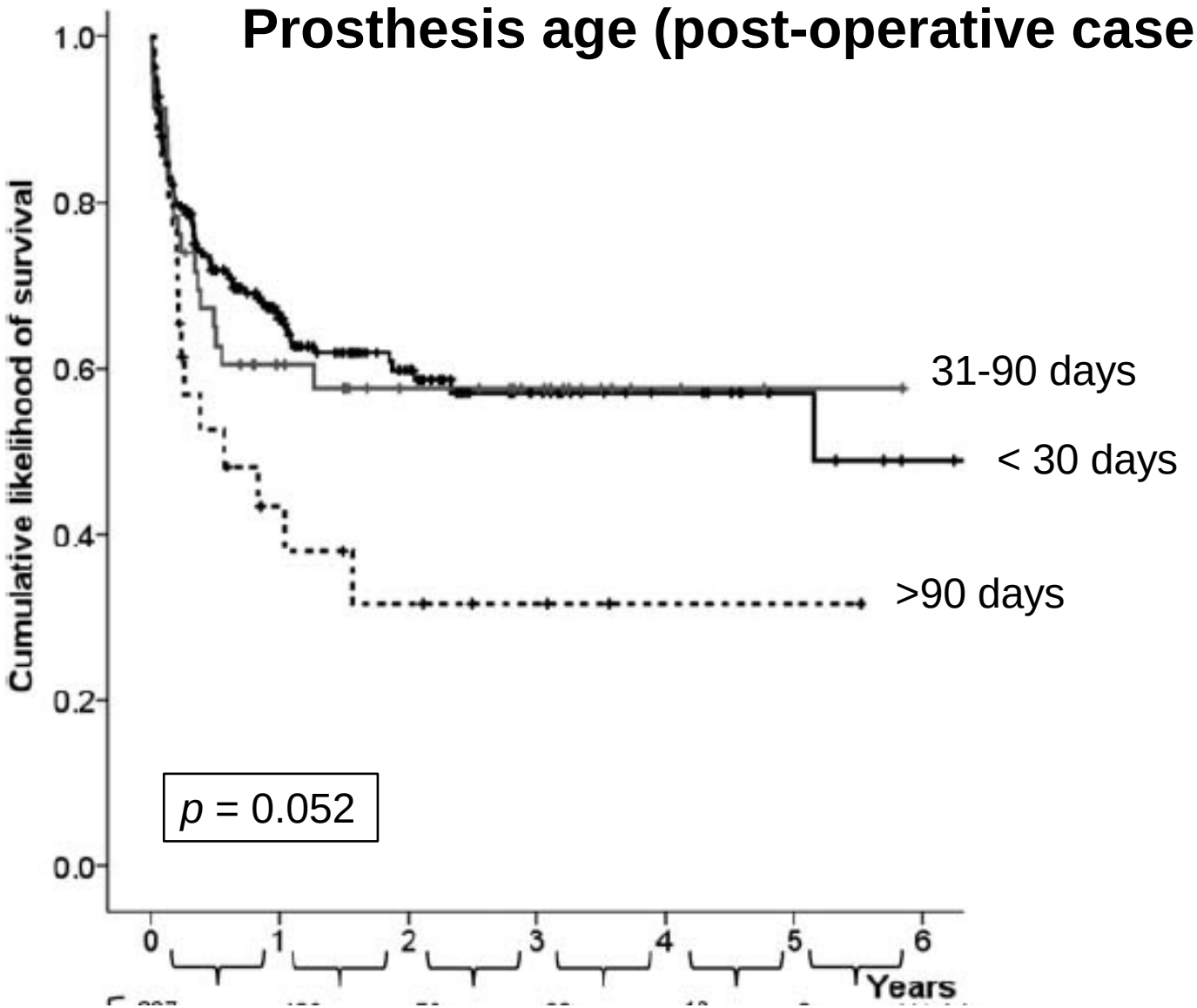
- Rifampin-based combo

Afterwards

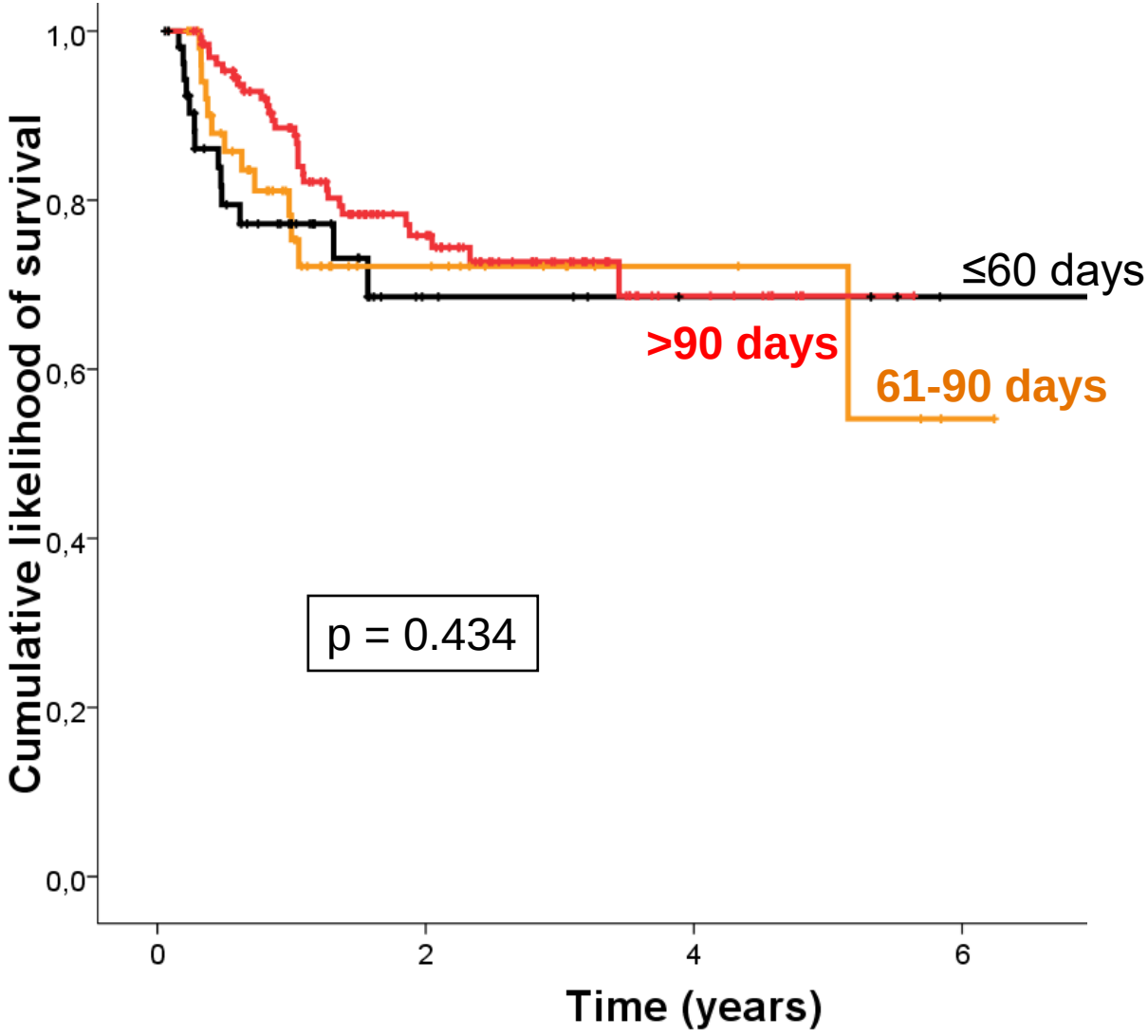
Ariza, 2017. Enferm Infecc Microbiol Clin

