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Evaluation of the etiological profile, age and findings in retrograde and voiding urethrocystography of men with urethral stricture

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This study aims to establish a profile of the urethral stricture disease in the studied population, in addition to evaluating the correlation between the etiology of urethral stricture, age and findings evidenced in the retrograde and voiding urethrocystography (RVUC) examination. This observational study was conducted at a single institution and included 135 men with urethral stricture. Patient's age and the etiology of stricture were determined. RVUC findings such as length, number, location, and degree of urethral lumen obstruction of urethral stricture, as well as other associated pathological urological findings, were also analyzed. The correlation between demographic parameters, including age and etiology, and RVUC findings was then statistically analyzed. Median age of the patients was 64 years (range: 18–89 years). The most frequent etiologies were iatrogenic (51.9%), idiopathic (20.0%), inflammatory (15.6%) and external traumatic (12.6%). The subgroup of patients over 45 years of age had higher percentages of urethral stricture regardless of the etiology. In the comparative analysis between the four etiology categories, age group and location were the two variables with a statistically significant association ($p = 0.001$ and < 0.001, respectively). The penile urethral segment represented almost half of the cases of stricture of inflammatory etiology (47.6%). In the membranous urethral segment, almost all cases of stricture were of iatrogenic etiology, representing 24.3% of all cases of iatrogenic etiology in the study. Comparative statistical analysis between the traumatic and non-traumatic etiology categories found that location and length were the only variables with a statistically significant association ($p < 0.001$ and $= 0.005$, respectively). In the penile urethral segment, stricture of non-traumatic etiology was the most frequent (33.3% versus 11.5%). In this study, strictures were only of traumatic etiology in the membranous (20.7%) and prostatic (6.9%) urethral segments. Strictures of non-traumatic etiology were the longest. In another supplementary analysis, a statistically significant association was evidenced between age group and the specific cause of urethral stricture ($p < 0.001$). Prostatectomy was the main specific cause of urethral stricture considering all age groups, representing 20.7% of all cases in the study and 25.2% of patients aged over 45 years. The idiopathic and urethral catheterization were more frequent causes proportionally in the subgroup of patients aged 45 years or less than in the subgroup aged over 45 years (41.7% versus 15.3%, 29.2% versus 6.3%, respectively). A more severe disease profile of urethral stricture was evidenced, with 83% of cases causing obstruction in more than 2/3 of the urethral lumen. In our study, there was a significant statistical association between the etiology and patient's age, and also between the etiology and stricture's location and length as demonstrated by the RVUC exam.

Keywords Urethral stricture, Etiology, Age groups, Cystography, Diagnosis, Diagnostic imaging, Urethroplasty

Etiology of urethral stricture has significant impact on location of stricture and chances of successful treatment. In addition to varying with location of urethral segment involved, etiology is greatly influenced by socioeconomic

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conditions of the region. Currently, in countries considered industrialized, most cases of anterior urethral stricture are due to occult or unrecognized blunt external perineal trauma or instrumentation (traumatic catheter placement or removal, chronic indwelling bladder catheterization, or transurethral surgery)[1].

Age is another important factor that can influence presentation of urethral stricture. In patients < 45 years old, the main causes are idiopathic, hypospadias surgeries and pelvic fractures, while in those > 45 years old, transurethral resection and idiopathic causes are more common. An important cause of multifocal/panurethral anterior urethral stricture disease is urethral catheterization, while pelvic fracture is a major cause of posterior urethral stenosis[2].

Retrograde and voiding urethrocystography (RVUC) is still the most commonly used imaging technique for evaluation of the male urethra worldwide, which provides important information for diagnosis and staging of urethral stricture disease[1,3].

The objective of this study is to establish a profile of the disease urethral stricture in the studied population. Additionally, our study evaluated the correlation between etiology, age group and RVUC findings shown in men with urethral stricture.

Methods

This is an observational and a non concurrent cohort study. Patient data were collected prospectively.

