ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1983, p. 731-737
0066-4804/83/050731-07$02.00/0

Vol. 23, No. 5

Ceftriaxone Therapy of Bone and Soft Tissue Infections in Hospital and Outpatient Settings

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Received 8 November 1982/Accepted 6 March 1983

Ceftriaxone, a broad-spectrum cephalosporin with a markedly extended half-life, was administered to 100 patients with 56 bone and 44 soft tissue infections. Sixty-eight received 1 g twice daily, and 32 received 2 g once daily intravenously. Overall, 91% had a satisfactory clinical response, with similar efficacies in both treatment regimens. In six patients, failure to achieve a cure correlated well with the development of resistance to ceftriaxone during therapy in *Enterobacter* and *Pseudomonas* species (two cases) and with superinfection with *Bacteroides fragilis* (four cases). In 41 patients, intravenous drug therapy was continued after discharge from the hospital. In this group, 1,093 patient-days of hospitalization were saved, amounting to $150,020 in cost savings. The prolonged half-life facilitated the administration of ceftriaxone in this setting.

Ceftriaxone is a new cephalosporin that combines a broad antibacterial spectrum with an extended half-life of 8 h (10), about four times as long as that of most others. Most *Enterobacteriaceae*, *Streptococcus*, and *Haemophilus* species are inhibited by concentrations less than 1 μg/ml; *Staphylococcus aureus* is inhibited by 4 μg/ml; and the majority of *Pseudomonas aeruginosa* strains are inhibited by 8 μg/ml (6, 11)—concentrations easily exceeded in the serum up to 24 h after a 1- or 2-g intravenous infusion (10).

Many patients with infections of bone and soft tissue caused by these bacteria remain hospitalized after any necessary surgical drainage or debridement for the sole reason of receiving intravenous antibiotics, either because the bacteria are resistant to oral antibiotics or because of the need for high serum levels of antibiotic. Continued hospitalization, sometimes for as long as 6 weeks, is costly, prevents the patient from returning to his family or job, and occupies a hospital bed that could be utilized for more acutely ill patients. Using the prolonged half-life and expanded antibacterial spectrum of ceftriaxone, we administered ceftriaxone intravenously once or twice daily to patients with bone or soft tissue infections in hospital and outpatient settings.

MATERIALS AND METHODS

Patient selection. Patients were admitted to the study if they had clinical symptoms and signs of infection which were confirmed by isolation of a ceftriaxone-susceptible organism. If cultures obtained at the inception of therapy were sterile or yielded ceftriaxone-resistant organisms, the patient was dropped from the study and safety testing was continued. Soft tissue infections consisted of cellulitis or deep open wounds surrounded by cellulitis. Gram-stained specimens of drainage from wounds and from cellulitis were examined in all cases for the presence of polymorphonuclear leukocytes and homogeneous populations of organisms (except for polymicrobial infections). Bone infections showed inflammatory changes within bone on X ray or biopsy. Infected prostheses were identified by obtaining positive cultures of purulent material adjacent to the prosthesis and visualizing the same organisms in Gram stains of the drainage.

Patient treatment. All patients were initially hospitalized in one of five Northern Virginia hospitals, The Fairfax Hospital (Falls Church), The Alexandria Hospital (Alexandria), The Mount Vernon Hospital (Alexandria), The Commonwealth Hospital (Fairfax), and The National Hospital (Arlington). The patients had infections in which ceftriaxone would be expected to be effective as a sole agent. After written consent was obtained, ceftriaxone was administered intravenously in 1-g doses every 12 h or in 2-g doses every 24 h for 3 to 56 days. Initially, in phase II testing, the patients received the former dosage regimen. Subsequently, in phase III testing, the patients were administered the latter dosage regimen. All patients below age 15 were treated with 50 mg per kg per day in divided dosage. In 41 patients, treatment with ceftriaxone was begun in the hospital and was self-administered at home intravenously, according to the procedure described previously (8).