Staphylococcal PJI managed by DAIR




Prosthesis age (post-operative cases)
Cumulative likelihood of survival
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
Years
31-90 days
< 30 days
>90 days
p = 0.052

Influence of the length of therapy



Staphylococcal PJI managed by DAIR

Ref	Design	N (dair)	Etiology	Conclusions
Byren, 2009	Observational Retrospective 1 center	112	Various	Length of therapy did not predict the likelihood of failure
Bernard, 2010	Observarional, retrospective, 1 center	60	Various (mostly staphylococci)	6 weeks ≈ 12 weeks
Puhto, 2012	Observational, retrospective, pre-post design 1 center	86	Various (mostly staphylococci)	8 weeks ≈ 12 weeks (hips) or 6 weeks (knees)
Chaussade, 2017	Observational, retrospective, multicenter	87	Various (mostly staphylococci)	6 weeks ≈ 12 weeks

Staphylococcal PJI managed by DAIR

Short Communication

Short- versus long-duration levofloxacin plus rifampicin for acute staphylococcal prosthetic joint infection managed with implant retention: a randomised clinical trial ☆

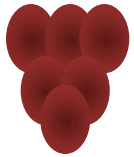
Jaime Lora-Tamayo [1,*], Gorane Euba [2], Javier Cobo [3], Juan Pablo Horcajada [4], Alex Soriano [5], Enrique Sandoval [6], Carles Pigrau [7], Natividad Benito [8], Luis Falgueras [9], Julián Palomino [10], María Dolores del Toro [11], Alfredo Jover-Sáenz [12], José Antonio Iribarren [13], Mar Sánchez-Somolinos [14], Antonio Ramos [15], Marta Fernández-Sampedro [16], Melchor Riera [17], Josu Mirena Baraia-Etxaburu [18], Javier Ariza [2], Prosthetic Joint Infection Group of the Spanish Network for Research in Infectious Diseases—REIPI

Int J Antimicrob Agents. 2016; 48: 310-6

- **Design** – open, comparative, randomized clinical trial

- **Setting** – 17 Spanish hospitals (REIPI), from 2009 to 2013

Staphylococcal PJI managed by DAIR



Eligible Patient
- Acute staphylococcal infection
- Debridement + Implant Retention

Hypothesis of non-inferiority

Main goal: cure rate

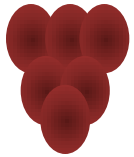
Short schedule = 8 weeks
Both knee & hip prosthesis

Rifampin 600 mg/d
Levofloxacin 750 mg/d

Standard schedule
- Hip prosthesis = 3 months
- Knee prosthesis = 6 months

$\Delta = 15\%$; $\alpha=0.05$; $1-\beta = 0.80$; loss rate = 10% → 195 patients

Staphylococcal PJI managed by DAIR



172 patients with acute staphylococcal PJI

Exclusion criteria

112 excluded
- 48 (28%) resistance to LVX or RIF
- 19 (11%) other treat. > 7 days
- 17 (10%) prosthesis removal
- 12 (7%) debridement delay > 21d
- 16 (9%) other

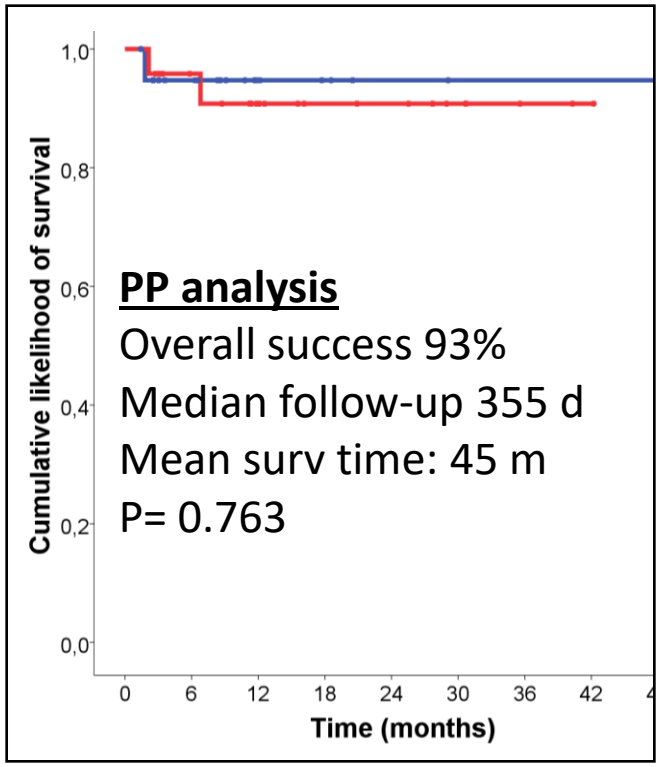
63 (35%) randomized
Intention-to-treat
- 33 long arm
- 30 short arm

