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Short- versus standard-course intravenous antibiotics for peri-prosthetic joint infections managed with debridement and implant retention: a randomised pilot trial using a desirability of outcome ranking (DOOR) endpoint

Laurens Manning[1,2,3,*], Sarah Metcalf[4], Michael Dymock[3], Owen Robinson[2,5,6,7], Benjamin Clark[2], Renjy Nelson[8,9], David L Paterson[10], Piers Yates[1,11], Mark Loewenthal[12,13], David Dewar[13,14], Paul Huggan[15], Joshua S Davis[12,16], in collaboration with the Australasian Society for Infectious Diseases Clinical Research Network

[1] *Medical School, University of Western Australia, Harry Perkins Research Institute, Fiona Stanley Hospital, Murdoch, Western Australia*
[2] *Department of Infectious Diseases, Fiona Stanley Hospital, Perth, Western Australia*
[3] *Wesfarmers Centre for Vaccines and Infectious Diseases, Telethon Kids Institute, Perth, Western Australia, Australia*
[4] *Department of Infectious Diseases, Christchurch Hospital, New Zealand*
[5] *Department of Infectious Diseases, Royal Perth Hospital, Perth, Western Australia, Australia*
[6] *PathWest Laboratory Medicine, Perth, Western Australia, Australia*
[7] *College of Science, Health, Engineering and Education, Murdoch University, Western Australia, Australia*
[8] *Infectious Diseases Department, Royal Adelaide Hospital, Adelaide, South Australia*
[9] *Faculty of Health and Medical Sciences, University of Adelaide, South Australia*
[10] *University of Queensland Centre for Clinical Research, Royal Brisbane and Womens Hospital Campus, Brisbane, Queensland, Australia*
[11] *Department of Orthopaedic Surgery, Fiona Stanley Hospital, Perth, Western Australia, Australia*
[12] *Department of Infectious Diseases, John Hunter Hospital, Newcastle, NSW, Australia*
[13] *School of Medicine and Public Health, University of Newcastle, NSW, Australia*
[14] *Department of Orthopaedic Surgery, John Hunter Hospital, Newcastle, NSW, Australia*
[15] *Waikato District Health Board, Hamilton, New Zealand*
[16] *Global and Tropical Health Division, Menzies School of Health Research, Charles Darwin University, Darwin, NT, Australia*

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ABSTRACT

Background: Peri-prosthetic joint infection (PJI) is a devastating complication of joint replacement surgery. Determining the optimal duration of intravenous (IV) antibiotics for PJI managed with debridement and implant retention (DAIR) is a research priority.

Methods: Patients undergoing DAIR for early and late-acute PJI of the hip or knee were randomised to receive 2 (short-course) or 6 (standard-course) weeks of IV antibiotics, with both groups completing 12 weeks of antibiotics in total. The primary endpoint of this pilot, open-label, randomised trial was a 7-point ordinal desirability of outcome ranking (DOOR) score, which accounted for mortality, clinical cure and treatment adverse events at 12 months. Duration of IV treatment was used as a tiebreaker, with shorter courses ranked higher. Outcome adjudication was performed by expert clinicians blinded to the allocated intervention (Australia and New Zealand Clinical Trials Registry ACTRN12617000127303).

Results: 60 patients were recruited; 31 and 29 were allocated to short- and standard-course treatment, respectively. All had an evaluable outcome at 12 months and were analysed by intention-to-treat. Clinical cure was demonstrated in 44 (73%) overall; 22 (71%) in the short-course group and 22 (76%) in the standard-care group (P=0.77). Using the DOOR approach, the probability that short- was better than standard-course treatment was 59.7% (95% confidence interval 45.1-74.3).

Conclusions: In selected patients with early and late-acute PJI managed with DAIR, shorter courses of IV antibiotics may be appropriate. Due to small sample size, these data accord with, but do not confirm, results from other international trials of early transition to oral antibiotics.

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1. Background

Peri-prosthetic joint infection (PJI) is a devastating complication of joint arthroplasty, resulting in pain, suffering, impaired mobility, prolonged hospitalisation, and broad-spectrum antibiotic therapy with accompanying societal and economic costs [1–3]. The burden of PJI is likely to rise due to increasing incidence of primary arthroplasty operations and the overall prevalence of joint replacements in the wider population [4].

Early post-operative and late-acute PJIs are commonly managed with open debridement, antibiotics, modular component exchange and irrigation of the joint [5], followed by antibiotics (debridement and implant retention; DAIR). Reported treatment success rates for this management approach vary widely [6], but are thought to be dependent on patient, microbiological and treatment factors, and the outcome measures applied. With a few notable exceptions, most studies are retrospective and there are few randomised controlled trials to guide management [7,8]. There are few data exploring choice or duration of antibiotics, given either orally or intravenously (IV), after DAIR. This uncertainty is reflected in international guidelines. The Infectious Diseases Society of America (IDSA), Musculoskeletal Infection Society (MSIS) and Australian Therapeutic Guidelines recommend 2 to 6 weeks of IV antibiotics following DAIR, without guidance or evidence about how to choose this duration [9,10].

