

Prophylaxis with Teicoplanin and Cefuroxime Reduces the Rate of Prosthetic Joint Infection after Primary Arthroplasty

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The aim of this study was to compare the prosthetic joint infection (PJI) rate after total joint arthroplasty in two consecutive periods of treatment with different antibiotic prophylaxes: cefuroxime versus cefuroxime plus teicoplanin. We retrospectively reviewed 1,896 patients who underwent total hip arthroplasty or total knee arthroplasty between March 2010 and February 2013. From March 2010 to August 2011, patients received 1.5 g of cefuroxime during induction of anesthesia and another 1.5 g 2 h later (the C group). From September 2011, 800 mg of teicoplanin was added to cefuroxime (the CT group). Throughout the period studied, there were no variations in pre- or postoperative protocols. Univariate and multivariate analyses were performed to evaluate independent predictors of PJI. There were 995 (55.7%) patients in the C group and 791 (44.3%) in the CT group. Patients in the CT group had a significantly lower PJI rate than patients in the C group (1.26% versus 3.51%, P = 0.002). There were no infections due to *Staphylococcus aureus* in the CT group (0% versus 1.6% in the C group, P < 0.001). A stepwise forward Cox regression model identified male sex (hazard ratio [HR], 3.85; 95% confidence interval [CI], 2.09 to 7.18), a body mass index of $\geq 35 \text{ kg/m}^2$ (HR, 2.93; 95% CI, 1.37 to 6.27), the presence of lung disease (HR, 2.46; 95% CI, 1.17 to 5.15), and red blood cell transfusion (HR, 3.70; 95% CI, 1.89 to 7.23) to be independent variables associated with a higher risk of PJI. The addition of teicoplanin to cefuroxime during primary arthroplasty was associated with a significant reduction in the global PJI rate due to a reduction of infection s caused by Gram-positive bacteria.

Drosthetic joint infection (PJI) after total hip arthroplasty (THA) or total knee arthroplasty (TKA) is a devastating complication. According to a recent retrospective study performed in the United States from 2001 to 2009, the number of procedures for infected arthroplasty significantly increased over that interval (1). Several reasons could explain this finding, including the fact that candidates for surgery are progressively older and have more comorbidities or the increase in the rate of resistance to cephalosporins among common pathogens involved in orthopedic infections (2). The most recent guidelines for antimicrobial prophylaxis during surgery recommend the administration of cefazolin for total joint arthroplasty; however, the authors consider it to be logical to provide prophylaxis with an agent active against methicillin-resistant Staphylococcus aureus (MRSA) for any patient known to be colonized with this Gram-positive pathogen (3). A meta-analysis of clinical trials comparing beta-lactams to glycopeptides concluded that both regimens had similar levels of effectiveness for preventing surgical site infection (4-6), but the etiology of the infection varied. In the glycopeptide arms, infections due to MRSA were less frequent and were balanced by an increase in the incidence of infections due to methicillin-susceptible S. aureus (MSSA) (4, 7). In addition, prophylaxis with glycopeptides has been associated with a higher rate of infection due to Gram-negative bacilli (8).

In order to avoid the risks of switching the prophylaxis from a cephalosporin to a glycopeptide, some authors advocate for dual prophylaxis. In our institution in 2002, there was a progressive increase in the number of MRSA infections among patients who underwent surgery for femoral neck fracture. The addition of teicoplanin to cefuroxime was associated with a significant decrease in the global rate of infection, particularly infections due to MRSA

but also infections due to other staphylococci (9). Recently, other authors have retrospectively reviewed their experience with dual prophylaxis (vancomycin plus cefazolin) versus prophylaxis with cefazolin alone in primary arthroplasty (10). Although the rate of MRSA infections was significantly reduced, the rate of MSSA infections increased and the global infection rate was not significantly different (1.1% for patients treated with vancomycin plus cefazolin versus 1.4% for patients treated with cefazolin alone).

In our institution, the standard antibiotic prophylaxis for primary arthroplasty consisted of 1.5 g of cefuroxime administered during the induction of anesthesia (30 min before incision) and a second dose of 1.5 g of cefuroxime administered 2 h after the first dose (11). The prevalence of PJI between 2009 and 2010 was 2.4%, and the main pathogens were *S. aureus* and coagulase-negative staphylococci (CoNS) (12). In order to reduce the infection rate, the prophylaxis was modified by the addition of 800 mg of teicoplanin to cefuroxime, and the infection rate was compared with

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that obtained during a previous period in which cefuroxime alone was used.