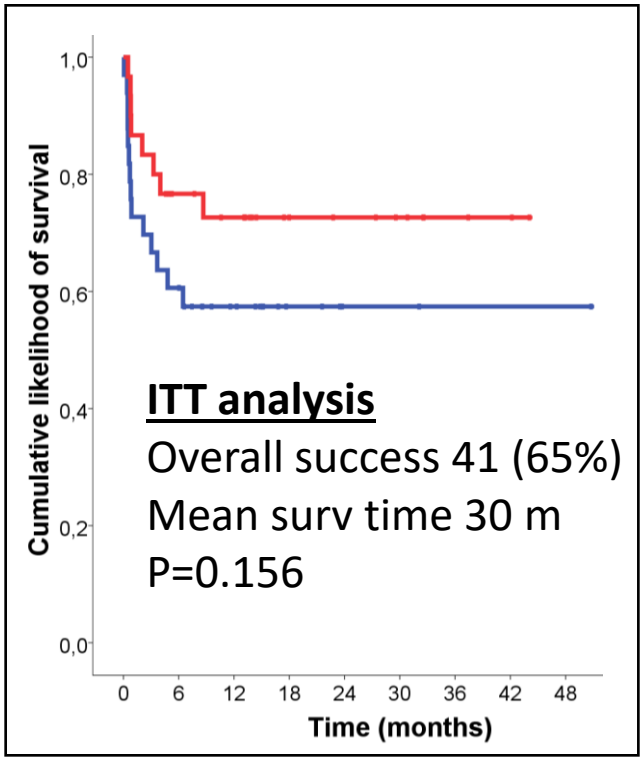
19 non-evaluable (13 in the long arm)
- 10 (53%) toxicity to ATB
- 2 (11%) early prosth. Removal
- 5 (26%) lost of follow-up
- 2 (11%) protocol violation

44 patients for PP analysis
- 20 long arm
- 22 short arm

Aim 2 – Efficacy of a short schedule of levofloxacin + rifampin

	Long arm (n=33)	Short arm (n=30)	*p*
Polymicrobial infection	9 (27%)	2 (7%)	**0.046**

