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A survey of peritonitis and exit-site and/or tunnel infections in Japanese children on PD

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Abstract To obtain data on peritonitis and exit-site and/or tunnel infections (ESI/TI) in Japanese children undergoing peritoneal dialysis (PD) from January 1999 through June 2003, we surveyed 22 members of the Japanese Study Group of Pediatric Peritoneal Dialysis (JSPPD) by questionnaire. One hundred and thirty patients were eligible. Seventy episodes of bacterial peritonitis occurred in 45 patients (0.17 episodes/patient-year), and 123 ESI/TI occurred in 60 patients (0.29 episodes/patient-year). S. aureus and MRSA were found to be the causative organisms in 39% and 13% of the peritonitis episodes, and in 59% and 20% of the ESI/TI, respectively. Tunnel infection was found in 55% of the MRSA peritonitis episodes. Eleven percent of the peritonitis episodes relapsed, and 19% needed hemodialysis. One patient died due to MRSA peritonitis. The PD catheter was removed in all fungal and 78% of MRSA peritonitis. However, the type

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M. Honda Department of Pediatrics, Tokyo Metropolitan Children's Hospital, Tokyo, Japan of organism did not influence the need for catheter-related surgery for ESI/TI. Neither peritonitis nor ESI/TI was prevented by the use of a swan-neck catheter, a downwardpointing exit site, povidone iodine exit-site care, bathing instruments, or nasal mupirocin. In conclusion, MRSA peritonitis was not uncommon in children in Japan, was frequently associated with tunnel infections, and had a poor outcome. No association was found between the occurrence of infection and preventive measures previously reported as effective. Alternative approaches are needed in children, especially for MRSA.

Keywords Peritoneal dialysis (PD) · Children · Peritonitis · Exit-site and/or tunnel infections (ESI/TI) · Multicenter survey · MRSA

Introduction

Prevention of peritonitis and exit-site and/or tunnel infections (ESI/TI) is essential for successful long-term peritoneal dialysis (PD). Based on an annual survey conducted in the years 1991–2001 by The Japanese Study Group of Pediatric Peritoneal Dialysis (JSPPD), the incidence of peritonitis in children on PD was 0.31 episodes/patient-year [1], higher than in adults [2]. ESI/TI also tended to occur more frequently in children, and were often associated with peritonitis.

In another JSPPD survey from 1981 through 1991, 11 of 72 (15%) deaths in children on PD resulted from peritonitis, and 12 (17%) from other infections [3]. In a more recent JSPPD survey from 1991 through 2003, only 2 out of 55 (3.6%) deaths were due to peritonitis, while deaths from cardiovascular complications increased from 26% to 36% [4]. Although the peritonitis-related mortality rate has decreased, peritonitis remains the most common cause of treatment failure in children; between 1991 and 2001 it was responsible for 44% of all transfers to hemodialysis (HD) [1]. In patients on PD for less than five years, 58% of the transfers to HD were caused by peritonitis. Furthermore, in children on long-term PD, we reported that severe perito-

nitis was a possible risk factor for encapsulating peritoneal sclerosis [5–6], a life-threatening complication.

We now report our analysis of data from a retrospective multicenter survey of peritonitis and ESI/TI in children on PD in Japan, and the impact of different preventative procedures [7-8] on such infections in children.

Patients and methods

This survey was conducted exclusively by committee members of the Japanese Study Group of Pediatric Peritoneal Dialysis (JSPPD). These committee members belonged to 22 hospitals, each of which had treated more than ten pediatric PD patients from the start of its PD program. A questionnaire was sent to the committee members in July 2003. The survey was independently approved by the local ethics committee of each hospital.

Patients were eligible for the survey if they were on PD and were 15 years or younger on 1st January 1999, and were still on PD on 31st December 2000. Therefore, all patients had been continuing PD for at least two years. New patients starting PD and those terminating PD between 1st January 1999 and 31st December 2000 were excluded. One hundred thirty patients were registered, representing 75% of all 173 Japanese PD patients 15 years or younger from 132 hospitals and dialysis centers treating pediatric PD patients, as identified by the Annual National Survey of JSPPD in 2001 [1].

