Antimicrobial strategies and multidisciplinary care in prosthetic joint infections

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Chapter 4

Targeted oral antimicrobial regimens for Gram-negative prosthetic joint infections: a prospective multicenter study

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Abstract

Objectives: Fluoroquinolones (FQ) are considered the most effective antimicrobial treatment for Gram-negative prosthetic joint infections (GN-PJI). Alternatives are needed due to increasing FQ resistance and side effects. We aimed to compare different targeted antimicrobial strategies for GN-PJI managed by debridement, antibiotics and implant retention (DAIR) or one-stage revision surgery (1SR) and to review the literature of oral treatment options for GN-PJI.

Methods: In this prospective, multicenter, registry-based study, all consecutive patients with a PJI caused by a GN microorganism (including mixed infections with Gram-positive microorganisms), managed with DAIR or 1SR from 2015 to 2020, were included. Minimum follow-up was one year. Patients received targeted therapy with either oral FQ, oral cotrimoxazole or with intravenous or oral β-lactams. Survival analysis was performed with use of Kaplan-Meier and Cox proportional hazards models to identify factors potentially associated with treatment failure.

Results: Seventy-four patients were included who received either FQ (n=47, 64%), cotrimoxazole (n=13, 18%) or β-lactams (n=14, 18%). Surgical strategy consisted of DAIR (n=72) or 1SR (n=2). Median follow-up was 449 days (interquartile range 89–738 days). Failure free survival did not differ between the FQ (72%) and cotrimoxazole (92%) groups (log rank, p=0.13). This outcome did not change when excluding all pseudomonal PJI in the FQ group.

Conclusions: Cotrimoxazole is a potential effective targeted antimicrobial therapy for patients with GN-PJI. A randomized controlled trial is needed to confirm the findings of this study.

Introduction

Gram-negative (GN) bacteria are the causative pathogen in 11-22% of prosthetic joint infections (PJI) (1, 2). Treatment with fluoroquinolones (FQ) is recommended as the first-line (oral) antimicrobial therapy for patients with GN-PJI (3-6). This recommendation is based on the high biological availability and good diffusion of FQ into bone and synovial fluid and the presumed anti-biofilm activity of FQ extrapolated from results of several in vitro models (7-11). However, clinical studies on the effectiveness of FQ for PJI are scarce, of low quality, and heterogeneous with respect to outcome (12-19). Furthermore, the global emergence of FQ resistant GN-PJI and the high discontinuation rate of FQ in patients with PJI due to side-effects necessitate other effective (oral) antimicrobial treatment strategies (16, 20, 21).

Cotrimoxazole could be an effective alternative to FQ because of good bone diffusion and high biological availability, yet clinical data on the use of cotrimoxazole for GN-PJI is nearly absent (11, 14, 18, 19, 22). Therapy with β-lactam antibiotics for GN-PJI was as effective as oral FQ in one small study (14).

In 2015, five hospitals in the Netherlands specialized in PJI care coordinated their protocols for the treatment of PJI and set up a prospective register to evaluate their management of PJI. The protocol regarded both FQ and cotrimoxazole as equally suitable first-line therapy for the oral treatment phase for GN-PJI taken into account both effectivity and antimicrobial stewardship: cotrimoxazole has a higher threshold for development of resistance than FQ. In the protocol, β-lactams were considered a second-line option. In this prospective study we aimed to compare the effectiveness of these antimicrobial strategies for patients with GN-PJI treated with debridement, antibiotics and implant retention (DAIR) or one-stage revision surgery (1SR).

Patients and methods

Ethics

The study was approved by the institutional review board of Leiden University Medical Center with a waiver of written informed consent and conducted according to Dutch law and regulations regarding medical research. All patients were informed by their treating physician about the registry and were included unless they chose to opt out.

