Treatment of Pneumonia and Other Serious Bacterial Infections with Cephapirin

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Nineteen patients with pneumonia due to *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, or *Escherichia coli* were treated with 4 to 18 g of cephapirin daily. There were three treatment failures. One patient each with pneumonia due to *E. coli* or *S. pneumoniae* died despite apparent eradication of the pathogen. Lobar pneumonia due to *K. pneumoniae* progressed during therapy in a third patient to lung gangrene, necessitating pneumonectomy. Five additional patients with pneumococcal pericarditis or septic bursitis, empyema, cannula-associated bacteremia, and thoractomy wound infection due to *S. aureus* were cured. All isolates of *S. aureus*, *S. pneumoniae*, and group A *Streptococcus* were inhibited by 0.8 µg of cephapirin per ml; minimal inhibitory concentrations of cephalothin were similar. Ninety percent of *K. pneumoniae*, 85% of *Proteus mirabilis*, 73% of *E. coli*, and 30% of *Enterobacter* were inhibited by 12.5 µg cephapirin per ml. All isolates of *Pseudomonas*, *Serratia* and indole-positive *Proteus* had a cephapirin minimal inhibitory concentration of >100 µg/mg. Serum concentrations after intravenous and intramuscular injection were similar to those reported for cephalothin. The intramuscular injections were moderately painful, and intravenous infusions caused phlebitis in three of nine patients treated with doses up to 18 g per day. Cephapirin appears comparable to cephalothin in vitro and is an effective agent in treatment of infection due to *S. aureus* and *S. pneumoniae*.

Cephapirin is a new cephalosporin antibiotic with an in vitro antibacterial spectrum similar to that of cephalothin (1, 6). Cephapirin is poorly absorbed following oral administration and must be given parenterally. Early reports suggested that the drug produced moderate pain after intramuscular administration but caused little pain or phlebitis when given by the intravenous route (3, 4, 7). In particular, it was reported to be better tolerated by the intravenous route than cephalothin (9). However, three recent comparisons of the incidence of phlebitis associated with cephapirin and cephalothin therapy have not resulted in consistent findings (5, 8, 13). Other adverse effects have been infrequent in patients receiving cephapirin therapy (10). In particular, renal toxicity has not been noted, in contrast to it being commonly associated with cephaloridine and infrequently with cephalothin (2). Experimental nephrotoxicity in laboratory animals has not been observed with cephapirin (11, 15). A serum-sickness-like syndrome has been documented in volunteers who received intermittent intrave-

nous injections of either cephapirin or cephalothin in doses of 8 g per day for up to 28 days (13).

The present study was undertaken to evaluate the clinical efficacy of cephapirin in patients with moderately severe and severe bacterial infections, especially pneumonia. We also compared the in vitro activities of cephapirin, cephalothin, and cephaloridine against a large number of clinical isolates and measured cephapirin serum levels in patients on various dose regimens.

MATERIALS AND METHODS

Clinical and microbiological studies. Twenty-four patients with infections due to *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae* were treated. Of these, 18 had significant underlying disease and 12 were 60 years of age or older. All but 2 had intrathoracic infections.

Cultures of sputum were obtained in all pneumonia patients prior to therapy except for three (numbers 9, 20, and 21) in whom transtracheal aspirations were performed because of their inability to produce ade-

quate sputum spontaneously. All aspirate and sputum specimens were Gram-stained and examined by one of the investigators to determine the predominant organism. At least one blood culture was obtained in every patient before institution of cephalirin therapy. Chest roentgenograms were obtained before, during, and after treatment to determine the extent of pneumonia and to assess response to therapy. In patients with pericarditis, empyema, wound infection, and septic bursitis, specimens for Gram stain and culture were obtained by aspiration of the involved site.

Sputum and direct aspirate specimens were cultured aerobically on sheep blood and MacConkey agars. Pneumococci were identified on blood agar and confirmed by optochin (ethylhydrocupreine) sensitivity. Isolates of *S. aureus* were coagulase and mannitol positive. *E. coli* and *K. pneumoniae* were identified by their typical colony appearance on MacConkey agar, the presence or absence of motility, and their characteristic performance in the indole, methyl red, Voges-Proskauer, and citrate biochemical reactions. The *K. pneumoniae* isolated in patient 23 was identified as type 1 by the Center for Disease Control, Atlanta, Ga.

