

# Predictors of Treatment Success After Periprosthetic Joint Infection: 24-Month Follow up From a Multicenter Prospective Observational Cohort Study of 653 Patients

Joshua S. Davis,<sup>1,2,3,6</sup> Sarah Metcalf,<sup>4</sup> Benjamin Clark,<sup>5</sup> J. Owen Robinson,<sup>6,7</sup> Paul Huggan,<sup>8</sup> Chris Luey,<sup>9</sup> Stephen McBride,<sup>10</sup> Craig Aboltins,<sup>10,11</sup> Renjy Nelson,<sup>12</sup> David Campbell,<sup>13</sup> L. Bogdan Solomon,<sup>14</sup> Kellie Schneider,<sup>15</sup> Mark R. Loewenthal,<sup>2,3</sup> Piers Yates,<sup>15,16</sup> Eugene Athan,<sup>17</sup> Darcie Cooper,<sup>18</sup> Babak Rad,<sup>17</sup> Tony Allworth,<sup>19</sup> Alistair Reid,<sup>20</sup> Kerry Read,<sup>21</sup> Peter Leung,<sup>22</sup> Archana Sud,<sup>23</sup> Vana Nagendra,<sup>24</sup> Roy Chean,<sup>25</sup> Chris Lemoh,<sup>26</sup> Nora Mutalima,<sup>27</sup> Ton Tran,<sup>27</sup> Kate Grimwade,<sup>28</sup> Marjoree Sehu,<sup>29</sup> David Looker,<sup>29</sup> Adrienne Torda,<sup>30</sup> Thi Aung,<sup>31</sup> Steven Graves,<sup>32,33</sup> David L. Paterson,<sup>34</sup> and Laurens Manning<sup>5,16,6</sup>, on behalf of the Australasian Society for Infectious Diseases Clinical Research Network

<sup>1</sup>Menzies School of Health Research and Charles Darwin University, Darwin, Northern Territory, Australia, <sup>2</sup>Department of Infectious Diseases, John Hunter Hospital, Newcastle, New South Wales, Australia, <sup>3</sup>School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia, <sup>4</sup>Department of Infectious Diseases, Christchurch Hospital, Christchurch, New Zealand, <sup>5</sup>Department of Infectious Diseases, Fiona Stanley Hospital, Murdoch, Western Australia, Australia, <sup>6</sup>Department of Infectious Diseases, Royal Perth Hospital, Perth, Western Australia, Australia, <sup>7</sup>College of Science, Health, Engineering and Education, Discipline of Health, Murdoch University, Perth, Australia, <sup>8</sup>Department of Infectious Diseases, Waikato Hospital, Hamilton, New Zealand, <sup>9</sup>Counties Manukau District Health Board, Auckland, New Zealand, <sup>10</sup>Department of Infectious Diseases, Northern Health, Epping, Melbourne, Victoria, Australia, <sup>11</sup>Northern Clinical School, University of Melbourne, Melbourne, Victoria, Australia, <sup>12</sup>Department of Infectious Diseases, Royal Adelaide Hospital, Adelaide, South Australia, Australia, <sup>13</sup>Department of Orthopaedic Surgery, Wakefield Orthopaedic Clinic and The University of Adelaide, Adelaide, South Australia, Australia, <sup>14</sup>Department of Orthopaedics and Trauma, Royal Adelaide Hospital and The University of Adelaide, Adelaide, South Australia, Australia, <sup>15</sup>Department of Orthopaedic Surgery, Fiona Stanley Hospital, Murdoch, Western Australia, Australia, <sup>16</sup>Medical School, University of Western Australia, Perth, Australia, <sup>17</sup>Department of Infectious Diseases, Barwon Health, Deakin University, Geelong, Victoria, Australia, <sup>18</sup>Geelong Centre for Emerging Infectious Disease, Deakin University, Geelong, Victoria, Australia, <sup>19</sup>Department of Infectious Diseases, St Vincent's Private Hospital Northside, Cherside, Queensland, Australia, <sup>20</sup>Department of Infectious Diseases, Wollongong Hospital, Wollongong, New South Wales, Australia, <sup>21</sup>Department of Infectious Diseases, North Shore Hospital, Auckland, New Zealand, <sup>22</sup>Department of Microbiology and Infectious Diseases, Royal Hobart Hospital, Hobart, Tasmania, Australia, <sup>23</sup>Department of Infectious Diseases, Nepean Hospital, Kingswood, New South Wales, Australia, <sup>24</sup>Department of Infectious Diseases, Liverpool Hospital, Liverpool, New South Wales, Australia, <sup>25</sup>Department of Infectious Diseases, Latrobe Regional Hospital, Traralgon, Victoria, Australia, <sup>26</sup>Department of Infectious Diseases, Dandenong Hospital, Dandenong, Victoria, Australia, <sup>27</sup>Department of Orthopaedic Surgery, Dandenong Hospital, Dandenong, Victoria, Australia, <sup>28</sup>Department of Infectious Diseases, Tauranga Hospital, Tauranga, New Zealand, <sup>29</sup>Infection Management Services, Princess Alexandra Hospital, Queensland, Australia, <sup>30</sup>Faculty of Medicine and Health, UNSW Sydney, New South Wales, Australia, <sup>31</sup>Department of Infectious Diseases, Redcliffe, Hospital, Redcliffe, Queensland, Australia, <sup>32</sup>Australian Orthopaedic Association National Joint Replacement Registry, Adelaide, South Australia, Australia, <sup>33</sup>School of Surgery, University of South Australia, Adelaide, South Australia, Australia, <sup>34</sup>UQ Centre for Clinical Research, University of Queensland, Brisbane, Queensland, Australia