Study Design

This is a multicenter, prospective, registry-based observational study. The quality registry entailed five regional hospitals in the south-west of the Netherlands that harmonized treatment for patients with PJI, as described in a previous publication (23). The treatment protocol was drafted by all participating physicians before start of data collection. In every participating center, a multidisciplinary team (MDT), consisting of orthopedic surgeons, infectious diseases physicians and/or clinical microbiologists, discussed treatment decisions and protocol deviations on a weekly basis. Data were stored in a secured online database.

Data Collection and Treatment Protocol

All adult patients diagnosed with a GN-PJI between January 1, 2015 and November 3, 2020 were eligible for inclusion. Patients treated with DAIR or 1SR were included to focus on the effectiveness of antimicrobial therapy in patients with a newly placed or retained implant while patients treated with two-stage revision or resection arthroplasty were excluded. Patients with polymicrobial PJI were not excluded. The diagnostic and surgical procedures were standardized in all centers. Perioperative cultures were obtained prior to the start of empiric antimicrobial therapy which consisted of flucloxacillin in acute PJI or vancomycin in chronic PJI. In case of DAIR, empiric GN coverage with an aminoglycoside (or ceftazidime in case of a contra-indication for aminoglycosides) was added for a maximum of 48 hours awaiting Gram-stain and definitive cultures. Targeted therapy against GN bacteria consisted of one to two weeks of intravenous (IV) β-lactam antibiotics followed by four to 11 weeks of monotherapy with oral ciprofloxacin or levofloxacin 500 mg twice-daily or oral cotrimoxazole 960 mg (trimethoprim 160 mg / sulfamethoxazole 800 mg)twice-daily. In case of resistance or side effects, patients were treated with β-lactams for the entire treatment duration. The decision to treat with either FQ or cotrimoxazole was always made by the MDT; the considerations for this choice were not collected in the database.

Definitions

PJI was defined as recommended by the 2013 Infectious Diseases Society of America (IDSA) guideline on PJI (3). The main outcome was treatment failure which was defined as: I. Surgical debridement after antimicrobial treatment had ended, II. Removal of the prosthesis III. Start of suppressive antimicrobial therapy, IV. Death attributable to PJI.

PJIs were classified as either: early postoperative (less than one month after initial surgery), chronic (symptoms more than three weeks and diagnosis more than one month after surgery) and acute hematogenous (symptoms less than three weeks in a previously asymptomatic patient).

Patients were stratified in to one of three targeted treatment strategies: FQ, cotrimoxazole or β-lactam. Patients in the FQ and cotrimoxazole group were treated for at least 50% of the treatment duration with oral FQ or oral cotrimoxazole, respectively. Patients in the β-lactam group received a β-lactam for the entire treatment duration (IV only or IV followed by oral therapy).

Statistical Analysis

Baseline clinical characteristics were summarized using descriptive statistics. To compare differences between antimicrobial strategies chi-square test or Fishers exact test (in case *one or more expected values are less than 5*) was used for categorical variables and one-way analysis of variance or Kruskal Wallis tests for continuous variables. To compare failure free survival between groups (counting from the day of DAIR or 1SR), Kaplan-Meier estimates were performed. Patients were censored at the time of death if the cause was not attributable to PJI. A Cox proportional hazards regression model was used to determine the association of baseline characteristics and antimicrobial strategy with treatment failure. Survival SPSS Statistics for Windows was used (IBM SPSS Statistics for Windows, Version 29.0.0, Armonk, NY).

Results

Seventy-four patients were included in the study (Figure 1).

