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The impact of our acquired experience on endoscopic injection treatment outcomes of vesicoureteral reflux during the first ten years of practice

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ABSTRACT

Introduction: Endoscopic injection treatment (EIT) for vesicoureteral reflux (VUR) correction is widely accepted as an optimal method for more than thirty years. However, it is still in its infancy in many pediatric surgical centers. It presents variable cure rates, with many factors affecting its successfulness.

Objectives: We aimed to identify how accumulated endoscopic experience affected the VUR resolution success rates, in association with a variety of characteristics, since the beginning of practicing the technique. We attempt to improve patient selection.

Patients and Methods: The outcomes of 53 children, corresponding to 78 refluxing ureteral units (RUUs), treated with endoscopic injection during the first years of practice (2010-2016), and 26 children with 42 RUUs during the latest years (2017-2020), were compared. Characteristics such as age, gender, VUR grades, preoperative voiding cystogram and dimercaptosuccinic acid scintigraphy, side, laterality were analyzed in relation with outcome of the groups of the study population. Outcomes presenting statistically significant differences were considered related to experience.

Results: Refluxing ureters of the second group presented significant improved endoscopic treatment success rates and also significant reduced need for open surgery. The second group of experienced performance presented significant improved success rates in younger children, in girls, in children with bilateral VUR or duplex ureteral system, and when reflux presented at the filling phase of voiding cystourethrogram. Furthermore, the second group of experienced performance presented significant improved success rates in ureteral units of a duplex system or with grade III and high grades IV-V VUR.

Conclusion: Our initial experience with EIT has been promising. Boys, and children with bilateral VUR or duplex ureteral system should be treated by more experienced endoscopic surgeons. Furthermore, high grade VUR is a predisposing factor for endoscopic treatment failure, performing by less experienced surgeons. Pediatric surgeons must upgrade their learning curve, initiating their experience, and developing their surgical skills with more simple cases before expanding their practice to more complicated.

Implication for health policy/practice/research/medical education:
Endoscopic Injection treatment of vesicoureteral reflux is safe and a viable alternative against open surgical ureteral reimplantation and long-term antibiotic prophylaxis. Over the few past years, there have been advances in the identification of risk factors that predict the effectiveness of management options of children with urinary tract infection, renal scarring and vesicoureteral reflux. The challenges and controversies in guidelines for vesicoureteral reflux intervention result in a more "case by case"- risks/benefits basis treatment planning. The aim of this study is to present our initial experience with endoscopic VUR management and investigate the predictive value of factors related to acquired endoscopic experience that could influence outcome.

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Original

Introduction

The endoscopic injection treatment (EIT) is recommended as the first-line therapy for children with vesicoureteral reflux (VUR), when intervention is required (1,2). Though the method is older than 20 years, it is still in its infancy in many pediatric surgical centers. It is considered preferable to ureteral reimplantation with open surgery, which may be reserved for exclusive use in children not responding to EIT (2). Furthermore, parents of children with VUR are very likely to express a preference for EIT among all alternative options proposed (3), because it is a minimally invasive outpatient procedure, with low morbidity and a lower overall cost (4). EIT has variable reported cure rates of 67-93% (5-7), with differences in study design, methodology, and inclusion criteria of patients. Concerns about its long-term efficacy and delayed complications have resulted in a controversy over its real usefulness (6). Furthermore, many preoperative, perioperative and postoperative factors (age, high VUR grade, neuropathic bladder, phase of VCUG - voiding cystourethrogram in which VUR is initially presented, occurrence of double ureters, endoscopic technique, amount of injected material, etc) have been controversially implicated in EIT success rates, but there is not yet agreement on which of them are the most influential for endoscopic VUR resolution.

EIT success seems to be affected by the operator's experience. In the era of surgical competencies, a learning curve is a well-known phenomenon (8). Independently of the technique used, there is a learning curve associated with endoscopic VUR correction (9). A multivariate analysis has shown that experience is an independent predictor of endoscopic VUR correction rates (10). A combination of adequate experience and great skill in EIT should obtain favorably comparable results to ureteral reimplantation, because there is a strong belief that nearly all endoscopic failures are related to unrecognized or unappreciated technical errors (2). A positive correlation is found to exist between years of experience and the ability to perform the procedure (11). The precise variables of VUR that change their response under the EIT learning curve with time are not known.