Data on each episode of peritonitis and ESI/TI occurring during the observation period from 1st January 1999 through 30th June 2003 were reviewed. Data collected included time and age at the start of PD and at the onset of infection, causative organisms, potential causes of peritonitis, patient and catheter outcomes, antibiotic treatment protocols, catheter type and direction of exit-site, time of catheter insertion, cleansing and bathing methods, and whether or not nasal mupirocin was used for *Staphylococcus aureus* nasal carriers before the onset of infection.

Peritonitis was defined as the presence of cloudy PD effluent with more than 100 white blood cells/mm³ and more than 50% polymorphonuclear cells, in accordance with the ISPD guidelines [9]. ESI/TI was diagnosed from at least one of: purulent discharge, marked pericatheter swelling, redness and/or tenderness of the sinus tract of the PD catheter. Organisms were considered pathogens only when they were cultured from a purulent discharge from the exit site. Relapse of peritonitis or ESI/TI was defined as the occurrence of infection with the same organisms within four weeks of completing antibiotic treatment for the initial episode. A relapse was regarded as part of one single episode of peritonitis or ESI/TI. These definitions were agreed to at the JSPPD Annual Meeting, before the questionnaire was sent out.

Data were expressed as mean \pm SD unless otherwise indicated. For statistical analyses, StatView-J 5.0 (Abacus Concepts, Berkeley, CA, USA) was used. We used the Mann–Whitney U test to determine differences in age between groups with and without infectious episodes and incidences by age group. Differences between groups with and without a catheter-type or other preventative procedures were analyzed using the chi-squared test. The chisquared test was also used to determine differences in causes and catheter outcomes between MRSA peritonitis and peritonitis by other organisms. The Kruskal–Wallis test was mainly used to analyze the impacts of causative organisms and the treatment protocol on the patients and catheter outcomes. A P value of less than 0.05 was considered statistically significant. Data were reviewed by the JSPPD committee members participating in the survey at the Annual Meeting in 2004.

Results

Epidemiology

Among the 130 patients, 72 episodes (2 viral and 70 bacterial) of peritonitis occurred in 47 (36%) patients over the 4.5-year period. We excluded the two episodes of viral peritonitis from the analysis; one was related to mumps infection and the other to an unidentified virus infection. Both episodes improved without antibiotic treatment.

Bacterial peritonitis occurred in 45 (35%) of 128 patients (0.17 episodes/patient-year). The mean age at the start of PD for the patients with bacterial peritonitis was 6.9 ± 4.8 years, and it was 8.6 ± 4.5 years in those without peritonitis (*P*=0.05). The mean age at the first episode of bacterial peritonitis in the survey period was 10.3 ± 5.4 years, and the average time on PD before the first peritonitis episode was 3.4 ± 3.0 years. One hundred and twenty-three episodes of ESI/TI occurred in 60 (46%) patients (0.29 episodes/patient-year). The mean age at the start of PD for the patients with ESI/TI was 7.3 ± 4.7 years, and for those without ESI/TI it was 8.6 ± 4.6 years (*P*=0.08). The mean age at the first episode of ESI/TI in the survey period was 10.2 ± 5.0 years, and the average time on PD prior to the first ESI/TI was 2.9 ± 2.6 years.

Fifty-nine patients (45%) had neither bacterial peritonitis nor EST/TI. Thirteen patients (10%) experienced only bacterial peritonitis, and 26 (20%) only ESI/TI, while 32 patients (25%) had both. Peritonitis occurred 1–4 times, and ESI/TI 1–14 times per patient. Twenty-nine patients (64%) had a single episode of peritonitis, ten patients had two episodes, three patients three, and three patients had four episodes. A single episode of ESI/TI occurred in 39 patients (65%), two episodes in eleven, three in three, and more than three episodes in seven patients.

In the patients aged six years or younger at the start of PD (n=52), 26 patients (50%) had bacterial peritonitis, and 19 patients (25%) over the age of six years had it (n=76). The incidence of bacterial peritonitis was 0.24 episodes/ patient-year in the patients aged six years or younger at the start of PD, higher than the 0.11 episodes/patient-year rate in those over six years old (P=0.01). Also, the incidence of ESI/TI was 0.32 episodes/patient-year in the patients aged six years or younger at the start of PD, tending to be higher than the 0.24 episodes/patient-year rate seen in those over

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six years, a difference that was not statistically significant (P=0.09).