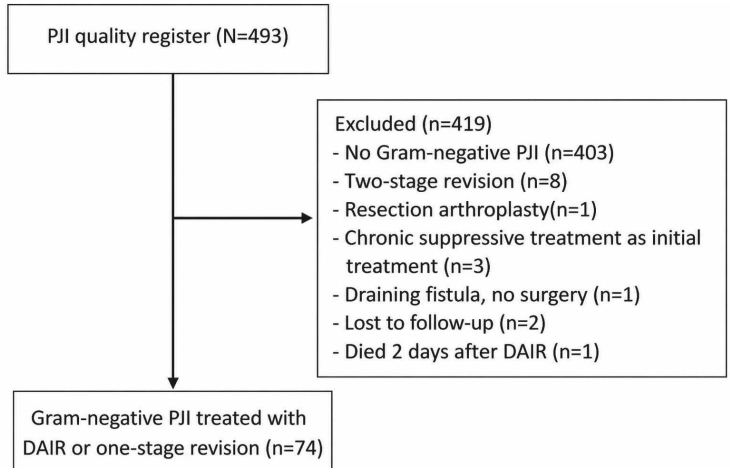

Figure 1. *Inclusion flowchart.*
PJI: prosthetic joint infection; DAIR: debridement, antibiotics and implant retention

Clinical characteristics of all patients and stratified per antimicrobial strategy are summarized in table 1. The majority of patients had a hip PJI and 57% of the infections was polymicrobial. Three patients (4%) had FQ-resistant GN microorganisms and were treated with cotrimoxazole (n=1) or β-lactams (n=2). Patients in the β-lactam group had more chronic infections, tumor endoprostheses, polymicrobial infections, pseudomonal infections and coinfections with enterococcal species compared to the other two groups.

Table 1. Baseline characteristics of cohort of Gram negative prosthetic joint infections, stratified per antimicrobial strategy

	All n=74	Fluoroquinolones n=47	Cotrimoxazole n=13	β-lactams n=14
General characteristics				
Male sex (%)	31 (42)	22 (47)	4 (31)	5 (36)
Age, years (mean, SD)	70 (12)	69 (13)	74 (9)	71 (11)
Joint				
Hip	55 (74)	37 (79)	8 (61)	10 (71)
Knee	17 (23)	10 (21)	4 (31)	3 (21)
Upper limb	2 (3)	0	1 (8)	1 (7)
Revised implant[a]	17 (23)	11 (23)	2 (15)	4 (29)
Tumor endoprosthesis	8 (11)	4 (9)	1 (8)	3 (21)
Previous PJI[b]	5 (7)	2 (4)	1 (8)	2 (14)
Comorbidities				
Diabetes Mellitus, n (%)	18 (24)	13 (28)	2 (15)	3 (21)
Chronic kidney disease (eGFR <60mL/min)	11 (15)	4 (9)	4 (31)	3 (21)
Rheumatoid arthritis	3 (4)	0	2 (15)	1 (7)
Immunosuppressants	7 (10)	4 (9)	2 (15)	1 (7)
Malignancy	10 (14)	4 (9)	2 (15)	4 (29)
Reported smoking (n=42)	15 (36)	11 (23)	2 (15)	2 (14)
Body mass index (median, IQR)	30 (26–34)	30 (28–35)	26 (25–30)	30 (24–34)
Clinical presentation				
Fistula	2 (3)	1 (2)	0	1 (7)
C-reactive protein (median, range)	54 (17–210)	68 (21–241)	42 (13–226)	42 (15–173)
Bacteremia	6 (8)	4 (9)	1 (8)	1 (7)
Timing infection				
Early postoperative (<3 weeks)	42 (57)	28 (60)	7 (54)	7 (50)
Acute hematogenous	26 (35)	17 (36)	5 (38)	4 (29)
Chronic PJI (>3 weeks symptoms)	6 (8)	2 (4)	1 (8)	3 (21)
Days from first symptoms to surgery (median, IQR)	5 (3–9)	4 (2–8)	6 (4–24)	8 (3–15)

Table 1. Baseline characteristics of cohort of Gram negative prosthetic joint infections, stratified per antimicrobial strategy *(Continued)*

