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Retrospective analysis of mortality and morbidity of pediatric systemic lupus erythematosus in the past two decades

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A total of 153 pediatric systemic lupus erythematosus patients (131 girls and 22 boys) under 18 years of age who were newly diagnosed between 1980 and 2001 were retrospectively analyzed. All patients were followed up until death, loss of follow-up, or December 31, 2002. The mean follow-up duration was 6.11 ± 9.02 years. There were no differences in sex and family history between the 1980-to-1990 cohort and the 1991-to-2001 cohort. The rate of complications of infection, skeletal manifestation, and end-stage renal disease were significantly higher in the 1980-to-1990 cohort (p=0.007, 0.001, and 0.000, respectively). Infection was the leading cause of death, and there were no differences in the cause of death between the 2 cohorts except end-stage renal disease (p=0.005). The survival rate was significantly worse in the 1980-to-1990 cohort than in the 1991-to-2001 cohort (p=0.0012). The 2 significant poor prognostic factors were being female and the development of end-stage renal disease. We conclude that the mortality and morbidity of SLE has improved over the past 2 decades. It may be associated with newer treatment modalities and better supportive care available recently.

Key words: Morbidity, mortality, systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease, which involves multiple organs. The disease has a female predominance. It may present as articular and mucocutaneous involvement, renal disease, hematological abnormalities, and central nervous system disease [1]. Approximately 25% of all cases of SLE occur in the first 2 decades of life [2]. Despite advances in diagnosis and management, complications still cause substantial morbidity [3]. The survival of SLE patients improved in the past 50 years, with 5-year survival increasing from 50% in 1955 to 94% in 1994 [4]. This improvement has been attributed to a number of different factors, including the more judicious use of corticosteroids, refinements in immunosuppressive therapy, more effective treatment of hypertension and cardiovascular disease, and greater availability of dialysis and renal transplantation [4]. Since literature of mortality and morbidity in pediatric SLE in Taiwan is limited, we retrospectively reviewed the mortality and morbidity of pediatric SLE between 1980 and 2001 in a medical center in Taiwan.

Materials and Methods

From 1980 to 2001, medical records of patients who fulfilled the American Rheumatism Association (ARA) 1982 revised criteria for SLE under 18 years of age at National Taiwan University Hospital (NTUH) were retrospectively reviewed. One hundred and fifty-three patients (131 girls and 22 boys) who were newly diagnosed between 1980 and 2001 were enrolled. All patients were followed up until death, loss of follow-up, or December 31, 2002. In the loss of follow-up group, telephone contacts for recent condition and management were done.

The demographic factors such as sex, birth date, family history, onset age, date of diagnosis and death, and duration of follow-up were recorded. The initial presentations including the ARA criteria and other symptoms such as Raynaud's phenomenon, alopecia, lymphadenopathy, and weight loss were recorded. The laboratory data at diagnosis of SLE were collected as follows: proteinuria, cellular cast, increased creatinine (>1 mg/dL), hemolytic anemia, leukopenia (<4000 / mm^3), lymphopenia (<1500 /mm^3), thrombocytopenia (<100 000 /mm^3), positive anti-double strand DNA (anti-dsDNA), anti-Smith antibody (anti-Sm), anti-ribonucleoprotein antibody (anti-RNP), anti-SSA, anti-SSB, anti-scl-70, low C3 (<80 mg/dL), low C4 (<20 mg/dL), positive rheumatoid factor, and elevated erythrocyte sediment rate (ESR) (>20 mm at 1 h/>40 mm at 2 h). The complications and causes of death in SLE patients were analyzed. Infection was defined as

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infection needed to be hospitalized. The infection rate was calculated as infected patients divided by all patients. End-stage renal disease (ESRD) was defined as the time of initiation of dialysis or renal transplantation. Therapeutic strategies and medications were also recorded.

To compare the differences of mortality and morbidity, all patients were divided into 2 cohorts: the 1980-to-1990 cohort and the 1991-to-2001 cohort. The 1980-to-1990 cohort was designated as the "old" cohort and the 1991-to-2001 cohort as the "new" cohort. The differences between these 2 cohorts were compared using the chi-square test and independent *t* test. The mortality rate was defined as the number of deaths divided by the total number of patients. Survival probabilities were estimated using the Kaplan-Meier method. The survival differences were compared by the log-rank statistic test. The prognostic factor of survival was analyzed by multivariate logistic regression. A *p* value less than 0.05 was considered significant.