The experimental protocols of this study were approved by the Research Ethics Committee of Professor Fernando Figueira Institute of Integral Medicine (IMIP) through the competent official Brazilian government system Plataforma Brasil (approval number: 2.766.270). All experiments of the present study were performed in accordance with relevant guidelines and regulations. After approval by the Research Ethics Committee, this study included 135 male patients diagnosed with urethral stricture from July 2018 to December 2021 at a single institution. After agreeing to participate and signing Informed Consent Form, each patient had a form filled out with their clinical data related to urethral stricture and also with data referring to findings shown in RVUC exam (location, length, number of areas of stricture, degree of urethral lumen obstruction and other relevant associated pathological urological findings, such as stress bladder, reduced bladder capacity, vesicoureteral reflux (VUR), elevated post-void residual, bladder or urethral diverticulum, bladder stone, late effects of hydrodistension proximal to the point of stricture).

The inclusion criteria of the study were: All male patients over 18 years of age with urethral stricture treated at the Urology outpatient clinic who understood and accepted participation in the study, signing the Free and Informed Consent Form; All cases of urethral stricture were accepted into the study, including recurrent cases, with a history of previous treatment for urethral stricture and with other associated urological pathologies. No patient included in this study presented a history of urethral tumor.

Three analyzes related to etiology were performed. The first one considered 4 etiological groups: iatrogenic, idiopathic, inflammatory, and external traumatic. The second analysis divided etiology into only 2 groups: traumatic and non-traumatic. The third one analyzed specific causes, such as types of procedures responsible for iatrogenic etiology.

Patients were further sub-categorized by age into 2 groups: ≤45 years of age; and > 45 years of age. An age limit of 45 years was chosen as the likelihood of iatrogenic manipulation of urethra increases above this age.

For statistical analyses, the following tests were used: Pearson's Chi-square, Fisher's Exact, Likelihood Ratio, Mann-Whitney, Kruskal-Wallis, Shapiro-Wilk. Significance level considered was $p < 0.05$ and confidence interval was 95%. Programs EXCEL (2020) and IBM SPSS version 25 were also used.

Results

Patient's age ranged from 18 to 89 years, with a median of 64 years. 82.2% of patients were over 45 years old.

Most common etiology was iatrogenic (51.9%), followed by idiopathic (20%), inflammatory (15.6%) and traumatic (12.6%). In a specific subanalysis of iatrogenic etiology, causes highlighted were prostatectomy (20.7%), trans-urethral resection (TUR) (16.3%) and urethral catheterization (10.4%) (Tables 1, 2 and 3).

In a comparative analysis between the four etiology categories, age group and location were the two variables with statistically significant association with etiology ($p = 0.001$ and < 0.001, respectively). Sub-group of patients > 45 years old had the highest percentages of urethral stricture diagnoses, regardless of etiology: inflammatory (95.2%), iatrogenic (90.0%), external traumatic (64.7%) and idiopathic (63%). Regarding location, penile urethral segment presented almost half of all cases of stricture with inflammatory cause (47.6%), and much fewer cases of other etiologies: idiopathic (22.2%), external traumatic (11.8%) and iatrogenic (11.4%). In membranous urethral segment, almost all strictures were iatrogenic (94.4%), representing 24.3% of all iatrogenic cases in the study. Almost half of urethral strictures of external traumatic etiology (47.1%) affected more than one urethral segment simultaneously (Table 1).

Comparative statistical analysis between traumatic and non-traumatic etiology categories found that location and length were the only variables with statistically significant association with etiology ($p < 0.001$ and $= 0.005$, respectively). In the penile urethral segment, urethral strictures of non-traumatic etiology (33.3% of all non-traumatic strictures) were considerably more common than of traumatic etiology (11.5% of all traumatic strictures). Traumatic strictures were predominantly diagnosed in the membranous (20.7%) and prostatic (6.9%) urethral segments. Median length was greater in urethral strictures of non-traumatic etiology (2.5 cm vs. 1.5 cm, $p = 0.005$) (Table 2).