	All n=74	Fluoroquinolones n=47	Cotrimoxazole n=13	β-lactams n=14
Microbiology, n (%)				
Escherichia coli	18 (24)	9 (19)	3 (23)	6 (43)
Enterobacter species	18 (24)	14 (30)	4 (31)	0
Pseudomonas aeruginosa	14 (19)	10 (21)	0	4 (29)
Proteus species	16 (22)	10 (21)	0	6 (43)
Klebsiella species	14 (19)	6 (13)	4 (31)	4 (29)
Other Gram-negative[a] Fluoroquinolone resistance	11 (15) 3 (4)	7 (15) -	4 (31) 1 (8)	- 2 (14)
Polymicrobial PJI	42 (57)	26 (55)	6 (46)	10 (71)
+ staphylococci	25 (34)	15 (32)	4 (31)	6 (43)
+ enterococci	17 (23)	6 (13)	3 (23)	8 (57)
+ streptococci	10 (14)	7 (15)	2 (15)	0

Abbreviations: SD, standard deviation; PJI, prosthetic joint infection; eGFR, estimated glomerular filtration; IQR, interquartile range;

[a]Minimum of 1 revision surgery of the same implant as the current PJI. [b]Minimum of 1 previous infection of the same implant as the current PJI.

Data on treatment, follow-up and outcome are shown in Table 2. Median follow-up time was 449 days (interquartile range (IQR) 89–738 days). The raw success rates were 69% (51/74) for the entire cohort, 72% (34/47) in the FQ group, 92% (12/13) in the cotrimoxazole group and 36% (3/14) in the β-lactam group. The median duration of antimicrobial treatment was 64 days (IQR 42–87 days) in the FQ group, 57 days (IQR 41–101 days) in the cotrimoxazole group and 42 days (IQR 19–65 days) in the β-lactam group, including patients who failed during therapy. Patients in the β-lactam group underwent a re-DAIR more often and received empirical GN antimicrobial therapy less often than patient in the FQ and cotrimoxazole group. In the β-lactam group, five patients were switched to oral therapy and nine received IV antibiotics for the entire treatment duration. None of the patients were treated with combination therapy for GN pathogens during the targeted antimicrobial phase.

Table 2. Treatment characteristics and outcome stratified per antimicrobial strategy

	All n=74	Fluoroquinolones n=47	Cotrimoxazole n=13	β-lactams n=14	P value
Days of follow-up (median, IQR)	449 (89–738)	446 (90–738)	473 (368–736)	98 (20–797)	
Surgical treatment strategy (n, %)					
DAIR	73 (97)	47 (100)	11 (85)	14 (100)	
RE-DAIR needed	38 (51)	24 (51)	4 (31)	10 (71)	0.08[a]
One-stage revision procedure	2 (3)	0	2 (15)	0	
Empirical antimicrobial Gram-negative coverage	48 (65)	33 (70)	11 (85)	4 (29)	<0.01[a]
Days of antimicrobial treatment[c] (median, IQR)	56 (42–88)	64 (42–87)	57 (43–101)	42 (19–65)	0.08[b]
Intravenous	15 (10–24)	14 (9–24)	15 (9–20)	17 (14–44)	
Oral	44 (34–71)	47 (34–70)	47 (42–86)	35 (19–66)	
Failure	23 (31)	13 (28)	1 (8)	11 (64)	<0.01[a]
Days to failure (median, range)	42 (8–535)	69 (8–275)	365	33 (14–535)	

Abbreviations: DAIR, Debridement, Antibiotics, Implant Retention; IQR, interquartile range;
[a]Calculated with Fisher exact test. [b]Calculated with Kruskal Wallis test. [c]including failed patients.

Figure 2 shows the survival curves for both the cotrimoxazole and the FQ group which did not differ statistically significant (log rank, p=0.13). This outcome did not change when excluding all pseudomonal PJI from the analysis (log rank, p=0.14). The β-lactam group was not included in this analysis because it differed too much in baseline characteristics with the FQ and cotrimoxazole groups.

