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Oral vs Intravenous Antibiotics for Fracture-Related Infections
The POvIV Randomized Clinical Trial

Major Extremity Trauma Research Consortium (METRC)

IMPORTANCE Fracture-related infection (FRI) is a serious complication following fracture fixation surgery. Current treatment of FRIs entails debridement and 6 weeks of intravenous (IV) antibiotics. Lab data and retrospective clinical studies support use of oral antibiotics, which are less expensive and may have fewer complications than IV antibiotics.

OBJECTIVE To evaluate the effectiveness of treatment of FRI with oral vs IV antibiotics.

DESIGN, SETTING, AND PARTICIPANTS The POvIV multicenter, prospective randomized clinical trial was conducted across 24 trauma centers in the US among patients aged 18 to 84 years who had fracture repair or arthrodesis with fixation with implants and developed an FRI without radiographic evidence of osteomyelitis. Patients were enrolled between March 2013 and September 2018 and followed up for 12 months after hospitalization for treatment of their FRI.

INTERVENTION Oral vs IV antibiotics following FRI.

MAIN OUTCOMES AND MEASURES The primary outcome was number of surgical interventions, and the primary hypothesis was noninferiority of oral vs IV antibiotics with respect to the number of study injury–related surgical interventions by 1 year. Unadjusted modified intent-to-treat (mITT) and adjusted per-protocol (PP) analyses were prespecified. A post hoc adjusted mITT analysis was conducted to resolve discrepancies between the results of the prespecified mITT and PP analyses. Recurrence of a deep surgical site infection was a key secondary outcome.

RESULTS Among 233 total patients, mean (SD) age was 46.0 (13.9) years, and 53 patients were female (22.7%). The mean number of surgical interventions within 1 year was 1.3 and 1.1 for the oral and IV groups, respectively. The upper bound of the 95% confidence interval of the mean difference with unadjusted mITT analysis was 0.59, which was lower than the prespecified noninferiority margin of 0.67, indicating noninferiority of oral to IV antibiotics. Adjusted PP analysis did not support noninferiority of the number of reoperations. A post hoc adjusted mITT analysis also showed noninferiority. The treatment effects estimates for the key secondary outcome of reinfection showed a similar pattern as those for the primary outcome.

CONCLUSIONS AND RELEVANCE In this prospective randomized clinical trial, oral antibiotic treatment was noninferior to IV treatment with respect to the primary outcome of number of surgical interventions based on mITT analysis. However, there is some uncertainty in these findings based on preplanned and post hoc secondary analyses. A similar pattern of treatment effect estimates was observed for the secondary outcome of recurrence of infection.

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Visual Abstract

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Supplemental content

Group Information: The Major Extremity Trauma Research Consortium (METRC) authors appear at the end of the article.

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Fracture-related infection (FRI) is a common and serious complication following fracture fixation surgery.[1] This is particularly true for open fractures, which are common in civilian and combat-related injuries.[2] The development of an infection prolongs recovery and increases the risk of nonunion, amputation, sepsis, and death.[3-7] Current FRI treatment regimens throughout North America and Europe require patients with infections to receive prolonged intravenous (IV) antibiotic therapy for 6 weeks or more following surgical debridement.[8-10] However, prolonged IV therapy is associated with increased costs and risks of line occlusion, sepsis, and thrombosis. On the other hand, several studies have demonstrated the efficacy of oral fluoroquinolones for bone and joint infections.[11-14] In addition, oral linezolid is active against antibiotic-resistant organisms. Oral antibiotics treat a range of typical pathogens in orthopedics and have penetration into bone and joint fluid.[15-24] Emerging literature supports successful use of lower-cost oral antibiotic therapy for the management of adult[24] and pediatric infections for shorter duration of IV antibiotics and overall shorter duration of all antibiotics.[25-30]

The main aim of the POvIV randomized clinical trial was to compare oral vs IV antibiotics for 6 weeks for the treatment of FRI after fracture fixation or joint fusion. The primary hypothesis was that the mean number of study injury-related surgical interventions by 1 year in the oral group would be noninferior to that of the IV group.

Key Points

Question How do oral vs intravenous (IV) antibiotics affect reoperation and reinfection rates after fracture-related infection treatment?