Minimal inhibitory concentrations (MIC) for *S. aureus* and gram-negative bacilli were determined by an agar dilution method in Mueller-Hinton agar. Antibiotic-containing plates were inoculated by a multiple inoculator apparatus (14) with a 100-fold dilution of an overnight Trypticase soy broth culture. The MIC for pneumococci and group A streptococci were determined in Mueller-Hinton agar containing 5% defibrinated sheep blood. These plates were inoculated with a 10-fold dilution of an overnight Todd-Hewitt broth culture.

Laboratory studies performed in all patients before, during, and after cephalirin therapy included hematocrit, leukocyte count and differential, urinalysis, blood urea nitrogen, serum creatinine, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), and serum bilirubin.

Serum level studies. Blood was drawn at varying times during courses of therapy from selected patients for determination of cephalirin concentration. Antibiotic levels were determined by the method of Bran et al. (4), except that 6-mm filter paper disks were loaded with 25 μ liters of serum from capillary tubes and assay plates were incubated at 37 C for 18 h. All assays were performed in quadruplicate.

Treatment schedules. Intramuscular injections of 1 g in 2 ml of sterile water were administered into the gluteal muscle mass. For intravenous infusions, each gram of the drug was dissolved to a concentration of 1 g/20 ml in 5% dextrose in water. The infusions were given over 20 to 30 min through small-gauge steel needles maintained at a given infusion site for 48 to 72 h.

RESULTS

Clinical results. Table 1 summarizes clinical data on the patients treated with cephalirin. All but 1 of the 11 patients with pneumococcal

pneumonia were cured. They defervesced within 1 to 7 days (mean, 2.8 days) after institution of therapy. In addition to the isolation of pneumococci from sputum or aspirates in all patients with pneumonia, and from blood cultures of two patients, examination of pretreatment sputum or transtracheal aspirates showed a predominance of gram-positive diplococci in all patients. The dose of cephalirin employed for pneumococcal pneumonia was 4 g per day except in patient 9, who received 6 g per day. Five patients, including one with pneumococcal bacteremia (patient 5), were treated for 5 days or less. All defervesced abruptly within 24 h of institution of cephalirin and remained well after therapy was discontinued. Follow-up sputum cultures invariably showed absence of pneumococci within 72 h of institution of therapy, and serial chest roentgenograms showed complete resolution of the pneumonic processes within 3 weeks in all patients. Patient 10, a 73-year-old man, admitted moribund with pneumonia and congestive heart failure, died suddenly on day 4 of therapy. At autopsy, some resolution of the pneumonia was evident, and cultures of lung, spleen, and blood were sterile. Patient 12, with lymphosarcoma, purulent pericarditis, and bacteremia, required emergency pericardiectomy and drainage in addition to 6 g of cephalirin per day. Therapy resulted in resolution of the pericarditis and eradication of pneumococci from blood and pericardial drainage fluid. Patient 24 had lobar pneumonia involving three lobes, presumed due to pneumococci. Initial sputum Gram stain showed a predominance of gram-positive diplococci. Although sputum and blood cultures did not grow out the pneumococci, this patient defervesced within 5 days, and complete resolution was observed on chest roentgenography by day 10 after institution of cephalirin.

Seven patients with *S. aureus* infections were treated with cephalirin. In three patients with pneumonia (numbers 15 to 17), pretreatment Gram stain of sputum showed the predominant organism to be large gram-positive cocci in clumps. These three patients were only moderately ill, and all defervesced within 72 h of institution of cephalirin therapy. Follow-up sputum cultures showed disappearance of staphylococci within 5 to 11 days, and the pulmonary infiltrates cleared within 5 to 14 days. Patient 14 with cannula-associated phlebitis and bacteremia defervesced within 48 h of removal of the cannula and institution of cephalirin therapy; local signs of inflammation disappeared within 10 days. Three patients with closed-space infec-