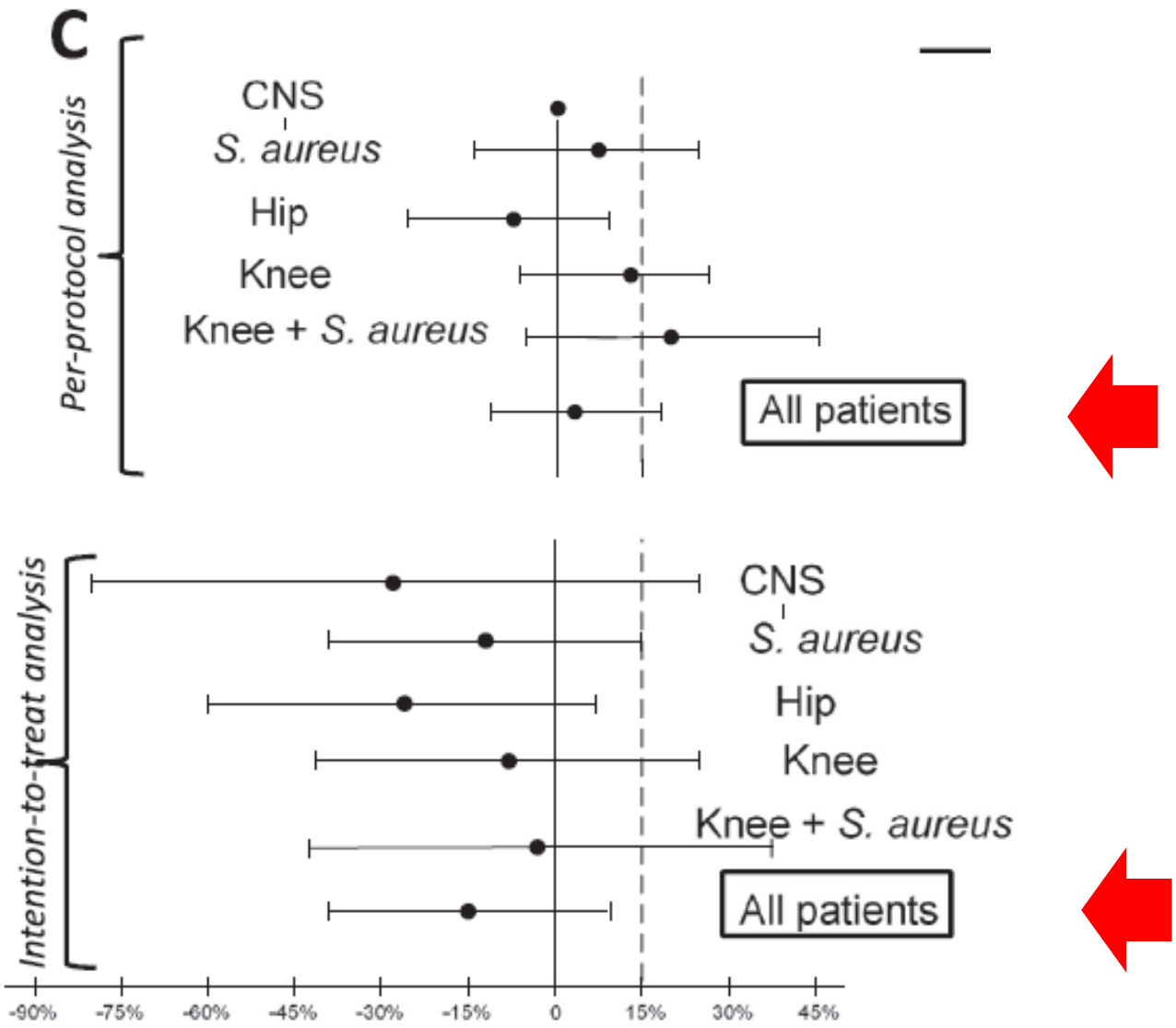




Short arm

Long arm

Staphylococcal PJI managed by DAIR

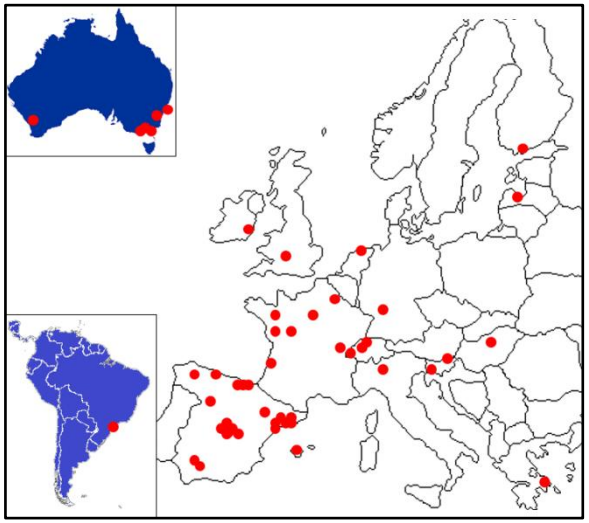


STREPTOCONGA

Streptococcal PJI managed by DAIR

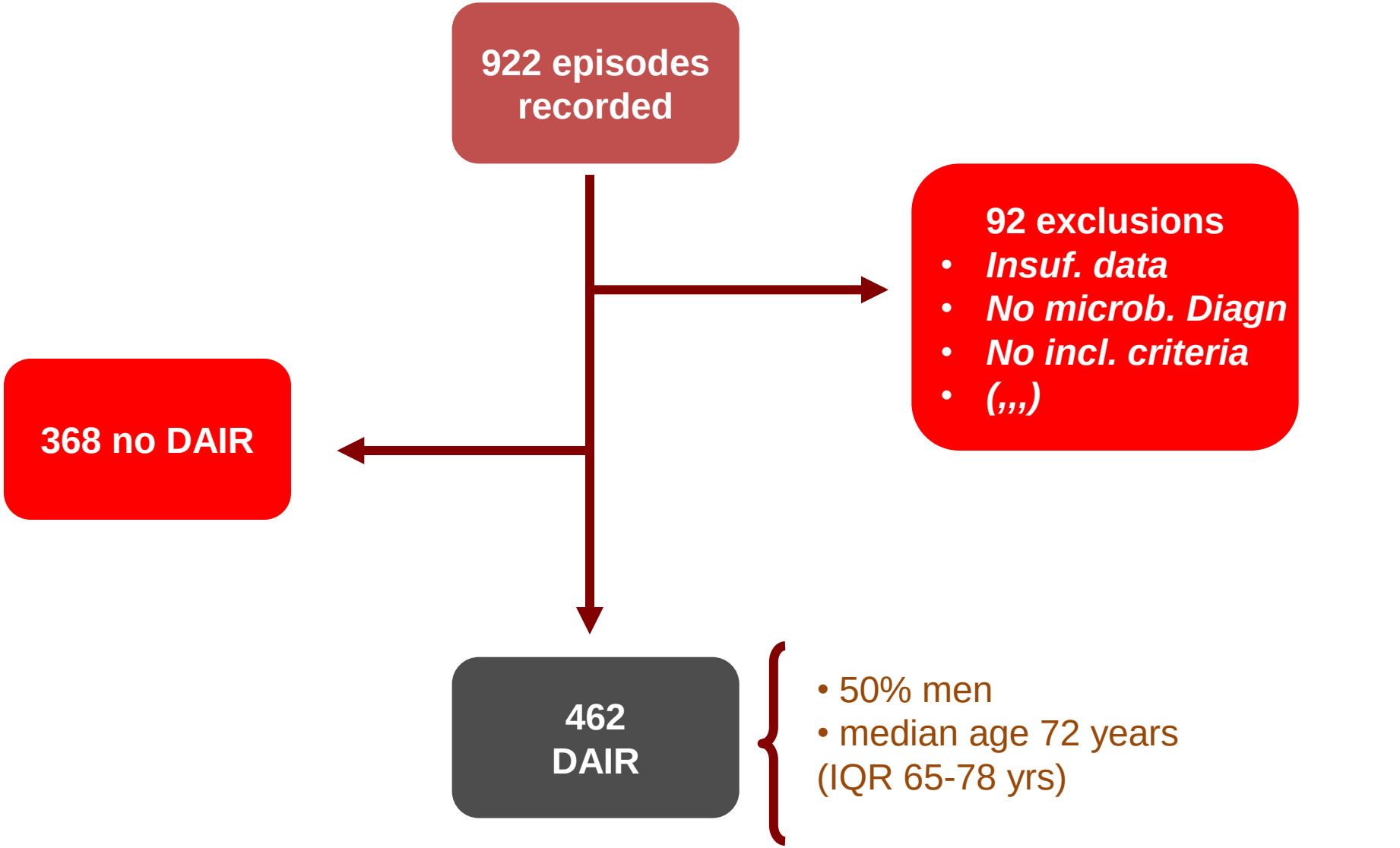
The Not-So-Good Prognosis of Streptococcal Periprosthetic Joint Infection Managed by Implant Retention: The Results of a Large Multicenter Study

Jaime Lora-Tamayo,[1,2] Éric Senneville,[3] Alba Ribera,[2,4,5] Louis Bernard,[6,7] Michel Dupon,[8] Valérie Zeller,[9] Ho Kwong Li,[5] Cédric Arvieux,[7,10] Martin Clauss,[11] Ilker Uçkay,[12] Dace Vigante,[13] Tristan Ferry,[14] José Antonio Iribarren,[15] Trisha N. Peel,[16] Parham Sendi,[17] Nina Gorišek Miksić,[18] Dolors Rodríguez-Pardo,[2,19] María Dolores del Toro,[2,20] Marta Fernández-Sampedro,[2,21] Ulrike Dapunt,[22] Kaisa Huotari,[23] Joshua S. Davis,[24] Julián Palomino,[2,20] Danielle Neut,[25] Benjamin M. Clark,[26] Thomas Gottlieb,[27] Rihard Trebše,[28] Alex Soriano,[2,29,30] Alberto Bahamonde,[31] Laura Guío,[2,32] Alicia Rico,[33] Mauro J. C. Salles,[34] M. José G. Pais,[35] Natividad Benito,[2,36] Melchor Riera,[2,37] Lucía Gómez,[38] Craig A. Aboltins,[39] Jaime Esteban,[40] Juan Pablo Horcajada,[41] Karina O'Connell,[42] Matteo Ferrari,[43] Gábor Skaliczki,[44] Rafael San Juan,[1,2] Javier Cobo,[2,45] Mar Sánchez-Somolinos,[2,46] Antonio Ramos,[47] Efthymia Giannitsioti,[48] Alfredo Jover-Sáenz,[49] Josu Mirena Baraia-Etxaburu,[50] José María Barbero,[51] Peter F. M. Choong,[52] Nathalie Asseray,[7,53] Séverine Ansart,[7,54] Gwenäel Le Moal,[7,55] Werner Zimmerli,[11] and Javier Ariza[2,4]; for the Group of Investigators for Streptococcal Prosthetic Joint Infection[a]