Findings In this randomized clinical trial, oral antibiotics were noninferior to IV with respect to the primary outcome of number of surgical interventions in the unadjusted modified intent-to-treat (mITT) analysis as well as in a post hoc adjusted mITT analysis, but not in the prespecified, adjusted per-protocol analysis.

Meaning Oral and IV antibiotics appear to have similar results treating infection after fracture surgery in terms of the primary outcome of number of surgical interventions and the secondary outcome of reinfection in the preplanned, unadjusted analysis; however, the findings are less clear in additional preplanned and post hoc secondary analyses conducted due to crossover and imbalance between randomized groups.

Methods

Trial Design

The POvIV study was a prospective, multicenter randomized clinical trial comparing oral vs IV antibiotic therapy in patients with FRI following extremity fractures. Its design has been described previously.[31] The study protocol and statistical analysis plan (SAP) are included in Supplement 1 and Supplement 2, respectively. A total of 24 trauma centers participated (eAppendix 2 in Supplement 3). The POvIV study protocol, including the informed consent form, was approved by the Johns Hopkins Bloomberg School of Public Health institutional review board, the Department of Defense Human Research Protection Office, and the institutional review board at each participating center. The study was conducted under the Major Extremity Trauma Research Consortium (METRC).[32]

Participants

Patients between the ages of 18 and 84 years who had a fracture that had previously undergone repair or arthrodesis with internal fixation with metal implants and developed an FRI that was treated with surgery were eligible for inclusion in this study. Complete details of inclusion and exclusion criteria are contained in the protocol publication[31] (and further expanded upon in eAppendix 1 in Supplement 3). Deep surgical site infection (SSI) was defined based on modified US Centers for Disease Control and Prevention criteria and involved only patients whose infections were treated operatively.[33] The definition of FRI was not in common use at initiation of this study, but all patients fit the definition.[34] Patients with osteomyelitis, defined as radiographic evidence of bone erosion or sequestrum in the setting of a deep infection, were excluded from this study.

Intervention

Patients were only randomized if (1) cultures indicated organisms were sensitive to available oral or IV antibiotics or if diagnosed with a culture-negative infection, (2) patients had no drug allergies or interactions, and (3) the surgeon and infectious disease team determined the patient could be treated using either oral or IV antibiotics. Patients randomized to the IV group were permitted to receive adjuvant therapy of oral rifampin and be considered adherent. After providing written informed consent and meeting all eligibility criteria, patients were randomized 1:1 in randomly permuted blocks stratified by clinical center. Patients were to be followed up for 1 year after discharge from the initial infection hospitalization.

Outcomes

The primary outcome was the number of study injury-related surgical interventions within 1 year after discharge from the initial infection hospitalization. A key secondary end point for this study was recurrence of a deep SSI requiring surgical treatment by 1 year, which was adjudicated by a masked panel of 3 orthopedic surgeons. Other secondary outcomes included nonunion between 6 and 12 months, treatment failure by 1 year, and rehospitalization due to complications of the study injury by 1 year.

Statistical Analysis

All outcomes were analyzed under a modified intention-to-treat (mITT) approach in which all patients except inappropriate enrollments, late ineligible patients, or refusals were analyzed according to the treatment group to which they were randomly assigned. The planned sample size for the study was 132 patients per treatment group based on noninferiority for the primary outcome.[31] A zero-inflated Poisson model was used to estimate the treatment-specific mean number of study injury-related surgical interventions, and it was assumed that

this outcome distribution would have a mean of 2.2 and variance of 4.2. A 95% 1-sided, upper confidence interval for the difference in means (Oral − IV) was computed. Oral antibiotics were considered noninferior to IV if the mean difference was less than or equal to 0.67 based on input from the protocol committee. Treatment-specific probabilities and risk differences of reinfection by 1 year were estimated using Kaplan-Meier methods. A noninferiority margin for reinfection was not set a priori. Treatment-specific descriptive statistics were computed for the secondary outcomes of nonunion, treatment failure, and rehospitalization due to complications.