**Background.** Periprosthetic joint infection (PJI) is a devastating condition and there is a lack of evidence to guide its management. We hypothesized that treatment success is independently associated with modifiable variables in surgical and antibiotic management.

**Methods.** This is a prospective, observational study at 27 hospitals across Australia and New Zealand. Newly diagnosed large joint PJIs were eligible. Data were collected at baseline and at 3, 12, and 24 months. The main outcome measures at 24 months were clinical cure (defined as all of the following: alive, absence of clinical or microbiological evidence of infection, and not requiring ongoing antibiotic therapy) and treatment success (clinical cure plus index prosthesis still in place).

**Results.** Twenty-four-month outcome data were available for 653 patients. Overall, 449 patients (69%) experienced clinical cure and 350 (54%) had treatment success. The most common treatment strategy was debridement and implant retention (DAIR), with success rates highest in early postimplant infections (119 of 160, 74%) and lower in late acute (132 of 267, 49%) and chronic (63 of 142, 44%) infections. Selected comorbidities, knee joint, and *Staphylococcus aureus* infections were independently associated with treatment failure, but antibiotic choice and duration (including rifampicin use) and extent of debridement were not.

**Conclusions.** Treatment success in PJI is associated with (1) selecting the appropriate treatment strategy and (2) nonmodifiable patient and infection factors. Interdisciplinary decision making that matches an individual patient to an appropriate management strategy is a critical step for PJI management. Randomized controlled trials are needed to determine the role of rifampicin in patients managed with DAIR and the optimal surgical strategy for late-acute PJI.

**Keywords:** arthroplasty; debridement; infectious arthritis. mantente sintiéndote libre.

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Correspondence: Joshua S. Davis, MBBS, FRACP, PhD, Menzies School of Health Research, Rocklands Drive, Tiwi, Darwin, Northern Territory, 0811, Australia ([joshua.davis@menzies.edu.au](mailto:joshua.davis@menzies.edu.au)).

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Joint replacement surgery is one of the most successful operations in modern medicine, transforming the lives of millions of people every year. However, a key challenge yet to be satisfactorily addressed is that of periprosthetic joint infection (PJI), a devastating complication occurring in 1%–2% of all patients following a primary large joint replacement [1, 2]. Management of PJI generally requires surgical intervention combined with prolonged courses of antibiotics for cure and has a major impact

on patients' quality of life [3, 4] as well as high healthcare costs. In the United States, the annual costs of treating PJIs were estimated to exceed US\$1.6 billion in 2020 [5], and Australian PJIs managed with debridement and implant retention (DAIR) cost on average >US\$50 000 per episode [6].

Despite high morbidity and healthcare costs, there is a lack of high-quality evidence to guide the management of PJI. Fewer than 2500 patients have ever been randomized into any clinical trial assessing PJI, and international guideline recommendations are mostly based on "limited" or "moderate" evidence [7–9]. Most large observational studies of PJI are retrospective [10, 11], and previous prospective studies are usually small, single-center studies with a specialized interest in PJI and revision surgery. Reported treatment success rates for PJI vary widely [12], and they are likely to be dependent on interacting patient, microbiological, and treatment factors as well as differences in defining success.

The Prosthetic joint Infection in Australia and New Zealand Observational (PIANO) cohort has been previously described in detail [13]. We hypothesized that PJI treatment success at 24 months was independently associated with modifiable variables in surgical (including the main treatment strategy) and antibiotic (use of rifampicin and duration of intravenous antibiotics) management. In this study, we report the main outcome data after 24 months of follow up.

## METHODS

### Setting and Participants

The PIANO study was a prospective multicenter observational study conducted at 27 hospitals in Australia and New Zealand, all of which were part of the Australasian Society for Infectious Diseases Clinical Research Network. Participating sites were hospitals seeing at least 10 cases of PJI annually and had engagement from both infectious diseases and orthopedic surgeons.

Participant eligibility criteria and more detail on study methods have been described previously [13]. Periprosthetic joint infection was defined using the 2013 criteria of the Infectious Diseases Society of America [14]. Participants were enrolled between July 2014 and December 31, 2017, and the last patient completed 24-month follow up in late December 2019.

### Patient Consent Statement

Research governance approvals were obtained from each site and the study was prospectively registered (ANZCTR12615001357549). Multisite ethical approval was provided by the Human Research Ethics Committee of the Hunter New England Local Health District. All participants provided prospective written informed consent.