Objectives

The present study aims to identify how the surgeon's experience affects EIT outcome in children with VUR. Our hypothesis is that during the primary period of EIT application by surgeons with less experience, a carefully preoperative risk-factors-based patient selection must be performed. This might be proved if we detected better results in more recent patients compared to earlier ones, by focusing on some characteristics, all the way back to the period we began performing the procedure.

Patients and Methods

Study design

We performed a retrospective review of children who underwent endoscopic correction of VUR at the Department of Pediatric Surgery of the Hippocrateion General Hospital at Thessaloniki-Greece, during a period of ten years (January 2010-January 2020). All patients enrolled in the study presented with grade II-V VUR, confirmed by VCUG, following febrile urinary tract infection (UTI) incidents (International system I-V of radiographic grading of VUR was used). Patients with double ureter systems were also included in this study. A dimercaptosuccinic acid scintigraphy (DMSA) study was performed preoperatively in all patients, both for the evaluation of the relative renal function, and for renal scarring detection. Relative renal function less than 44% was defined as deficient, independently of renal scar presence. Indications for endoscopic intervention included persistent VUR grade ≥ II, or febrile UTI breakthrough with the patient being on medical treatment for at least 12-24 months, DMSA defect or new renal scars, and parental preference. Children presenting voiding dysfunction were not included in the study. A combination of hydrodistension injection (HIT) and subureteral transurethral injection (STING) technique was used. All endoscopic injections were completed by the same team of pediatric surgeons, each of whom was the single operator in a case-by-case rotation. All surgeons were pediatric surgery specialists and certified for EIT, after training in courses and educational programs in reference centers. All procedures were performed, with the patient under general anesthesia, at a day-care basis. The patients were divided into two groups in accordance with time, an early group I (2010-2016) and a late group II (2017-2020). All patients were on a postoperative follow-up protocol from one to three years. Postoperative control VCUG was performed at the third month after endoscopic injection. Every patient with subsequent febrile UTI during the follow-up period underwent further VCUG and DMSA assessment. The diagnosis of a febrile UTI was set in every child who presented with temperature more than 38°C and positive urine culture (bacterial culture count more than 10^5 of a single organism). VUR resolution was defined as complete cessation, or downgrading from grades IV-V to grade I. In patients with persistent or recurrent VUR, a repeated second, and if necessary, a third injection correction attempt after six months were performed respectively. All patients were kept on prophylaxis with antibiotics, until VCUG-determination of VUR resolution after the last endoscopic injection, or until surgical ureteral reimplantation. Antibiotic prophylaxis was stopped in patients with persistent grade II single system VUR after three failed endoscopic attempts. These patients

remained under surveillance by a pediatric nephrologist, evaluating a possible postinfectious upgrading of VUR and new DMSA scar formation or relative renal function deterioration. Open ureteral reimplantation was recommended for patients with persistent grade III or greater of single system VUR after three failed endoscopic attempts, for double ureter system with persistent grade II VUR after three failed endoscopic attempts, and for patients with persistent grade II single system VUR who presented new renal scar and/or deterioration of relative renal function after a new febrile UTI.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Hippocrateion Hospital approved this study. The institutional ethical committee at the University of Patras School of Medicine approved all study protocols. Accordingly, written informed consent taken from all participants before any intervention. This study was extracted from the Ph.D., thesis of the first author at this university (Thesis # 2013: 614/25-2-2013).

Data analysis

We analyzed the final outcomes (total reinjections, endoscopic VUR resolution rates, post injection febrile UTIs, and ureteral reimplantations) separately for each time group of children and compared them to identify if the pediatric surgeons' acquired experience was a possible major success factor. Furthermore, the refluxing ureteral units (RUUs) of the corresponding children were grouped and compared accordingly. The following were included as accompanying comparable factors between the two study groups: gender, age, VUR grades, side and laterality, presentation of reflux during the filling or voiding phase of preoperative VCUG, preoperative DMSA defects, and ureteral duplication. Statistical analysis was performed using the IBM SPSS software version 24.0 (IBM Corp, Armonk, NY, USA). Categorical variables were expressed as absolute counts and/or frequencies and were compared by Pearson's chi square and Fisher's exact tests. A P value < 0.05 was considered as significant.