There was also a statistically significant association ($p < 0.001$) between etiology and age group when specific causes of urethral stricture were analyzed within the iatrogenic, inflammatory, and traumatic categories. Prostatectomy and TUR were important causes, only seen in patients > 45 years. Prostatectomy was the main cause of urethral stricture in our study (20.7%), and specifically in the sub-group > 45 years (25.2%). TUR

Variable	Etiology				*p*-value
	Idiopathic	Iatrogenic	External Traumatic	Inflammatory	
	n (%)	*n* (%)	*n* (%)	*n* (%)	
	(27)	(70)	(17)	(21)	
Total sample	**27 (100.0)**	**70 (100.0)**	**17 (100.0)**	**21 (100.0)**	
Age range (years) (option 1)					$p^{(1)} < 0.001$*
18 to 59	19 (70.4)	16 (22.9)	12 (70.6)	6 (28.6)	
60 to 69	4 (14.8)	25 (35.7)	3 (17.6)	9 (42.9)	
70 or more	4 (14.8)	29 (41.4)	2 (11.8)	6 (28.6)	
Age range (years) (option 2)					$p^{(2)} = 0.001$*
Over 45	17 (63.0)	63 (90.0)	11 (64.7)	20 (95.2)	
Up to 45	10 (37.0)	7 (10.0)	6 (35.3)	1 (4.8)	
RVUC(**)– Location					$p^{(3)} < 0.001$*
Bulbar	10 (37.0)	22 (31.4)	5 (29.4)	6 (28.6)	
Penile	6 (22.2)	8 (11.4)	2 (11.8)	10 (47.6)	
Membranous	–	17 (24.3)	1 (5.9)	–	
Prostatic	–	5 (7.1)	1 (5.9)	–	
Multiple	11 (40.7)	18 (25.7)	8 (47.1)	5 (23.8)	
Degree of obstruction of the urethral lumen					$p^{(2)} = 0.474$
< 1/3	–	1 (1.4)	–	–	
1/3 – 1/2	2 (7.4)	2 (2.9)	1 (5.9)	–	
1/2–2/3	2 (7.4)	12 (17.1)	–	3 (14.3)	
> 2/3	23 (85.2)	55 (78.6)	16 (94.1)	18 (85.7)	
Degree of obstruction of the urethral lumen - recategorized					$p^{(2)} = 0.533$
≤ 2/3	4 (14.8)	15 (21.4)	1 (5.9)	3 (14.3)	
> 2/3	23 (85.2)	55 (78.6)	16 (94.1)	18 (85.7)	
Number of urethral stricture points					$p^{(2)} = 0.656$
1	22 (81.5)	59 (84.3)	13 (76.5)	19 (90.5)	
More than 1	5 (18.5)	11 (15.7)	4 (23.5)	2 (9.5)	
Associated findings on examination (RVUC**)					$p^{(1)} = 0.074$
Yes	9 (33.3)	26 (37.1)	8 (47.1)	14 (66.7)	
No	18 (66.7)	44 (62.9)	9 (52.9)	7 (33.3)	
Total					
Assessment of the length of urethral strictures according to etiology (4 groups)					
Statistic	**Etiology**				
	Idiopathic	**Iatrogenic**	**External Traumatic**	**Inflammatory**	**p-value**
Median (Length)	2.00	1.50	1.50	3.00	$p^{(4)} = 0.131$
P25	1.00	1.00	1.00	1.25	
P75	5.00	3.00	4.32	6.50	

Table 1. Assessment of the study's variables according to etiology (4 groups). (*) Statistical significance level $p < 0.05$. (**) RVUC: Retrograde and Voiding Urethrocystography. (1) Using Pearson's Chi -square test. (2) Using Fisher's Exact test. (3) Using the Likelihood Ratio test. (4) Kruskal-Wallis test. Obs.: Length in centimeter (cm).

represented 16.3% of total cases and 19.8% of men > 45 years. Urethral catheterization and idiopathic causes were much more common proportionally in subgroup of patients aged ≤ 45 years (29.2% vs. 6.3%, 41.7% vs. 15.3%, respectively) (Table 3).

This study also showed the presence of obstruction involving > 2/3 of urethral lumen due to stricture in 83%, and associated RVUC abnormalities in 42.2% of the cases (Table 2).