Causative organisms and potential causes of peritonitis

Gram-positive organisms were isolated more frequently than other organisms, and were found in 64% of the peritonitis episodes and in 72% of ESI/TI patients (Table 1). *S. aureus* was the single most common organism, causing 39% of peritonitis episodes and 59% of ESI/TI. Methicillin-resistant *S. aureus* (MRSA) caused 9/27 (33%) of the peritonitis cases and 25/73 (34%) of ESI/TI cases were due to *S. aureus*. MRSA was responsible for 13% of all episodes of peritonitis, and 20% of all episodes of ESI/TI.

MRSA peritonitis occurred more frequently in younger children. The mean age of onset of MRSA peritonitis was 7.1 \pm 5.1 years, compared to 11.2 \pm 5.0 years of age for peritonitis caused by other organisms (*P*=0.02).

Tunnel infection was thought to be the likely cause of peritonitis in 23%, touch contamination during dialysis bag exchanges in 7%, unknown in 61%, and other causes in 9% of the cases. While a tunnel infection was found in five of the nine (55%) cases of MRSA peritonitis, it was found in 11 (18%) of the 61 cases caused by other organisms (P=0.04). Antibiotics had been used to treat upper respiratory infections or for prophylaxis of infections after surgery within the preceding four weeks in eight (11%) of the peritonitis episodes.

Patient and catheter outcomes

PD could be continued after the peritonitis had subsided without relapse and also without transfer to HD in 48 (69%) of the 70 episodes. Relapse occurred in eight (11%) episodes of peritonitis; however, PD could be continued without interruption. Gram-positive species other than MRSA were found in six (75%) of these eight episodes of relapse. HD was necessary in 13 (19%) episodes of peritonitis, and of these, three were temporary (23%) and ten required permanent transfer to HD (77%). Of these ten episodes transferred to permanent HD, the causative organisms were fungus in five (50%), MRSA, MSSA and coagulase-negative staphylococcus (CNS) in one episode each, and unknown in two episodes. One patient (2%) died due to MRSA peritonitis.

Catheter removal or replacement was performed in 27 episodes (39%) of peritonitis, including seven MRSA, four MSSA, five fungal, five gram-negative, two CNS and four of unknown etiology. Catheter replacement was performed in 21 episodes, and the mean time to catheter removal was 33 ± 30 days after the onset of peritonitis. In 17 of these 21 cases, the catheter was removed and replaced at the same time. Catheter removal without replacement was performed in six episodes. In all five episodes of fungal peritonitis, the catheter was removed and the patients were transferred to HD as soon as fungus was detected, all within two weeks of the onset of peritonitis. While seven episodes (78%) of MRSA peritonitis required catheter removal or replacement, only six of the 36 (17%) episodes caused by other gram-positive species did so (P=0.01).

Among the ESI/TI, 89 (72%) of 123 episodes subsided without relapse and also without developing peritonitis, 18 (15%) relapsed, nine (7%) did not improve, and seven (6%) developed peritonitis. Fifteen of 25 (60%) episodes related to MRSA subsided without relapse and also without developing peritonitis, and 49 of 64 (77%) episodes caused by other gram-positive species did so. Catheter replacement or revision was needed in 33 (27%) of the ESI/TI episodes, including catheter replacement in 11, unroofing of the catheter cuff in 18, and exit-site revision in four. Seven of 25 (28%) episodes caused by MRSA required catheter-related operations, and 19 of 64 (30%) episodes caused by other gram-positive species did so. The type of organism did not appear to influence the patient outcome and also the need for a catheter-related operation.