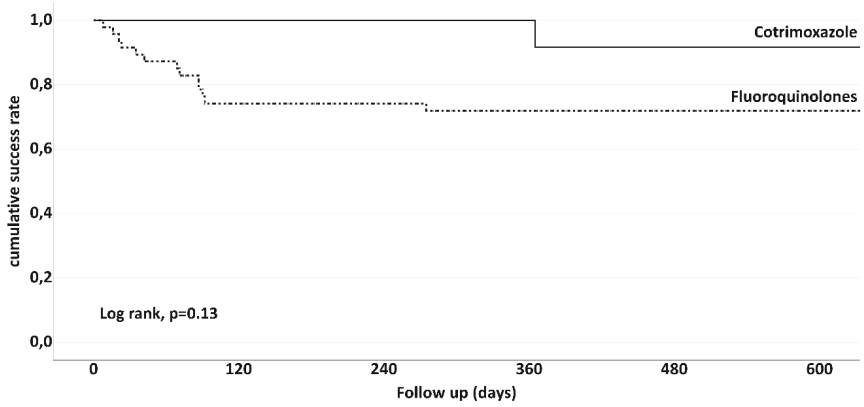

Figure 2. *Survival analysis for Gram-negative prosthetic joint infections treated with DAIR or one-stage revision, related to antimicrobial treatment strategy.*

The presence of a tumor endoprosthesis, not receiving empirical GN antimicrobial coverage, and coinfection with enterococci were associated with failure in univariable analysis (Table 3). Multivariable analysis was not performed due to the small number of patients in the cotrimoxazole and β-lactams groups.

Table 3. Univariable analysis of clinical characteristics possibly associated with failure

	Failure n (%)	Univariable analysis HR (95% CI)	P value
Patient factors			
Age >70	10 (26)	0.67 (0.29–1.54)	0.35
Smoker	7 (47)	0.82 (0.52–1.28)	0.38
On Immunosuppressants	1 (14)	0.40 (0.05–2.98)	0.37
Diabetes mellitus	4 (22)	0.56 (0.19–1.65)	0.29
Implant type			
Knee (vs hip and upper limb)	7 (41)	1.53 (0.63–3.71)	0.35
Previous PJI[a]	2 (40)	1.69 (0.40–7.23)	0.48
Revised implant[b]	7 (41)	1.74 (0.71–4.23)	0.22
Tumour endoprosthesis	5 (63)	3.10 (1.14–8.47)	0.03

Table 3. Univariable analysis of clinical characteristics possibly associated with failure *(Continued)*

	Failure n (%)	Univariable analysis HR (95% CI)	P value
Microbiology			
Pseudomonas aeruginosa	7 (50)	2.35 (0.97–5.73)	0.06
Enterococcus species coinfection	9 (53)	2.51 (1.08–5.82)	0.03
Polymicrobial infection	16 (38)	1.87 (0.77–4.54)	0.17
Treatment			
>7days between first symptoms to _surgery	6 (24)	0.68 (0.27–1.71)	0.41
No empirical treatment covering _Gram-negative microorganisms	12 (46)	2.60 (1.12–6.01)	0.03

The abbreviations used in the table are as follows: HR - hazard ratio; CI - confidence interval; PJ – prosthetic joint infection.

[a]Minimum of 1 previous infection of the same implant as the current PJI. [b]Minimum of 1 revision surgery of the same implant as the current PJI

Discussion

In this prospective multicenter study, patients with GN-PJI who received targeted oral antimicrobial monotherapy with cotrimoxazole after DAIR or 1SR had similar outcomes as patients who received FQ, although numbers were small. The overall success rate of 69% is in line with other observational studies on GN-PJI who reported success rates between 64% and 86% (15, 17, 19, 22). To the best of our knowledge, this is the first study that compared specific oral antimicrobial strategies for GN-PJI.