Shorter course IV antibiotic durations are an accepted standard in Europe [11,12], whereas in Australia and New Zealand (NZ), most patients with PJI receive exactly 6 weeks of IV antibiotics [5]. In addition, a large trial in the United Kingdom (OVIVA trial) showed that early transition to oral antibiotics was non-inferior to 6 weeks of IV antibiotics in a heterogeneous group of bone and joint infections [13]. Although the OVIVA trial was designed as a pragmatic trial, generalisable to all bone and joint infections, fewer than 25% of the participants had a DAIR procedure for a PJI and the trial was not designed with PJI-specific primary outcomes. In a survey of Australasian Infectious Diseases physicians, 2 versus 6 weeks of IV antibiotics for PJI managed with DAIR was ranked as the most important infectious disease research priority [14].

Regional variation between Europe and Australasia in duration of parenteral antibiotics and uncertainty in international guidelines indicated there was clinical equipoise across different settings at the time this trial was commenced. In this open-label, randomised pilot trial we aimed to compare short (2 weeks) with standard (6 weeks) duration of parenteral antibiotics using a desirability of outcome ranking (DOOR) endpoint designed for PJI managed with DAIR [15]. The 7-point DOOR ordinal score was developed to account for survival at 12 months, clinical cure of the PJI and treatment-related adverse effects.

2. Methods

2.1. Study sites and ethical approvals

The PIANOFORTE (Prosthetic joint Infection in Australia and NZ: cOmparing diFferent antibiOtic strategies in a Randomised Trial Evaluation) is a prospective, binational, multicentre, open-label, randomised pilot trial, conducted at 6 hospitals in Australia and NZ, recruited through the Australasian Society for Infectious Diseases Clinical Research Network (ASID CRN). Ethical approvals were obtained from each site and the study was prospectively registered (ACTRN12617000127303). All participants provided written informed consent.

2.2. Participants

Adult patients (>18 years old) with an early or late-acute PJI of either hip or knee joint were eligible. Early infections were defined as occurring within 30 days of the index arthroplasty and late-acute PJI were defined as presenting >30 days after the index arthroplasty, but with 21 days or fewer of symptoms prior to diagnosis, in the absence of a sinus tract [5].

2.3. Diagnostic criteria for a peri-prosthetic infection (PJI)

A PJI diagnosis reflected international guidelines at the time the study was designed [9]. A PJI was confirmed by the presence of at least one of the following: i) increased leukocyte count or neutrophil percentage in preoperative synovial fluid aspirate (synovial fluid white blood cell count over 1700 cells/μL or neutrophil percentage greater than 65%); ii) visible pus around the prosthesis at operation without alternative explanation; iii) acute inflammation of peri-prosthetic tissue ($\geq$5 neutrophils per high power field); iv) two or more pre-operative or intraoperative cultures (blood, synovial fluid, peri-prosthetic tissue, or sonication fluid) that yielded the same organism (indistinguishable based on genus and species identification or common antibiogram) or vi) pure growth of *Staphylococcus aureus*, beta-haemolytic streptococci or aerobic Gram-negative bacilli from a single synovial fluid or intraoperative tissue/fluid specimen were eligible.

2.4. Inclusion and exclusion criteria

Inclusion criteria were: i) suitable for management by DAIR, with a stable implant, and no sinus or septic shock, ii) one or more causative organisms identified, iii) Gram-positive and Gram-negative organisms susceptible to rifampicin or ciprofloxacin, respectively, iv) an adequate debridement procedure (defined as extensive open debridement with the exchange of removable parts) performed within 21 days of the onset of symptoms and v) randomisation completed within 14 days of the first adequate DAIR procedure.

Participants were excluded if they: i) had an additional diagnosis requiring more than 2 weeks of IV antibiotics in the opinion of the site investigators (e.g. *S. aureus* endocarditis), ii) were not treated with curative intent, iii) were unlikely to survive for more than 12 months (in the opinion of the site investigator), iv) were significantly immunosuppressed, v) at least one causative organisms was *Cutibacterium* spp., vi) one or more of the causative organisms were “difficult-to-treat”, including Gram-negative anaerobes, fungi, mycobacteria, vancomycin-resistant Enterococci or carbapenem-resistant Gram-negative bacilli, vii) were not competent to provide informed consent, viii) treating clinicians were unwilling for the participant to be enrolled, ix) prior enrolment in the PIANOFORTE or x) were unwilling or unlikely to be accessible to complete trial-related scheduled visits.

2.5. Recommended antibiotic treatments

The IV antibiotic(s) chosen needed to be appropriate for the causative organisms. Regimens included i) flucloxacillin or cefazolin for Gram-positive organisms susceptible to methicillin, ii) ampicillin or penicillin for Gram-positive organisms susceptible to penicillin, iii) vancomycin, teicoplanin or daptomycin for methicillin-resistant organisms or for participants with severe beta-lactam hypersensitivity reactions, iv) ceftriaxone for susceptible Gram-negative infections or v) piperacillin-tazobactam,

* Corresponding author: A/Prof Laurens Manning, Medical School, University of Western Australia, Harry Perkins Research Institute, Fiona Stanley Hospital, PO Box 404, Bull Creek 6149, Western Australia, Australia. Tel.: +61 8 61611156.
E-mail address: laurens.manning@uwa.edu.au (L. Manning).

meropenem or ertapenem for ceftriaxone non-susceptible Gram-negative organisms. Two IV antibiotics were permitted for polymicrobial infections. For the most common parenteral antibiotics, dosing was in accordance with the Therapeutic Guidelines of Australia, which recommend total daily doses of 8 g and 6 g for flucloxacillin and cefazolin, respectively. Vancomycin dosing is based on trough concentrations of 15-20 mg/L for intermittent dosing and 20-25 mg/L for continuous infusions [16].