TABLE 1. Clinical data of patients treated with cephapirin

Strain and patient no.	Age (years) and sex	Diagnosis	Site of isolation	Admission fever (F) ^a	Initial leukocyte count	Initial chest X ray ^b	Underlying disease	Daily dose (g)/duration (days)	Result
<i>S. pneumoniae</i> 1	72 F	Pneumonia	Sputum	102 (38.9)	3,800	RML consolidation	Carcinoma of lung	4/8	Improved, died later of carcinoma Cured
2	87 F	Pneumonia	Sputum	101 (38.3)	16,800	RLL, LLL consolidation	Heart failure, obstructive lung disease	4/10	
3	47 M	Pneumonia	Sputum	103 (39.4)	31,800	RLL bronchopneumonia	Obstructive lung disease	4/5	Cured
4	60 M	Pneumonia	Sputum	101 (38.3)	10,600	LLL consolidation	Alcoholism	4/5	Cured
5	24 F	Pneumonia	Sputum, blood	102.8 (39.4)	24,800	LLL consolidation		4/4	Cured
6	57 M	Pneumonia	Sputum	102.2 (38.9)	6,500	RLL bronchopneumonia	Cirrhosis, influenza	4/8	Cured
7	33 F	Pneumonia	Sputum, blood	102.4 (38.9)	8,400	LLL consolidation	Systemic lupus erythematosus, influenza	4/9	Cured
8	65 F	Pneumonia	Sputum	101 (38.3)	9,500	Lingular consolidation	Obstructive pulmonary disease, influenza	4/9	Cured
9	68 F	Pneumonia	Transtacheal aspirate	103.6 (40.0)	22,500	LLL consolidation	Carcinoma of pancreas	6/10	Improved, died later of carcinoma Cured
10	73 M	Pneumonia	Sputum	101 (38.3)	6,300	RLL consolidation	Heart failure	4/4	Died
11	46 M	Pneumonia	Sputum	99.2 (37.2)	10,600	RLL bronchopneumonia	Mitral stenosis	4/4	Cured
12	45 M	Purulent pericarditis	Pericardial fluid, blood	102 (38.9)	8,600	Pericardial effusion	Lymphosarcoma	6/9	Cured
<i>S. aureus</i> 13	40 M	Empyema	Thoracentesis	101 (38.3)	9,100	Pleural effusion		4-6/12	Cured
14	75 F	Intravenous cannula-associated bacteremia	Blood, catheter tip	103.8 (40.0)	11,900		Heart failure	6/10	Cured
15	76 M	Pneumonia	Sputum	103 (39.4)	2,700	RLL bronchopneumonia	Lymphosarcoma	4-6/7	Cured

TABLE 1—Continued

16	Pneumonia	76 M	Sputum	103.4 (39.4)	15,600	Bilateral diffuse bronchopneumonia	Diabetes mellitus	4-6/9	Cured
17	Pneumonia	17 M	Sputum	103.2 (39.4)	9,900	LLL bronchopneumonia		4/5	Cured
18	Pericardiectomy wound infection	35 M	Sputum, thoracotomy wound	104 (40.0)	12,200	LLL consolidation with effusion	Relapsing pericarditis	4-6/10	Cured
19	Septic bursitis	52 F	Olecranon bursa	102 (38.9)	16,700			4/10	Cured
<i>E. coli</i> 20	Pneumonia	74 F	Transtacheal aspirate	102 (38.9)	14,800	LUL, LLL consolidation	Diabetes mellitus, heart failure	4-6/5	Died
<i>K. pneumoniae</i> 21	Pneumonia	61 M	Transtacheal aspirate	99.6 (37.8)	17,200	RLL, LLL bronchopneumonia	Chronic renal failure	4/10	Cured
22	Pneumonia	34 M	Sputum, pleural fluid	102 (38.9)	3,400	LLL consolidation and effusion	Alcoholic cirrhosis	12-18 ^c /16	Cured
23	Pneumonia	50 M	Sputum, lung	104 (40.0)	2,200	RUL consolidation		12-18 ^c /16	Failure
Unknown ^d 24	Pneumonia	85 F		103 (39.4)	30,000	RUL, RML, LLL consolidation	Heart failure	4/10	Cured

^a Numbers in parentheses represent the approximate Celsius equivalent.

^b RML, Right middle lobe; RLL, right lower lobe; LLL, left lower lobe; RUL, right upper lobe; LUL, left upper lobe.