Fluoroquinolones

The cure rate of 72% with targeted monotherapy with FQ in our cohort is comparable to other reported success rates of FQ for GN-PJI (14, 15, 19). FQ are the most studied oral antibiotics in bone and joint infections (BJI) and most clinical studies date from the 1980s and 90s and were focused on osteomyelitis (24-26). High biological availability and good bone penetration made FQ an attractive oral alternative to IV therapy (27). Two randomized trials on the oral treatment of GN osteomyelitis compared oral ciprofloxacin with IV antimicrobial therapy. In the first trial by Greenberg *et al.* (n=30) treatment was successful in 10/14 patients (71%) on ciprofloxacin and in 15/16 patients (94%) on IV antibiotics (not specified) (28). In the second trial by Gentry *et al.* (n=59) oral ciprofloxacin (success rate 77%) was as effective as IV β-lactams with or without aminoglycosides (success rate 79%) (29). Three observational studies, of patients with GN osteomyelitis treated with oral FQ, reported outcomes that were similar to these two trials (24-26). To best of our knowledge, randomized controlled

trial data comparing different oral antimicrobial strategies for the treatment of GN osteomyelitis are absent.

Data from in vitro experiments and foreign body animal models on the effect of different antibiotics on GN microorganisms favor FQ over cotrimoxazole in *Escherichia coli and Stenotrophomonas maltophilia* biofilms and FQ over β-lactams in *Pseudomonas aeruginosa* biofilms (7-10). The IDSA 2013 guideline recommendation of oral ciprofloxacin for GN-PJI was based on expert opinion and two small observational studies reporting success rates of 80% (in five patients with GN-PJI treated with cefepime-FQ combination) and 80% (in 47 patients with GN-PJI treated with DAIR and ciprofloxacin) (4, 18, 30). Since 2013, seven additional cohort studies were published that analyzed the antimicrobial treatment of GN-PJI (Table 4). Rodriguez-Pardo *et al.* (n=174) concluded that the use of FQ was protective against failure in GN-PJI treated with DAIR (hazard ratio (HR) 0.22, 95% confidence interval (CI) 0.13–0.37) (19). Tornero *et al.* (n=62) reported that antimicrobial regimens not containing FQ were strongly associated with failure (odds ratio 6.5, 95%CI 1.8–23.8) (31). Both studies compared any FQ use (monotherapy with FQ and combination therapy containing FQ) with all other antimicrobial regimens that did not contain FQ. It is likely that confounding by indication and immortal time bias influenced outcomes in these studies (32). Further, the findings of these two studies were not confirmed by Fantoni *et al.* (n=82), Wouthuyzen-Bakker *et al.* (GN-PJI, n=48), and Papadoupolos *et al.* (n=131) who did not report an association between the use of FQ and improved outcome in GN-PJI (13, 16, 17). To date, only Grossi *et al.* (n=76) compared two different antimicrobial regimens for GN-PJI: oral FQ preceded by IV β-lactams was as effective as an entire course of IV β-lactams without FQ (HR 0.73 95%CI 0.19–2.77) (14). However, in this study, the majority of patients in both the oral FQ group (51/58, 88%) and the IV β-lactam group (11/18, 61%) received combination therapy, often with cotrimoxazole, making the effectiveness of monotherapy with FQ and β-lactams difficult to assess.

Table 4. Observational studies reporting on the effects of oral antimicrobial treatment on the outcome of Gram-negative prosthetic joint infections

Reference	Number of GN cases	Population	Surgical management	Variable	Outcome
Martinez-Pastor *et al.* 2010	7	ESBL+ GN PJI	DAIR		*Success rate*
				monotherapy: cotrimoxazole (n=4)	75%
Aboltins *et al.* 2011	17	PJI	DAIR followed by chronic suppression		*Success rate*
				monotherapy: ciprofloxacin (n=12)	92%
				amoxicillin/clavulanic acid (n=3)	67%
				ciprofloxacin + amoxicillin/clavulanic acid (n=2)	100%
Jaen *et al.* 2012	47	PJI	DAIR		*Success rate*
				any use fluoroquinolone[a] (n=35) vs no fluoroquinolone (n=12)	69% vs 58%, p=0.25[c]
				monotherapy: fluoroquinolone (n=28)	82%
Rodriguez-Pardo *et al.*[e] 2014	173	PJI	DAIR		*Association with failure*
				any use of ciprofloxacin (n=124)	HR 0.22 (0.13–0.37) p<0.00[b]
					Success rate
				any use ciprofloxacin[a]	79%
				any use of cotrimoxazole[a] (n=10)	50%
Tornero *et al.* 2014	62	PJI	DAIR		*Association with failure*
				no fluoroquinolone (n=14)	OR 6.5 (1.8-23.8), p=0.01[f]
Grossi *et al.*[d] 2016	76	PJI	DAIR, 1SR, 2SR		*Association with failure*
				no fluoroquinolone (n=18)	HR 0.75 (0.21 – 2.63) p=0.65[b]
					Success rate
				monotherapy: fluoroquinolone (n=7)	71%
				any use of fluoroquinolone[a] (n=58)	78%
				any use of cotrimoxazole[a] (n=19)	84%