Results

The baseline data of 153 patients (22 boys and 131 girls) are summarized in Table 1. Nine patients had a family history of SLE. The onset age was 13.14 ± 5.99 years and the age at diagnosis was 13.54 ± 5.55 years. There were no differences between sex distribution, family history, and death age between the 2 cohorts. The onset age and diagnosed age were significantly older in the new cohort than in the old cohort (p=0.042 and 0.017, respectively). The follow-up duration was significantly shorter in the new cohort (5.31 ± 6.9 years) than in the old cohort (7.66 ± 11.59 years) with p=0.002. The total number of loss of follow-up patients was 29 (19%) without any difference between the 2 cohorts.

The characteristics including ARA criteria and other manifestations and laboratory data at diagnosis are summarized in Table 2. The frequent characteristics at diagnosis were anti-nuclear antibody (ANA), immunologic disorder, hematologic disorder, and malar rash. There were 20 patients with alopecia, 19 with lymphadenopathy, 7 with Raynaud's phenomenon, 7 with weight loss, and 1 with recurrent parotitis. The frequent characteristics of laboratory data were low C3, elevated ESR, low C4, and positive anti-dsDNA.

Infection was the leading complication (Table 3). The identified pathogens included herpes zoster (19.6%), *Salmonella* (7.2%), *Escherichia coli* (5.2%), *Candida* (4.6%), *Staphylococcus* (2%), and *Enterobacter*, *Pseudomonas*, *Acinetobacter*, *Proteus*, *Pneumococcus*, *Mycobacterium tuberculosis*, *Cryptococcus*, *Shigella*, *Morganella*, *Corynebacterium*, *Klebsiella*, *Citrobacter*, and *Enterococcus*. The neurologic manifestations included encephalopathy (5 cases), brain infarction (3), psychoses (3), seizures (2), and myelopathy (1). The cardiovascular manifestations included limb vasculitis (2), venous thrombosis (2), acute myocardial infarction (1), and dissection of aortic aneurysm (1). The skeletal manifestations included osteonecrosis (10), compression fracture (2), and synovitis (1). The ocular manifestations included retinopathy (6), glaucoma (3), and cataract (2). Others included acute renal failure (5), antiphospholipid syndrome (4), pancreatitis (3), lupus pneumonitis (2), superior mesenteric artery (SMA) syndrome (1), enteropathy (1), and obstructive uropathy (1). Comparing the differences between the 2 cohorts, there were significant declines recently in infection, skeletal manifestations, and ESRD (p=0.007, 0.001, and 0.000, respectively).

The frequent drugs for treatment were oral corticosteroids (95.4%), antimalarials (64.1%), and azathioprine (64.1%) (Table 4). The other immunosuppressive agents included cyclosporin A (23 cases) and methotrexate (1). The increased medication recently included antimalarials, cyclophosphamide pulse therapy, and other immunosuppressive agents (cyclosporin A) (p=0.000, 0.015, and 0.016, respectively).

Table 1. Baseline data of SLE patients in 2 different periods of cohort study

Category	Cohort study period		Total	*p*
	1980-1990 n = 52 (%)	1991-2001 n = 101 (%)	n = 153 (%)	
Sex (male:female)	5:47	17:84	22:131	NS
Family history	3 (5.8)	6 (5.9)	9 (5.9)	NS
Age of onset (yrs)	12.45 ± 5.27	13.49 ± 6.23	13.14 ± 5.99	0.042
Age at diagnosis (yrs)	12.80 ± 5.30	13.92 ± 5.53	13.54 ± 5.55	0.017
Follow-up duration (yrs)	7.66 ± 11.59	5.31 ± 6.90	6.11 ± 9.02	0.002
Death age (yrs)	17.83 ± 11.27	16.89 ± 7.55	17.49 ± 10.05	NS
No. of loss of follow-up	12 (23.1)	17 (16.8)	29 (19.0)	NS

Abbreviations: SLE = systemic lupus erythematosus; NS = not significant

Table 2. Characteristics and laboratory data at diagnosis in SLE patients in 2 different periods of cohort study