MATERIALS AND METHODS

All patients who underwent TKA or THA between March 2010 and February 2013 were prospectively registered in a database. For this study, only patients undergoing primary surgeries were selected. Patients with femoral neck fracture were excluded from the study. Relevant patient information was gathered: demographics (age and gender), comorbidities (having or not having one of the following entities: hypertension, diabetes mellitus, malignancy, liver disease, lung disease, or chronic renal failure), body mass index (BMI), drug allergies, preoperative performance status (measured by use of the American Association of Anesthesiology [ASA] classification, laterality, type of implant (TKA or THA), duration of surgery, duration (in days) of hospitalization, preoperative and postoperative (day +4) hemoglobin value, and the need for red blood cell transfusion.

From March 2010 to August 2011, antibiotic prophylaxis consisted of 1.5 g of cefuroxime administered during the induction of anesthesia (infused over 5 to 10 min starting 30 min before the surgical incision) and another 1.5 g of cefuroxime administered 2 h later. From September 2011 it was decided to add one dose of 800 mg of teicoplanin during the induction of anesthesia (infused over 15 min after the infusion of cefuroxime). Thus, we defined two groups of patients according to the type of antibiotic prophylaxis: one group of patients who received only cefuroxime (the C group) and one group of patients who received cefuroxime and teicoplanin (the CT group). Surgeries were performed in an operating room with a nonlaminar airflow, and throughout the study period there were no variations in the preoperative washing protocol, the method of skin preparation, the hand hygiene solutions used, the type of sterilization of surgical equipment, the surgical team, surgical techniques, or operating theaters. Screening for S. aureus carriers was not performed, and antibiotic-loaded cement was never used in these patients. The Ethical Committee of our institution approved the study.

After being discharged, the patients were followed up according to the protocol of our hospital, which includes a first visit 1 month after surgery and a second visit 3 months after surgery. One patient was excluded from the analysis because he died 10 days after surgery due to nonseptic post-operative complications. PJI was defined according to recent criteria (13). All patients with an early PJI were taken back to the operating room for debridement, and six deep samples of synovial fluid or periprosthetic tissue were submitted to the Microbiology Laboratory.

Continuous variables were expressed as median and interquartile range (IQR) and, according to the Kolmogorov-Smirnov test of normality, were compared by use of the Student t test or the Mann-Whitney U test. Continuous variables were also categorized as an age of <70 years and an age of \geq 70 years; BMIs of <30 kg/m², 30 kg/m² to 35 kg/m², and \geq 35 kg/m²; and durations of surgery of <105 min and \geq 105 min. Categorical variables were compared by the chi-square test or Fisher's exact test when necessary. The Kaplan-Meier survival method was used to estimate the cumulative probability of failure due to PJI within the first 100 days after surgery. A stepwise forward Cox regression model was performed to identify independent variables associated with infection within 100 days after surgery. All variables included in the univariate analysis were included in the multivariate analyses. The presence of an interaction and the role of confounding factors were evaluated. Statistical significance was defined as a two-tailed P value of < 0.05. The analysis was performed using SPSS, version 19.0, software (SPSS, Inc., Chicago, IL, USA).

RESULTS

A total of 1,896 patients were included in the study, but 110 (5.8%) were excluded due to allergy to penicillin. The median age of the cohort was 71.5 years (IQR, 64 to 77 years), and 1,196 (66.9%) were female. There were 1,290 (72.7%) TKAs and 496 (27.8%) THAs. Forty-five (2.5%) patients had a PJI within the first 100

days after surgery. The baseline characteristics of the patients according to outcome are shown in Table 1. Male sex (4.4% for the C group versus 1.6% for the CT group, P < 0.001), the presence of lung disease (5.4% versus 2.2%, P = 0.031), the median duration of surgery (85 min versus 95 min, P = 0.010), and the need for a red blood cell transfusion (6.2% versus 2.1%, P = 0.002) were variables associated with a higher infection rate.