Table 4. Observational studies reporting on the effects of oral antimicrobial treatment on the outcome of Gram-negative prosthetic joint infections *(Continued)*

Reference	Number of GN cases	Population	Surgical management	Variable	Outcome
Tornero *et al.* 2016	21	PJI	DAIR		*Success rate*
				any use of fluoroquinolone[a] (n=19) vs monotherapy: cotrimoxazole (n=2)	94% vs 0%, p=0.01[c]
Wouthuyzen-Bakker *et al.* 2019	48	Late acute PJI	DAIR		*Success rate*
				fluoroquinolone (n=35) vs no fluoroquinolone (n=13)	66% vs 62%, p=0.79[c]
Papadoupolos *et al.* 2019	131	MDR and XDR	DAIR, 1SR, 2SR, RA		*Success rate*
		PJI			No effect on outcome (data not provided in publication)
Fantoni *et al.* 2019	82	PJI	DAIR, 1SR, 2SR, RA	fluoroquinolone (n=not provided)	*Association with failure*
					HR 0.73 (0.19–2.77) p=0.64[b]
Hanssen *et al.* 2024	74	PJI	DAIR, 1SR	monotherapy: fluoroquinolone (n=47) vs cotrimoxazole (n=13)	72% vs 92%
					p=0.13

Abbreviations: PJI, prosthetic joint infection; DAIR, Debridement, Antibiotics, Implant Retention; 1S,: one-stage revision; 2SR, two stage revision; RA, resection arthroplasty; HR, hazard ratio; MDR, multidrug resistant; XDR, extensively drug resistant; OR, odds ratio; SMX-TMP, sulfamethoxazole/trimethoprim; ESBL, extend spectrum beta-lactamase. [a]All antimicrobial regimens containing this drug, including combination therapy [b]Cox regression; [c]Chi square test; [d]Most antibiotic treatment regimens in this study consisted of combination therapy; [e]24 patients from this study were also included in the study of *Jaen et al.* from 2012; [f]Logistic regression; [g]Fisher Exact test

Taking all these data into consideration, it is not certain if FQ are the most effective antimicrobials for GN-PJI. In addition to this equipoise, several reasons necessitate the search for effective alternative strategies, most importantly the rising incidence of FQ resistant GN infections, also in PJI (16, 33). Second, the European Medicine Agency initiated a program in 2019 to limit the use of FQ due to serious side effects which may arise like irreversible neuropathy, tendon rupture and the formation and rupture of aortic aneurysms. Lastly, drug adherence to FQ in combination with other drugs can be problematic: unplanned drug discontinuation occurred in 36% of patients on rifamycin with FQ compared to 3% of patients on rifamycin without FQ in patients with staphylococcal PJI (20). FQ monotherapy is reported to be well tolerated with a <4% discontinuation rate(34).