Due to crossover, the mITT effect could be attenuated toward the null of no treatment difference. To address this concern, a secondary analysis was performed that estimated the per-protocol (PP) effect for the primary outcome and secondary reinfection outcome. Specifically, inverse probability of treatment weighting was used to estimate treatment effects adjusted for measured confounders. The SAP prespecified an unadjusted mITT analysis and an adjusted PP analysis with prespecified covariates. As part of the peer review process, we were asked to explain the differences between the unadjusted mITT and adjusted PP analyses. In doing so, we identified important imbalances between the 2 treatment groups in the mITT analysis, which led to the addition of an adjusted analysis of the mITT effect. This also led to the inclusion of 2 additional covariates in the models that had not been prespecified in the SAP: (1) biological sex and (2) an Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association (AO/OTA)[35] type C fracture pattern.

Results

Patients

Of 2059 patients screened, 921 patients were eligible for inclusion, and 242 patients were randomized between March 2013 and September 2018. Patient flow is provided in the **Figure**. The study reached 88% of the enrollment target, with 115 patients in the oral group and 118 patients in the IV group. Among 233 total patients, mean (SD) age was 46.0 (13.9) years; 53 patients were female (22.7%) and most patients were male (180 patients [77%]). The largest subgroup of patients was in the tibia or fibula group (64.4%), followed by femur (6.9%) and radius or ulna (6.9%) fractures. Of 233 study participants, the observed time from definitive fixation or fusion to infection was less than 3 months for 125 patients (54%), 3 to 6 months for 36 patients (15%), 6 to 12 months for 28 patients (12%), longer than 12 months for 43 patients (18%), and unknown for 1 patient (0.4%) (**Table 1**; eTable 1 in Supplement 3). Despite randomization, the treatment groups were imbalanced, with the IV group having more male patients, type C fractures, and debridements for the index infection. There were no appreciable differences in follow-up time between patients randomized to the oral group compared with the IV group (median [IQR] follow-up time: oral, 373 days [352-411]; IV, 377 days [349-415]).

At discharge from the index infection hospitalization, 7 patients assigned to the oral group (6.1%) received IV antibiotics, and 12 patients assigned to IV (10.2%) received oral antibiotics only. Of patients randomized to and receiving IV antibiotics, 15 patients received adjuvant oral rifampin only and 2 received adjuvant oral rifampin plus additional oral antibiotics. Of the 7 patients randomized to the oral group who received IV antibiotics, 2 patients received adjuvant oral rifampin and 5 did not. The mean (SD) number of days of baseline antibiotic coverage was 39.3 (11.0) in the oral group and 40.7 (18.4) in the IV group. In the group randomized to oral antibiotics, 41% received linezolid, and in the group randomized to IV, 29% received vancomycin. For those who received only oral treatment, the mean (SD) duration of baseline antibiotic coverage was 38.6 (11.3) days; 41% of these patients received linezolid. For those who received any IV antibiotics, the mean (SD) duration of baseline antibiotic coverage was 41.5 (18.4) days; 34% of these patients received vancomycin.