Results

A total of 79 children (age 12 months-15 years, mean 5.6 years, 58 girls and 21 boys), where included in the study. Of these, 53 were treated with EIT from 2010 to 2016 comprising study group I, and 26 to the period from 2017 to 2020 comprising group II. Children of group I corresponded to 78 RUUs, while those of group II corresponded to 42 RUUs. The characteristics of children (age distribution, gender, laterality, VUR presentation at filling or voiding phase of VCUG, preoperative DMSA and double ureteral system) are shown in Table 1. The characteristics of the two groups expressed in RUUs (side, VUR grades, and double ureteral system) are shown in Table 2.

The outcomes of EIT correction of VUR were compared between the two groups of children. Successful EIT, need of open surgery, and febrile UTIs rates did not present statistically significant differences (Table 3, Figures 1-2). However, when comparisons were performed regarding RUUs, significant differences were found. More precisely, the second group presented statistically improved EIT success rates ($P=0.024$), and significant less need of open ureteral reimplantations ($P=0.035$) (Table 4, Figures 1-2). A total of 155 reinjection attempts were performed in the first group, and 75 in the second respectively. The two groups did not present significant differences related to the number of injection attempts (Table 4, Figure 3).

Comparison of the success rates regarding the population characteristics, showed statistically significant improved results in children under the age of six years ($P=0.031$), in girls ($P=0.018$), in cases of bilateral VUR ($P=0.006$), and in children who presented VUR from the filling phase of the retrograde cystourethrography ($P=0.024$) (Table 5). Furthermore, male gender ($P=0.040$), bilateral VUR

Table 1. Characteristics of the two groups of children with vesicoureteral reflux, treated with endoscopic injection

Children characteristics	Children total (n=79)	Children group I (n=53)	Children group II (n=26)	*P* value
<6 years	36	24	12	0.942
≥6 years	43	29	14	
Females	58	39	19	0.962
Males	21	14	7	
Unilateral VUR	38	28	10	0.230
Bilateral VUR	41	25	16	
VUR at filling phase of VCUG	48	30	18	0.280
VUR at voiding phase of VCUG	31	23	8	
DMSA ≤ 44%	49	32	17	0.666
DMSA > 44%	30	19	11	
Single ureteral system	71	49	22	0.278
Double ureteral system	8	4	4	

Abbreviations: VUR, vesicoureteral reflux; VCUG, voiding cystourethrography; DMSA, dimercaptosuccinic acid scintigraphy.

Table 2. Characteristics of the two groups of refluxing ureteral units treated with endoscopic injection

RUUs characteristics	RUUs total (n=120)	RUUs group I (n=78)	RUUs group II (n=42)	*P* value	
Right sided	55	35	20	0.773	
Left sided	65	43	22		
VUR grade II	52	38	14	0.105	0.366
VUR grade III	38	21	17	0.128	
VUR grade IV	21	13	8	0.743	
VUR grade V	9	6	3	0.898	
VUR grades II-III	90	59	31	0.825	
VUR grades IV-V	30	19	11		
Single ureteral systems	112	74	38	0.357	
Double ureteral systems	8	4	4		

Abbreviations: RUUs, refluxing ureteral units; VUR, vesicoureteral reflux.

Table 3. Compared outcomes of children with vesicoureteral reflux

79 Children	Children Group I (n=53)	%	Children Group II (n=26)	%	*P* value
Successful EIT	30	56.6	20	76.9	0.078
Open surgery	17	32.1	4	15.4	0.114
Post-injection febrile UTIs	8	15.1	3	11.5	0.668

Abbreviation: EIT, endoscopic injection treatment.

($P=0.003$), and duplex ureteral system ($P=0.004$) seem to be significant preoperative factors that predispose to EIT failure in children performing by surgeons with less endoscopic experience (Table 5, Figure 4).