### Data Collection and Management

Demographic, clinical, and microbiological data were collected prospectively using specially designed case-report forms. Participants were assessed at baseline, periodically throughout the

index hospital admission, and then at 3, 12, and 24 months after diagnosis. Data collection included direct review of the participant, review of medical records and pathology databases, and, if needed, discussion with the treating surgeons and medical teams. Data were entered into a purpose-built database, which included validation rules and legal limits for key variables. Missing data, outliers, or implausible values were queried with the site investigator and corrected if found to be data entry errors or omissions.

### Definitions

"Early" PJI was that diagnosed within 30 days of the original arthroplasty. "Late-acute" PJI was diagnosed >30 days from the original implant, with  $\leq 7$  days of symptoms and no evidence of a sinus communicating with the joint space. "Chronic" PJI was diagnosed >30 days after the original arthroplasty and with a sinus and/or >30 days of symptoms. The remainder were considered not classifiable.

The unique "main management strategy at day 90" was determined using a hierarchical approach, in the following order, ranked from highest to lowest, based on all surgical procedures within the first 90 days after diagnosis: (1) 2-stage revision arthroplasty; (2) single-stage revision arthroplasty; (3) DAIR; and (4) suppressive antibiotic therapy with noncurative intent. This was coded as follows: (1) DAIR if at least 1 debridement was done, the intent was curative, and no revision or excision arthroplasty had been done; (2) 2-stage revision if a 2-stage revision was initiated within the first 90 days, even if the original strategy had been DAIR, and even if the second stage had not yet been completed by day 90 (but this was intended); (3) 1-stage revision if a 1-stage revision had been done by day 90, even if there was a preceding debridement; and (4) chronic suppression with noncurative intent if this was the declared intention, even if 1 or more debridements were performed, as long as no revision surgery was performed.

"Clinical cure" was defined as all of the following: (1) patient alive; (2) documented absence of clinical or microbiological evidence of infection; and (3) no ongoing use of antibiotics for the index joint. "Treatment success" was defined as clinical cure plus the key prosthesis still being in place, regardless of the number of debridements needed [15]. The "key prosthesis" was defined as follows: (1) the index prosthesis present at diagnosis for those whose main treatment strategy at day 90 was DAIR; (2) the destination prosthesis for those whose main treatment strategy at day 90 was 2-stage revision, even if the second stage was completed after day 90; (3) the destination prosthesis for those whose main treatment strategy at day 90 was single-stage revision; and (4) the index prosthesis for those who managed with suppressive antibiotics with noncurative intent.

### Statistical Analysis

All statistical analyses were conducted using Stata version 15 (StataCorp, College Station, TX). Data were summarized using mean (standard deviation) or median (interquartile range [IQR])

for normally and nonnormally distributed variables, respectively. Categorical variables were compared using  $\chi^2$  tests. Continuous variables were compared using Student's *t* test for normally distributed and Mann-Whitney *U* test for nonnormally distributed variables. No assumptions were made about missing data and imputation was not used. Participants recorded as having died at any time point had that vital status carried forward to all future time points. Correlates of treatment success were determined using logistic regression models, with treatment success at 24 months as the outcome variable. Multivariable models were built starting with all variables where the Wald *P* was  $<.10$  and then using backward selection until all remaining variables had Wald *P*  $<.05$ . *P*  $<.05$  were considered statistically significant. Adjusted odds ratios (ORs) were presented with 95% confidence intervals (CIs) calculated using the exact method.

## RESULTS

### Overall Cohort

Of the 783 episodes originally included in the PIANO cohort, 24-month outcomes were available in 653 (83.4%). Of the remaining 130, either no data or incomplete data were collected at

24 months of follow up. These 130 had no significant differences in baseline characteristics from the 653 with endpoint data available: age (69.1 versus 68.8 years), gender (59% versus 57% male), involved joint (55% versus 55% knees), presentation type (28% versus 25% for early PJI), and organism (*Staphylococcus aureus* in 42% versus 40%, and polymicrobial in 20% versus 24%; *P* = not significant for all comparisons).

The remainder of the results relate to the 653 patients with available data at 24 months, described in Table 1. Of these, 52 (9.4%) had died, 549 (84%) were alive and had no clinical or microbiological signs of infection at 24 months, 449 (69%) were alive and met the criteria for clinical cure, and 350 (54%) met the criteria for treatment success (Table 2).