There were 995 (55.7%) patients who received only cefuroxime as antibiotic prophylaxis (the C group) and 791 (44.3%) patients who received cefuroxime and teicoplanin prophylaxis (the CT group). Patients in the CT group had a lower rate of PJI than patients who received only cefuroxime (1.26% versus 3.51%, P =0.002). Figure 1 shows the cumulative probability of being free of PJI within the first 100 days of follow-up for each group (P =0.003, log-rank test). The evolution of the PJI rate according to the microorganism isolated (a Gram-positive or a Gram-negative microorganism) is shown in Fig. 2.

Patients in the CT group had a lower PJI rate due to Grampositive microorganisms (0.9%) than patients in the C group (2.9%) (P = 0.002), whereas no differences in the PJI rate due to Gram-negative microorganisms were found between the two groups (0.6% for the C group versus 0.4% for the CT group, P =0.739). The microorganisms isolated from both groups are shown in Table 2. There were no infections due to *S. aureus* in the CT group (0% versus 1.6% in the C group, P < 0.001), and there was a nonsignificant reduction in the prevalence of infection due to coagulase-negative staphylococci (1.5% in the C group versus 0.76% in the CT group, P = 0.145).

The baseline characteristics of patients according to prophylaxis group are shown in Table 3. The median BMI value (29.9 kg/m² in the C group versus 29.3 kg/m² in the CT group, P = 0.004) and the median duration of surgery (90 min in the C group versus 85 min in the CT group, P = 0.002) were significantly higher in the C group than in the CT group. Because these variables were also associated with a higher risk of infection, they were analyzed separately, and the results are shown in Table 4. The rate of PJI was lower in all subgroups, but among patients with a BMI of <30 kg/m², the difference was not statistically significant.

All variables studied in the univariate analysis (age, male sex, BMI, ASA classification of III or IV, hypertension, diabetes mellitus, malignancy, liver disease, lung disease, chronic renal failure, left side, duration of surgery, site, red blood cell transfusion, and prophylaxis group) were included in a multivariate analysis (hemoglobin values were excluded due to colinearity with the need for red blood cell transfusion). A stepwise forward Cox regression model identified male sex (hazard ratio [HR], 3.875; 95% confidence interval [CI], 2.091 to 7.183), a BMI of \geq 35 kg/m² (HR, 2.932; 95% CI, 1.370 to 6.275), the presence of lung disease (HR, 2.463; 95% CI, 1.178 to 5.151), and red blood cell transfusion (HR, 3.703; 95% CI, 1.896 to 7.231) to be independent variables associated with a higher risk of PJI. Addition of teicoplanin to the antibiotic prophylaxis rather than the use of cefuroxime alone was associated with a lower risk of infection (HR, 0.355; 95% CI, 0.170 to 0.740) (Table 5).

DISCUSSION

Reducing the PJI rate is of utmost importance to avoid severe consequences for patients, including additional surgeries, prolonged antibiotic therapy, and a poor functional outcome, which also lead to increased economic costs (1, 14). Antibiotic prophy-