When success rates regarding RUUs were compared, there were significant differences with improved EIT results in VUR grade III ($P=0.039$), in high grades IV-V VUR ($P=0.026$), and in single ureteral systems ($P=0.038$) of the second group (Table 6). Furthermore, higher grades of VUR ($P<0.001$) and especially grades IV-V ($P=0.001$), and duplex ureteral system ($P=0.002$) seem to be significant preoperative factors that predispose to EIT failure in RUUs performing by surgeons with less endoscopic experience (Table 6, Figure 4).

Discussion

As EIT is an endoscopic procedure performed by a single operator, training may present difficulties (11). The learning curve for EIT can be longer than usually expected, because its learning is based solely in sight (12). There is a difference in EIT training, between an urologist who is more familiar with endoscopy, and a pediatric surgeon (12). Inexperienced performers should ideally practice endoscopic VUR correction only under expert observation, until they have satisfactorily learned the procedure (12).

Success rates increased from 60% for the first 20 of 292 injections in 134 patients, to 80% for the last 20 attempts have been reported (13). Other researchers reported EIT success rates of high levels after 35-40 attempts (12). Herz et al reported 46% success rate in 28 RUUs of 18 children during the first 6 months of their study, and 93% overall success rate in 84 RUUs of 56 children during the subsequent 18 months (4).

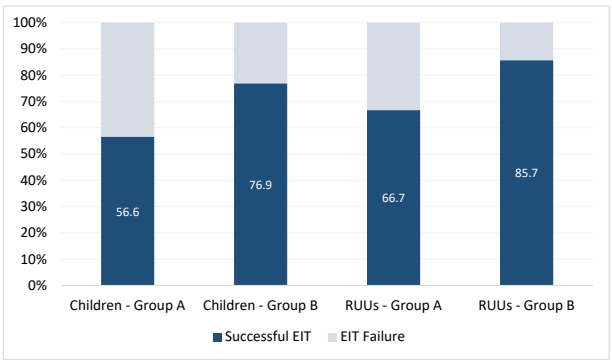

Figure 1. EIT Successful rates. Abbreviations: EIT, endoscopic injection treatment; RUUs, refluxing ureteral units.

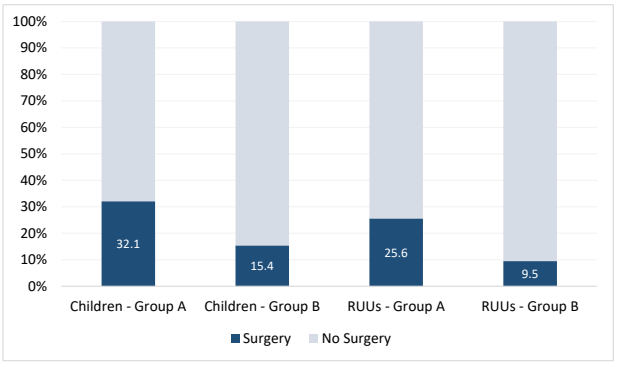

Figure 2. Ureteral Reimplatation rates. Abbreviation: RUUs, refluxing ureteral units.

Table 4. Compared outcomes of refluxing ureteral units

120 RUUs	RUUs Group I (n=78)	%	RUUs Group II (n=42)	%	*P* value
Successful EIT	52	66.7	36	85.7	**0.024**
Total reinjections*	77	49.7	33	44	0.419
Second reinjection attempts	44	28.4	21	28	0.525
Third reinjection attempts	33	21.3	12	16	0.144
Open surgery	20	25.6	4	9.5	**0.035**

Abbreviations: RUUs, refluxing ureteral units; EIT, endoscopic injection treatment.
*A total of 110 reinjections attempts were performed in the study population (n group I =77, n group II =33).
*A total of 230 injection attempts were performed in the study population (n group I =155, n group II =75).