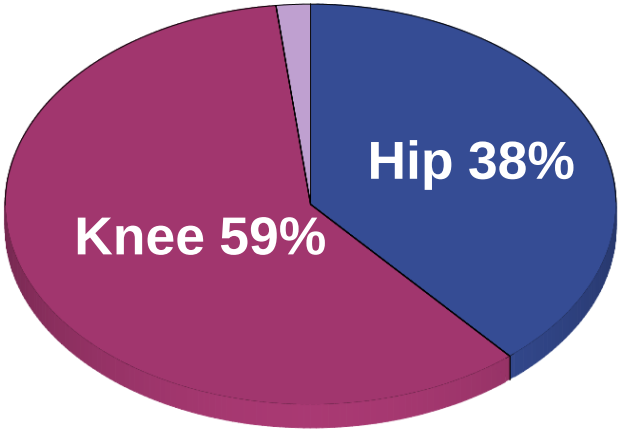


- 52 hospitals (15 nations)
- 2003-2012
- PJI caused by streptococci
  - No superinfections
  - Polymicrobial cases allowed

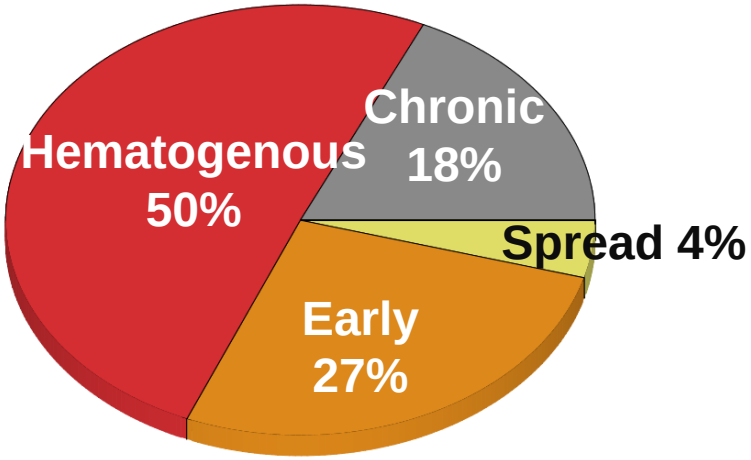
Streptococcal PJI managed by DAIR



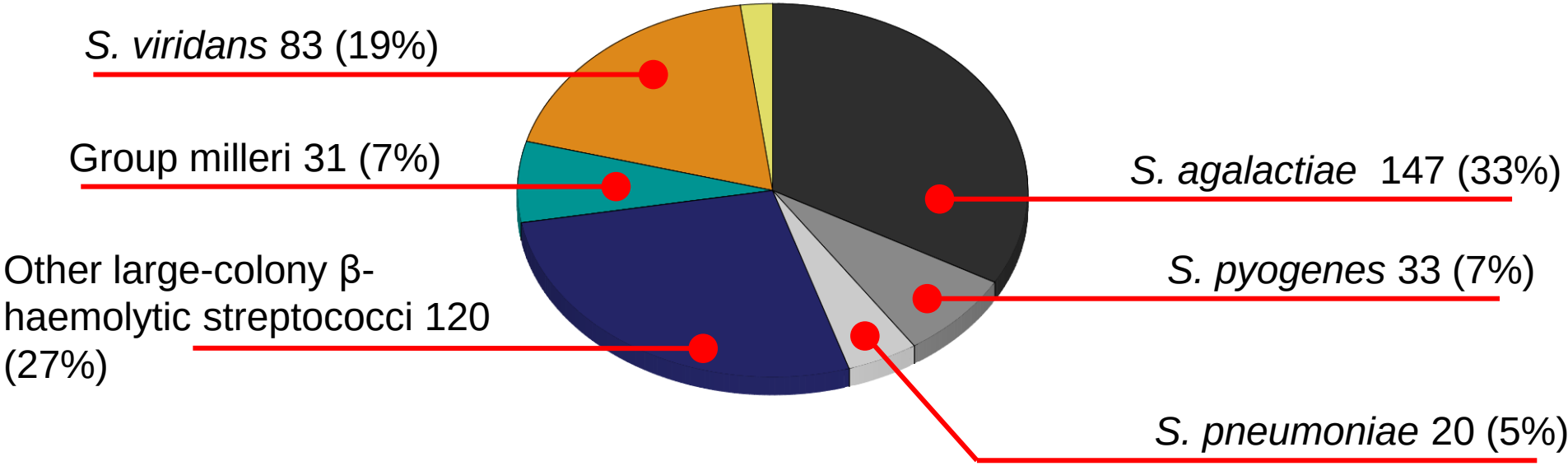
Streptococcal PJI managed by DAIR



Prosthesis location



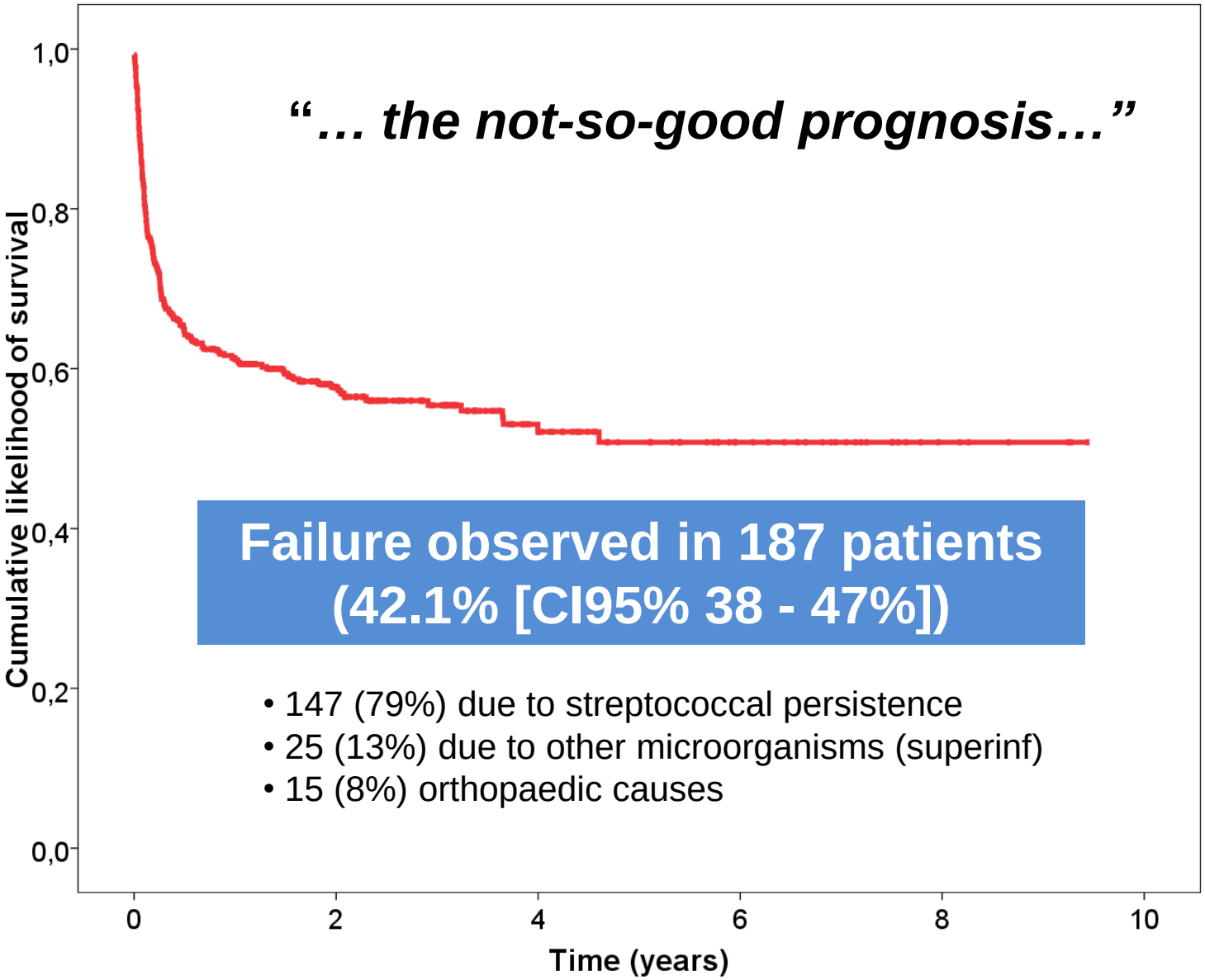
Type of infection



Streptococcal PJI managed by DAIR

DIFFERENCES AMONG STREPTOCOCCAL SPECIES		*S. agalactiae*	*S. pyogenes*	*S. pneumoniae*	Other large-col beta-haemolyt	Group milleri	*S. viridans*	p
Sex (women)		57%	55%	**45%**	**37%**	58%	58%	**0.013**