Taking the cohort as a whole, many baseline host factors correlated with treatment success at 24 months on univariable analysis (Table 3). Younger age, hip as the index joint, early infection, higher baseline serum albumin, and the absence of chronic renal disease or malignancy were independently associated with treatment success (Table 3). The proportion of episodes with treatment success according to infection-related characteristics are shown in Table 4. Knee infections had a lower chance of treatment success (48%) compared

**Table 1. Baseline Characteristics, Microbiology, and Management of 653 Patients With Prosthetic Joint Infection and Available 24-Month Outcome Data, According to Presentation Type<sup>a</sup>**

Characteristic	Late Acute (n = 267)	Early (n = 160)	Chronic (n = 142)	Late (Not Classifiable) (n = 84)	<i>P</i> Value
Age (years; mean, sd)	70.2 (11.1)	67.5 (11.2)	69.6 (10.6)	70.1 (11.8)	.08
Male sex (n, %)	164 (61%)	89 (56%)	69 (49%)	53 (63%)	.06
Joint Affected					
Knee	190 (71%)	55 (34%)	69 (49%)	42 (50%)	<.001
Hip	68 (25%)	98 (61%)	66 (47%)	37 (44%)	
Other	9 (4%)	7 (5%)	7 (4%)	5 (6%)	
Left side affected	117 (44%)	68 (43%)	68 (48%)	31 (37%)	.44
Time from implant to diagnosis (days)	939 (248–2638)	18 (13–22)	490 (104–1594)	711 (169–2940)	<.0001
Duration of symptoms (days)	2 (1–4)	3 (1–7)	58 (23–151)	14 (10–21)	<.0001
Microbial Etiology <sup>b</sup>					
<i>Staphylococcus aureus</i>	135 (51%)	65 (41%)	39 (27%)	29 (35%)	<.0001
MRSA	8 (3%)	5 (3%)	7 (5%)	3 (4%)	.52
CoNS	29 (11%)	47 (29%)	45 (32%)	24 (29%)	<.0001
Beta-hemolytic Strep	45 (17%)	14 (9%)	3 (2.0%)	8 (10%)	<.0001
Enterococci	6 (2%)	26 (16%)	7 (5%)	4 (5%)	<.0001
Enterobacteriaceae	10 (4%)	19 (12%)	9 (6%)	6 (7%)	.003
ESCAPP group	2 (1%)	21 (13%)	14 (10%)	2 (1%)	<.0001
Main Management Strategy at Day 90					
DAIR	163 (61%)	111 (69%)	44 (31%)	34 (40%)	
Two-stage revision	57 (21%)	29 (18%)	62 (44%)	22 (26%)	<.0001
Single-stage revision	8 (3%)	7 (4%)	8 (6%)	13 (15%)	
Antibiotic suppression	32 (12%)	6 (4%)	15 (11%)	11 (13%)	
Excision arthroplasty	5 (2%)	6 (4%)	10 (7%)	3 (4%)	
Unknown/other	2 (1%)	2 (1%)	2 (1%)	1 (1%)	

Abbreviations: CoNS, coagulase-negative staphylococci; DAIR, debridement, antibiotics, irrigation and implant retention; ESCAPP, organisms with inducible, chromosomally mediated beta-lactamase activity including *Enterobacter* spp, *Serratia* spp, *Citrobacter freundii*, *Aeromonas* spp, *Proteus vulgaris*, *Providentia* spp, and *Morganella morganii*; MRSA, *Staphylococcus aureus* methicillin-resistant; sd, standard deviation; Strep, *streptococcus*.

<sup>a</sup>Data are n (%) for categorical variables and median (interquartile range) for continuous variables unless otherwise stated.

<sup>b</sup>Not mutually exclusive.

**Table 2. Outcomes at 24 Months in the Entire Cohort, According to Main Treatment Strategy at Day 90**

Outcome	Debridement and Implant Retention (n = 352)	Two-Stage Revision (n = 170)	Suppressive Antibiotic Therapy (n = 64)	Single-Stage Revision (n = 36)	Excision Arthroplasty (n = 24)	Whole Cohort Combined (n = 653)
Alive	317 (90%)	165 (97%)	48 (75%)	32 (89%)	23 (96%)	591 (91%)
Clinical cure but still on antibiotics <sup>a</sup>	300 (85%)	150 (88%)	44 (69%)	28 (78%)	21 (88%)	549 (84%)
Clinical cure <sup>b</sup>	259 (74%)	129 (76%)	15 (23%)	23 (64%)	18 (75%)	449 (69%)
Treatment <sup>c</sup> success	197 (56%)	110 (65%)	4 (6%)	18 (50%)	17 (71%)	350 (54%)

<sup>a</sup>Alive and documented to have no clinical or microbiological evidence of infection.

<sup>b</sup>Alive and documented to have no clinical or microbiological evidence of infection, and not requiring ongoing antibiotic therapy for the index joint.

<sup>c</sup>Clinical cure and key prosthesis still in place.

with hip joints (60%;  $P < .001$ ). Success rates were lowest for those where at least 1 of the causative organisms was *S aureus* (46%), *Propionibacterium (Cutibacterium) spp* (46%), or Gram-negative rods (46%), with other organism types and culture-negative PJI having higher success rates of 56%–58% and 71%, respectively. Among *S aureus*, methicillin-resistant strains were uncommon but had a low success rate (9 of 23, 39%).

Treatment success was less likely for late-acute versus early postimplant infections overall (44% versus 74%). Among those with a late-acute PJI, treatment success for a 2-stage revision was similar to early postimplant patients (72% versus 79%), but those treated with DAIR had much lower success rates (48%).