Antibiotic treatment

Initial antibiotic treatment protocols varied widely, including drug choices, routes (Table 2), dosages, and duration of administration. For bacterial peritonitis, initial antibiotics were given intraperitoneally in 59 episodes (84%),

Organisms			Number of peritonitis episodes (%)	Number of ESI/TI episodes (%)
Gram-positive species	Total gram-positive		45 (64.3)	89 (72.4)
	Staphylococcus aureus	Total	27 (38.6)	73 (59.3)
		Methicillin-sensitive (MSSA)	18 (26.2)	48 (39.0)
		Methicillin-resistant (MRSA)	9 (12.9)	25 (20.3)
	Other gram-positive		18 (26.2)	16 (13.0)
Gram-negative species			10 (14.3)	14 (11.4)
Fungus			5 (7.1)	3 (2.4)
Culture negative			10 (14.3)	16 (13.0)
Total			70 (100)	123 (100)

Table 1 Causative organisms in
peritonitis and ESI/TI

Table 2 Initial antibiotic routes in peritonitis and ESI/TI

Routes	Number of peritonitis	Number of ESI/TI	
	episodes (%)	episodes (%)	
Intraperitoneally	40 (57.1)	8 (6.5)	
Intraperitoneally and intravenously	19 (27.1)	5 (4.1)	
Intravenously	8 (11.4)	15 (12.2)	
Orally	1 (1.4)	59 (48.0)	
Orally and intravenously	0	17 (13.8)	
Orally and intraperitoneally	0	6 (4.9)	
Locally	0	6 (4.9)	
Unknown	2 (2.9)	7 (5.7)	
Total	70 (100)	123 (100)	

although intravenous antibiotics were also prescribed in 19 of those (32%). Intravenous antibiotics were used with or without intraperitoneal antibiotics in 27 episodes (39%). Regardless of the route of administration, cephalosporins were the most commonly used antibiotics. There were 40 cases of bacterial peritonitis where antibiotics were only given intraperitoneally; first- or second-generation cephalosporins were given in 13 episodes, first- or secondgeneration cephalosporins combined with third-generation cephalosporins in 13, a cephalosporin combined with an aminoglycoside in 12, and glycopeptides (vancomycin) in two. Although vancomycin was used as the initial treatment in four of the nine episodes of MRSA peritonitis, catheter removal or replacement was needed in all four. Antifungal drugs were not knowingly used in the five episodes of fungal peritonitis, but all improved after transfer to HD.

In ESI/TI, antibiotics were given orally as the initial treatment in 82 episodes (67%), although intravenous antibiotics were also administered in 21% and intraperitoneal antibiotics in 7% of those. Of the oral antibiotics used in ESI/TI, cephalosporins were the most common (44

episodes). Trimethoprim/ sulfamethoxazole was used in 11, minomycin in seven, penicillins in six, rifampin in five, macrolides in four, and others in five cases.

Catheters and preventative procedures

All patients except one used catheters with double cuffs; the most common catheter was the swan-neck type, which was used in about 70% of the patients. The intraperitoneal portion of the catheter was either straight or curled. The former was the most common, being used in more than 80% of the patients. The type of catheter used did not differ between the patients with and without infections (Tables 3 and 4).

The exit site was pointing downwards in 64% of patients with bacterial peritonitis, and in 71% of those without peritonitis. The exit site was also pointing downwards in 77% of the patients with ESI/TI and in 67% of those without. The duration of the break-in periods (the time between catheter insertion and start of PD) was less than two weeks in 92% of the patients.

Povidone-iodine solution was used as an exit-site cleansing agent in 64% of patients with bacterial peritonitis, in 72% of those without peritonitis, in 73% of patients with ESI/TI, and in 66% of those without such infection.

Sealing devices for protecting the exit site during bathing were used in 53% of the patients with bacterial peritonitis, in 49% of those without peritonitis, in 55% of patients with ESI/TI, and in 44% of those without ESI/TI.

Nasal application of mupirocin ointment to *S. aureus* nasal carriers was used in only 6% of all patients, and no association was found between the occurrence of infections and the use of mupirocin.

Discussion

There have been no detailed reports about causative organisms, antibiotic regimens and preventative proce-

 Table 3 Factors potentially influencing the occurrence of bacteria peritonitis (N=128)

Number of patients with/without episodes of peritonitis		With (45)	Without (83)
Catheter types*, direction of exit-site, and duration of break period, n (%)	Subcutaneous part of catheter (swan neck: straight)	29 (64%):16	61 (73%):22
	Intraperitoneal part of catheter (straight: curled)	39 (87%):16	67 (81%):16
	Swan neck catheter (intraperitoneal straight type)	23 (51%)	49 (81%):16
	Direction of exit-site (intraperitoneal: lateral: upward)	29 (64%):7:9	59 (71%):4:20
	>2 weeks after catheter insertion	10 (8%)	
Exit-site cleansing agent, bathing method, and use of mupirocin, n (%)	Cleansing agent (providone iodine: chlorhexidine: others)	29 (64%):14:2	60 (72%):18:5
	Bathing method (closed: open: shower) Use of nasal mupirocin	24 (53%):13:8 8 (6%)	41 (49%):18:14