To complete a minimum total antibiotic duration of 12 weeks, highly bioavailable oral antibiotics were recommended. For those with one or more Gram-positive causative organisms, this was rifampicin 300-450 mg twice daily (starting within 2 weeks) plus a companion agent determined by the treating clinician(s), based on susceptibility profile and patient tolerability. Recommended companion agents were fusidic acid, ciprofloxacin, doxycycline or amoxicillin for streptococcal or enterococcal PJI. Ciprofloxacin (500-750 mg twice daily) was recommended as a single agent for aerobic Gram-negative rods. Mixed Gram-positive and -negative infections were treated with ciprofloxacin plus rifampicin.

2.6. Antibiotic-related complications

Major IV antibiotic-related complications were defined by any of the following: i) death as a result of antibiotic-induced AE, ii) new hospital admission or prolongation of existing admission as a result of antibiotic-induced AE, iii) catheter-related bloodstream infection, iv) peripherally-inserted central catheter (PICC)-related deep vein thrombosis, v) acute kidney injury defined as >1.5-fold increase in serum creatinine, or glomerular filtration rate decrease by 25%, vi) *Clostridium difficile*-associated diarrhoea (CDAD), vii) anaphylaxis or angioedema, or viii) raised liver enzymes >10 fold the upper limit of normal (ULN). Minor antibiotic-related complications were any AE attributable to IV or oral antibiotics not covered in the above list, including, but not limited to: i) rash, ii) non-CDAD antibiotic-related diarrhoea, iii) asymptomatic leukopenia or eosinophilia ($>0.5 \times 10^9$ cells/L), iv) raised liver enzymes <10 times ULN, v) nausea and/or vomiting or vi) peripheral oedema related to sodium content of antibiotic infusions.

2.7. Antibiotic duration

"Day zero" for the duration of antibiotics was considered the date of first "adequate" DAIR procedure, defined as open (rather than arthroscopic), with removal of all infected/necrotic tissue and exchange of modular components.

Patients randomised to the standard- or short-course treatment arms received at least 42 or 14 days of IV antibiotics from the date of the first adequate operative debridement, respectively. In both arms, treating clinicians had the discretion to extend the IV antibiotic duration.

Trial visits occurred at baseline, and 4 and 12 months following enrolment. Laboratory data were collected at enrolment and 2 weeks, 4-8 weeks, 12 weeks and 1 year. Oxford knee and hip scores were collected at the final visit. At any time, details relating to attributable antibiotic adverse events (AE) were captured (defined in supplementary file 1).

2.8. Outcome measures

At 12 months, participants were assigned a score from most to least desirable outcome.

1 Clinical cure with no antibiotic-related complications
2 Clinical cure with minor antibiotic-related complications
3 Clinical cure with major antibiotic-related complications
4 Lack of clinical cure, with no antibiotic-related complications
5 Lack of clinical cure, with minor antibiotic-related complications
6 Lack of clinical cure, with major antibiotic-related complications
7 Death from any cause

Clinical cure was defined as all the following: i) alive, ii) no clinical or microbiological evidence of infection, iii) original, non-modular prosthesis still present and iv) no use of ongoing antibiotic therapy for the index joint at 12 months.

Secondary outcomes were: i) clinical cure at 12 months, ii) Oxford joint scores at 12 months, iii) major adverse antibiotic events and iv) duration of IV antibiotics. Post-hoc exploratory analyses of C-reactive protein (CRP) concentrations over time were also performed.

2.9. Outcome adjudication

Outcome adjudication was performed by a committee comprising a specialist infectious diseases physician and two specialist orthopaedic surgeons blinded to the allocated treatment. After training, each adjudicator determined an ordinal score for every participant. Discordant results were resolved by consensus.

2.10. Statistical analyses

The statistical plan was confirmed prior to the end of the trial (Supplementary file).

The DOOR method proposes that participants are ranked under the following constraints:

1 When ranking the outcomes of two patients with different overall clinical outcomes, the patient with a better overall clinical outcome receives a higher rank.
2 When ranking the outcomes of two patients with the same overall clinical outcome, the patient with a shorter duration of IV antibiotic use receives a higher rank.

Once a DOOR score was assigned, the trial arms were assessed by comparing the distributions of rankings between arms. The primary analysis was by intention-to-treat (ITT), regardless of the actual duration of IV antibiotic therapy received. A per-protocol analysis was also performed. For the standard- and short-course this included those receiving 35-56 days and 10-21 days of IV antibiotics, respectively.

To formally compare the distributions of DOOR between treatment groups, we utilised the method reported by the authors of the original DOOR approach [15] to provide a probability that a randomly selected individual from the intervention group had a better DOOR than a randomly selected individual from the standard of care group. We estimated this probability with the proportion of between-treatment pairwise comparisons in which the former individual has a better DOOR than the latter. A 95% confidence interval (CI_{95}) was then computed for this estimate using a Mann-Whitney normal distribution approximation. Bivariate comparisons for categorical variables were performed using a Fisher's Exact or Chi-squared test, and for comparisons of median values, a Mann-Whitney U test was performed. Exploratory multivariable analyses were performed using logistic regression with clinical cure as the dependent variable. All analyses were performed using R [17].