Patient evaluation. An investigator examined each patient before beginning therapy, at least twice weekly while he or she was on therapy, and after therapy. Cultures were performed before therapy, 2 days after the initiation of therapy, and after therapy. The follow-

ing studies were done before therapy, twice weekly during therapy, and at the conclusion of therapy: urinalysis, complete blood count, platelet count, direct Coombs test, prothrombin time, blood urea nitrogen, serum creatinine, serum glucose and electrolytes, serum calcium and phosphorus, and hepatic enzymes. Leukopenia was defined as a white blood cell count less than 4,800/mm^3, and eosinophilia was defined as an absolute eosinophil count greater than 300/mm^3. In patients with osteomyelitis, X rays were obtained at the initiation and completion of therapy. Susceptibility to ceftriaxone was determined for each clinical isolate by the Kirby-Bauer method, using 30-μg ceftriaxone disks. A zone of inhibition of 17 mm was considered to indicate susceptibility. The minimum inhibitory concentrations (MICs) were determined by a standard twofold serial dilution method with tryptic soy broth, using the conventional inoculum of 10^5 organisms per ml (3). The serum levels of ceftriaxone were assayed by the agar well method, using *Escherichia coli* ATCC 1346 (1).

Response to therapy was determined on microbiological grounds as well as on clinical grounds for all infections. Cure was defined as the complete resolution of signs of infection accompanied by sterilization of the infected site at the conclusion of therapy. In the case of osteomyelitis, initial cultures were taken from bone, and follow-up cultures were evaluated from deep within the wound. When culture specimens were no longer available, the assessment of response was made on clinical grounds only. For osteomyelitis, radiological re-evaluation was performed at the conclusion of therapy. If radiological signs of healing were observed along with the subsiding of signs of inflammation for at least 1 year after therapy, a patient was considered cured. However, relapses in patients "cured" of osteomyelitis have been known to occur several decades after an apparent cure, so that further follow-up is necessary. Clinical improvement was determined by the signs of infection subsiding in the patient, but further therapy (drainage, debridement, change to another drug due to drug reaction) being required. In these cases, follow-up cultures that showed either persistence of the initial isolate or superinfection by a new organism were differentiated from colonization by the finding on Gram-stained specimens of polymorphonuclear leukocytes and homogeneous populations of organisms, in addition to clinical correlation.

RESULTS

Ceftriaxone was administered to 100 patients with bone or soft tissue infections. Sixty-six were in males and 34 were in females, ages 2 to 86 years (mean = 45). The duration of therapy was from 3 to 56 days, with a mean of 25 days. Twenty-seven patients had diabetes mellitus, and three patients were alcoholics. Six patients with infections of the foot had severe peripheral vascular disease without diabetes. Three patients had underlying malignancies, but only one was leukopenic. Five patients were receiving steroids: one because of increased intracranial pressure due to an astrocytoma, two because of rheumatoid arthritis, one because of systemic lupus erythematosis, and one because of sprue.

Sixty-eight patients with 30 soft tissue and 38 bone infections received the drug twice daily in phase II studies, and 32 patients with 14 soft tissue and 18 bone infections received it once daily in phase III. The patients in the former group ranged from 2 to 83 years of age (mean = 42), and those in the latter group ranged from 24 to 86 years (mean = 51). There were 45 males and 23 females in the former group and 21 and 11, respectively, in the latter group. The mean durations of therapy were 25 and 24 days, respectively, with respective ranges of 3 to 56 days and 5 to 51 days. In the former group, 35 of 68 patients (51%) were considered to have underlying diseases interfering with their ability to combat infection, and in the latter category, 18 of 32 patients (56%) suffered from underlying diseases. Serum levels ranged from a peak of 40 to 200 μg/ml (mean = 98) and a trough of 16 to 150 μg/ml (mean = 56), using a dose of 1 g intravenously every 12 h. When 2 g of ceftriaxone was administered as a single dose every 24 h, the peak levels ranged from 150 to 250 μg/ml (mean = 180) with trough levels of 14 to 100 μg/ml (mean = 34). The wide ranges reflect varied creatinine clearances in these patients.

The 44 skin and soft tissue infections consisted of 5 traumatic wounds, 13 postoperative wounds, 8 ulcers of the lower extremities, 14 cases of cellulitis, and 4 intraabdominal abscesses. Three of the patients were bacteremic, one with an hepatic abscess (*Serratia*), one with multiple soft tissue abscesses on steroids for an astrocytoma (*S. aureus*), and the third with sacroileitis (*S. aureus*).