Category	Cohort study period		Total n = 153 (%)	*p*
	1980-1990 n = 52 (%)	1991-2001 n = 101 (%)		
ARA criteria				
Malar rash	42 (80.1)	76 (75.2)	118 (77.1)	NS
Discoid lesion	0 (0)	3 (3.0)	3 (2.0)	NS
Photosensitivity	13 (25)	25 (24.8)	38 (24.8)	NS
Oral ulcer	8 (15.4)	32 (31.7)	40 (26.1)	0.030
Arthritis	25 (48.1)	63 (62.4)	88 (57.5)	0.090
Serositis	9 (17.3)	14 (13.9)	23 (15.0)	NS
Renal disorder	33 (63.5)	57 (56.4)	90 (58.8)	NS
Neurologic disorder	5 (9.6)	2 (2.0)	7 (4.6)	0.032
Hematological disorder	40 (76.9)	82 (81.2)	122 (79.7)	NS
Immunological disorder	43 (82.7)	94 (93.1)	137 (89.5)	0.047
ANA	50 (96.2)	100 (99.0)	150 (98.0)	NS
Others				
Raynaud	3 (5.8)	4 (4.0)	7 (4.6)	NS
Alopecia	4 (7.7)	16 (15.8)	20 (13.1)	NS
Lymphadenopathy	6 (11.5)	13 (12.9)	19 (12.4)	NS
Weight loss	2 (3.8)	5 (5.0)	7 (4.6)	NS
Laboratory data				
Proteinuria	31/52 (59.6)	54/101 (53.5)	85/153 (55.6)	NS
Cellular cast	18/52 (34.6)	33/101 (32.7)	51/153 (33.3)	NS
Increased creatinine	12/50 (24.0)	15/98 (15.3)	27/148 (18.2)	NS
Hemolytic anemia	24/52 (46.2)	44/101 (43.6)	68/153 (44.4)	NS
Leukopenia	14/52 (26.9)	39/101 (38.6)	53/153 (34.6)	NS
Lymphopenia	29/52 (55.8)	61/101 (60.4)	90/153 (58.8)	NS
Thrombocytopenia	10/52 (19.2)	20/101 (19.8)	30/153 (19.6)	NS
Anti-dsDNA	40/50 (80.0)	89/101 (88.1)	129/151 (85.4)	NS
Anti-Sm	10/29 (34.5)	19/72 (26.4)	29/101 (28.7)	NS
Anti-RNP	15/27 (55.6)	28/72 (38.9)	43/99 (43.4)	NS
Anti-SSA	12/24 (50.0)	38/72 (52.8)	50/96 (52.1)	NS
Anti-SSB	7/24 (29.2)	15/72 (20.8)	22/96 (22.9)	NS
Anti-scl-70	8/24 (33.3)	7/72 (9.7)	15/96 (15.6)	0.006
Low C3	48/52 (92.3)	95/100 (95.0)	143/152 (94.1)	NS
Low C4	44/51 (86.3)	86/100 (86.0)	130/151 (86.1)	NS
Rheumatoid factor	5/23 (21.7)	8/44 (18.2)	13/67 (19.4)	NS
Elevated ESR	41/46 (89.1)	64/76 (84.2)	105/122 (86.1)	NS

Abbreviations: SLE = systemic lupus erythematosus; ARA = American Rheumatism Association; ANA = antinuclear antibody; Anti-Sm = anti-Smith antibody; Anti-RNP = anti-ribonucleoprotein antibody; ESR = erythrocyte sedimentation rate; NS = not significant

The age of mortality was 17.49 ± 10.05 years. The overall mortality rate was 21.6% at 5 years and 28.8% at 10 years. The overall survival probability was 75. 5% at 5 years and 63.1% at 10 years. In the old cohort, the 5-year survival probability was 60.4% and the 10-year survival probability was 44.4%. In the new cohort, these numbers were 85.2% and 77.5%, respectively. Survival was significantly worse in the old cohort than in the new cohort as calculated using the log-rank test (p=0.0012) (Fig. 1). On a univariate analysis, being male was a good prognostic factor on survival (p=0.011). Increased creatinine, decreased hemoglobulin, and serositis at diagnosis were poor prognostic factors (p=0. 009, 0.087, and 0.031, respectively). Apart from this, complications of ESRD, neurologic, skeletal, and ocular manifestations were also poor prognostic factors (p=0. 006, 0.073, 0.023, and 0.048, respectively). Using multivariate logistic regression analysis, only sex and ESRD complications were significant. About the medication, using cyclophosphamide had adverse effects on survival (p=0.018), while using at least 6 times of cyclophosphamide pulse therapy, antimalarials, and azathioprine were good (p=0.064, 0.000, and 0.004, respectively). By multivariate analysis, cyclophosphamide, antimalarials, and azathioprine were significant.