2.11. Sample size justification

The PIANOFORTE was explicitly designed as a pilot trial with no formal sample size calculation. A total of 60 participants was based on the likely recruitment rates at participating sites that could inform a larger definitive trial.

Table 1
Clinical and laboratory characteristics according to treatment allocation

	Total(n=60)	Short-course(n=31)	Standard-course(n=29)
Age, years; median (IQR)	67 (61-76)	67 (60-77)	67 (61-73)
Sex, male (%)	38 (63.3)	21 (67.7)	17 (58.6)
Affected joint, knee (%)	48 (70%)	26 (84)	17 (59) [f]
Body mass index, kg/m^2; median (IQR)	32.3 (29.3-37.9)	33.4 (29.4-40.1)	31.7 (29.1-35.7)
Prosthesis age, days; median (IQR)	622.5 (35.5-2729.5)	1143 (331-3377)	102 (25-1092)
Early PJI (prosthesis age <30 days; n [%])	13 (22%)	4 (13%)	9 (31%)
Duration of symptoms before diagnosis, days; median (IQR)	3 (1.75-5)	3 (1-6)	3 (2-4)
Duration of symptoms before DAIR, days; median (IQR)	4 (2-6.25)	4 (2-8)	5 (2-6)
Surgical procedure performed prior to adequate DAIR; n (%)	9 (15%)	3 (9.7%)	6 (20.7%)
Repeat debridement procedure after adequate DAIR; n (%)	7 (11.7%)	3 (9.7%)	4 (13.8%)
Co-morbidities			
Diabetes mellitus, present; n (%)	16 (26. 7%)	11 (35.5%)	5 (17.2%)
Chronic renal impairment, present; n (%)	4 (6.7%)	1 (3.2%)	3 (10.3%)
History of cancer, present; n (%)	2 (3.3%)	1 (3.2%)	1 (3.4%)
Cirrhosis, present; n (%)	1 (1. 7%)	1 (3.2%)	0 (0%)
Rheumatoid arthritis, present; n (%)	5 (8.3%)	4 (12.9%)	1 (3.4%)
Congestive cardiac failure, present; n (%)	3 (5%)	2 (6.5%)	1 (3.4%)
Ischaemic heart disease, present; n (%)	6 (10%)	2 (6.5%)	4 (13.8%)
Cerebrovascular disease, present; n (%)	3 (5%)	0 (0%)	3 (10.3%)
Microbiology			
Methicillin-susceptible *Staphylococcus aureus*; n (%)	30 (50%)	14 (45.2%)	16 (55.2%)
Group B Streptococcus; n (%)	9 (15%)	3 (9.7%)	6 (20.7%)
Group C/G Streptococcus; n (%)	6 (10%)	4 (12.9%)	2 (6.9%)
Staphylococcus lugdunensis; n (%)	3 (5%)	0 (0%)	3 (10.3%)
Other coagulase-negative staphylococci; n (%)	7 (11. 7%)	4 (12.9%)	3 (10.3%)
Other; n (%)	10 (16.7%)	8 (25.8%)	2 (6.9%)
Polymicrobial; n (%)	4 (6.7%)	2 (6.5%)	2 (6.9%)
Baseline bloods			
CRP, mg/L; median (IQR)	260 (136-332)	295 (154-326)	230 (120-340)
Total white cell count, x 10^9 cells/L; median (IQR)	13.1 (10.3-15.9)	14.3 (11.9-16.7)	12.3 (10.2-14.9)
Creatinine, µmol/L; median (IQR)	85 (67-114)	84 (64-109)	92 (65-141)
Albumin, g/L; median (IQR)	29 (24-36)	32 (26-36)	28 (23-36)

IQR, interquartile range; PJI, peri-prosthetic joint infection; DAIR, debridement and implant retention; CRP, C-reactive protein.

2.12. Data management and randomisation

Participants were randomised in a 1:1 ratio to using permuted blocks of size 4 or 6 stratified by hip or knee PJI. The random allocation sequence was generated by an independent statistician. To maintain allocation concealment, none of the investigators had REDCap® randomisation privileges. Treatment allocation was concealed until eligibility and consent were confirmed. Study data were collected and managed using REDCap® (version 9.2.5 Vanderbilt University) [18].