The 56 bone infections included eight infected prostheses: three total hip replacements (*S. aureus*, *Staphylococcus epidermidis*, and *Enterobacter cloacae*), one total knee replacement (*S. epidermidis*), one intramedullary rod for a fractured tibia (*S. aureus*), one Hoffman apparatus for a fractured tibia (*S. epidermidis*), one set of screws for a trimalleolar fracture (*S. aureus*), and one metallic compression plate for a fractured femur (*S. aureus*).

Bone infections not complicated by prosthesis infection were categorized by (i) whether this was the initial therapeutic episode or a recurrent infection, and (ii) etiology (13). Nine of the 38 cases (24%) treated with 1 g twice daily and 5 of 18 (27%) treated with 2 g once daily were recurrences. There were seven hematogeneous cases, all initial episodes and all treated with 1 g of ceftriaxone twice daily. There were 20 cases of osteomyelitis complicated by vascular insufficiency. All were in the feet of patients with diabetes mellitus. Fourteen were initial episodes, and six were recurrences. Thirteen were

TABLE 1. Bacteria isolated from patients receiving ceftriaxone

Organism	No. of infections eradicated/ total (%)	Mean (range) MIC (μg/ml)
Staphylococcus aureus	46/49 (96)	4.6 (1.25–10)
Enterobacter sp.	9/11 (84)	0.6 (0.1–6.25)
Serratia marcescens	6/7 (90)	3.7 (0.6–10)
Pseudomonas aeruginosa	8/13 (62)	10 (5–20)
Escherichia coli	8/8 (100)	2.3 (0.6–5)
Klebsiella pneumoniae	7/7 (100)	1.2 (0.6–2.5)
Streptococcus sp.	12/13 (92)	0.18 (0.05–0.3)
S. epidermidis	3/4 (75)	2.6 (0.3–5)
Proteus mirabilis	2/2 (100)	
Citrobacter diversus	1/1	
Haemophilus influenzae	2/2	
Morganella morganii	1/1	
Anaerobic organisms[a]	5/5	

[a] *Propionibacterium acnes, Streptococcus, Bacteroides fragilis*, and *Peptococcus* sp.

treated with 1 g of ceftriaxone twice daily, and seven were treated with 2 g once daily. Twenty-one cases were infected from a contiguous septic focus, 12 treated by the former regimen and 9 by the latter. Fourteen were initial episodes, and seven were recurrences.

Bacteria infecting the wounds were identified in all cases and were shown to be ceftriaxone sensitive by disk testing. A total of 123 organisms were isolated, of which all but 5 were aerobic or facultative, reflecting our bias against treating anaerobic organisms with this drug. The types of bacteria were evenly distributed between the two dosage regimens. MICs were determined for 85 of 123 isolates (Table 1). Eighteen infections were polymicrobial.

Efficacy. Bacteria were eradicated in 110 instances of the 123 isolates, or in 88 of 100 infections (Table 1). The rate of eradication was lowest for *P. aeruginosa* (62%), but this correlated with failure to achieve a clinical cure in only two cases. Bacterial persistence was noted in eight patients (12%) receiving divided dosage and in four patients (12%) receiving a single dosage of ceftriaxone. Two isolates of *E. cloacae* and one isolate of *P. aeruginosa* developed resistance to ceftriaxone during therapy. Four developed *B. fragilis* superinfection, and one developed *Streptococcus faecalis* superinfection.

Cure or improvement was noted in 91 of 100 patients (91%). The efficacy rates were similar in both the divided-dosage group (89%) and the once-daily dosage group (94%). Of the soft tissue infections treated with 1 g of ceftriaxone twice daily (Table 2), two clinical failures were noted. In one case, the patient expired from an overwhelming case of *E. coli* mediastinitis complicated by acute renal failure, and in the second case, clinical failure was attributed to *Bacteroides fragilis* superinfection of a diabetic foot ulcer. Seven patients in this group improved clinically but failed to achieve a cure. One of these became superinfected with *B. fragilis* and *S. faecalis*. Two patients were cured by surgery or by local therapy, and four patients required prolonged courses of oral antibiotics after clinical improvement on ceftriaxone.