Primary Outcome

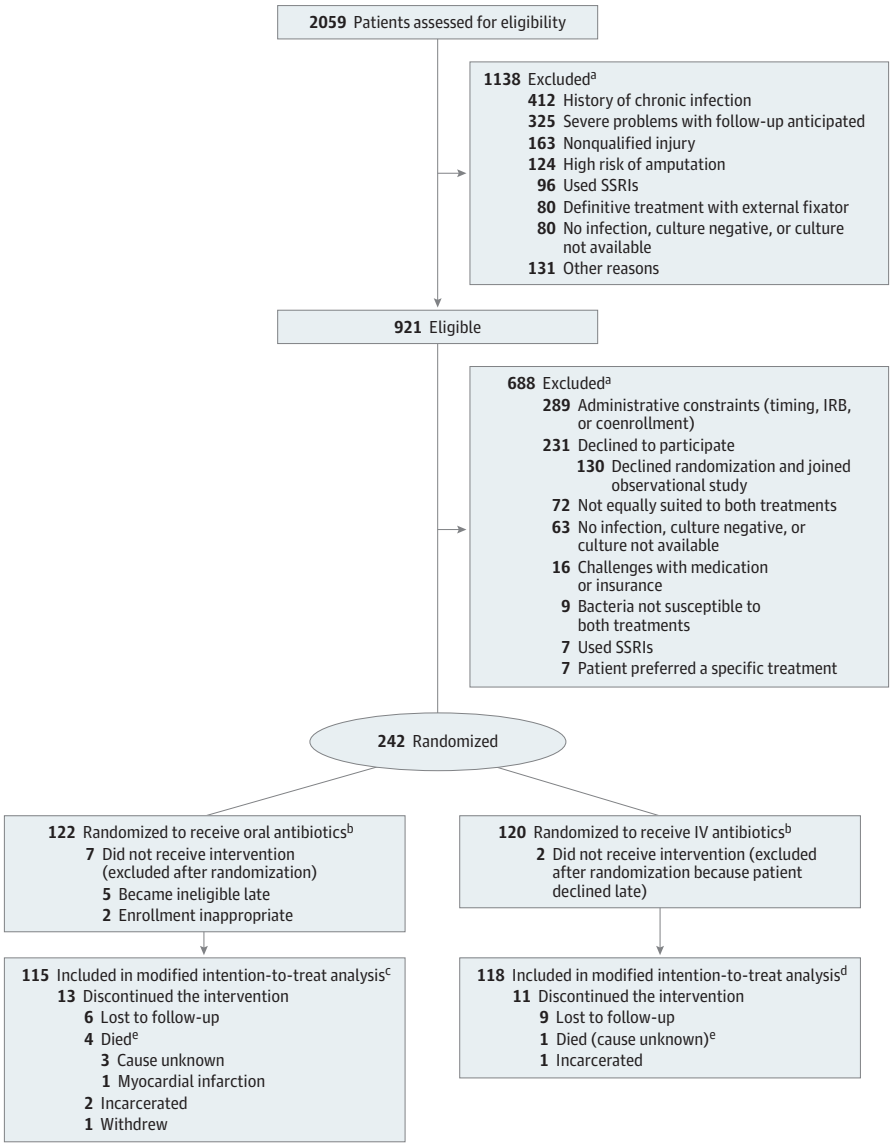
The total number of observed study injury-related surgical interventions within 1 year after discharge from the initial infection hospitalization was 137 in the oral group (1.32 interventions per person-years of follow-up; 52 patients had 0 interventions) and 118 in the IV group (1.09 interventions per person-years of follow-up; 56 patients had 0 interventions). The estimated mean number of study injury-related surgical interventions based on the zero-inflated Poisson unadjusted model was 1.32 (95% CI, 1.00-1.66) and 1.09 (95% CI, 0.83-1.36) for the oral and IV groups, respectively. The estimated difference in means was 0.23; the upper bound of the 95% 1-sided confidence interval was 0.59. This was lower than the prespecified noninferiority margin of 0.67, indicating noninferiority of oral to IV antibiotics in terms of the primary outcome. The estimated mean number of study injury-related surgical interventions based on the zero-inflated Poisson adjusted model was 1.34 (95% CI, 1.01-1.70) and 1.04 (95% CI, 0.79-1.32) for the oral and IV groups, respectively. The estimated difference in means was 0.30; the upper bound of the 95% 1-sided confidence interval was 0.65. This was also lower than the prespecified noninferiority margin of 0.67 (**Table 2**).

In the secondary PP analysis, the estimated mean number of study injury-related surgical interventions within 1 year was 1.39 (95% CI, 1.05-1.74) and 1.03 (95% CI, 0.78-1.30) for the oral only and any IV groups, respectively. The estimated difference in means was 0.35, and the upper bound of the 95% 1-sided confidence interval was 0.71. This was greater than the prespecified noninferiority margin, indicating insufficient evidence to conclude noninferiority. The unadjusted percentage of patients with no secondary surgeries was similar in oral and IV groups in the mITT (45.2% vs 47.5%) and PP (45.0% vs 47.8%) analyses (Table 2).

Secondary Reinfection Outcome

The number of recurrences of deep SSI observed within 1 year of discharge was 35 in the oral group (30.4% of patients, with 0.44 infections per person-year) and 38 in the IV group (32.2% of patients, with 0.41 infections per person-year). In the mITT unadjusted analysis, estimated probabilities of reinfection within 1 year were nearly identical between groups: 33.3% (95%

Figure. CONSORT Diagram



IRB indicates institutional review board; IV, intravenous; SSRI, selective serotonin reuptake inhibitor.

[a]Multiple reasons for exclusion were possible.

[b]A total of 19 patients crossed over to receive a treatment to which they were not randomized (7 patients in the oral antibiotics group received any IV antibiotics, and 12 patients randomzied to IV antibiotics received only oral antibiotics).