There were 50 deaths in the follow-up duration and the causes of death are summarized in Table 5. Infection was again the most frequent cause of death. The identified pathogens included 13 *Pseudomonas*, 4

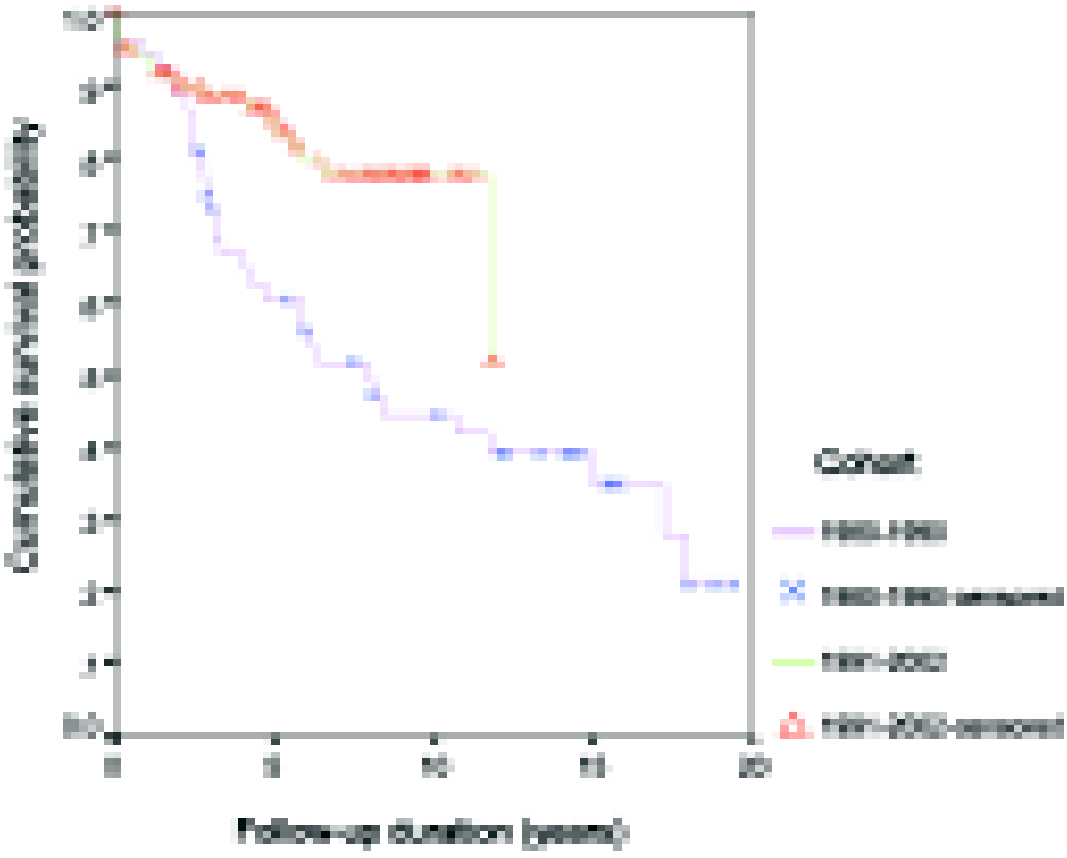

Fig. 1. Survival curve in systemic lupus erythematosus patients (p=0.0012 by the log-rank test of Kaplan-Meier method).