TABLE 1 Baseline characteristics of patients according to outcome^a

	Result for patients with:		
Characteristic	No PJI $(n = 1,741)$	PJI $(n = 45)$	P value ^b
Median (IQR) age (yr)	72 (64–77)	70 (62.5–76.5)	0.320
No. (%) of patients ≥70 yr of age	1,008 (57.9)	24 (53.3)	0.540
No. (%) of patients by gender			
Female	1,175 (67.5)	19 (42.2)	< 0.001
Male	566 (32.5)	26 (57.8)	
Median (IQR) BMI (kg/m ²)	29.6 (26.6–32.8)	30.5 (26.9–35.0)	0.143
No. (%) of patients with BMI of:			0.151
<30 kg/m ²	939 (54.1)	21 (46.7)	
$30 - <35 \text{ kg/m}^2$	552 (31.8)	13 (2.3)	
\geq 35 kg/m ²	246 (14.2)	11 (24.4)	
No. (%) of patients with preoperative ASA classification of:			
I or II	1,410 (81.1)	34 (75.6)	0.351
III or IV	329 (18.9)	11 (24.4)	
No. (%) of patients with the following comorbidity:			
Hypertension	905 (52.0)	25 (55.6)	0.636
Diabetes mellitus	222 (12.8)	7 (15.6)	0.504
Malignancy	116 (6.7)	1 (2.2)	0.361
Liver disease	33 (1.9)	2 (4.4)	0.220
Lung disease	157 (9.0)	9 (20.0)	0.031
Chronic renal failure	14 (0.8)	0 (0)	1.000
No. (%) of patients with the following laterality:			
Left	863 (50.5)	22 (50.0)	0.951
Right	847 (49.5)	22 (50.0)	
Median (IQR) duration of surgery (min)	85 (75–105)	95 (85–122.5)	0.010
No. (%) of patients with duration of surgery of \geq 105 min	440 (25.3)	16 (35.6)	0.118
No. (%) of patients with arthroplasty at the following site:			
Knee	1,260 (72.4)	30 (66.7)	0.399
Hip	481 (27.6)	15 (33.3)	
Median (IQR) Hg value (g/dl)			
Preoperative	137 (128–145)	143 (126–152.5)	0.154
Postoperative	113 (104–121)	114 (104–122.5)	0.722
No. (%) of patients with the following red blood cell transfusion amt:	181 (10.4)	12 (26.7)	0.002
1 unit	25 (1.4)	0 (0)	0.173
2 units	126 (7.2)	9 (20.0)	
\geq 3 units	30 (0.7)	3 (6.7)	
No. (%) of patients in the following prophylaxis group:			
Cefuroxime	960 (55.1)	35 (77.8)	0.002
Cefuroxime + teicoplanin	781 (44.9)	10 (22.2)	

^a PJI, prosthetic joint infection; IQR, interquartile range; BMI, body mass index; Hg, hemoglobin.

^b Boldface values indicate statistically significant differences.

laxis has been demonstrated to be efficacious when the following basic principles are fulfilled: selection of an antibiotic that covers the majority of potential contaminant microorganisms, administration of the antibiotic 10 to 30 min before incision, and read-ministration of the dose when surgery lasts more than 2 times the half-life of the antibiotic (15).

Although in our institution these rules are followed in 99% of cases, according to internal audits, *S. aureus* was the most com-

mon microorganism isolated during the first period of the study, when cefuroxime alone was used (Table 2). During this period, patients with a BMI of \geq 30 kg/m² had a PJI rate of 4.5% (Table 4). Potential explanations for this finding are (i) the low level of blood flow into fat (25 to 30 ml/min/100 g of tissue, <5% of cardiac output), (ii) the higher glomerular filtration in obese patients (16), and (iii) the high MIC₉₀ of cefuroxime (2 mg/liter) for *S. aureus* and coagulase-negative staphylococci (CoNS; 32 mg/liter)



FIG 1 Cumulative probability of being free of PJI within the first 100 days of follow-up for each antibiotic prophylaxis group. —, cefuroxime prophylaxis; ----, cefuroxime and teicoplanin prophylaxis.

 TABLE 2 PJI rate and microorganisms isolated according to

 prophylaxis group

Variable	No. (%) of patients		
	C group (<i>n</i> = 995)	CT group (<i>n</i> = 791)	P value ^a
Presence of PJI	35 (3.5)	10 (1.3)	0.002
Gram-positive microorganism ^b	29 (2.9)	7 (0.9)	0.002
Gram-negative microorganism	6 (0.6)	3 (0.4)	0.739
Polymicrobial infection	8 (0.8)	6 (0.8)	0.914
Microorganism			
Staphylococcus aureus	16 (1.6)	0 (0)	< 0.001
Methicillin-resistant S. aureus	5 (0.5)	0 (0)	0.046
CoNS	15 (1.5)	6 (0.8)	0.145
Methicillin-resistant CoNS	10 (1.0)	3 (0.4)	0.122
Enterococcus faecalis	2 (0.2)	1(0.1)	0.842
Escherichia coli	3 (0.3)	2 (0.3)	0.847
Pseudomonas aeruginosa	2 (0.2)	3 (0.4)	0.847
Klebsiella pneumoniae	0(0)	1(0.1)	0.908
Proteus mirabilis	1 (0.1)	0(0)	0.908
Enterobacter cloacae	1(0.1)	1(0.1)	0.871
Morganella morganii	0 (0)	1 (0.1)	0.908
Citrobacter koseri	1 (0.1)	0 (0)	1.000

^a Boldface values indicate statistically significant differences.