Table 5. Compared success rates according to the characteristics of children

	Successful EIT total	Successful EIT group I	Successful EIT group II	*P* values	
79 Children	50/79 (63.3%)	30/53 (56.6%)	20/26 (76.9%)		
< 6 years	21/36 (58.3%)	11/24 (45.8%)	10/12 (83.3%)	**0.031**	0.309
≥ 6 years	29/43 (67.4%)	19/29 (65.5%)	10/14 (71.4%)	0.698	
Females	40/58 (69%)	23/39 (59%)	17/19 (89.5%)	**0.018**	**0.040**
Males	10/21 (47.6%)	7/14 (50%)	3/7 (42.9%)	0.757	
Unilateral VUR	35/38 (92.1%)	25/28 (89.3%)	10/10 (100%)	0.552	**0.003**
Bilateral VUR	15/41 (36.6%)	5/25 (20%)	10/16 (62.5%)	**0.006**	
VUR at filling phase of VCUG	29/48 (60.4%)	15/30 (50%)	14/18 (77.8%)	**0.043**	0.224
VUR at voiding phase of VCUG	21/31 (67.7%)	15/23 (65.2%)	6/8 (75%)	0.610	
DMSA ≤44%	30/49 (61.2%)	18/32 (56.3%)	12/17 (70.6%)	0.327	0.975
DMSA >44%	20/30 (66.7%)	13/21 (61.9%)	7/9 (77.8%)	0.398	
Single ureteral systems	46/71 (64.8%)	29/49 (59.2%)	17/22 (77.3%)	0.140	**0.004**
Double ureteral systems	4/8 (50%)	1/4 (25%)	3/4 (75%)	0.157	

Abbreviations: EIT, endoscopic injection treatment; VUR, vesicoureteral reflux; VCUG, voiding cystourethrography; DMSA, dimercaptosuccinic acid scintigraphy.

The success of endoscopic VUR therapy appears to be dependent on correct technique (4). The basic principle of EIT is to create a new anti-reflux mechanism at the ureteral orifice, thereby allowing the ureteral mucosa to coapt during bladder filling and prevent urine reflux. Technical errors, such as ineffective needle sites and low injected volumes, as well as uncertain endpoints, most likely comprise the major reasons for failure (14).

As experience with EIT has been gained, several modifications and technical improvements were applied to the original description aiming to improve results. Modifications included ureteral hydrodistension, needle placement in an intra-ureteral submucosal position when possible, needle placement in an accurate site and depth to provide sufficient space for the injected material, and increased amount of injected agent volume (4,12). Extrusion of material if the needle is too superficial, and decreased coaptation may occur if the needle is too deep (4). The injected material volume is under the surgeon's exclusive control, constrained by the upper acceptable limit beyond which the material is likely to migrate, or

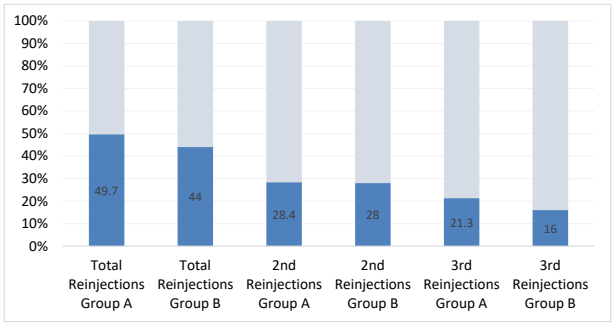

Figure 3. RUUs' reinjection rates. Abbreviation: RUUs, refluxing ureteral units.

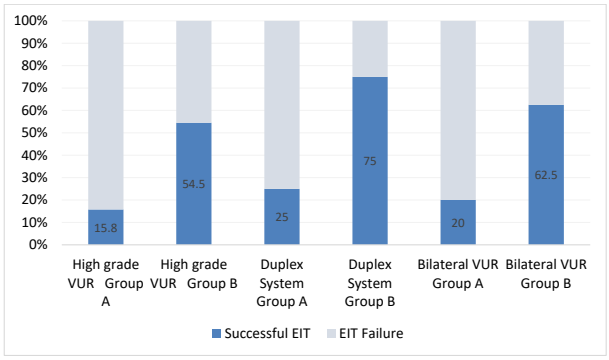

Figure 4. Significant Risk Factors. Abbreviations: EIT, endoscopic injection treatment; VUR, vesicoureteral reflux.