Age (years)		72	70	75	71	75	72	0.206
Renal chronic impairment		8%	18%	15%	10%	10%	6%	0.307
Rheumatoid arthritis		4%	**18%**	5%	9%	7%	**15%**	**0.033**
Immunosuppressive therapy		7%	18%	5%	12%	10%	13%	0.318
Location (knee)		59%	58%	60%	73%	42%	46%	**0.001**
Revision prosthesis		22%	18%	20%	20%	26%	31%	0.508
Type of infection	Early (< 3 m)	**31%**	**49%**	5%	24%	19%	28%	**0.007**
	Hematogenous	**47%**	**42%**	**90%**	50%	55%	47%	
	Chronic (>3 m)	16%	6%	5%	22%	26%	21%	
Polimicrobial infection		12%	21%	10%	13%	16%	**27%**	0.065

Streptococcal PJI managed by DAIR

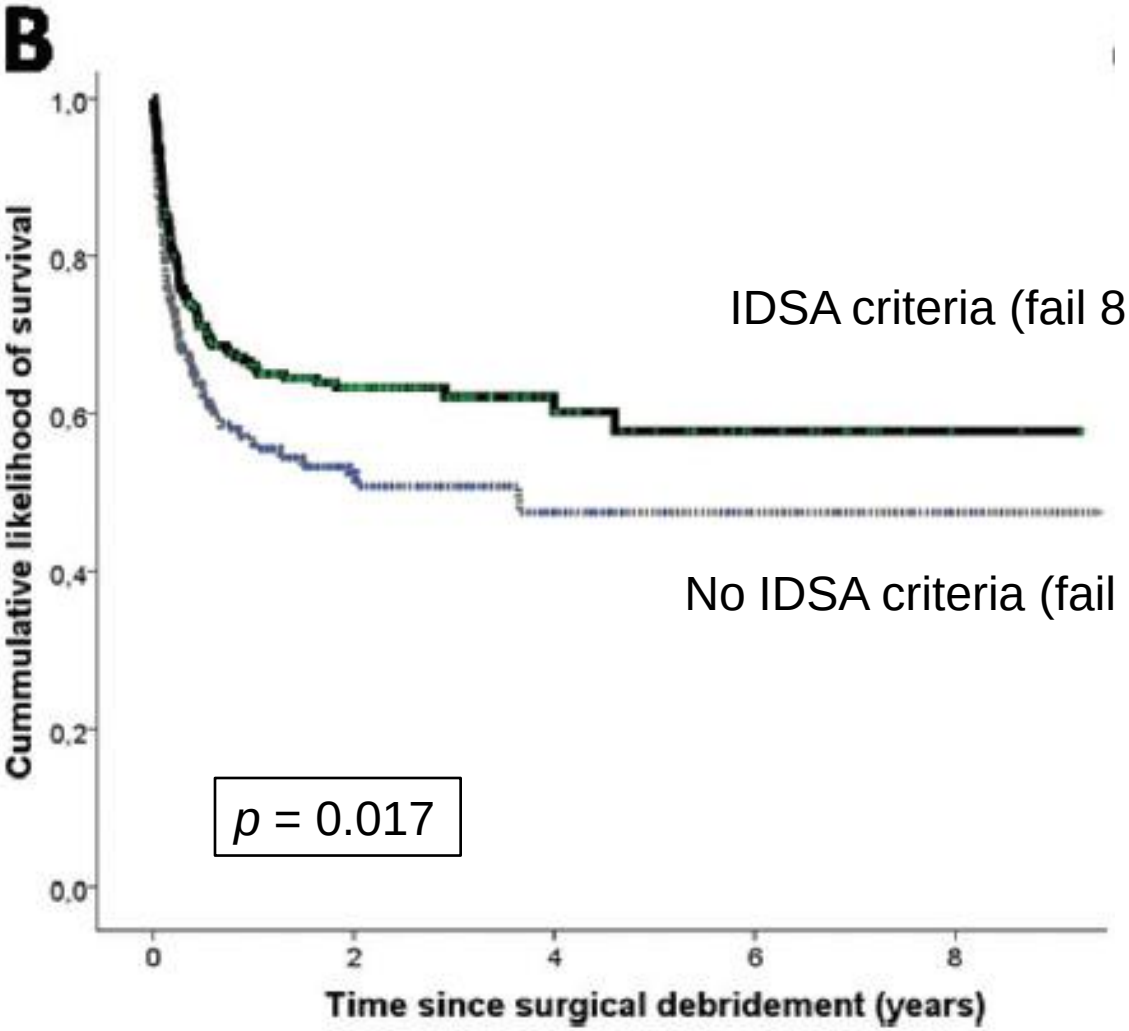


"… the not-so-good prognosis…"