^c Treated concurrently with 1 g of kanamycin per day.

^d Presumed to be *S. pneumoniae*.

tions (numbers 13, 18, and 19) required surgical procedures in addition to cephalapirin therapy, including lung decortication, drainage of an extrapleural abscess, and incision of an olecranon bursa, respectively. Patient 13 became afebrile by day 7 of cephalapirin treatment (day 4 post-lung decortication); patients 18 and 19 both were afebrile on day 3 of cephalapirin therapy. *S. aureus* could no longer be recovered from drainage from the infected sites by 5, 15, and 15 days, respectively, after institution of cephalapirin.

Four patients (numbers 20 to 23) with gram-negative bacillary pneumonia received cephalapirin. The diagnosis was established by the demonstration of gram-negative rods in predominance in smears and recovery of *E. coli* or *K. pneumoniae* in cultures from transtracheal aspirates in patients 20 and 21, and from sputum and pleural fluid or lung tissue in patients 22 and 23. Patient 20, a 74-year-old woman, died of *E. coli* pneumonia on day 5 of treatment. Examination of the pretreatment transtracheal aspirate showed sparse gram-positive cocci and numerous gram-negative bacilli, but only *E. coli* was recovered on culture. On day 4 of treatment a repeat transtracheal aspirate showed only gram-negative bacilli and culture again grew out only *E. coli*. The MIC of both isolates was 25 $\mu\text{g/ml}$. Autopsy showed severe confluent bronchopneumonia involving three lobes, but lung cultures were sterile and no bacteria were seen in tissue sections. Two of three patients with *K. pneumoniae* infections were cured, including patient 22, an alcoholic male with severe lobar pneumonia. He required several thoracenteses for management of early empyema and received concurrent kanamycin therapy. He defervesced within 8 days and *K. pneumoniae* was eradicated from sputum and pleural fluid within 10 days of institution of therapy. Patient 23 with severe lobar pneumonia due to type 1 *K. pneumoniae* fared less well. He had been ill for 5 days before institution of therapy and developed gangrene of most of the right lung, necessitating pneumonectomy. Despite therapy with large doses of cephalapirin and kanamycin which eradicated *K. pneumoniae* from sputum, the patient remained febrile. The pathogen was recovered from necrotic lung resected on day 27 of illness, 7 days after cephalapirin therapy was discontinued. MIC of pre- and post-treatment isolated was 3.1 $\mu\text{g/ml}$.

Adverse effects. There were no instances of drug-induced anemia, neutropenia, eosinophilia, or renal toxicity. There were, however,

nine patients who developed elevated SGOT values during therapy. Seven had been given cephalapirin intramuscularly and two (patients 14 and 22) had been treated intravenously. In the latter two, elevated SGOT levels were noted before treatment as well, but significant elevations (greater than 50 units) occurred during intravenous therapy. In all cases, SGOT values diminished after therapy ended. Serum creatinine phosphokinase levels were not measured.

The most striking adverse effect was severe watery diarrhea in patient 12 treated with 6 g per day intravenously for 7 days. Culture of diarrhea fluid yielded no pathogenic microorganism. The diarrhea subsided 3 days after cephalapirin therapy ended.

Local tolerance on injection was good in many patients; however, 10 of 23 who received some or all of their doses intramuscularly reported some pain after the injection. In only one case was the pain severe enough to necessitate stopping therapy. Evidence of phlebitis (redness and a palpable venous cord at the infusion site) developed in three of nine patients given intravenous cephalapirin. Of the two patients who developed severe phlebitis, one received 6 g daily for nine days and the other received 12 to 18 g daily for 16 days. Another patient who was given 12 to 18 g intravenously daily for 16 days had evidence of mild phlebitis.

In vitro results. All pneumococcal isolates from study patients had MIC of 0.1 μg or less per ml. Patients' *S. aureus* isolates were all inhibited by 0.4 μg of cephalapirin per ml, and the *K. pneumoniae* isolates by 6.25 μg or less per ml. These organisms were included with other concurrent hospital isolates in studies of the comparative in vitro activity of cephalapirin, cephalothin, and cephaloridine. Cephalapirin was somewhat more active than cephalothin against group A streptococci and pneumococci, but less active than cephaloridine (Fig. 1). Cephalapirin inhibited all strains of pneumococci at a concentration of 0.1 $\mu\text{g/ml}$ and all group A streptococci at 0.05 $\mu\text{g/ml}$. Cephalapirin and cephalothin showed almost identical anti-staphylococcal activity, inhibiting all 100 strains of *S. aureus* at 0.8 $\mu\text{g/ml}$ (Fig. 2).