Table 6. Compared success rates according to the characteristics of refluxing renal units

	Successful EIT total	Successful EIT group I	Successful EIT group II	*P* value	
120 RUUs	88/120 (73.3%)	52/78 (66.7%)	36/42 (85.7%)		
Right sided	39/55 (70.9%)	22/35 (62.9%)	17/20 (85%)	0.686	0.082
Left sided	49/65 (75.4%)	30/43 (69.8%)	19/22 (86.4%)	0.141	
VUR grade II	49/52 (94.2%)	35/38 (92.1%)	14/14 (100%)	0.555	
VUR grade III	30/38 (78.9%)	14/21 (66.7%)	16/17 (94.1%)	**0.039**	<0.001
VUR grade IV	8/21 (38.1%)	3/13 (23.1%)	5/8 (69.5%)	0.070	
VUR grade V	1/9 (11.1%)	0/6 (0%)	1/3 (33.3%)	0.333	
VUR grades II-III	79/90 (87.8%)	49/59 (83.1%)	30/31 (96.8%)	0.059	**0.001**
VUR grades IV-V	9/30 (30%)	3/19 (15.8%)	6/11 (54.5%)	**0.026**	
Single ureteral systems	84/112 (75%)	51/74 (68.9%)	33/38 (86.8%)	**0.038**	**0.002**
Double ureteral systems	4/8 (50%)	1/4 (25%)	3/4 (75%)	0.157	

Abbreviations: EIT, endoscopic injection treatment; VUR, vesicoureteral reflux; RUUs, refluxing ureteral units.

extrude, or cause obstruction (15). Learning the correct position (axis, angle, and depth) of needle placement and the capable agent injected volume, are vital for the long-term VUR resolution (4,12). The lack of tactile feedback when inserting the needle, and of knowledge regarding optimal limits on the amount of bulking agent, render training in EIT difficult (12). A higher volume of injected agent implied a technically more difficult injection (15). Endoscopic failure with normal appearing mounds is not surprising, because the appearance of the mound as an end-point of injection should be cautioned since this is totally subjective (14). A proposed method to monitor the technique, and to ensure that adequate material has been injected at the appropriate location in order to ensure VUR resolution, is the intraoperative performed post-injection cystogram (8). Intraoperative identification of ureteral orifice hydrodistension degree immediately following injection, would be optimal (15).

EIT cure rates related to the surgeon are increasing, and the requirement for reinjections decreases as experience with the technique is improving (16,17). Experience and adjustments in clinical-surgical practice are associated with a reduced ureteral reimplantation rate (18). With increasing experience, not only high-grade primary VUR, but also reflux in double ureteral system is considered eligible for EIT (19). On the other hand, failures are seen even in the best surgical series, despite many surgeons are likely to have reached the threshold for acceptable results based on the learning curve (15).

There is not any standardized teaching of the EIT procedure (20). There are ex-vivo and computer simulation programs that help increasing EIT success rates (11,21). Simulation training allows for surgeon's practice in a realistic setting and stress-free environment, with opportunity to focus on the acquisition of surgical skills (like inappropriate cystoscope movements and correct needle placement), without inherent risk of harm to the patient, and worry about surgical outcome (11,21). These may shorten the early learning curve and provide a greater understanding of the technical components of successful EIT, especially before patient contact (11,21).

Conclusion

In our effort to improve EIT success rate by patient selection, we recommend that patients with characteristics such as younger age, male gender, bilateral VUR, reflux presentation at the filling phase of VCUG, double ureteral systems, and more severe VUR grades should be treated by more experienced practitioners. Pediatric surgeons must upgrade their learning curve, initiating their experience and developing their surgical skills with more simple cases before expanding the indications to more difficult cases.

Limitations of the study

The study presented certain limitations. The number of patients of the study population is limited. Larger series of patients are mandatory to extract more secure conclusions. All procedures were not performed by a single, but by a team of three operators. DMSA scarring evaluation and cut-off about 40% in relative renal function could possibly give more significant results. Follow-up period of children who underwent EIT the last year of the study was shorter. The retrospective nature of data based on case records was another limitation, rendering the need of performing more prospective studies.

Authors' contribution

SR conceived the manuscript. SR and XS wrote the manuscript and revised it. IS prepared tables and graphs. SR and GT were included in preparing the concept and design. AK and AV critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript, and critically evaluated the intellectual contents. All authors have read and approved the manuscript's content and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no known competing

interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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