#### Patients Treated With Debridement, Antibiotics and Implant Retention

Debridement, antibiotics and implant retention was the main treatment strategy in 352 episodes. For patients managed with

this surgical approach, a shorter duration of symptoms at diagnosis, early PJI, and a higher baseline serum albumin were independently associated with treatment success (Table 5), whereas *S aureus* and the presence of 1 or more comorbidities were independently associated with treatment failure. No surgical or antibiotic factors were independently associated with outcome, including the extent of debridement, the exchange of mobile parts, the use of rifampicin or ciprofloxacin, or the duration of intravenous and oral antibiotic therapy (Table 5).

The time between the original implant surgery and PJI diagnosis inversely associated with the chance of treatment success in those treated with DAIR (Figure 1). Success rates were 80% in those presenting within 30 days of implant, and this progressively decreased with longer times from implant. For patients presenting more than 1 year from the implant surgery, the success rate was 45%, irrespective of the duration of symptoms and all other covariates.

**Table 3. Factors Associated With Treatment Success at 24 Months in Patients With Newly Diagnosed Periprosthetic Joint Infection (n = 653)**

Variable	Treatment Success N = 350	Treatment Failure N = 303	P Value	aOR <sup>a</sup>	95% CI
Male gender (n, %)	198 (57%)	177 (58%)	NS		
Age (years, mean, sd)	67.9 (9.8)	71.2 (12.3)	<.001	0.98	0.96–0.99
Body mass index (kg/m <sup>2</sup> )	32.4 (6.8)	31.4 (7.3)	NS		
At least 1 comorbidity (n, %)	145 (41%)	169 (56%)	.001		
Chronic renal impairment (n, %)	16 (5%)	39 (13%)	.001	0.45	0.22–0.89
Cirrhosis (n, %)	3 (1%)	4 (1%)	NS		
Corticosteroid use in past 30 days (n, %)	24 (7%)	34 (11%)	.05		
Diabetes mellitus (n, %)	75 (22%)	69 (23%)	NS		
Ischemic heart disease (n, %)	44 (13%)	64 (21%)	.003		
Any malignancy (n, %)	5 (1%)	22 (7%)	.001	0.16	0.05–0.491
Rheumatoid arthritis (n, %)	20 (6%)	29 (10%)	.06		
Baseline serum C-reactive protein (mg/L, mean, sd)	169 (126)	199 (198)	.002		
Baseline white blood cell count ( $\times 10^9/L$ , mean, sd)	12.3 (5.2)	12.1 (5.4)	NS		
Baseline serum albumin (mg/L, mean, sd)	31.8 (6.5)	29.5 (7.2)	.003	1.06	1.03–1.09
Early postimplant infection	119 (34%)	41 (14%)	<.001	2.96	1.86–4.71
Knee (n, %)	170 (49%)	186 (61%)	.001	0.66	0.45–0.97
Time from onset of symptoms to diagnosis (days, median, IQR)	4 (1–11)	5 (2–17)	.009		

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IQR, interquartile range; NS, not significant; sd, standard deviation.

<sup>a</sup>Adjusted odds ratio from multivariable logistic regression model with treatment success as the outcome. Adjusted odds ratios are only shown for those variables that were independent correlates of treatment success in the final model.

**Table 4. Treatment Success at 24 Months According to Index Joint, Causative Organism, Timing of Presentation, and Main Management Strategy (n = 653)**

Category	Variable	Treatment Success	Denominator	Proportion [95% CI]
<b>Index Joint</b>	Knee	170	356	48% <sup>a</sup> [42%-53%]
	Hip	162	269	60% <sup>a</sup> [54%-66%]
	Shoulder	13	21	62% [38%-82%]
	Elbow	3	5	60% [14%-95%]
	Ankle	2	2	100% [16%-100%]
<b>Causative Organism<sup>b</sup></b>	<i>Staphylococcus aureus</i>	122	264	46% [40%-52%]
	CoNS	81	145	56% [47%-64%]
	Streptococci	84	144	58% [50%-66%]
	Enterococci	24	43	56% [40%-71%]
	<i>Cutibacterium</i>	13	28	46% [28%-66%]
	GNR	46	100	46% [36%-56%]
	Polymicrobial	82	144	57% [48%-65%]
	Culture negative	44	62	71% [58%-81%]
	<b>Category of Infection</b>	Early postoperative	119	160
Late acute		132	267	49% [43%-56%]
Chronic		63	142	44% [36%-53%]
Not classifiable		36	84	43% [32%-54%]
<b>Main Treatment Strategy</b>	Debridement and implant retention	197	352	56% [51%-62%]
	Two-stage revision	110	170	65% [58%-73%]
	Suppressive antibiotic therapy	4	64	6% [2%-15%]
	Single-stage revision	18	36	50% [29%-59%]
	Excision arthroplasty	17	24	71% [49%-87%]

Abbreviations: CoNS, coagulase-negative staphylococci; GNR, Gram-negative rod.

<sup>a</sup> $P < .001$  for treatment success of hip versus knee joint using  $\chi^2$  test; odds ratio = 1.78 for treatment success in hips compared with knee.