There was only one failure in the group with soft tissue infections treated with a single daily 2-g dose of ceftriaxone (Table 2). This patient had an infection surrounding an anal fistula caused by a malignant tumor and could only be improved with irradiation. Three patients improved but were not cured while on ceftriaxone: one with cellulitis surrounding a bursa who required a bursectomy, and two who developed adverse drug reactions requiring discontinuation of ceftriaxone.

In patients with bone infections treated with 1 g of ceftriaxone twice daily (Table 3), two patients became superinfected with *B. fragilis*, both of whom had foot infections complicated by vascular insufficiency. One patient failed, and another was improved. A second failure was attributed to the development during therapy of resistance to ceftriaxone in an *E. cloacae* isolate infecting a tibia and fibula from a contiguous focus. Other failures were attributed to vascular insufficiency in two cases of small bones of the feet infected (one initially and one recurrently) with *S. aureus* in diabetics who required amputation for cure, and to a recurrent *S. epidermidis* infection involving a total knee prosthesis requiring prosthesis removal. Removal of a hip prosthesis infected by *E. cloacae* was also required to cure one patient who improved on, but could not be cured by, ceftriaxone. Seven others who improved on, but were not cured by, ceftriaxone required prolonged oral antibiotics due to subtotal resolution of signs of infection. Four of these were recurrent infections. Another patient required further local wound care to be cured, and in two other cases, drug therapy was discontinued due to an adverse reaction attributable to ceftriaxone before cure could be achieved.

There was one failure in the group of patients with bone infections treated with 2 g of ceftriaxone once daily (Table 3): an *S. aureus* infection of the foot complicated by vascular insufficien-

TABLE 2. Response of skin and soft tissue infections to ceftriaxone

Dosage regimen	Diagnosis	No. of cases	Clinical response (no. of cases)			Bacteriological response (no. of cases)		
			Cured	Improved	Failed	Eradicated	Persisted	Superinfected
1 g every 12 h	Cellulitis	10	8	2		10		
	Traumatic wound infection	5	4	1		5		
	Postoperative wound infection	8	6	1	1	4	3	1
	Foot ulcer infection	6	3	2	1	4	1	1
	Intraabdominal abscess	1		1		1		
2 g every 24 h	Cellulitis	4	3	1		4		
	Postoperative wound infection	5	4	1		5		
	Foot ulcer infection	2	1	1		1	1	
	Intraabdominal abscess	3	2		1	1	2	

cy. The development of ceftriaxone resistance was noted in a recurrent *E. cloacae* foot infection, complicated by vascular insufficiency, which improved but was not cured. One infected tibia stabilized by an intramedullary rod was improved on, but was not cured by, ceftriaxone. Two initial cases of polymicrobial osteomyelitis of the hand bones from a contiguous source were improved on ceftriaxone but required prolonged oral antibiotics thereafter to be cured. One final reason for improvement without cure was the discontinuation of ceftriaxone due to an adverse drug reaction.

Of all bone infections, only 6 of 14 recurrent episodes were cured (42%), compared with 27 of 42 initial episodes (64%). Four of eight prosthesis infections were cured (50%), as were 10 of 20 bone infections complicated by vascular insufficiency (50%). Osteomyelitis from a hematogenous source was cured in 4 of 7 patients (57%), and that due to a contiguous septic focus was cured in 15 of 21 patients (71%). The cure rates were roughly equivalent between the two dosage regimens.

In all groups, nine patients were deemed to be failures. This was attributable to *B. fragilis* superinfection (two cases), to the development of ceftriaxone resistance during therapy of an *E. cloacae* infection (one case), and to a recurrent total knee prosthesis infection (one case); the remainder were thought to have failed in large part due to their underlying diseases: osteomyelitis complicated by vascular insufficiency (three cases), infection involving a tumor (one case), and an overwhelming case of mediastinitis complicated by renal failure (one case).

Adverse drug reactions. We observed occasional adverse reactions attributable to ceftriaxone (Table 4). Ten patients (10%) developed diarrhea, which in three was severe enough to stop the drug. All patients with diarrhea were tested for *Clostridium difficile* toxin in the stool.