Cephalapirin was less active than cephalothin and cephaloridine against isolates of *E. coli*, inhibiting 73% of the isolates at a concentration of 12.5 $\mu\text{g/ml}$ compared to 80% and 96% of strains inhibited by cephalothin and cephaloridine, respectively (Fig. 3). The activities of the three cephalosporins did not differ significantly against isolates of *K. pneumoniae*, *Proteus mirabilis*, or *Enterobacter*. Cephalapirin inhib-

FIG. 1. Cumulative percentage of inhibition of isolates of group A *Streptococcus* and *S. pneumoniae*. Numbers in parentheses refer to the number of isolates tested.

ited 90% of *K. pneumoniae*, 85% of *P. mirabilis*, and 30% of *Enterobacter* at a concentration of 12.5 $\mu\text{g/ml}$. MIC of the three cephalosporins was 100 μg or greater per ml for 15 strains each of *Pseudomonas aeruginosa* and indole-positive *Proteus* and 10 strains of *Serratia*.

Serum levels. Peak serum levels in patients

FIG. 2. Cumulative percentage of inhibition of 100 *S. aureus* isolates.

FIG. 3. Cumulative percentage of inhibition of isolates of *E. coli*, *Klebsiella*, *P. mirabilis*, and *Enterobacter*. Numbers in parentheses refer to the number of isolates.

given 1-g intramuscular doses were measured 1 h after injection (Table 2). The values ranged from 4.3 to 40.0 $\mu\text{g/ml}$, with a mean of 10.1 $\mu\text{g/ml}$. Cephapirin activity disappeared rapidly from the blood in most cases so that 4 h after injection the mean level was 1.3 $\mu\text{g/ml}$.

Significant elevations of serum cephapirin levels were observed in two patients. Patient 20 had concentrations of 40.0, 34.0 and 12.2 $\mu\text{g/ml}$ 1, 2 and 3 h after a 1-g intramuscular dose on day 4 of treatment. At the time, she was in heart failure and had a blood urea nitrogen content of 42 mg/100 ml. Patient 21 had twice weekly hemodialysis for chronic renal failure and received 1-g intramuscular doses every 6 h for *K. pneumoniae* bronchopneumonia. On day 8 of treatment, immediately prior to beginning dialysis, and 6 h after his last dose, he had a cephapirin serum level of 78.4 $\mu\text{g/ml}$. At the beginning of the dialysis he received 1 g of cephapirin intravenously. Subsequent serum levels during the dialysis were: 30 min postdose, 126.4 $\mu\text{g/ml}$; 1 h postdose, 70.4 $\mu\text{g/ml}$; and 4 h postdose, 52.0 $\mu\text{g/ml}$. No untoward effects were noted in these two patients as a result of the elevated levels.

DISCUSSION

Cephapirin is highly active in vitro against isolates of *S. aureus*, pneumococci, and group A *Streptococcus*. Its anti-staphylococcal activity was virtually identical to that of cephalothin. Large inocula of all staphylococcal isolates were inhibited by 0.8 μg of both agents per ml. In another study large inocula of penicillin-resistant *S. aureus* were killed in vitro at cephapirin

concentrations of 5 μg or less per ml (15). This suggests that cephapirin may, like cephalothin, be resistant to staphylococcal penicillinase. The in vitro activity of cephapirin against pneumococci and group A streptococci was intermediate between that of cephaloridine and cephalothin. All isolates were inhibited by the three cephalosporins at concentrations of 0.2 μg or less per ml. The small differences in antibacterial activity of the three agents are unlikely to be important factors in the successful management of infections due to these organisms. Isolates of *Enterobacteriaceae* were much less susceptible to cephapirin. This agent and cephalothin showed similar in vitro activity against isolates of *P. mirabilis* and *K. pneumoniae*, but cephapirin was less active against *E. coli*. The latter finding agrees with the results of other studies (3, 7). *Pseudomonas*, indole-positive *Proteus*, and *Serratia* were highly resistant.