3. Results

A total of 327 patients were screened and 61 (18.7%) participants were recruited between May 2017 and November 2019. One participant was randomised but subsequently found to be ineligible and was excluded (symptoms >21 days and immunosuppressed). There were 25 potentially eligible participants who were not recruited, including 20 (80%) who declined to participate (Fig. 1). Of 31 randomised to the short-course treatment arm, 28 (90.1%) received between 10 and 21 days of IV antibiotics. In the standard-course arm, 28 (96.6%) received between 35 and 56 days of treatment (Fig. 2); the median (interquartile range [IQR]) duration of IV antibiotic treatment was 15 (14-17.5) days in the short-course group and 42 (42-44) days in the standard-course group. The baseline clinical characteristics, co-morbidities and baseline laboratory values of the participants enrolled, according to treatment allocation, are shown in Table 1. Thirteen (21.7%) PJIs were classed as early (diagnosed within 30 days of the arthroplasty operation) with 9 and 4 in the standard-course and short-course groups, respectively (P=0.12). The median (IQR) time between arthroplasty and PJI diagnosis was 622.5 (35.5-2729.5) days. The median (IQR) duration of symptoms prior to diagnosis was 3 (1.75-5) days and prior to the DAIR procedure was 4 (2-6) days, respectively. Nine patients (3 and 6 in the short- and standard-course groups, respectively) underwent a debridement procedure prior to the first adequate debridement. Seven (3 and 4 in the short- and standard-course groups, respectively) had a further debridement after the first adequate debridement. Methicillin-susceptible *S. aureus* (MSSA) was identified in 30 (50%) participants. Methicillin-resistant *S. aureus* (MRSA) was not identified. Except for the prosthesis age at PJI diagnosis (median 102 [25-1092] versus 1143 (331-3377] days; P=0.015) and proportion of knee (compared with hip) joints affected (84% versus 59%, P=0.045), the two groups were well-matched, with no significant differences in any of the socio-demographic or clinical variables (Table 1). The initial parenteral antibiotic regimens according to treatment group are provided (Supplementary Table). Flucloxacillin (23; 38.3%), cefazolin (12; 20%) and cefazolin plus vancomycin (9; 15%) were initially prescribed for most participants. Rifampicin (median daily dose 600 mg), rifampicin plus ciprofloxacin (median daily dose 1000 mg) and rifampicin plus fusidic acid (median daily dose 1000 mg) use was documented in 52 (86.7%), 20 (33.3%) and 14 (23.3%) participants, respectively. The median (IQR) time from first adequate debridement to starting rifampicin was 8 (5.5-14) days. There were no apparent differences between parenteral antibiotic choices or the use of rifampicin according to treatment allocation.

The distribution of DOOR scores according to treatment allocation are shown (Table 2). The primary ITT analysis, applying DOOR with the duration of IV antibiotics used as a tiebreaker (shorter courses ranked higher), demonstrated that the probability

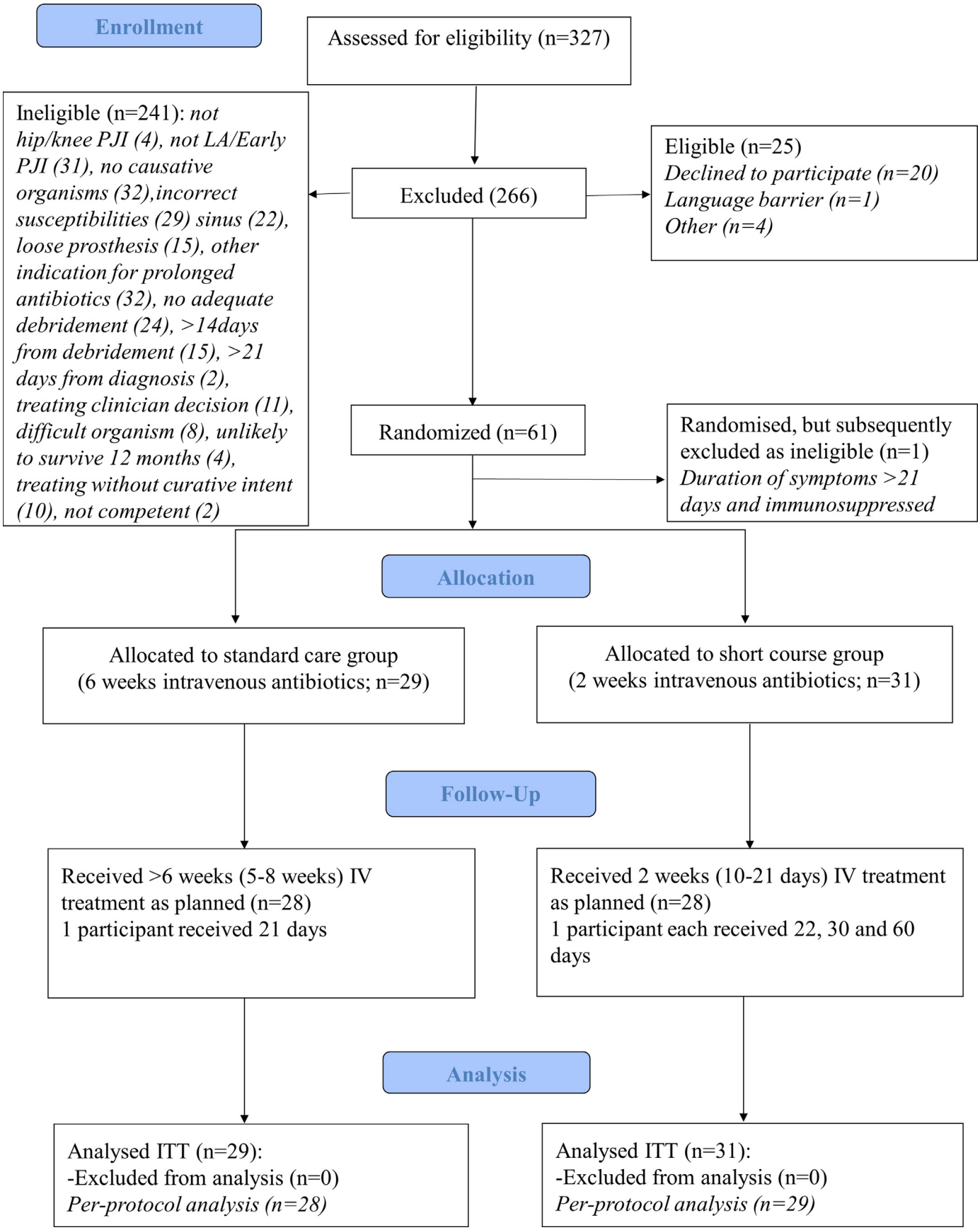

Fig. 1. Consort diagram for patients with peri-prosthetic joint infections managed with debridement and implant retention and enrolled into short- versus standard-course intravenous antibiotic trial. PJI; peri-prosthetic joint infection; LA, late-acute; ITT; intention-to-treat.