Failure observed in 187 patients (42.1% [CI95% 38 - 47%])

- 147 (79%) due to streptococcal persistence
- 25 (13%) due to other microorganisms (superinf)
- 15 (8%) orthopaedic causes

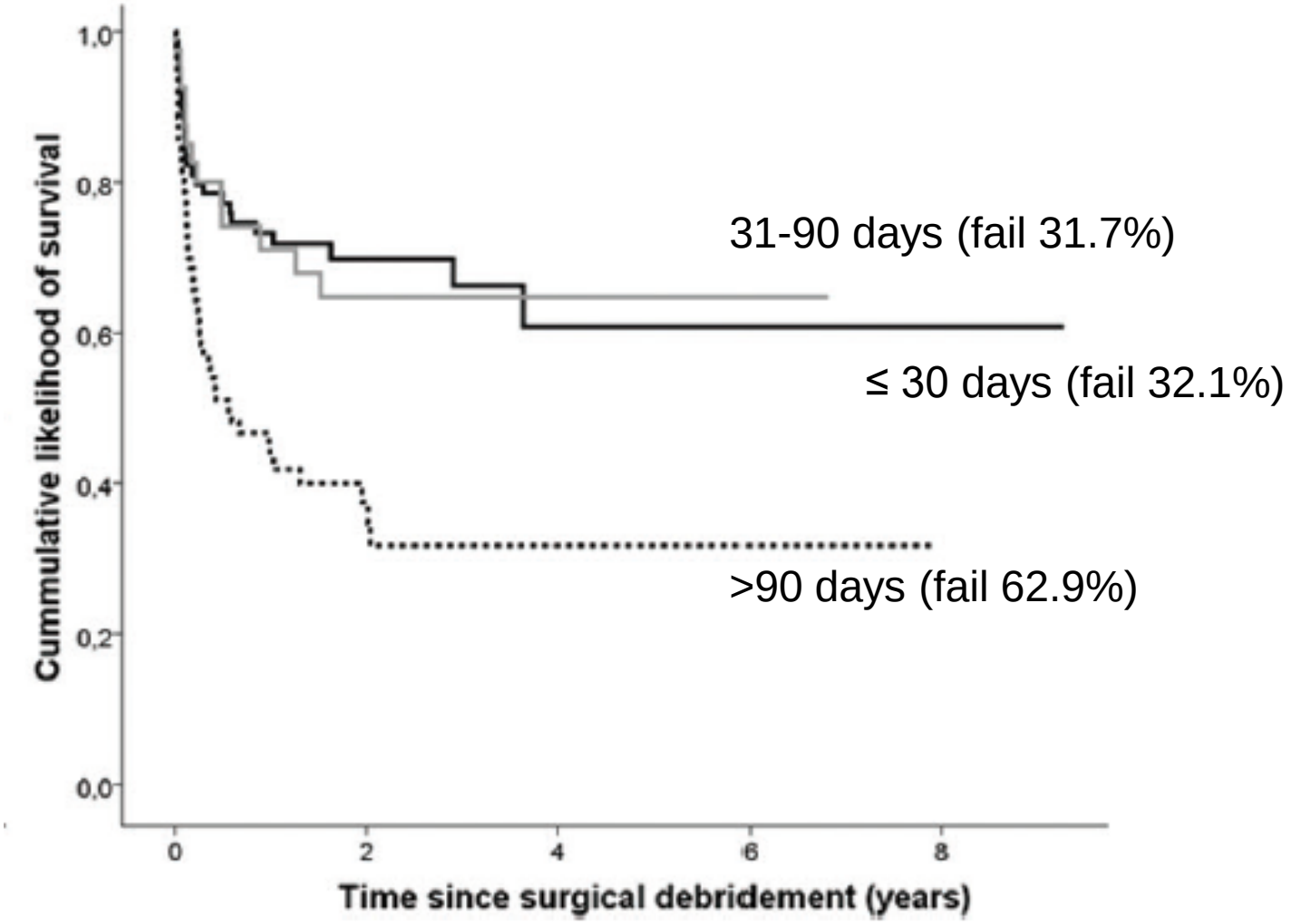
Streptococcal PJI managed by DAIR



IDSA criteria (fail 81/221 = 37%)

No IDSA criteria (fail 116/223 = 52%)

Failure rate according to prosthesis age (post-operative cases)