[c]A total of 42 participants had <365 days of follow-up, and 73 participants had ≥365 days of follow-up (90% of expected person-time of follow-up).

[d]A total of 46 participants had <365 days of follow-up, and 72 participants had ≥365 days of follow-up (92% of expected person-time of follow-up).

[e]No patient death was determined to be study related.

CI, 24.2%-42.5%) for the oral group and 32.5% (95% CI, 23.9%-41.6%) for the IV group (treatment difference for oral − IV, 0.71% [95% CI, −11.8% to 13.6%]). The mITT adjusted estimates of reinfection were 34.8% (95% CI, 24.4%-46.0%) for oral and 30.5% (95% CI, 21.7%-40.0%) for IV (treatment difference for oral − IV, 4.3% [95% CI, −9.4% to 18.3%]) (**Table 3**).

With regard to the PP analysis, the number of recurrences of infection observed within 1 year of discharge was 38 (31.7% of patients, with 0.47 infections per person-year) in the oral only group and 35 (31.0% of patients, with 0.38 infections per person-year) in the any IV group. The adjusted estimated probabilities of reinfection in the PP analysis within 1 year were 37.7% (95% CI, 26.9%-49.3%) for oral only and 29.8% (95% CI, 20.8%-39.1%) for any IV (treatment difference for oral only − any IV, 7.9% [95% CI, −6.6% to 22.6%]) (Table 3).

Other Secondary Outcomes

Nonunion between 182 to 365 days was observed in 5 patients in each randomized group (oral, 4.3%; IV, 4.2%), with equal event rates during the time period (0.14 events per year). In patients who received oral only or any IV antibiotics, 6 and 4 patients, respectively, experienced a nonunion between 182 and 365 days (oral only: 5.0% of patients, with 0.17 events per person-year vs any IV: 3.5% of patients, with 0.11 events per person-year).

eTable 2 in Supplement 3 reports on treatment failures within 1 year: 42 patients in each randomized group (oral, 36.5% vs IV, 35.9%) were observed to fail treatment, with 0.55 vs 0.50 failures per person-year in the oral and IV groups, respectively. In those who received oral only and any IV, 45 patients (37.5%) and 39 patients (34.8%), respectively, experienced a

Table 1. Participant Demographic Characteristics

Characteristic	No. (%)			
	Assigned		Per protocol	
	Oral (n = 115)	IV (n = 118)	Oral only (n = 120)	Any IV (n = 113)
Age, y				
18-34	29 (25)	31 (26)	30 (25)	30 (27)
35-54	52 (45)	57 (48)	59 (49)	50 (44)
55-80	34 (30)	30 (25)	31 (26)	33 (29)
Mean (SD)	46.4 (13.7)	45.6 (14.2)	45.8 (13.2)	46.2 (14.8)
Sex				
Female	31 (27)	22 (19)	30 (25)	23 (20)
Male	84 (73)	96 (81)	90 (75)	90 (80)
Race and ethnicity[a]				
Black	19 (17)	31 (26)	23(19)	27 (24)
Hispanic	8 (7)	6 (5)	9 (8)	5 (4)
White	82 (71)	78 (66)	81 (68)	79 (70)
Other[b]	6 (5)	3 (3)	7 (6)	2 (2)
Major daily activity				
Working or active duty	72 (63)	77 (65)	79 (66)	70 (62)
Going to school	2 (2)	4 (3)	2 (2)	4 (4)
Something else	40 (35)	37 (31)	39 (33)	38 (34)
Missing	1 (1)	0	0	1 (1)
Education				
≤High school	69 (60)	72 (61)	76 (63)	65 (58)
Some college	45 (39)	44 (37)	44 (37)	45 (40)
Refused or did not know	0	2 (2)	0	2 (2)
Missing	1 (1)	0	0	1 (1)
Comorbid conditions				
Diabetes	20 (17)	12 (10)	16 (13)	16 (14)
Liver disease	4 (3)	11 (9)	5 (4)	10 (9)
Kidney disease	10 (9)	4 (3)	8 (7)	6 (5)
Heart disease	48 (42)	53 (45)	47 (39)	54 (48)
Immunosuppression				
HIV	4 (3)	2 (2)	4 (3)	2 (2)
Without insurance	13 (11)	15 (13)	16 (13)	12 (11)
BMI, mean (SD)[c]	29.2 (7.3)	30.2 (8.9)	29.2 (7.0)	30.3 (9.2)
Tobacco use				
Never	39 (34)	43 (36)	41 (34)	41 (36)
Former	35 (30)	33 (28)	37 (31)	31 (27)
Current	39 (34)	42 (36)	41 (34)	40 (35)
Missing	2 (2)	0	1 (1)	1 (1)
Drug allergy	6 (5)	6 (5)	6 (5)	6 (5)
Substance use disorder	5 (4)	9 (8)	3 (3)	11 (10)
Depression	10 (9)	13 (11)	9 (8)	14 (12)
VR-12 preinjury health status				
Excellent	31 (27)	37 (31)	32 (27)	36 (32)
Very good	36 (31)	33 (28)	38 (32)	31 (27)
Good	31 (27)	28 (24)	34 (28)	25 (22)
Fair	11 (10)	15 (13)	12 (10)	14 (12)
Poor	5 (4)	5 (4)	4 (3)	6 (5)
Missing	1 (1)	0	0	1 (1)
Preinjury VR-12 Physical Component Score, mean (SD)	48.8 (10.9)	49.8 (11.0)	49.2 (10.7)	49.4 (11.2)
Preinjury VR-12 Mental Component Score, mean (SD)	54.6 (11.4)	55.5 (9.8)	55.2 (11.0)	54.9 (10.2)