Cotrimoxazole

Twelve of 13 patients (92%) in our study were successfully treated with oral cotrimoxazole after two weeks of IV β-lactams. This high success rate compared to FQ could not be explained by the absence of *Pseudomonas aeruginosa* infections. Good bone penetration and high biological availability make cotrimoxazole a drug of interest for treating BJI (11). However, clinical data that inform on cotrimoxazole for BJI are limited and derived mainly from observational studies on staphylococcal infections, of which two included PJI (35-39). Stein *et al.* successfully treated 11 of 20 patient (55%) with multi drug resistant staphylococcal PJI managed with implant retention or revision surgery between 1989 and 1997 (39). Deconinck *et al.* reported a success rate of 71% in 28 patients with PJI treated with cotrimoxazole. All patients in this study were treated with a combination of two or more antibiotics and 47% of the infections were caused by a GN microorganism but outcome of GN-PJI was not provided (36).

The outcome of GN-PJI treated with cotrimoxazole is mentioned in four other small case series with a combined success rate of 69% in 35 patients, but most of these patients received double or even triple therapy, often with FQ or β-lactams (14, 19, 22, 40). Possible explanations for the lesser use of cotrimoxazole are feared toxicity and the reported inferiority of cotrimoxazole compared to FQ in in vitro biofilm and foreign body animal models (8, 10). With respect to side effects, cotrimoxazole had to be discontinued due to side effects in only 6–18% of patients in BJI cohorts (36-37). Still, possible bone marrow and renal toxicity, skin disorder and drug-drug interactions, should be taken into account when prescribing this drug, especially in the elderly PJI population.

β-lactam antibiotics

Patients in our study who were treated with β-lactams had a high failure rate of 64% and median time to failure was 50% shorter compared to patients who were treated with FQ. This poor outcome might be explained by the overrepresentation of risk factors for failure in the β-lactam group: chronic PJI, no empirical antimicrobial coverage for the causative GN microorganism, pseudomonal infections, enterococcal co-infections, polymicrobial PJI and more re-DAIRS. However, this could not be statistically analyzed due to the small sample size of this group. Unfavorable clinical findings could have led to a continuation of the IV therapy with β-lactams instead of switching to an oral regimen with cotrimoxazole or FQ resulting in selection bias of more high-risk patients in the β-lactam group. Low biological availability of β-lactams might also explain the poor outcome in patients who were switched to an oral β-lactam. In the aforementioned study of Grossi *et al.*, IV β-lactams were equally effective as FQ for GN-PJI, yet the majority of patients were treated with combination therapy and only seven patients received monotherapy IV β-lactams (14). Therefore, given the paucity and bias of the available data, it is not possible yet to provide evidence based recommendations for or against β-lactam monotherapy for GN-PJI.

Strengths and limitations

Strengths of this study are its prospective design and the clearly defined monotherapy strategies. This approach is less prone to bias than studies in which one antimicrobial strategy (e.g. all regimens containing FQ, including combination therapies) is compared with all other treatments combined (e.g. all regimens not containing FQ). The disadvantage of combining several strategies in one group is the risk of wrongfully rejecting a possibly effective strategy within that combined group. It is difficult to assess the effectiveness of a single drug when combination therapies are included.

Our study was limited by the small group of patients treated with cotrimoxazole and β-lactams and larger studies are obviously needed to confirm our findings. Second, the study population was heterogeneous due to the inclusion of patients with polymicrobial PJI and chronic PJI, but these are also patient groups for whom data are needed to inform clinicians about the most optimal treatment. The study was designed to include both patients treated with DAIR and 1SR but due to the low number of 1SR (n=2) the results cannot be extrapolated to this treatment strategy. Thirdly, the considerations for the choice for either FQ or cotrimoxazole were not recorded, so confounding by indication cannot be excluded. With the exception of the absence of pseudomonal PJI in the cotrimoxazole group, baseline characteristics were not different between cotrimoxazole and FQ and both strategies were equally divided

over the participating centers. Lastly, the database does not contain information on side-effects, so the safety of the three strategies could not be assessed.

Conclusions

Current recommendations for the treatment of GN-PJI are based on in vitro models, experimental foreign body animal models and limited conflicting clinical data. The data from this study suggest that cotrimoxazole is a promising antimicrobial treatment option for GN-PJI in selected patients but its safety and effectivity compared to FQ need be determined in larger observational studies and, ideally, a randomized controlled trial.

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