Discussion

The present study showed a very high incidence of iatrogenic urethral strictures, corresponding to more than half of all cases as shown in Table 1. This differed significantly from what was shown in the study by Mathur et al., which recorded a much lower incidence of iatrogenic stricture (26.8%)[4]. In our study, prostatectomy was the main isolated cause of urethral stricture (20.7%). This finding contradicts literature data, which do not indicate prostatectomy as one of main causes of urethral stricture, such as the study by Lumen N. et al., which showed a rate of only 3.3%. This higher rate found in the present study might be explained by the common use of large non-silicone urethral catheters. Another interesting finding of our study was the stricture location in penile,

Variable	Type of etiology			p-value
	Non-traumatic	Traumatic	Total group	
	n (%)	n (%)	n (%)	
	(48)	(87)	(135)	
Age range (years) (Option 1)				$p^{(1)} = 0.060$
18 to 59	25 (52.1)	28 (32.2)	53 (39.3)	
60 to 69	13 (27.1)	28 (32.2)	41 (30.4)	
70 or more	10 (20.8)	31 (35.6)	41 (30.4)	
Age range (years) (option 2)				$p^{(1)} = 0.246$
Over 45	37 (77.1)	74 (85.1)	111 (82.2)	
Up to 45	11 (22.9)	13 (14.9)	24 (17.8)	
RVUC (**) – Location				$p^{(1)} < 0.001$*
Bulbar	16 (33.3)	27 (31.0)	43 (31.9)	
Penile	16 (33.3)	10 (11.5)	26 (19.3)	
Membranous	-	18 (20.7)	18 (13.3)	
Prostatic	-	6 (6.9)	6 (4.4)	
Multiple	16 (33.3)	26 (29.9)	42 (31.1)	
Degree of obstruction of the urethral lumen				$p^{(2)} = 0.952$
< 1/3	-	1 (1,1)	1 (0.7)	
1/3 – 1/2	2 (4.2)	3 (3,4)	5 (3.7)	
1/2–2/3	5 (10.4)	12 (13.8)	17 (12.6)	
> 2/3	41 (85.4)	71 (81.6)	112 (83.0)	
Degree of obstruction of the urethral lumen – recategorized				$p^{(1)} = 0.573$
≤ 2/3	7 (14.6)	16 (18.4)	23 (17.0)	
> 2/3	41 (85.4)	71 (81.6)	112 (83.0)	
Number of urethral stricture points				$p^{(1)} = 0.689$
1	41 (85.4)	72 (82.8)	113 (83.7)	
More than 1	7 (14.6)	15 (17.2)	22 (16.3)	
Associated findings on examination (RVUC**)				$p^{(1)} = 0.320$
Yes	23 (47.9)	34 (39.1)	57 (42.2)	
No	25 (52.1)	53 (60.9)	78 (57.8)	
Total	**48 (100.0)**	**87 (100.0)**	**135 (100.0)**	
Assessment of the length of urethral strictures according to 2 etiological groups (non-traumatic and traumatic)				
Statistic	**Etiology**			**p-value**
	Non-traumatic	**Traumatic**	**Total group**	
Median (Length)	2.50	1.50	2.00	$p^{(3)} = 0.005$*
P25	1.00	1.00	1.00	
P75	5.75	3.00	3.00	

Table 2. Assessment of the study's variables according to the type of etiology with two groups (non-traumatic and traumatic). (*) Statistical significance level $p < 0.05$. (**) RVUC: Retrograde and Voiding Urethrocystography. (1) Using Pearson's Chi -square test. (2) Using Fisher's Exact test. (3) Mann-Whitney test. Obs.: Length in centimeter (cm).

bulbar and multiple segments of urethra in a significant percentage of post-prostatectomy cases (42.8%), unlike the remaining patients (57.2%) who presented strictures in more expected locations due to the procedure: vesicourethral anastomotic site, membranous and prostatic urethral segments. This finding could be explained by history of urethral catheterization in all these cases, which might be a concomitant factor causing stricture also in anterior urethra. Radiotherapy was responsible for 3% of urethral strictures, consistent with 1-13% rate reported in the literature[5–7].

The rate of urethral stricture caused by TUR (mostly monopolar) was 19.4% and similar to that found by Lumen N. et al.[2]. Another similar finding was that TUR and idiopathic etiologies were the main causes of bulbar urethral stricture in our study (23.3% of cases each), similar to the literature that describe bulbomembranous urethral segment as the most affected site by post-TUR stricture, followed by fossa navicularis and penile urethra[8–10]. Although risks of post-TUR syndrome, blood loss, and clot retention have decreased over time, risk of urethral stricture has remained the same[11,12].