Abbreviations: BMI, body mass index; IV, intravenous; VR-12, Veterans RAND 12-Item Health Survey.

[a] Participants self-reported race by responding to the following question: "What race do you consider yourself to be? Please choose one or more of the following: White, African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, Other." The original question for self-reported ethnicity was, "Are you of Latino or Hispanic origin?" with a binary yes/no response. For this table, race and ethnicity were reported as a composite variable, wherein anyone identifying as being of Latino or Hispanic origin was categorized as Hispanic. Among non-Hispanic participants, categories of Black and White included those who identified solely as African American or White, respectively.

[b] Those identifying as more than 1 race or as a race other than those listed was categorized as Other.

[c] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Number of Study Injury–Related Surgical Interventions by 1 Year Post Initial Infection

	mITT			Per protocol		
	Oral (n = 115)	IV (n = 118)	Oral − IV	Oral only (n = 120)	Any IV (n = 113)	Oral only − any IV
Participants with no OR trips, No. (%)	52 (45.2)	56 (47.5)	NA	54 (45.0)	54 (47.8)	NA
Total OR trips, No.	137	118	NA	144	111	NA
Person-years of follow-up, truncated at 1 y, No.	103.7	108.1	NA	106.6	105.2	NA
Surgical interventions per person-year of follow-up						
Crude mean	1.32	1.07	NA	1.36	1.02	NA
Estimated mean, zero-inflated Poisson (95% CI)						
Unadjusted[a]	1.32 (1.00 to 1.66)	1.09 (0.83 to 1.36)	0.23 (95% CI upper bound, 0.59)	NA	NA	NA
Adjusted[b]	1.34 (1.01 to 1.70)	1.04 (0.79 to 1.32)	0.30 (95% CI upper bound, 0.65)	1.39 (1.05 to 1.74)	1.03 (0.78 to 1.30)	0.35 (95% CI upper bound, 0.71)

Abbreviations: IV, intravenous; mITT, modified intent-to-treat; NA, not applicable; OR, operating room.

[a] Unadjusted analysis not performed for per-protocol groupings.

[b] Analysis adjusts for the following covariates: age, body mass index, insurance status, duration of hospital stay to treat initial infection, preinjury general health, time between final fixation and initial infection, retention of surgical implants at fracture site, number of debridements, gram-negative infection, gram-positive infection, kidney disease, diabetes, substance use disorder, sex, and fracture pattern C.

Table 3. Number of Reinfections by 1 Year Post Initial Infection

	mITT			Per protocol		
	Oral (n = 115)	IV (n = 118)	Oral − IV	Oral only (n = 120)	Any IV (n = 113)	Oral only − any IV
Reinfections within 1 y, No. (%)	35 (30.4)	38 (32.2)	NA	38 (31.7)	35 (31.0)	NA
KM estimate of probability of reinfection within 1 y (95% CI)						
Unadjusted[a]	33.3% (24.2% to 42.5%)	32.5% (23.9% to 41.6%)	0.7% (−11.8% to 13.6%)	NA	NA	NA
Adjusted[b]	34.8% (24.4% to 46.0%)	30.5% (21.7% to 40.0%)	4.3% (−9.4% to 18.3%)	37.7% (26.9% to 49.3%)	29.8% (20.8% to 39.1%)	7.9% (−6.6% to 22.6%)

Abbreviations: IV, intravenous; KM, Kaplan-Meier; mITT, modified intent-to-treat.