The peak serum level was measured in our patients about 1 h after a 1-g intramuscular dose. In patients with normal renal function, little drug was present longer than 4 h after a 1-g parenteral dose. The mean serum concentration 1 h after a 1-g intramuscular dose was 10.1 $\mu\text{g/ml}$, very similar to the mean serum level attainable with a comparable dose of cephalothin. This concentration was well above the MIC of all isolates of *S. aureus*, pneumococci, and group A *Streptococcus*, but was below the MIC of many isolates of *Enterobacteriaceae*. Two patients with abnormal renal function, one of whom was anuric and on a hemodialysis program, had considerably elevated serum levels without recognized toxicity. Hemodialysis was effective in partially removing cephapirin from the blood, as documented by McCloskey et al. (12).

Half of the patients treated were 60 years of age or older, and many had severe underlying disease. Despite these adverse prognostic factors the infectious processes of 21 of the 24 patients were eradicated. The clinical results observed with cephapirin therapy were satisfactory in patients with infection due to *S. pneumoniae* and *S. aureus*. All seven patients with staphylococcal infection were cured, although removal of a foreign body in one and surgical drainage of abscesses in three others was certainly of major therapeutic importance. One elderly male died during therapy of pneumococcal pneumonia despite eradication of the pneumococci from the lungs. Eleven others with proven and one with suspected pneumococcal infections were cured. Although only four patients with gram-negative

TABLE 2. Cephapirin serum levels

Treatment	Patient no.	Dose interval (h)	Serum level ($\mu\text{g/ml}$)			
			1 ^a	2	3	4
Intramuscular dose (1 g)	1	6	4.3	3.4		0
	3	6	9.9	7.6		3.4
	7	6	9.0	8.6		3.1
	11	6	17.6	8.6		0
	17	6	10.6	3.0		0
	19	6	13.0	7.6		1.3
	18	4	6.9	3.8		1.6
	20	4	40.0	34.0	12.2	
Intravenous dose (1 g)	2	6	22.0	5.7	1.8	
	13	4	7.0	4.1	1.0	
Intravenous dose (2 g)	22	4	30.4	20.0		18.5

^a Time (hour) after dose.

bacillary pneumonia were treated, the results were disappointing. One elderly female died during therapy of *E. coli* pneumonia from hypoxia, severe congestive heart failure, and uncontrollable ventricular arrhythmias despite apparent eradication of the pathogen from lung tissue. In another patient severe lobar pneumonia (*Klebsiella*) progressed to virtually total gangrene of one lung despite cephapirin treatment of 12 g or more daily. The responsible pathogen was isolated in pure culture from surgically resected tissue and showed identical cephapirin MIC to the pretreatment isolate.

Seven patients who received cephapirin by the intramuscular route developed elevated SGOT values. This abnormality may be related to muscle damage at injection sites and has been observed by others (4). We did not observe any instances of rash, eosinophilia, or neutropenia, adverse reactions which have been reported by other investigators (3, 4, 10, 15). Only two patients received long-term intravenous administration of cephapirin. In neither case was there any evidence of the serum-sickness type of adverse reaction noted by Sanders et al. (13). The only severe adverse effect noted was profuse watery diarrhea in one patient that subsided after cephapirin treatment was discontinued.

Cephapirin is an effective antimicrobial agent in the treatment of pneumococcal and staphylococcal infection, but may be less satisfactory in the treatment of gram-negative bacillary infection involving sites other than the urinary tract. In contrast to early opinions (4, 9), it may not be better tolerated by patients than cephalothin. Many of our patients who received intramuscular cephapirin complained of pain at injection sites, and severe phlebitis was observed in two patients who received intravenous cephapirin. Recent evidence from one double-blind, cross-over design trial suggests that the potential of cephapirin to produce phlebitis may be equivalent to that of cephalothin (5), though in another study of different design cephapirin produced less phlebitis than cephalothin (8), and in a third study phlebitis was seldom observed after administration of either agent (13). The eventual role of cephapirin in antibacterial chemotherapy will likely depend on further comparative trials of efficacy and toxicity.

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