*All patients except one used catheters with double cuffs

Table 4 Factors potentially influencing the occurrence of EST/TI (N=130)

Number of patients with/without episodes of ESI/TI			Without (70)
Catheter types*, direction of exit-site, n (%)	Subcutaneous part of catheter (swan neck: straight)	44 (73%):16	50 (71%):20
	Intraperitoneal part of catheter (straight: curled)	53 (88%):7	63 (90%):7
	Swan neck catheter (intraperitoneal straight type)	38 (63%)	41 (56%)
	Direction of exit-site (intraperitoneal: lateral: upward)	46 (77%):5:9	47 (67%):4:19
Exit-site cleansing agent, bathing method, n (%)	Cleansing agent (providone iodine: chlorhexidine: others)	44 (73%):11:5	46 (66%):17:7
	Bathing method (closed: open: shower)	33 (55%):21:6	31 (44%):23:16

*All patients except one used catheters with double cuffs

dures for peritonitis and ESI/TI in children on PD in Japan. In Japan, a few hospitals treat only a very small number of children, unlike most dialysis centers that treat only adults. The present survey was conducted via questionnaire, which was sent exclusively to the facilities of JSPPD committee members. Although the number of facilities associated with committee members accounts for only 17% of all hospitals and centers managing pediatric PD patients, committee members were actually managing about 75% of all pediatric patients in Japan. In our survey, the proportion of patients using automated PD was unknown; however, according to the Annual National Survey of JSPPD in 2001 [1], more than 80% of the patients were prescribed automated PD.

In a previous JSPPD survey, we found that the risk of peritonitis or ESI/TI was highest in children younger than two years at the start of PD [3]. This survey also showed that the incidence of peritonitis was higher in children younger than this at the start of PD, while that of ESI/TI did not vary according to age. *S. aureus* was the most common cause of peritonitis in our patients. In a survey of Japanese adults, *S. aureus* was also the most common organism, detected in 20% of 448 episodes of peritonitis from 1994 to 1996 [2]. However, in reports from other countries on adults [10–12] and on children [9, 13–15], the most common organism remains CNS. One explanation for this difference might be the low rate of touch contamination as a cause of peritonitis in our survey, thereby reducing the incidence of coagulase-negative staphylococcal peritonitis.

In our survey, *S. aureus* was also the most common organism found in ESI/TI. Family members caring for young children on PD are believed to be important sources of *S. aureus* [16–17]. The incidence of nasal carriers of *S. aureus*, which was not determined in this survey, is reported to be high, ranging from 44% to 62% among pediatric PD patients [17]. Nasal mupirocin was applied to only 6% of those in our survey, mainly because it is only approved by the medical insurance system for MRSA infections in Japan. Applying mupirocin to exit sites has been reported to be highly effective [14]. Exit-site mupirocin for patients, combined with intranasal mupirocin for family members, could significantly reduce the number of *S. aureus* infections.

It is a major concern that MRSA accounted for one-third of peritonitis by *S. aureus*. In a recent Korean report on adults [12], *S. aureus* was the second most common cause of peritonitis; 35% was MRSA, similar to our finding.

According to the Mid-European Pediatric Peritoneal Study Group, 18% of *S. aureus* peritonitis was caused by MRSA in the period between 1993 and 1997 [15].

The type of organism that causes peritonitis affects the outcome [9, 13, 15]. Compared to the other organisms, peritonitis caused by MRSA or fungi was associated with worse outcomes in our survey. MRSA peritonitis occurred more frequently with concomitant tunnel infections and had a worse outcome. Of the nine episodes with MRSA peritonitis, catheter-related surgery was needed in 78%, although PD could be continued in 89%. One patient died due to MRSA peritonitis in this survey, while between 1991 and 2001 no deaths due to peritonitis were reported [1].