[a] Unadjusted analysis not performed for per-protocol groupings.

[b] Analysis adjusts for the following covariates: age, body mass index, insurance status, duration of hospital stay to treat initial infection, preinjury general health, time between final fixation and initial infection, retention of surgical implants at fracture site, number of debridements, gram-negative infection, gram-positive infection, kidney disease, diabetes, substance use disorder, sex, and fracture pattern C.

treatment failure within 1 year (oral only: 0.59 events per person-year vs any IV: 0.47 events per person-year).

eTable 3 in Supplement 3 reports on rehospitalization due to complications within 1 year. Overall, 42 patients (36.5%, with an event rate of 0.57 rehospitalizations per person-year) and 39 patients (33.1%, with an event rate of 0.44 rehospitalizations per person-year) were rehospitalized in the oral and IV groups, respectively. In those who received oral only and any IV antibiotics, 44 patients (36.7%, with an event rate of 0.58 rehospitalizations per person-year) and 37 patients (32.7%, with an event rate of 0.42 rehospitalizations per person-year) were rehospitalized, respectively. Patients in the any IV group also had an additional 3 admissions for line access, deep vein thrombosis, or line sepsis (multiple reasons possible) that required hospitalization. These events were not counted as part of the primary outcome.

Crossovers

The eFigure in Supplement 3 shows the flow of crossover patients, and eTables 4-6 in Supplement 3 compare the crossover patients to assigned patients. Relative to patients who crossed over from oral to IV antibiotics, patients who crossed over from IV to oral antibiotics were more likely to be male (75% vs 43%) or have less than a high school degree (83% vs 43%), were more uninsured (33% vs 14%), had more type C fractures (42% vs 29%), had more articular injuries (58% vs 29%), experienced more than 1 debridement (41% vs 29%), and had more anaerobic infections (17% vs 0%). The 19 crossovers occurred for a variety of reasons (eTable 6 in Supplement 3). Ten patients (6 switching from IV to oral antibiotics) refused their assigned treatment for reasons including pills being too large, IV use requiring a nursing home, IV use interfering with crutches, changing their mind, lack of insurance, and ulcerative colitis. Infectious disease physician preference was the reason for crossover in 4 patients. The crossover reason was unknown for 5 patients. Among 7 patients who crossed over from oral to IV treatment, 1 patient had a contributing event to the primary outcome of reoperation, and 0 patients had reinfections. Among 12 patients who crossed over from IV to oral antibiotics, 8 events (from 4 patients) contributed to the primary outcome of reoperation, and 3 patients had reinfections.

Discussion

To our knowledge, this is the largest prospective randomized clinical trial to evaluate the safety and efficacy of oral vs IV antibiotics for FRI. We found that oral treatment was noninferior to IV treatment in unadjusted and adjusted mITT analyses of the primary outcome of number of surgical interventions. However, the secondary PP analysis was not supportive of noninferiority, as the upper bound of the 95% confidence interval was 0.71, which was greater than the limit of 0.67 prespecified by the protocol committee based on clinical judgement.

Patients receiving oral vs IV antibiotics were observed to have similar reinfection rates in the unadjusted mITT analysis (PO, 33.3% vs IV, 32.5%); estimated differences increased between IV and oral groups in adjusted mITT and PP analyses. The higher failure rate among patients who crossed over from IV to oral antibiotics compared with patients who crossed over from oral to IV antibiotics may be due to several differences between the groups. Among crossover patients, the group crossing over from IV to oral antibiotics included more racial and ethnic minority individuals (67% vs 28%), more male patients (75% vs 43%), fewer patients with education after high school (17% vs 43%), more patients without insurance (33% vs 14%), more patients with type C fractures (42% vs 29%), those with longer mean [SD] time from fixation to first infection debridement (673.5 [1756.7] days vs 123.1 [178.3] days), and more anaerobic infections (17% vs 0%). The most striking difference was the mean (SD) time to infection presentation. Late presentation may make an infection harder to eradicate (eTables 2-5 in Supplement 3).[36]

Crude rates of treatment failure and rehospitalization for complications were slightly higher for oral vs IV antibiotics based on mITT and PP groupings; however, these differences are of uncertain clinical significance. Crude rates of nonunions between 6 months and 1 year were similar between groups.