^b Data for polymicrobial infections with Gram-positive microorganisms were included in the Gram-positive microorganism group.

(www.eucast.org/mic_distributions/). The first two explanations are potentially responsible for the low concentration of cephalosporins in adipose tissue of obese patients (17). Although cefazolin has a lower MIC_{90} (1 mg/liter), cefuroxime was preferred in our institution because it has better stability against class A and C

beta-lactamases (18, 19), and use of this antibiotic resulted in a lower infection rate than the use of cefazolin in a randomized trial in patients undergoing cardiac surgery (20).

The addition of a high dose of teicoplanin (800 mg) to cefu-



FIG 2 Evolution of the PJI rate according to the type of microorganism, a Gram-positive organism (GP) or a Gram-negative organism (GN).

TABLE 3 Characteristics of patients according to type of antibiotic prophylaxis^a

Characteristic	Result for the following group:		
	C group	CT group	P value ^b
	(n = 995)	(n = 791)	
Median (IQR) age (yr)	71 (64–77)	72 (64–78)	0.236
No. (%) of patients by gender			
Female	669 (67.2)	525 (66.4)	0.700
Male	326 (32.8)	266 (33.6)	
Median (IQR) BMI (kg/m ²)	29.9 (26.8–33.3)	29.3 (26.4–32.3)	0.003
No. (%) of patients with preoperative ASA classification of III or higher	185 (18.6)	155 (19.6)	0.590
No. (%) of patients with the following comorbidity:			
Hypertension	424 (42.6)	432 (54.6)	< 0.001
Diabetes mellitus	131 (13.2)	98 (12.4)	0.626
Malignancy	64 (6.4)	53 (6.7)	0.820
Liver disease	21 (2.1)	14 (1.8)	0.606
Lung disease	96 (9.6)	70 (8.8)	0.564
Chronic renal failure	8 (0.8)	6 (0.8)	0.914
Median (IQR) duration of surgery (min)	90 (75–105)	85 (75–100)	0.002
No. (%) of patients with arthroplasty at the following site:			
Knee	736 (74.0)	554 (70.0)	0.065
Hip	259 (26.0)	237 (30.0)	
Median (IQR) Hg value (g/dl)			
Preoperative	136 (128–145)	138 (128–147)	0.185
Postoperative	113 (104–121)	112 (104–122)	0.884
No. (%) of patients receiving a red blood cell transfusion	110 (11.1)	83 (10.5)	0.704

 $^{\it a}$ IQR, interquartile range; BMI, body mass index; Hg, hemoglobin.

^b Boldface values indicate statistically significant differences.

TABLE 4 PJI rate according to d	lifferent antibiotic prophylaxis and
different subgroups of patients	

	No. (%) of patients with PJI		
Patient subgroup (no. of patients) and PJI subgroup	C group $(n = 995)$	CT group $(n = 791)$	P value ^a
BMI of $<30 \text{ kg/m}^2 (n = 960)^b$			
РЈІ	13 (2.6)	8 (1.8)	0.383
PJI due to GP^c	9 (1.8)	6 (1.3)	0.558
BMI of $\geq 30 \text{ kg/m}^2 (n = 822)^b$			
РЈІ	22 (4.5)	2 (0.6)	0.001
PJI due to GP	20 (4.1)	1 (0.3)	0.001
Duration of surgery of <105 min $(n = 1,330)$			
PJI	21 (3.0)	8 (1.3)	0.037
PJI due to GP	20 (2.8)	5 (0.8)	0.007
Duration of surgery of ≥ 105 min ($n = 456$)			
РЈІ	14 (4.9)	2 (1.2)	0.037
PJI due to GP	9 (3.1)	2 (1.2)	0.223

^b In 4 cases the BMI was not available.