TABLE 3. Response of bone infections to ceftriaxone

Dosage regimen	Diagnosis	Initial episode or recurrence (no. of cases)	Clinical response (no. of cases)			Bacteriological response (no. of cases)		
			Cured	Improved	Failed	Eradicated	Persisted	Superinfected
1 g every 12 h	Hematogenous	Initial (7)	4	3		7		
	Vascular insufficiency	Initial (9)	4	3	2	7		2
		Recurrence (4)	2	1	1	4		
	Contiguous focus of infection	Initial (8)	7		1	7	1	
		Recurrence (4)	1	3		4		
	Prosthesis	Initial (5)	3	2		5		
		Recurrence (1)			1		1	
2 g every 24 h	Vascular insufficiency	Initial (5)	4		1	5		
		Recurrence (2)		2		1	1	
	Contiguous focus of infection	Initial (6)	4	2		6		
		Recurrence (3)	3			3		
	Prosthesis	Initial (2)	1	1		2		

TABLE 4. Adverse reactions to ceftriaxone

Reaction	No.[a]	No. requiring drug termination
Leukopenia	8	2
Rash	3	2
Drug fever	2	1
Phlebitis	1	0
Thrombocytosis	5	0
Thrombocytopenia	1	0
Eosinophilia	23	0
Diarrhea	10	3[b]
Antabuse-like reaction	1	1

[a] In 100 patients.

[b] One patient with diarrhea had positive *C. difficile* toxin assay in stool.

Only one case was positive, and this patient responded well to a short course of oral vancomycin in addition to stopping the ceftriaxone. Rash was noted in three patients (3%), in two of whom the drug was stopped. Fever attributable to ceftriaxone occurred in two instances (2%), requiring discontinuation of the drug in one. An Antabuse-like reaction similar to moxalactam reactions (7) occurred in one patient and recurred on rechallenge with alcohol. Phlebitis occurred in only one instance (1%). Laboratory abnormalities were noted during therapy: eosinophilia (23%), leukopenia (8%), thrombocytosis (5%), and thrombocytopenia (1%). Except for the leukopenia (mean 3,700/mm^3, range 2,000 to 4,700 mm^3), no laboratory abnormalities required discontinuation of ceftriaxone, and all returned to normal after the conclusion of treatment. The leukopenia occurred at a mean duration of 20 days of ceftriaxone therapy (range 7 to 39 days), and in two instances the drug was discontinued because of this side effect. In these two patients, the white blood cell count was 2,000 and 2,700/mm^3, respectively. Eosinophilia was associated with leukopenia in four instances, thrombocytopenia in one, and rash in two. The mean eosinophil count in 23 patients with eosinophilia was 850/mm^3 (range 420 to 2,100 mm^3).

Intravenous ceftriaxone administered in an outpatient setting. Forty-one patients of the 91 who were responding to ceftriaxone had their therapy continued by intravenous self-administration after discharge from the hospital, according to the previously described procedure (8). The inpatient portion of their therapy consisted of a mean of 8.8 days (range 0 to 24 days), and the outpatient portion was a mean of 25.4 days (range 6 to 43 days). One-half of these infections were caused by *S. aureus*. Of these patients, 30 were cured, 9 improved, and 2 failed, which was similar to the overall results. This program saved 1,093 total days of hospitalization. At a cost of $140 per day for a hospital bed, the net savings of this program amounted to $150,020, and it allowed the patients to return to their families and to their jobs earlier than otherwise would have been possible. Of the once-daily dosage regimen, 55% of the therapy was administered in the outpatient setting, compared with 35% of the divided-dosage regimen.

DISCUSSION

When ceftriaxone was given in this study to patients with bone or soft tissue infections, cure or clinical improvement occurred in 91 of 100 infections (91%). The efficacy rates were similar in both the group receiving 1 g twice daily (89%) and the group receiving 2 g once daily (94%). Soft tissue infections were most readily cured (70%), and only 7% failed on ceftriaxone therapy. Of these infections, the group that fared least well were the foot infections seen in patients with diabetes mellitus (four of eight [50%] were cured). Bone infections were more difficult to treat. Overall, only 33 of 56 (59%) were cured, with comparable efficacies in the divided-dosage regimen (55%) and the single-dosage regimen (67%). Patients with recurrent bone infections (42% cured), infected prostheses (50% cured), or osteomyelitis complicated by vascular insufficiency (50% cured) did least well. Although osteomyelitis from a hematogenous source (57% cured) fared slightly better, it was osteomyelitis from a contiguous focus (71% cured) that responded best of all to antibiotics. However, in this last group (osteomyelitis from a contiguous focus of infection), only initial cases responded well (79% cured). Merely 57% of recurrences were cured by ceftriaxone in this group. These results are slightly better than the figures of 60 and 25%, respectively, for initial and recurrent cases of osteomyelitis infected from a contiguous focus, reported previously (13). That study emphasized the necessity for surgery as an adjunct in the treatment of osteomyelitis, especially if it is recurrent and accompanied by devitalized bone. Our experience supports this concept. We also confirm the difficulty of treating prosthesis infections and the necessity of removal of the hardware in patients who fail to respond completely to medical therapy alone (12).