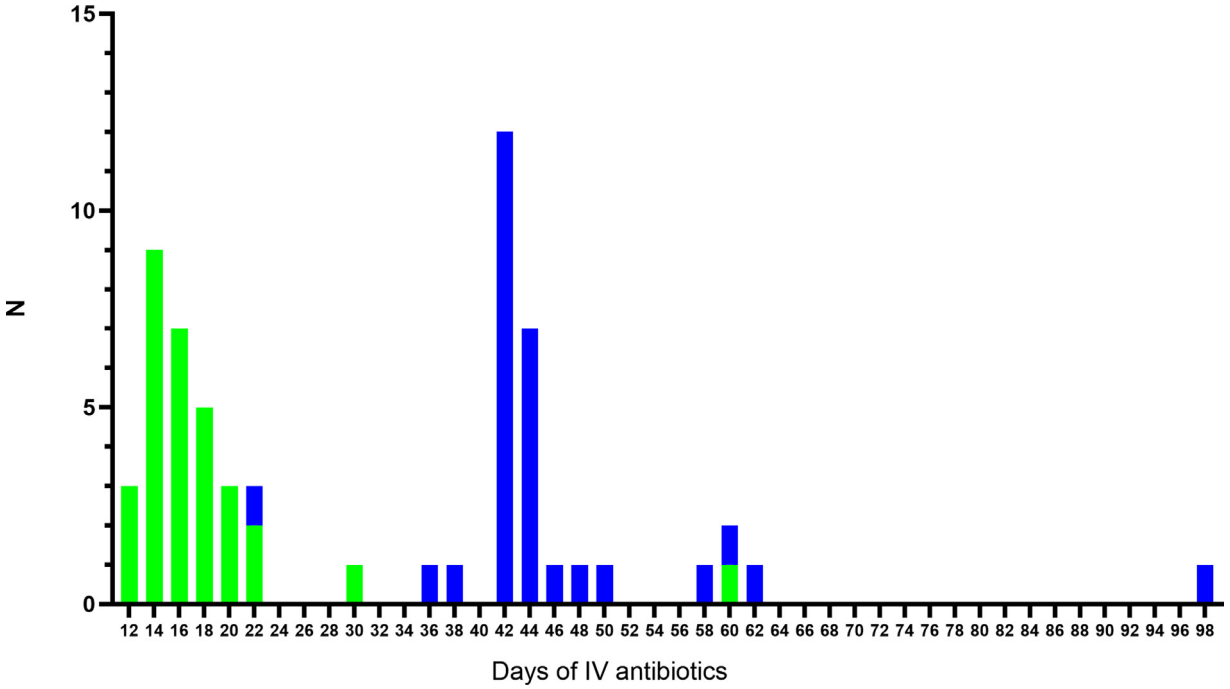

Fig. 2. Histogram of actual number of days of intravenous antibiotics received in patients allocated to short- (green) or standard- (blue) course treatment.

Table 2
Primary, secondary and exploratory outcomes according to treatment allocation

	Total (n=60)	Short-course (n=31)	Standard-course (n=29)
Prosthesis removal within 120 days	8 (13.3%)	4 (12.9%)	4 (14%)
Duration of IV (d) (median [IQR])****	26 (15-42)	15 (14-17.5)	42 (42-44)
Death at 1 year	3 (5%)	2 (6.4%)	1 (3.4%)
Prosthesis removal 120-365	5	1 (3.2%)	4 (13.8%)
Ongoing antibiotics at 365	5	2 (6.4%)	3 (10.3%)
DOOR (median [IQR])	2 (1-4)	2 (1-4)	2 (1-3.5)
DOOR Score1234567	162266613	81222502	81044111
Clinical cure (DOOR values 1-3)	44 (73%)	22 (71%)	22 (76%)
Oxford Score at 12 months	43 (33-46)	34 (30-46)	41.5 (32-45)
At least 1 major AE	9	4	5
CRP Change at 2 weeks (% of baseline)	81.5 (71.4-91.1)	85.5 (74.2-91.4)	79.3 (71.1-90.3)
CRP Change at 4 weeks (% of baseline)	89.6 (80.0-94.4)	90 (82.7-96.4)	85.0 (66.7-94.0)
CRP Change at 12 weeks (% of baseline)	97.1 (92.3-98.9)	97.9 (90.2-98.9)	95.6 (93.8-98.7)

IV, intravenous; d, days; IQR, interquartile range; DOOR, desirability of outcome ranking; AE, adverse event; CRP, C-reactive protein.
**** $P<0.0001$ compared between short-course and standard-course groups.

that a randomly selected individual from the short-course group had a higher DOOR than a randomly selected individual from the standard-course group (long-course antibiotics) was 59.7% (CI_{95} 45.1-74.3%). Analysis of participants completing the antibiotic durations per-protocol gave similar results (59.1% [CI_{95} 45.1-74.1%]).