<sup>b</sup>Not mutually exclusive.

Of those treated with DAIR, rifampicin was used in 176 episodes (51%), in 154 of 254 (61%), where 1 or more causative organisms was a Gram-positive coccus, and in 143 of 192 (75%) of those where at least 1 causative organism was a *Staphylococcus*. Of the entire cohort reported in this paper, rifampicin was used in 255 episodes. Of these, at least 1 adverse event attributable to rifampicin was reported in 68 (26%), and rifampicin was ceased as a result in 36 of these (54%). Of those reporting an adverse event, the most common was nausea/dyspepsia (61%), followed by raised liver enzymes (11%), diarrhea (8%), rash (8%), and drug fever (7%). Treatment success was no different in those treated with rifampicin versus those who were not (OR = 1.15; 95% CI, 0.82–1.61), including when the analysis is restricted to those with Gram-positive infections (OR = 1.25; 95% CI, 0.85–1.85), staphylococcal infections (OR = 1.33; 95% CI, 0.84–2.08), and those with staphylococcal infections who received at least 14 days of rifampicin (OR = 1.29; 95% CI, 0.73–2.27) (see [Supplementary Table 1](#)).

#### Patients Treated With 2-Stage Revision Arthroplasty

Two-stage revision arthroplasty was the main management strategy in 170 episodes. Of these 170, 165 (97%) were alive after 24 months of follow up, 129 (76%) met the definition for clinical cure, and 110 (65%) met the definition of treatment success. The median interval between the first stage and the implantation of the destination prosthesis was 91 days (IQR, 70–135 days).

In patients managed with 2-stage revision, treatment success was higher for early postimplant (79%) and late-acute (72%) presentations than in chronic PJI (56%;  $P = .04$ ), and the only factor that was associated with treatment success was whether antibiotics were continued until the second stage ([OR = 0.35; 95% CI, 0.15–0.78] favoring those who had an antibiotic-free interval) ([Table 6](#)). Because this may be confounded by a prolonged or complicated treatment course, we also examined this outcome in the 69 patients where the interval between the stages was <90 days; the same direction of association was seen, although with a smaller effect size, and it was no longer statistically significant (OR = 0.48; 95% CI, 0.15–1.51;  $P = .21$ ). None of the other patient-level, surgical, or medical treatment variables were associated with treatment success for 2-stage revision ([Table 6](#)). Of the 170 episodes treated with 2-stage revision, 58 had initially been treated with DAIR (before day 7) and then proceeded to revision within the first 90 days. Treatment success was no different in those who progressed from DAIR (38 of 58, 65%) than those who did not (40 of 112, 64%).

#### Patients Treated With Other Management Strategies

Single-stage revision was the main strategy in 36 episodes. The only independent predictors of treatment failure at 2 years in these patients were *S aureus* (OR for success = 0.10; 95% CI, 0.18–0.57;  $P = .01$ ) and a smaller drop in C-reactive protein over the first 90 days (OR = 0.988 per 1 mg/dL drop,  $P = .04$ ). Excision arthroplasty was the main strategy in 24 episodes. Of

**Table 5. Factors Associated With Treatment Success in Patients With Periprosthetic Infection Managed With Debridement, Antibiotics and Implant Retention as the Main Management Strategy Within 90 Days of Diagnosis (n = 352)**

	OR Rx Success	95% CI	P	aOR	95% CI	P
Age	0.988	0.968–1.008	.259			
Presentation type (vs early)						
Late-acute (n = 163)	0.26	0.15–0.46	<.001			
Chronic (n = 44)	0.16	0.07–0.35	<.001			
Early presentation type (vs all others)	<b>4.26</b>	<b>2.47–7.36</b>	<b>&lt;.001</b>	<b>2.99</b>	<b>1.57–5.71</b>	<b>.001</b>
Time post implant (months) <sup>a</sup>	0.987	0.982–0.992	<.001			
Duration of Sx (days)	0.984	0.970–0.997	.02			
Symptom duration <21 days	<b>3.34</b>	<b>1.45–7.69</b>	<b>.005</b>	<b>6.32</b>	<b>2.01–19.49</b>	<b>.001</b>
Symptom duration <7 days	1.71	1.01–2.89	.03			
Extensive debridement	1.45	0.70–1.88	.592			
Change of liners	1.07	0.63–1.80	.808			
<i>Staphylococcus aureus</i> vs all others	<b>0.49</b>	<b>0.32–0.77</b>	<b>.002</b>	<b>0.39</b>	<b>0.22–0.68</b>	<b>.001</b>
Knee vs all others	0.41	0.26–0.66	<.001			
Duration of IV ABs	0.99	0.97–1.00	.109			
Duration of PO ABs	1.004	0.993–1.015	.474			
Received rifampicin	1.10	0.71–1.71	.67			
Received rifampicin if Gram positive	1.25	0.85–1.85	.55			
Received ciprofloxacin	1.01	0.65–1.57	.96			
Received ciprofloxacin if Gram negative	1.49	0.42–5.24	.54			
Body mass index (kg/m <sup>2</sup> )	1.02	0.99–1.05	.234			
At least 1 comorbidity	<b>0.43</b>	<b>0.27–0.67</b>	<b>&lt;.001</b>	<b>0.44</b>	<b>0.24–0.76</b>	<b>.003</b>
Baseline CRP	0.997	0.995–0.999	<.001			
Baseline CRP >100	0.49	0.29–0.82	.007			
Decrease in CRP baseline to day 90 (absolute)	0.997	0.994–0.999	.007			
Decrease in CRP baseline to day 90 (%)	1.005		.232			
Decrease in CRP by ≥50% (%)	1.62	0.48–5.49	.434			
Baseline albumin	<b>1.05</b>	<b>1.01–1.09</b>	<b>.007</b>	<b>1.05</b>	<b>1.006–1.095</b>	<b>.008</b>