Enterobacter, 4 *Candida*, 3 *Klebsiella*, 2 *Pneumococcus*, 2 *Staphylococcus*, 2 *Aspergillus*, and 1 *each of Enterococcus*, herpes simplex virus, *Proteus*, *Bacteroides*, *Streptococcus intermedius*, *Acinetobacter*, *E. coli*, *Provideridia*, and *Trichospiron*. The second leading cause of death was massive bleeding due to disseminated intravascular coagulopathy or antiphospholipid syndrome. The neurologic symptoms included brain infarction (2 cases), organic brain syndrome (4), and seizure (3). The others included 4 congestive heart failure, 1 adrenal insufficiency, 1 liver cirrhosis, 1 ovarian carcinoma, and 1 IVC thrombosis. The only significant difference in the cause of death between the 2 cohorts was ESRD (34.4% in the old cohort decreased to 0% in the new cohort, p=0.005).

Discussion

Despite the advances in diagnosis and management,

Table 3. Complications in SLE patients in 2 different periods of cohort study

Category	Cohort study period		Total n = 153 (%)	p
	1980-1990 n = 52 (%)	1991-2001 n = 101 (%)		
Infection	32 (61.5)	39 (38.6)	71 (46.4)	0.007
Neurologic manifestation	8 (15.4)	7 (6.9)	15 (9.8)	0.096
Cardiovascular manifestation	4 (7.7)	4 (4.0)	8 (5.2)	NS
Skeletal manifestation	9 (17.3)	2 (2.0)	11 (7.2)	0.001
Ocular manifestation	4 (7.7)	8 (7.9)	12 (7.8)	NS
ESRD	13 (25.0)	5 (5.0)	18 (11.8)	0.000
Others	14 (26.9)	17 (16.8)	31 (20.3)	NS

Abbreviations: SLE = systemic lupus erythematosus; ESRD = end-stage renal disease; NS = not significant

Table 4. Treatment of systemic lupus erythematosus with different agents

Category	Cohort study period		Total n = 153 (%)	*p*
	1980-1990 n = 52 (%)	1991-2001 n = 101 (%)		
Oral corticosteroids	50 (96.2)	96 (95.0)	146 (95.4)	NS
Steroid pulse therapy[a]	22 (42.3)	50 (49.5)	72 (47.1)	NS
Antimalarials	14 (26.9)	84 (83.2)	98 (64.1)	0.000
Cyclophosphamide	24 (46.2)	38 (37.6)	62 (40.5)	NS
Cyclophosphamide pulse therapy[b]	4 (7.7)	24 (23.8)	28 (18.3)	0.015
Azathioprine	32 (61.5)	66 (65.3)	98 (64.1)	NS
NSAID	9 (17.3)	24 (23.8)	33 (21.6)	NS
Other immunosuppressive agent	3 (5.8)	21 (20.8)	24 (15.7)	0.016

Abbreviations: NSAID = nonsteroidal antiinflammatory drugs; NS = not significant

[a]Steroid pulse therapy denotes intravenous methylprednisolone ≥15 mg/kg/d for 3 days, maximum 1 g/d.

[b]Cyclophosphamide pulse therapy denotes at least 6 times of intravenous cyclophosphamide pulse therapy (0.5-1 g/m^2 monthly than quarterly).

complications attributable to SLE or the treatment itself continue to cause substantial morbidity [3]. Infections, coronary artery disease, and orthopedic management of osteonecrosis were prominent reasons for hospitalization [5]. In the present study, infection was the leading complication. The mechanisms of infectious complications were associated with the disease itself, although glucocorticoids and immunosuppressive drugs may increase the risks and the number of types of infections that develop [5]. The common reported infections included herpes zoster, *Salmonella* bacteremia, pneumococcal sepsis, and gram-negative polyarticular septic arthritis [5]. In the present study, herpes zoster was most common (19.6%), followed by *Salmonella*, *E. coli*, and *Candida* infections. Pneumococcal sepsis was rare in our report. The significant lower complication of infections in the new cohort may be associated with advances in antimicrobials and immunosuppressive agents. The role of daily oral glucocorticoids therapy in the pathogenesis of osteonecrosis is already well established [5]. There was significantly less osteonecrosis in the new cohort in our studies, and it may be associated with advances in the glucocorticoids usage as using other immunosuppressive agents to decrease the oral daily dose. The neurologic manifestations such as hypertensive encephalopathy, seizure, and psychosis were decreased in the new cohort, possibly due to better control of blood pressure and disease activity.