There were no significant differences for prosthesis removal within 4 months, prosthesis removal between 4 and 12 months, death within 12 months, the need for ongoing antibiotics at 12 months or Oxford joint scores at 12 months (Table 2). The median (IQR) DOOR was not different between the short- and standard-course groups (2 [1–4] and 2 [1-3.5], respectively; P=0.81). Five patients (8.3%) were still on suppressive antibiotics at 12 months, including 2 (6.4%) and 3 (10.3%) in the short- and standard-course groups, respectively (P=0.66).

There were 11 major AEs recorded in 9 participants: 5 in the standard-course group and 4 receiving short-course therapy. A PICC-line thrombosis and CDAD occurred in 1 participant each, both in the standard-course group. There were 9 patients with acute kidney injury (5 in the standard-course and 4 in the short-course groups).

Successful clinical cure (defined above; comprising DOOR scores of 1-3) was achieved in 44 patients (73%), with no significant differences between short- and standard-courses (22 [71%] and 22 [76%]; P=0.77). Clinical and laboratory correlates of clinical success or treatment failure are shown (Table 3). A multivariate analysis did not identify any independent factors associated with clinical failure, including a model that included the proportion of knee joints and prosthesis age.

The exploratory outcome of change in CRP over time according to clinical success or failure is shown (Fig. 3). The median percentage CRP change from baseline at 4 and 12 weeks was significantly higher in those with a successful outcome (91.4% [81.9-97.6] versus 82.2 [69.9-89.8]; P=0.04 and 98.3% [94.4-99] versus 91.1% [81.9-94.8], P=0.001).

4. Discussion

In this comparative trial of short- versus standard-course IV antibiotic therapy for early and late-acute PJI managed with DAIR, the probability that a randomly selected individual from the short-

Table 3
Clinical and laboratory factors associated with clinical success (ordinal score 1-3) in peri-prosthetic joint infections managed with debridement and implant retention

	Success (n=44)	Failure (n=16)
Age, years (median, IQR)	66 (60-74)	69 (65-77)
Sex, male (n, %)	28 (63.6)	10 (62.5)
Affected joint, knee (n, %)	31 (70)	11 (81)
Side, right (n, %)*	17 (38.6)	11 (68.8)
Body mass index, kg/m^2 (median, IQR)	33.8 (30.0-38.9)	30 (27.5-33.8)
Prosthesis age, days (median, IQR)	493 (29.5-2216.5)	844 (142-2920)
Duration of symptoms before diagnosis, days (median, IQR)	3 (1-6)	2 (2-4.5)
Duration of symptoms before DAIR, days (median, IQR)	4 (3-7.3)	3.5 (2-5)
Surgical procedure performed prior to adequate DAIR; n	7	2
Repeat debridement procedure after adequate DAIR; n	5	2
Oxford scores at 12 months*	42 (33-46)	32.5 (31-40.25)
Co-morbidities		
Diabetes mellitus, present; n	13	3
Chronic renal impairment, present; n	3	1
History of cancer, present; n	2	0
Cirrhosis, present; n	1	0
Rheumatoid arthritis, present; n	2	3
Congestive cardiac failure, present; n	1	2
Ischaemic heart disease, present; n	5	1
Cerebrovascular disease, present; n	3	0
Microbiology		
Methicillin-susceptible *Staphylococcus aureus*; n	21	9
Group B Streptococcus; n	7	2
Group C/G Streptococcus; n	4	2
Staphylococcus lugdunensis; n	6	1
Other coagulase negative staphylococci; n	2	1
Other; n	6	4
Polymicrobial; n	2	2
Blood culture positive; n	8	6
Baseline bloods		
C-reactive protein, mg/L; median (IQR)	239 (126-324)	278 (220-343)
Total white cell count, x 10^9 cells/L; median (IQR)	13.3 (10.6-16.1)	12.8 (10.2-14.4)
Creatinine, µmol/L; median (IQR)	80 (67-109)	100 (70-130)
Albumin, g/L; median (IQR)	31 (25-36)	28 (23-35)
Changes in CRP		
CRP Change at 2 weeks (% of baseline)	85.0 (74.2-92.6)	77.8 (59.0-87.2)
CRP Change at 4 weeks (% of baseline)*	91.4 (81.9-97.6)	82.2 (69.9-89.8)
CRP Change at 12 weeks (% of baseline)**	98.3 (94.4-99)	91.1 (81.9-94.8)

IV, intravenous; d, days; IQR, interquartile range; DAIR, debridement and implant retention; AE, adverse event; CRP, C-reactive protein
* $P<0.05$.
** $P<0.01$.

course group had a higher DOOR than a randomly selected individual from the standard-course group was approximately 60%. These data accord with recently published trials demonstrating non-inferiority of early transition to oral antibiotics for patients with diverse bone and joint infections, which included those with PJI managed with DAIR [13]. It should be noted that the results for the OVIVA trial were published after recruitment for PIANOFORTE was completed. Taken together, shorter courses of IV antibiotic therapy may be appropriate for carefully selected patients with PJI managed with DAIR, including in Australia and NZ where 6 weeks of parenteral therapy is the standard approach [5].