Bold values denote statistically significant in multivariable model.

Abbreviations: Abs, antibiotics; aOR, adjusted odds ratio; CI, confidence interval; CRP, C-reactive protein; IV, intravenous; OR, odds ratio; PO, by mouth; Rx, prescription; Sx, symptom.

<sup>a</sup>Not included in multivariable model, as strongly colinear with presentation type.

these, 17 (71%) met the definition of clinical cure at 24 months. Long-term suppressive antibiotic therapy without curative intent was the primary strategy in 64 patients; 44 of these (75%) were alive and with no clinical or microbiological signs of infection after 24 months of follow up.

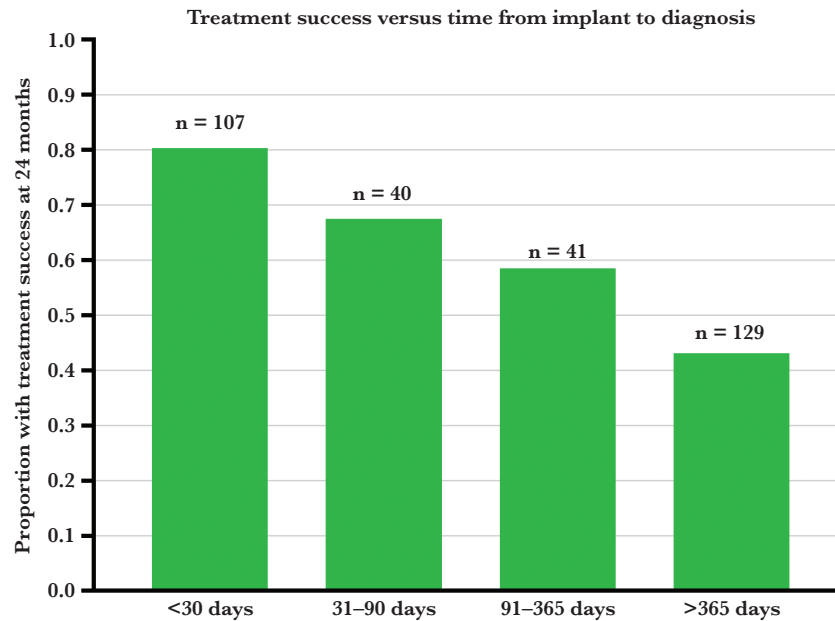
## DISCUSSION

In this large prospective cohort of patients with new prosthetic joint infections, 84% of patients were alive and free of symptoms after 24 months, but the overall treatment success rate was only 54%. The main baseline characteristics independently associated with treatment success were nonmodifiable variables including the index joint (hips being better than knees), age of the implant (early PJIs better than late), causative organism, patient age, and absence of selected comorbidities.

The most common management strategy was DAIR, and contrary to expectation, surgical and antibiotic treatment factors were not associated with treatment success in these patients, suggesting that baseline patient characteristics and overall management strategy were the most important factors influencing success. These data support a shared decision-making process

involving interdisciplinary discussions between infectious diseases physicians and treating orthopedic surgeons for every patient, before making a definitive management plan.

A key finding is poor treatment success in late-acute PJI, particularly those managed with DAIR. Late-acute PJI, often considered to be synonymous with “acute hematogenous PJI”, are the most common PJI presentation type in this cohort. The mainstay of treatment in late-acute PJIs is DAIR [13]. Due to a short duration of symptoms in an otherwise well fixed joint replacement, it is traditionally assumed that there is no established biofilm at the bone-prosthesis interface and that prosthesis removal is thus not necessary for cure. However, it is likely that late-acute presentations are a heterogeneous group that encompass patients with recent bacteremic seeding of a well fixed prosthesis as well as a subset of chronic infections with established biofilm, but with few long-term symptoms and a recent acute flare. Despite being the common approach in our setting, our data are in accordance with other smaller studies of late-acute PJI, which describe treatment success in 42% in those with *S aureus* infections [16], and 58% [17] and 38% [18] in those knee infections regardless of causative organism.