Renal involvement was noted in 40% to 80% of pediatric lupus patients [6]. Many efforts were made to avoid the complication of ESRD. For patients with severe lupus nephritis, an extended course of pulse cyclophosphamide therapy is more effective than a 6-month course of pulse methylprednisolone therapy in preserving renal functions [7]. The National Institutes of Health studies showed that a regimen of monthly intravenous pulses of cyclophosphamide was comparable to oral cyclophosphamide in terms of efficacy, but was less toxic [8]. The current, preferred regimen is monthly pulse intravenous cyclophosphamide for 6 months followed by quarterly pulses for 2 years [4]. The side effects of cyclophosphamide include premature ovarian failure, infection (most commonly herpes zoster), and possible malignancy. In our department, we regularly administered the preferred

Table 5. Causes of death in SLE patients

Category	Cohort study period		Total n = 50 (%)	*p*
	1980-1990 cohort n = 32 (%)	1991-2001 cohort n = 18 (%)		
Infection	25 (78.1)	13 (72.2)	38 (76)	NS
Active lupus	3 (9.4)	1 (5.6)	4 (8)	NS
ARDS	8 (25.0)	4 (22.2)	12 (24)	NS
ESRD	11 (34.4)	0 (0)	11 (22)	0.005
Massive bleeding	8 (25.0)	6 (33.3)	14 (28)	NS
Neurologic symptoms	4 (12.5)	5 (27.8)	9 (18)	NS
Others	10 (31.3)	3 (16.7)	13 (26)	NS

Abbreviations: SLE = systemic lupus erythematosus; ARDS = acute respiratory distress syndrome; ESRD = end-stage renal disease; NS = not significant

regimen of cyclophosphamide pulse therapy since 1993, and the complication of ESRD decreased significantly in the new cohort (p=0.000).

The leading causes of death in patients with SLE are infectious complications and clinical manifestations including acute vascular neurologic events, renal failure, and cardiovascular or pulmonary involvement [5]. Early deaths are usually due to active disease, whereas atherosclerosis is a leading cause of late deaths [9]. The present data confirm a previous report [10] that patients with SLE die more often from infections than from disease activity. There was no mortality of atherosclerosis in our pediatric patients. The most common infectious agents related to the mortality were *Pseudomonas*, *Enterobacter*, *Candida*, and *Klebsiella*. It seemed that nosocomial infection was predominant.

Recent studies have shown a greater reduction in mortality in lupus patients than in the general population [9]. Overall, the 10-year survival rate in retrospective series has been 75% to 85%, with more than 90% of patients surviving longer than 5 years [9]. In the present study, the 10-year survival probabilities improved from 44.4% in the old cohort to 77.5% in the new cohort.

Several features of SLE have been associated with mortality. Renal damage (but not active nephritis) had the highest risk, followed by those with thrombocytopenia, very active disease at presentation, and lung involvement [11]. In the present study, being male was a significant good prognostic factor, while the complication of ESRD was a poor prognostic factor. Cyclophosphamide pulse therapy, antimalarials, and azathioprine had good effects on survival, but cyclophosphamide had adverse effects. The use of cyclophosphamide (not the pulse therapy) may not decrease the development of ESRD and therefore had adverse effects on survival. The increased usage of antimalarials and cyclophosphamide pulse therapy in the new cohort and the decrease in ESRD complications may have contributed to the better survival in the new cohort. Further studies on the treatment of lupus nephritis should be launched. On the other hand, the more judicious use of corticosteroids, refinements in immunosuppressive therapy, appropriate antibiotics, more effective treatment of hypertension and cardiovascular disease, greater availability of dialysis and renal transplantation, and provisions for medical intensive care may also contribute to the improvement of survival in SLE patients [4,5].

In summary, reviewing the pediatric SLE patients in NTUH in Taiwan, we found that disease complications decreased recently, especially in infection, osteonecrosis and compression fracture, and ESRD. Being female and the development of ESRD were poor prognostic factors. Infection was the leading cause of death. The 10-year survival probabilities increased significantly from 44.4% in the 1980-to-1990 cohort to 77.5% in the 1991-to-2001 cohort (p=0.0012). Better medical care may contribute to these improvements.

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