^c GP, Gram-positive microorganism.

roxime was associated with a significant reduction in the incidence of PJIs due to Gram-positive microorganisms, but, interestingly, the reduction was particularly important in infections due to *S. aureus* (strains susceptible and resistant to methicillin) and among obese patients (Table 4). Recent guidelines for antimicrobial prophylaxis in surgery (3) concluded that recommendations for weight-based dosing for antimicrobial prophylaxis in obese patients cannot be made because data demonstrating clinically relevant decreases in the rates of surgical site infections from the use of such dosing strategies instead of standard doses in obese patients are not available in the published literature. Our result supports the concept that cefuroxime, even when it is used at 3 g (1.5 g before surgery and 1.5 g 2 h later), does not achieve concen-

TABLE 5 Independent predictors of PJI

Variable	P value	HR (95% CI)
Gender (male)	< 0.001	3.875 (2.091–7.183)
BMI <30 kg/m ² (reference) 30–35 kg/m ² ≥35 kg/m ²	0.510 0.006	l 1.266 (0.628–2.554) 2.932 (1.370–6.275)
Lung disease Red blood cell transfusion CT group vs C group	0.017 <0.001 0.006	2.463 (1.178–5.151) 3.703 (1.896–7.231) 0.355 (0.170–0.740)

trations in obese patients high enough to prevent infections caused by MSSA and CoNS. The addition of 800 mg of teicoplanin probably provides effective antibiotic concentrations at the periprosthetic and in adipose tissue (21), but also we cannot eliminate the possibility of a synergistic effect between beta-lactams and glycopeptides, which has been demonstrated *in vitro* against MRSA and glycopeptide-intermediate *S. aureus* strains (22, 23). On the other hand, it is evident that narrow- or expanded-spectrum cephalosporins are not adequate for preventing infections caused by CoNS strains with a high rate of methicillin resistance (24). The incidence of these infections was also reduced in our study when teicoplanin was used, although the difference was not statistically significant.

Teicoplanin was selected instead of vancomycin because teicoplanin can be infused over 20 min without the risk of red man syndrome and it has a better safety profile than vancomycin even at high doses (25). The use of a high dose of teicoplanin was based on a previously reported experience in cardiac surgery, whereby 400 mg of teicoplanin showed a lower efficacy than cloxacillin plus tobramycin in preventing infections caused by Gram-positive microorganisms (26). The explanation for these findings could be related to the high protein binding of teicoplanin (>90%), since only the free fraction of an antibiotic is microbiologically active (27).

The main drawback of our study is the retrospective nature of the analysis and the fact that patients were not randomized to receive teicoplanin or not. However, throughout the study period there were no changes in the hygiene protocol, the surgeons, or the operating theaters used. Furthermore, information on the most important variables potentially associated with PJI was collected, and a multivariate analysis was performed to avoid bias. In addition, the infection rate in other types of surgery, like colon surgery, remained stable during the study period, supporting the value of adding teicoplanin. Another limitation was the fact that the MIC of teicoplanin for those CoNS organisms isolated during the period of use of teicoplanin was not determined. This information would have been interesting, since the MIC₉₀ of teicoplanin for CoNS is 8 mg/liter (www.eucast.org/mic_distributions/) and could explain the lower efficacy of teicoplanin in preventing CoNS infection. Finally, the follow-up period of the study was 100 days, whereas the majority of authors recommend 365 days; however, recent studies (28) confirm that the majority of infections after arthroplasty occur within the first 3 months and only a minor number are detected afterwards, supporting the change made by the National Healthcare Safety Network (NHSN) in January 2013 to use a 90-day surveillance period for these procedures.

The incidence of vancomycin-resistant *Enterococcus faecium* (VRE) in our institution is low, and there was no change in the incidence of this microorganism during the study period. However, the impact of adding a glycopeptide as antibiotic prophylaxis in hospitals with a high incidence of VRE needs to be further evaluated.

In conclusion, the addition of 800 mg of teicoplanin to cefuroxime during primary arthroplasty was associated with a significant reduction in the global PJI rate due to a reduction in the incidence of infections caused by Gram-positive microorganisms. The dual prophylaxis was particularly effective against *S. aureus* in a population with a BMI of \geq 30 kg/m². According to these results, the addition of teicoplanin could be restricted to *S. aureus* carriers. In the future, it will be necessary to compare the efficacy of nasal

and skin decontamination of *S. aureus* carriers (29), the use of dual prophylaxis with a beta-lactam plus a glycopeptide, or both measures integrated in a bundle of measures, as suggested in a recent meta-analysis (30) considering not only the rate of PJI due to *S. aureus* but also the rate of PJI due to CoNS and other important epidemiological outcomes, such as the prevalence of VRE and mupirocin or chlorhexidine resistance.

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