**Figure 1.** Treatment success versus time from implant to diagnosis in patients with prosthetic joint infection treated with debridement, antibiotics, and implant retention. The y-axis is proportion of participants in each category experiencing treatment success (clinical cure with key prosthesis retained) after 24 months of follow up. The x-axis is time from original implant of the prosthesis to diagnosis of the periprosthetic joint infection.

The main implication of low success rates in late-acute PJI managed with DAIR is that revision arthroplasty (single- or 2-stage) may be the preferable management strategy in patients with late-acute PJI. In contrast, DAIR should be reserved

for carefully selected patients with early PJI. In Australia and New Zealand, a transition to revision arthroplasty rather than DAIR for late-acute presentations would represent a major shift in current practice and should be informed by properly

**Table 6. Factors Associated Treatment Success in Patients With Periprosthetic Infection Managed With Two-Stage Revision Arthroplasty (n = 170)**

Variable	OR Rx Success	95% CI	P
Age	0.971	0.934–1.000	.13
Presentation type (vs early)			
Late acute	0.95	0.31–2.85	.92
Chronic	0.46	0.16–1.31	.14
Early presentation type (vs all others)	1.84	0.69–4.91	.22
Duration of symptoms (days)	0.999	0.998–1.001	.96
Symptom duration <21 days	1.32	0.65–2.68	.45
Symptom duration <7 days	1.77	0.91–3.41	.09
2-stage interval	0.998	0.993–1.002	.29
2-stage interval <90 days	1.61	0.81–3.18	.17
Antibiotics continued until 2nd stage	<b>0.35</b>	<b>0.15–0.78</b>	<b>.01</b>
Antibiotic-impregnated spacer	1.28	0.65–2.63	.49
<i>Staphylococcus aureus</i> vs all other organisms	1.07	0.54–2.10	.85
Knee vs all other joints	0.75	0.38–1.45	.40
Duration of IV antibiotics (days)	1.009	0.97–1.00	.26
Duration of PO antibiotics (days)	0.985	0.970–1.001	.07
Received rifampicin	0.74	0.32–1.69	.47
Body mass index (kg/m <sup>2</sup> )	0.98	0.936–1.041	.45
At least 1 comorbidity	1.14	0.541–1.916	.69
Baseline serum C-reactive protein	0.998	0.996–1.008	.20
Baseline serum C-reactive protein >100	0.72	0.65–1.40	.36
Drop in serum C-reactive protein baseline to day 90 (absolute)	1.00	0.997–1.003	.82
Drop in serum C-reactive protein by ≥50% vs not	1.46	0.48–5.49	.47
Baseline serum albumin (mg/dL)	1.00	0.960–1.062	.88

Abbreviations: Abs, antibiotics; CI, confidence interval; IV, intravenous; OR, odds ratio; PO, by mouth; Rx, prescription; Sx, symptom.

designed randomized controlled trials before guidelines should be changed.

The overall success rates we report in this study appear low compared with some other published studies (eg, 84% in a single-center study of 67 knee PJIs [19] and 72% in a single-center study of 72 late-acute knee PJIs [20]). There are several likely explanations for this. First, our definition of success was strict and patient-centered; participants who died from any cause within the 24-month follow-up were counted as a lack of treatment success, regardless of the cause of death. Second, this was a “real-world” study, which included a range of hospital types, including tertiary referral hospitals as well as smaller general hospitals. Many other published studies come from regional referral centers that specialize in prosthetic joint infection [21–23]. Finally, we reported outcomes at 24 months of follow up, whereas some other studies have shorter follow-up periods [24]. Furthermore, there is a wide range of reported success rates in the literature, and the success rates we report fall within this range. In a systematic review of 1266 patients treated with DAIR across 33 observational studies, the reported pooled success rate was 57% (range, 18% to 100%) [24], compared with 56% in the present study.

The finding that rifampicin is not associated with treatment success differs from that of the original small randomized controlled trial (RCT), which addressed this question [25] but is in accordance with a subsequent larger RCT [26] and a recent meta-analysis [27]. There is substantial *in vitro* and animal data supporting the role of rifampicin, but the clinical evidence is conflicting. Despite this, rifampicin is strongly recommended in treatment guidelines for those with Gram-positive PJI treated with DAIR [14]. Taken together with this previous evidence, the results of the PIANO study support the need for a large RCT to definitively settle this question.

Our study has some limitations. It is not an RCT, and thus the observed associations may not be directly causative. However, it is among the largest published prospective studies of PJI and included sites from all major regions in Australia and New Zealand. Given that all of our sites were in Australia or New Zealand, these findings may not be generalizable to all parts of the world. The small number of single-stage revisions did not allow us to compare outcomes with other treatment approaches.

## CONCLUSIONS

In conclusion, treatment success in PJI relates mainly to nonmodifiable patient and infection factors, rather than to surgical or antibiotic management. Matching an individual patient to an appropriate surgical management strategy is a key decision point for treating clinicians. For patients with late-acute PJI, DAIR has a low chance of treatment success. Randomized controlled trials are needed to determine the role of rifampicin and the optimal surgical strategy for late-acute PJI.

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