Rates and predictors of treatment failure in *Staphylococcus aureus* prosthetic joint infections according to different management strategies: a multinational cohort study. The ARTHR-IS study group.

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Supplementary material

Table S1. Checklist of items according to STROBE document.

Title and abstract (a) Indicate the study design with a commonly used term in the title or abstract (b) Provide an informative and balanced summary in the abstract of what was done and what was found	Study design specified in title and abstract Balanced summary included in the abstract
Background/rationale Explain the scientific background and rationale for the investigation being reported	The scientific background and rationale are included in the Introduction
Objectives State specific objectives, including any prespecified hypotheses	Pre-specified hypothesis and objectives are stated in the Introduction
Study design Present key elements of study design early in the paper	Study design described in the first part of Methods
Setting Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Described in Methods
Participants (a) Give the eligibility criteria and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	Described in Methods This is not a matched study
Variables Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Defined in Methods
Data sources/ measurement For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Specified in Methods.
Bias Describe any efforts to address potential sources of bias	Selection bias: inclusion of consecutive cases. Information bias: use of well defined, standard, easy-to-collect variables (piloted). Immortal time bias: use of landmark analysis
Study size Explain how the study size was arrived at	Not applicable. All cases detected in the study period were included.
Quantitative variables Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Some quantitative variables were categorized according to clinical criteria to facilitate multivariate analyses.
Statistical methods	

(a) Describe all statistical methods, including those used to control for confounding	Included in Methods
(b) Describe any methods used to examine subgroups and interactions	Included in Methods
(c) Explain how missing data were addressed	Patients with missing data were excluded
(d) If applicable, explain how loss to follow-up was addressed	Not applicable
(e) Describe any sensitivity analyses	Included in Methods
Participants	
(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Included in Results (Figure 1)
(b) Give reasons for non-participation at each stage	Specified in Figure 1
(c) Consider use of a flow diagram	Figure 1
Descriptive data	
(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, table S4
(b) Indicate number of participants with missing data for each variable of interest	Figure 1
(c) Summarize follow-up time (eg, average and total amount)	Information at 18 months was available for all patients
Outcome data	
Report numbers of outcome events or summary	Figure 1, Figure S1, Table S3
Main results	
(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Specified in Results (Table 2)
(b) Report category boundaries when continuous variables were categorized	Specified in methods
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	
Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Specified in Methods and Results
Key results	
Summarize key results with reference to study objectives	Specified in Abstract and Discussion
Limitations	
Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Included in Discussion
Interpretation	
Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Included in Discussion
Generalizability	
Discuss the generalizability (external validity) of the study results	Included in Discussion
Funding	
	Included

Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

Table S2. Definitions of the key variables used

Inclusion criteria	
Microbiologically confirmed hip or knee *S. aureus* prosthetic joint infection diagnosed within the first year after primary arthroplasty	(1) Clinical criteria: at least one sign or symptom of PJI, including joint pain and/or swelling, or a sinus tract communicating with the prosthesis, and (2) Isolation of *S. aureus* from: (a) one or more joint aspirate cultures; (b) two or more periprosthetic tissue samples; and (c) blood cultures with no other obvious source of infection.
Surgical procedures	
Debridement, antibiotics, and implant retention (DAIR)	Surgical removal of infected and necrotic tissue and exchange of removable prosthetic components, i.e. polyethylene (plastic line) or mobile components (femoral head in some hip prostheses).
Prosthesis removal	Removal of part of the prosthesis components ("partial removal") or of all components ("total removal"). After removal, the options are specified below.
Prosthesis reimplantation	Implantation of a new prosthesis after removal of the previous one. This can be performed in one or two stages. Specific definitions - Partial reimplantation: only one component is replaced. This is usually performed in acute infections when a component is loose (cup or femoral component in hips; femoral or tibial component in knees). - Total reimplantation: all components are replaced. - One-stage replacement: the component(s) are removed and reimplanted in the same surgical procedure. - Two-stage replacement: the components(s) are replaced in two procedures: in the first, the component(s) are removed, a spacer with antibiotics is placed to maintain joint space, in the second, the component(s) are reimplanted.
Arthrodesis	All articular and prosthetic material are removed, and a nail is placed in order to achieve a permanent fixed joint between the bones. It is more frequently performed in knees, usually as a two-stage procedure.
Girdlestone resection	Resection of joint and prosthesis components without replacement and fixation in the hip.
Limb amputation	Amputation of the limb proximal to the joint. Usually performed when all previous procedures have failed but a severe life-threatening infection is present.
Additional debridement	Debridement(s) performed after any type of initial procedure performed, due to persistent surgical wound discharge, bleeding, haematoma or devitalized tissues without clear evidence of persistent infection.
Additional procedures not due to persistent infection	Surgery on the prosthetic joint not performed to control infection, such as debridement to remove devitalized tissue and haematomas, dislocation, plastic or reconstructive surgery, etc.
Treatment failure	
Death	Death related to SA-PJI
Clinical failure	For the first surgical procedure, any of the following: persistence/relapse of signs and symptoms of infection; need for additional course of antibiotics after the initial scheduled treatment; long-term suppressive antibiotic therapy; and removal of the prosthesis. For all surgical procedures performed, any of the following: persistence of signs and symptoms of infection at month 18; long-term suppressive antibiotic therapy; and removal of the prosthesis.

Significant functional loss	Severe impairment of limb function that impedes walking or makes walking very difficult, including a Girdlestone resection, arthrodesis or limb amputation.