To our knowledge, this is the first time a DOOR approach has been applied to PJI. Since the first publication of this approach [15], there have been no randomised trials completed using it as an endpoint for any infection, although it has been used as a post-hoc analysis of trial data [19] and in analyses of observational data [20,21]. The potential advantages of this method are that it takes into account the potential risks as well as benefits of antibiotic therapy. This enables a superiority rather than a non-inferiority comparison for trials comparing antibiotic treatment durations. One of the disadvantages of an ordinal method such as a DOOR is that it assumes equal weighting between each stratum. Further work is needed to develop an appropriately weighted DOOR endpoint for PJI research that takes into account patient-centred outcomes as well as conventional indicators of successful treatment.

A larger randomised trial to definitively address the optimal duration of IV antibiotic therapy in PJI managed with DAIR will be challenging. Clinician equipoise has likely been undermined by the publication of the OVIVA trial [13] and the gradual uptake of early oral switch of antibiotics for bone and joint infection. The current study, although underpowered, has shown a cure rate of 71% in the short-course group, and 76% in the standard-course group. Based on these data, a definitive non-inferiority trial with a 5% non-inferiority margin and 75% cure rate in the standard-course arm would need to recruit over 2500 participants to achieve 90% power.

In terms of design and implementation, the PIANOFORTE has several strengths. Although it was open-label and the participants were not blinded, the final outcome assessments that provided the ordinal score were undertaken by expert clinicians blinded to treatment allocation. The duration of IV antibiotics was randomly

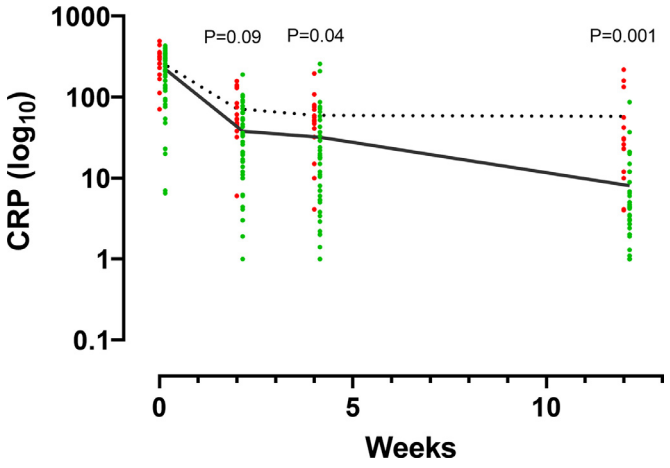

Fig. 3. C-reactive protein (CRP) measured over time according to successful (green) or unsuccessful (red) treatment for peri-prosthetic joint infection managed with debridement and implant retention.

allocated, most participants received the IV antibiotic duration allocated and an evaluable outcome was available for all participants.

Valuable lessons were learned from this trial despite the small sample size and pilot design. Firstly, there was no indication of a difference in outcomes between the standard- and short-course groups, which might provide additional reassurance for clinicians outside Europe and the United Kingdom that results from recent trials could be generalisable to their regions. Secondly, the clinical success rate was relatively high at approximately 75%, compared with a pooled estimate of 61% in a large meta-analysis of 99 studies [6]. This reinforces that appropriate patient selection is key determinant of outcome in patients with PJI treated with DAIR. Thirdly, DOOR may be an attractive alternative to traditional dichotomous outcomes applied in conventional trials. Finally, the dynamics of CRP over the first 12 weeks of treatment may be useful in predicting outcomes at 12 months.

This trial also had limitations. It was designed as a pilot trial, with no formal sample size calculation, to determine feasibility and refine the design of a potential future larger trial. For the reasons outlined above, such a trial is unlikely to be completed. Participants recruited to PIANOFORTE were highly selected and may not be generalisable to all patients with PJI managed with DAIR and clinical cure rates are likely to be lower in a less-selected cohort. Finally, we were not able to control for surgical factors such as the adequacy of debridement.

Major AEs related to PICC lines or antibiotic therapy were uncommon, occurring in 15% of participants. Most major AEs were episodes of acute kidney injury, which were evenly spread between standard-course and short-course IV treatment groups. Notably, PICC-associated blood stream infections, which are a potential downside of leaving PICC-lines in-situ for longer periods, were not observed. This was unexpected, given that rates of ~1-5% have been reported elsewhere [22, 23]. Similarly, only one participant in the standard-course group developed PICC-associated deep venous thrombosis (DVT). Considering that reported rates of PICC-associated DVT may be as high as 20% [24], this result was also unexpected. Taken together, these data indicate that an increased risk of severe PICC-associated complications should not necessarily be used to justify shorter courses of IV therapy.

In selected patients with early and late-acute PJI managed with DAIR, shorter courses of IV antibiotics may be appropriate. Due to small sample size, these data support, but do not confirm, the findings of other large scale international trials with early transition to oral antibiotics. However, these data demonstrate the feasibility of the DOOR approach in future trials in PJI, a condition where patient-centred factors such as antibiotic duration, AEs, joint scores and quality of life measurements may be as important as traditional dichotomous outcomes of treatment success or failure. Further work is required to refine a PJI-specific DOOR.

Declarations

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Competing Interests: None

Ethical Approval: Ethical approvals were obtained from each site and the study was prospectively registered (ANZCTR12615001357549). All participants provided written informed consent.

Randomised Controlled Trial: Australia and New Zealand Clinical Trials Registry ANZCTR12617000127303

Sequence Information: Not applicable

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2022.106598.

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