The OVIVA randomized clinical trial of oral vs IV antibiotic treatment for bone and joint infections[24] found equivalent results in patients randomly assigned to oral vs IV antibiotics with respect to treatment failure (13.2% vs 14.6%, defined as the presence of at least 1 clinical, microbiologic, or histological criterion and similar to this trial's reinfection criteria). The OVIVA trial enrolled patients from a general orthopedic patient population experiencing joint prosthetic infections (n = 225), osteomyelitis or diskitis (n = 425), or FRIs (n = 394 [63% with implant retention]). In contrast, all patients in the POvIV trial had an FRI with metal at the site, which makes infection eradication more challenging due to biofilm. Hence, the reinfection rate in the POvIV trial (all FRI patients) was much higher (32%) than the treatment failure rate in the OVIVA trial that included, but was not limited to, FRIs (14%). OVIVA investigators have not yet reported on the subgroup of patients with FRIs. Like POVIV, the OVIVA trial also suffered from noncompliance with assigned treatment; the degree of FRI crossover has not yet been reported.

Strengths and Limitations

The POvIV trial must be interpreted in light of its strengths and limitations. Major study strengths included randomization, prospective data collection, a multicenter approach, focus on patients with FRIs, and greater than 90% expected follow-up in both groups. Limitations include enrollment of just 88% of the prespecified sample size due to enrollment difficulties.[31] Another potential limitation was lack of masking of clinicians and patients. However, the primary outcome of number of surgeries or secondary outcome of reinfection are unlikely to have been influenced by a lack of masking.

Due to some crossover and lack of balance, we observed mITT effects (unadjusted and adjusted) that were attenuated toward the null relative to the adjusted PP analysis. Despite meeting the noninferiority margin based on mITT analyses of the primary outcome, the secondary PP analysis suggested fewer overall study injury-related surgical interventions for any IV vs oral antibiotics only groups. An important next step would be to compare these results to effects among the subgroup of patients in the OVIVA trial with FRIs.

Conclusions

In the POvIV randomized clinical trial, these data show that oral antibiotic use was noninferior to IV antibiotics with respect to the primary outcome of number of surgical interventions with the mITT analyses, but oral antibiotics did not demonstrate noninferiority with the secondary PP analysis. While there were similar rates of reinfection in the unadjusted mITT analysis, there were greater differences in rates with adjusted mITT and PP analyses. Clinicians and patients can use these data to inform shared decision-making regarding antibiotic care for FRIs.

ARTICLE INFORMATION

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Invited Commentary

Mixed Results With Oral Antibiotics for Fracture-Related Infections

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The paradigm shift from longer courses and intravenous (IV) administration of antibiotics to shorter courses and oral administration continues with this important contribution by Obremskey et al.[1] The authors report on a multicenter randomized clinical trial comparing the current treatment of fracture-related infections (FRI) with subsequent debridements up to 1 year, after 6 weeks of IV antibiotics vs oral antibiotics. It remains unknown whether IV and oral antibiotics in this study provided equivalent coverage and tissue penetration. Except for vancomycin (IV), linezolid (oral), and rifampin (oral) as an adjunct to IV therapy, the baseline antibiotics administered, doses, frequency, and blood levels for vancomycin are not stated. Assuming antibiotic coverage was adequately addressed, the authors have constructed an appropriate clinical trial.[2]

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The rates of patient loss after randomization (9/242 = 3.7%) and crossovers (19/233 = 8.2%) are not unusual for randomized clinical trials,[3] and follow-up was adequate. However, the use of the term *per-protocol analysis* for the analysis comparing patients who received only oral antibiotics or any IV antibiotics is unclear. It is our understanding that this analysis should be termed an *as-treated analysis* rather than a per-protocol analysis. A per-protocol analysis only analyzes data from participants who follow the protocol, excluding their data after they become nonadherent. An as-treated analysis considers the treatment actually received by the participant, regardless of adherence to their randomized assignment.[4]