Similarly to literature data, urethral catheterization was an important cause of urethral stricture in the present study, accounting for 10.4% of all cases. However, differing from the literature, it played an even greater etiologic role in patients ≤ 45 years old (29.2%). A proportionally higher rate of urethral catheterization causing

Etiology	Age range (years)			p-value
	Over 45	Up to 45	Total group	
	n (%)	n (%)	n (%)	
Idiopathic	17 (15.3)	10 (41.7)	27 (20.0)	$p^{(1)} < 0.001$*
Prostatectomy	28 (25.2)	–	28 (20.7)	
Urethritis	19 (17.1)	1 (4.2)	20 (14.8)	
TUR (**)	22 (19.8)	–	22 (16.3)	
Urethral catheterization	7 (6.3)	7 (29.2)	14 (10.4)	
Perineal trauma	7 (6.3)	4 (16.7)	11 (8.1)	
Genital trauma	1 (0.9)	–	1 (0.7)	
Pelvic fracture	2 (1.8)	2 (8.3)	4 (3.0)	
Urinary calculi elimination	1 (0.9)	–	1 (0.7)	
Penectomy	1 (0.9)	–	1 (0.7)	
Radiotherapy	4 (3.6)	–	4 (3.0)	
Endoscopic ureterorenolithotripsy	1 (0.9)	–	1 (0.7)	
Lichen sclerosus	1 (0.9)	–	1 (0.7)	
Total	**111 (82.2)**	**24 (17.7)**	**135 (100.0)**	

Table 3. Specific causes according to age group. (*) Statistical significance level $p < 0.05$. (**) TUR: Transurethral Resection. (1) Using Fisher's Exact test.

stricture would be expected in patients > 45 years old, when the odds of needing urinary tract manipulation increase considerably. In all the patients > 45 years old with stricture caused by urethral catheterization in this study, indications for catheterization were not for urological reasons, but rather due to cases of polytrauma, traumatic brain injury, and abdominal intestinal surgery. Eventually, lack of assistance by Urology Staff initially could explain this high incidence rate in this patient population. In our study, and similar to literature data, the location of the stricture caused by urethral catheterization involved mainly anterior urethra and multiple urethral segments, with only one case affecting the membranous urethra. As a limitation of the present study, exact data are missing regarding duration and type of urethral catheter used in some patients, as well as whether the urethral catheter insertion was traumatic or not.

Idiopathic urethral strictures were common (20%), as also observed in previous studies[13–18]. In posterior urethra, the cause is usually identified, which probably indicates that there are no idiopathic strictures in this area[2]. This data could be confirmed in our study, in which no idiopathic stenosis was found in posterior urethra.

In our study, urethritis was cause of urethral stricture in only 14.8% of cases, differing from studies on etiology of urethral stricture in countries where urethritis is still an important cause of stricture (54–66.5%)[19–21]. In these cases secondary to urethritis in our study, the penile urethra was involved in 45%, bulbar in 30% and simultaneous involvement of penile and bulbar urethras in the remaining 25% of patients.

External traumatic urethral strictures often involve the posterior urethra. The literature reports that pelvic fracture causing rupture of bulbomembranous junction is the main etiology of posterior urethral stenosis. In younger patients it remains an important etiology, but overall it is responsible for only 11.2% of strictures[22]. In our study, contrary to this data from the literature, 7 (41.1%) of the patients with external traumatic stricture presented stricture only in the bulbar or penile urethra, without involvement of the posterior urethra. Four patients were found to have urethral stenosis due to pelvic fractures, representing only 3% of all causes. This lower percentage compared to international literature may be explained by the fact that our patient sample is predominantly of a higher age group (82.2% over 45 years old). However, similarly to data from literature reported above, these four patients with urethral stenosis due to pelvic fracture were younger and, in all cases, there was severe involvement only of the posterior urethra. In 2 cases, there was simultaneous multiple involvement of membranous and prostatic segments. In the remaining 2 cases, the membranous urethra was affected alone in one patient and with prostatic urethra in other one. Unlike some reports in literature, there was no involvement of bulbar urethra in the 4 cases of urethral stenosis due to pelvic fracture, actually affecting only posterior urethra[4,13]. All cases of posterior urethral stenosis in this study were of iatrogenic and external traumatic etiologies. Another interesting result of our study related to traumatic strictures was that statistical analysis comparing median length of urethral stricture between the two categories of traumatic and non-traumatic etiologies indicated that length was greater in non-traumatic strictures than traumatic, with statistically significant difference ($p = 0.005$), compatible with literature data that post-traumatic urethral strictures tend to be short[4]. Santucci et al. demonstrated that the shortest urethral strictures that are favorable to treatment by urethroplasty with excision and primary anastomosis (EPA) are those of traumatic origin[23].