Fungal peritonitis is uncommon in children, as previously reported by Warady [18]. In our survey, fungal peritonitis had the worst catheter outcomes. For all episodes of fungal peritonitis, early catheter removal and transfer to HD were performed because those procedures were recommended by ISPD guidelines [8, 9].

Permanent HD was required in ten episodes (14%) of peritonitis. The need for HD transfer in all cases of fungus peritonitis contributed to the relatively high percentage of HD transfer in our survey. The Japanese survey of adults on PD found the rate of HD transfer due to peritonitis to be 16%, similar to our survey. Because HD is the preferred dialysis modality in Japan, patients with PD complications tend to be transferred to HD early.

Excepting the worse outcomes from MRSA and fungal peritonitis, we could not detect any clear relationships between the type of organism producing peritonitis and the need for catheter-related operations, partly because of the limited number of episodes. In adults, Bunke et al. reported that peritonitis due to S. aureus significantly increased the need for catheter removal and transfer to HD compared to other gram-positive infections, although the rate of MRSA was not described [10]. Kim et al. also reported high catheter removal rates in S. aureus infections compared with other gram-positive species, and found that methicillin-resistant CNS episodes showed higher catheter removal rates compared to methicillin-sensitive CNS[12]. Troidle et al. reported that 7.4% of patients with MRSA peritonitis died, while the mortality rate was only 1.3% in patients with MSSA peritonitis [19].

The treatment of peritonitis in children remains controversial. The 1996 ISPD recommendations for initial antibiotic treatment involved a first-generation cephalosporin and an aminoglycoside. In the 2000 ISPD pediatric guidelines [9], a first-generation cephalosporin combined with ceftazidime was recommended for children without risk factors for severe infections, similar to the protocol for adults [8]. For children with certain risk factors, a combined intraperitoneal administration of a glycopeptide and ceftazidime is recommended, despite concerns about increasing resistance to glycopeptide [8, 20]. Consequently, two different sets of guidelines for treatment of peritonitis in children on PD existed during the survey period and this probably contributed to the lack of uniformity in initial treatment in our survey. In addition, the treatment policies differed markedly among the participating hospitals. Intravenous antibiotics were used in 39% of all peritonitis episodes, with or without intraperitoneal antibiotics. However, only four (19%) of the 22 hospitals used them in most (82%) of the episodes. According to a survey on adult patients in Japan, intravenous antibiotics, as used in 72% of cases, were the most preferred treatment of peritonitis. A perceived risk of adverse effects on the peritoneal membrane might be one reason for preferring intravenous to intraperitoneal antibiotics [2]. Another reason might be to avoid mixed antibiotics in the peritoneal fluid. Although the current treatment of peritonitis relies on the intermittent intraperitoneal administration of antibiotics [15], further clarification of the optimal treatment of peritonitis in children is needed.

MRSA was the causative organism in a relatively high proportion of cases, and the initial antibiotics, including vancomycin, did not always influence remission rates in our survey. However, because there were only nine episodes of MRSA, this limited experience does not allow any solid conclusions to be drawn on the effectiveness of MRSA treatment.

Although sealing methods for the exit site during bathing were used in about 50% of patients, open bathing was also used in about 30% of patients without showing an increased infection rate. Because Japanese patients prefer to take a bath than to shower, open bathing for children is common practice when their exit site is intact.

Our results failed to confirm that techniques previously reported to be effective in preventing infections actually are effective. This was mainly because a large number of patients used these techniques regardless of infectious episodes, while relatively few patients did not use these techniques. The small number of patients and the disproportionate number using some of the techniques of preventing infectious complications limited the validity of comparing the efficacies of different procedures.

In conclusion, the incidence of both peritonitis and ESI/ TI in our survey was much lower than in previous reports. MRSA was not uncommon as a causative organism in Japan, and MRSA peritonitis frequently occurred with tunnel infections, and had a worse outcome. Even though the infection rates found in this survey are low, it is apparent that neither peritonitis nor ESI/TI were fully prevented by the use of swan-neck catheters, a downwardpointing exit site, povidone iodine solution, bathing instruments, or mupirocin—all approaches previously reported as effective. Alternative preventive approaches are needed for PD-related infections in children, especially for MRSA infections.

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