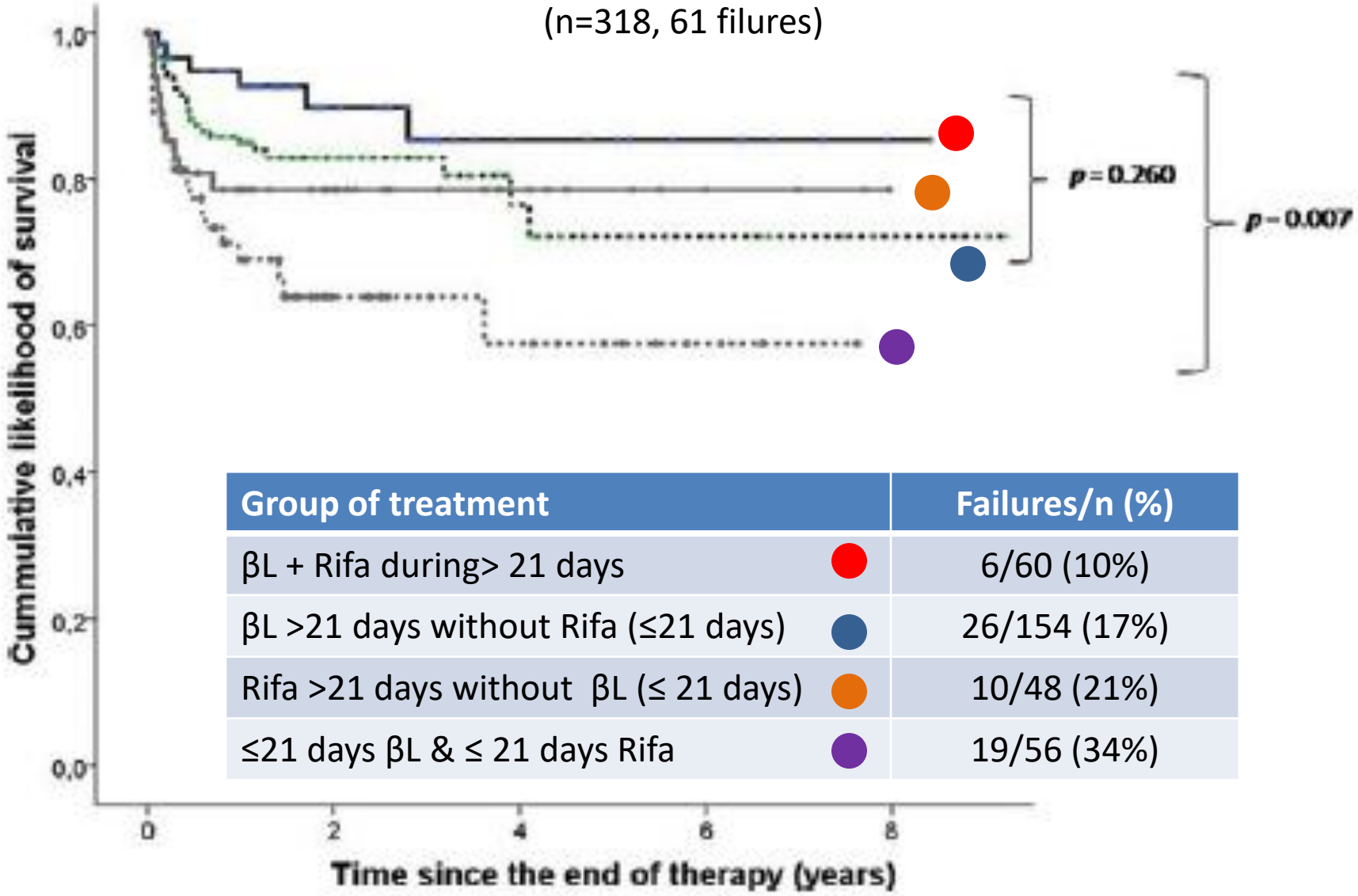


	Adjusted Hazard Ratio	
	All patients (n=444, fail 187)	**Cases not failing within the first 30 d. (n=389, fail = 132)**
Renal chronic failure	1.55 (0.97 – 2.48)	-
Rheumatoid arthritis	**2.36 (1.50 – 3.72)**	-
Immunosupr. therapy	-	1,66 (0.99-2.18)
Revision prosthesis	1.37 (0.96 – 1.90)	1.47 (0.99-2.18)
Chronic inf (>3 m)	**2.20 (1.51 – 3.20)**	**1.69 (1.10-2.60)**
Bacteremia	**1.69 (1.19 – 2.40)**	-
Symptoms dur. (x day)	-	**1.00 (1.00-1.00)**
Exchange remov. Comp	**0.60 (0.44 – 0.81)**	**0.65 (0.50-0.93)**
Need for ≥2 debrid.	1.38 (0.96 – 1-99)	**1.68 (1.10-2.57)**
Rifampin (per day)	-	**0.98 (0.96-0.998)**
Glyicopeptides (per day)	-	**1.04 (1.02-1.06)**
Co-trimoxazole (per day)	-	**1.04 (1.002-1.08)**

	Early failure (n=444, 55 fails)	Late failure (n=389; 71 fails)	Fail After (n=318, 61 fals)
Sex (female)	-	**0.51 (0.30-0.85)**	
Age (per year)	**1.04 (1.00-1.07)**		
Rheumatoid arthritis	**3.33 (1.40-7.93)**		
Immunosuppressive ther.	-	**2.64 (1.46-4.79)**	
Revision prosthesis	-	**1.77 (1.07-2.93)**	
Chronic infection (>3 mo)	**1.41 (1.10-1.81)**		**2.24 (1.24-4.05)**
Bacteremia	**2.23 (1.80-4.20)**		
S. Pyogenes	**3.31 (1.41-7.77)**		
Symptoms duration > 7d	-	**1.70 (1.05-2.75)**	
Polyethylene Exchange	-		**0.44 (0.26-0.76)**
≥2 desbridements	-	**2.45 (1.45-4.15)**	
B-lactams (no Rifa)		-	**0.48 (0.28-0.84)**
B-lactams (plus Rifa)		-	**0.34 (0.12-0.96)**
Quinolones (plus Rifa)		0.21 (0.03-1.54)	-
Glycopeptides (no Rifa)		**2.82 (1.43-5.53)**	-

Streptococcal PJI managed by DAIR

Patients not failing during treatment
(n=318, 61 filures)



Group of treatment	Failures/n (%)
βL + Rifa during> 21 days	6/60 (10%)
βL >21 days without Rifa (≤21 days)	26/154 (17%)
Rifa >21 days without βL (≤ 21 days)	10/48 (21%)
≤21 days βL & ≤ 21 days Rifa	19/56 (34%)

Final thoughts

- Multicenter study are needed
  - so we may produce statistically robust studies
  - so the sample keeps homogeneity

- Re. Staphylococcal PJI managed by DAIR
  - the success rate is ~ 55%
  - treatment with rifampin ameliorates the prognosis, including MRSA
  - MRSA infection does not necessarily carry a worse prognosis
  - treatment in the first days must focus planctonic bacteria
  - 8 weeks of treatment may be enough as long as things go well

Final thoughts

- Re. Streptococcal PJI managed by DAIR
  - the success rate is ~ 60%
  - no big differences are seen between streptococcal species
  - the mainstay of treatment are beta-lactams
  - addition of rifampin may ameliorate the prognosis

- Re. management with DAIR
  - Zimmerli's / IDSA criteria must be followed
  - the sooner the patient is operated the better, but no specific time limits have been found
  - post-operative PJI with prosthesis age <3 months are probably suitable for DAIR
  - the exchange of removable increases the odds of success

MERCI BEAUCOUP DE VOTRE ATTENTION

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