Table S3. Summary of outcomes for the different analyses.

	Rate of failure (95% CI)	Reason for failure		
		Related mortality	Clinical failure	Functional loss
First procedure	32.8 (25.2-41-3)	7.0%	21.1%	4.7%
First procedure: DAIR	31.3 (22.9-41.0)	6.0%	23.3%	2.0%
First procedure: removal	37.9 (22.6-56.0)	10.3%	13.8%	13.8%
All procedures	24.2 (17.5-32-3)	7.0%	8.5%	8.5%
First procedure: DAIR	21.2 (14.2-30.0)	6.0%	9.0%	6.0%
First procedure: removal	34.4 (19.8-52.7)	10.3%	6.9%	17.2%

Table S4. Characteristics of patients who underwent debridement, antibiotic therapy, and implant retention (DAIR) treated with and without rifampicin.

Variables	Rifampicin adjuvant treatment, n= 84 (%)	No rifampicin adjuvant treatment, n=15 (%)	*p* value
Age ≥80 years	18 (21.4)	3.0 (20.0)	1
Charlson index ≥2	29 (34.5)	7 (46.7)	0.394
Haemoglobin <10 mg/dl	28 (33.3)	8 (53.3)	0.155
C-reactive protein ≥100 mg/L	31 (39.2)	5 (35.7)	1
Body mass index >30	45 (53.6)	12 (80)	0.087
Hip fracture as the reason for arthroplasty	21 (25.0)	4 (26.7)	1
Radiological signs of infection[a]	4 (9.0)	1 (12.5)	0.763
Fever >38 ºC	18 (21.4)	4 (26.7)	0.737
Sinus tract at diagnosis	1 (1.2)	1 (6.7)	0.281
Methicillin-resistant *S. aureus*	17 (20.2)	3 (20.0)	1
Polymicrobial infection	23 (27.4)	8 (53.3)	0.068
Presence of bacteraemia	14 (16.7)	3 (20)	0.718
Polyethylene/mobile component replacement	52 (61.9)	6 (40)	0.155
Days from symptom onset to surgery <21	74 (88.1)	14 (93.3)	1
Appropriate indication for DAIR[b]	43 (51.2)	5 (33.3)	0.266
Inadequate empiric antimicrobial therapy	7 (10.8)	2 (22.2)	0.300

[a] Data available for 52 patients. Defined as presence of periprosthetic lucency or signs of prosthetic component loosening. [b] Performed <21 days from symptom onset to surgery, absence of sinus tract, and replacement of polyethylene or mobile components.

Table S5. Approval of the ethics committee of all participating centers.

Hospital	**Ethics Committee name**	**Reference Number**
Hospital Universitario Virgen Macarena. Seville, Spain.	CEI de los Hospitales Universitarios Virgen Macarena y Virgen del Rocío **(Master Ethics Committee)**	2019/030
Hospital Universitario Virgen del Rocio. Sevilla, Spain	CEI de los Hospitales Universitarios Virgen Macarena y Virgen del Rocío (Master Ethics Committee)	2019/030
Hospital Universitario Ramón y Cajal. Madrid, Spain	CEI del HU Ramón y Cajal	081/19
Hospital Universitario 12 Octubre. Madrid, Spain	CEIm Hospital 12 de Octubre	Nº CEIm: 19/118
Hospital Universitari Bellvitge. Barcelona, Spain.	CE de la Investigación Clínica del HU de Bellvitge	Acta 07/19
Hospital del Mar. Barcelona, Spain.	CEIm del Parc de Salut Mar	2019/8500
Hospital de la Santa Creu i Sant Pau /Sant Pau. Barcelona, Spain.	CEIm de la Fundació de Gestió Sanitària del Hospital de la	19/080 (OBS)

	Santa Creu i Sant Pau de Barcelona	
Humanitas Research Hospital. Milano, Italy	Comitato etico independiente IRCCS Istituto Clinico Humanitas	680/19
IRCCS Pol. S. Orsola. Bologna, Italy.	Comitato etico di Area Vasta Emilia Centro	2836/2019
Máxima Medical Center. Eindhoven, the Netherlands	Central EC of the Netherlands	N19.031
	Commissie Lokale Uitvoerbaarheid (Máxima Medisch centrum)	2019-047
Amphia Hospital,.Breda, Netherlands	Central EC of the Netherlands	N19.031
	CWC Amphia	19.157
Catharina Hospital. Eindhoven, the Netherlands	Central EC of the Netherlands	N19.031
	Catharina Ziekenhuis	nWMO-2019.124
Oxford University Hospitals NHS Foundation Trust. Oxofrd, UK.	NHS Foundation Trust	IRAS Reference: 265624
Norfolk and Norwich University Hospital. Norwich, UK	NHS Foundation Trust	IRAS Reference: 265624
North Manchester General Hospital	NHS Foundation Trust	IRAS Reference: 265624
Jena University Hospital. Jena, Germany	Universitats Klinikum Jena Ethik-Kommission	2019-1408
Centre Hospitalier Universitaire de Rennes. Rennes, France.	CNIL	2213705
Croix Rousse Hospital. Lyon. France.	CNIL	2213705
Centre Hospitalier Universitaire de Bordeaux. Bordeaux, France	CNIL	2213705

Figure S1. Cumulative proportion of SA-PJIs occurring after primary arthroplasty.