Fenton et al. found in their series that penile urethral strictures were more than 6 cm long (almost twice the length of bulbar strictures [3.3 cm]), highlighting the common need for urethral substitution with tissue transfer techniques in penile urethra[13]. In a more recent series, it was observed more than half of men over 65 years old undergoing urethroplasty required tissue transfer techniques, when EPA was not possible[24]. Similarly to series by Fenton et al., in our study, the length of strictures affecting only penile urethra was also almost twice that of strictures affecting only bulbar urethra .

Kinnaird et al. identified urethral stricture length and etiology as independent predictors of recurrence after urethroplasty in multivariate analysis of 604 urethroplasties. Multivariate regression identified lichen sclerosus, iatrogenic and infectious etiologies as independently associated with stricture recurrence. Stricture with length ≥ 5 cm recurred significantly more frequently (13.8% versus 5.9%) with Hazard Ratio: 2.3 (1.2–4.5; $p \leq 0.01$)[25]. Although our study did not evaluate therapeutic results, it demonstrated a severe urethral stricture disease profile in the studied population in that more than half of patients had iatrogenic urethral strictures (51.9%) and also significant amount of post-inflammatory stricture (15.6%), which are two etiologies considered by the study mentioned above as independent predictors of urethral stricture recurrence after urethroplasty[25]. This situation is further aggravated by a significantly higher rate of iatrogenic (90%) and inflammatory (95.2%) etiologies in patients over 45 years old, adding to all comorbidities more present with advancing age with negative influence on prognosis. Furthermore, our study demonstrated a very high rate of severe obstruction of urethral lumen by stricture, with 83% of strictures compromising more than 2/3 of urethral lumen, with a significant number of strictures with complete obstruction. Another finding of our study in favor of a more severe profile of urethral stricture is the presence of associated pathological changes in RVUC in almost half of patients (42.2%), many of which already suggest important repercussions on urinary tract due to stricture. In our study, the urethral stricture median length was 2 cm, much lower than the previously reported cut-off point of 5 cm for worse prognosis. However, in post-inflammatory urethral strictures, median length was closer to 5 cm (3 cm), followed by idiopathic (2 cm), external traumatic (1.5 cm) and iatrogenic (1.5 cm) etiologies. When statistical analysis considered only the two categories of etiology (traumatic and non-traumatic), the median length was much greater in non-traumatic stricture (2.5 cm) than traumatic (1.5 cm), with statistically significant difference ($p = 0.005$).

Our study has the limitation of being observational with its inherent biases. In many cases, urethral stricture etiology was not documented in the hospital medical records and this information depended exclusively on memory and recollection of participating patients regarding their clinical history, in addition to physical examination performed in the outpatient clinic. Another limitation of this study was the use of a convenience sampling for the included patients.

Conclusion

Etiology and age are important impact factors on urethral stricture presentation and evolution. Our study showed that the etiology of urethral stricture has a statistically significant association with both the patient's age and the location of the urethral stricture in RVUC. There was also a statistically significant association between the etiology and the length of urethral stricture when comparing the 2 etiological groups non-traumatic and traumatic. An inflammatory etiology occurred in older individuals and was associated with more extensive and, therefore, more complex strictures. There was no statistically significant association between etiology and other findings provided by RVUC.

Data availability

All data of this study are available in the manuscript, tables, supplementary material and related files.

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Author contributions

R.B.F. conceived the idea and primary hypotheses of the study; R.B.F. and S.V.C.L. developed the project; R.B.F. collected and analyzed the data; R.B.F. wrote the manuscript; F.T.L.N., G.A.C., F.E.M. and S.V.C.L. critically reviewed and edited the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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