Bacterial eradication occurred for 110 of the 123 isolates. These figures compare favorably with rates reported for other cephalosporins and aminoglycosides. Ceftriaxone was especially effective in curing *S. aureus*, *Streptococcus* (non-Group D), *Haemophilus influenzae*, *E. coli*, *Klebsiella*, and *Serratia* infections of soft tissue and bone. Of the nine clinical failures, two became superinfected with *B. fragilis*, one developed in vitro resistance to ceftriaxone during

therapy (*E. cloacae*), and six failed to improve, presumably due to their underlying disease (diabetes mellitus with peripheral vascular disease, tumor, acute tubular necrosis, and a prosthesis infection). Although the eradication of *Pseudomonas* from wounds occurred less frequently than with other pathogens (62 versus 93%), clinical response was observed in 9 of 11 patients infected with *Pseudomonas*. In three instances, bacteria became resistant to ceftriaxone during therapy (two *E. cloacae* and one *P. aeruginosa*). Development of resistance during therapy has been reported with other beta-lactams (5, 7, 9).

In addition to the acquisition of resistance to ceftriaxone by *Pseudomonas* and *Enterobacter* during therapy, the main deficiencies in its spectrum are *B. fragilis* (MIC_{90} = 100 μg/ml) and *S. faecalis* (MIC_{50} = ≥100 μg/ml) (6, 11). We observed *B. fragilis* superinfection in four patients who were being treated with ceftriaxone, as well as one case of *S. faecalis* superinfection, as had been the case with moxalactam (14).

The third-generation cephalosporins are distinguished by differences in pharmacokinetics and penetration into various body compartments. For example, the ability of moxalactam to achieve high cerebrospinal fluid levels has made it the drug of choice for gram-negative bacillary meningitis, except for *Pseudomonas* strains (4). The high biliary levels associated with cefoperazone have made it a valuable agent in the treatment of cholangitis due to susceptible bacteria, and its hepatic route of excretion allows it to be used in renal failure without adjustment of dosage (2). The prolonged serum half-life of ceftriaxone (8 h), its distinguishing feature, is approximately four times greater than those of the other third-generation cephalosporins (10). We took advantage of this feature and continued ceftriaxone therapy by intravenous self-administration in 41 patients after discharge from the hospital, resulting in a savings of 1,093 patient-days of hospitalization or $150,020. Most patients returned to work while they self-administered infusions of ceftriaxone. Although it is our experience that any antibiotic can be self-administered by an outpatient up to a maximum of four infusions a day, the ability to give an antibiotic such as ceftriaxone once or twice daily facilitates the program merely from the standpoint of time. It is our opinion that the favorable pharmacokinetics of ceftriaxone may be beneficial to hospitalized patients, as well in terms of labor costs, in the preparation and administration of intravenous medications and in tolerance of parenterally administered drugs.

Ceftriaxone was generally well tolerated. However, we were forced to discontinue ceftriaxone therapy in nine patients because of rash (two cases), leukopenia (two cases), diarrhea (three cases), drug fever (one case), and an Antabuse-like reaction (one case). We feel it especially important to follow closely the white blood cell count in outpatients, as this is the only serious side effect that is clinically asymptomatic.

In summary, ceftriaxone is an effective medication in the treatment of bone and soft tissue infections caused by susceptible organisms, as long as the patient is monitored for *B. fragilis* superinfection as well as for the development of ceftriaxone resistance in *Pseudomonas* and *Enterobacter* species during therapy. Dosage regimens of 2 g once daily or 1 g twice daily are approximately equally effective in the treatment of bone and soft tissue infections. However, the single daily dosage regimen facilitates the intravenous self-administration of this drug to outpatients.

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