Recent Advances in Hypospadias

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***Abstract**: Hypospadias is a common urological malformation. Hypospadiology is a complex subspecialty that deals with mind boggling number of surgical procedures intended to cure this malformation. In this review the authors summarize the most significant recent advances in hypospadiology.*

INTRODUCTION

Hypospadias is the second most common human birth defect with an incidence of 1 in 250 male births. Hypospadias repair is one of the two leading problems which have helped to define modern pediatric urology; the other being the management of vesicoureteric reflux. The earliest recorded medical description of hypospadias dates back to the second century AD when the term 'hypospadias' was used by Galen. The primary management of hypospadias during the first millennium was limited to distal amputation of the penis (Heliodorus and Antyllus 100-200 AD). The faculty of 'hypospadiology' has undergone revolutionary advances over the decades. The plethora of surgical techniques is a reflection of the 'then' medical knowledge and surgical finesse. Advances in the understanding of the anatomy and embryology of the penis, development of finer surgical instruments and suture materials, improved safety of modern anesthesia, and embracement of psychological principles have resulted in improved outcome of hypospadias. However, even today, hypospadias repair which is more of an '*artistic endeavo*r' remains a challenge for surgeons, patients and parents[1].

CHANGING EPIDEMIOLOGICAL TRENDS

There are several reports claiming rising prevalence of hypospadias over the past 3 decades[2,3]. However, such increases tend to be localized to specific regions or time periods. Paulozzi et al[4] observed an increase from 20 to 40 per 10,000 live births between 1986 and 1993; Lund et al[5] from Denmark reported an increased from 0.24% in 1977 to 0.52% in 2005, corresponding with an annual increase in prevalence of 2.4%. The prevalence was not related to increasing maternal age in the Danish study[5]. Porter et al[6] observed no significant increase in the prevalence of hypospadias in Washington State between 1987 and 2002. However, the risk of hypospadias increased with advancing maternal age, white race and pre-existing non-gestational diabetes. Similarly, Fisch et al[7] could not find any increase in New York State between 1992 and 2005.

ETIOLOGY OF HYPOSPADIAS: NEWER INSIGHTS

The virilization of the genital tubercle results in phallic growth and urethral tubularization. It is brought about by the androgen signaling cascade which involves testosterone biosynthesis, peripheral conversion of testosterone to dihydrotestosterone (DHT) and interaction of both the hormones with androgen receptors. Altered androgen signaling either at the genetic or hormonal level can account for the development of hypospadias. Yucel et al[8] demonstrated 40% hypospadias in genetically engineered heterozygous mice mutant for ephrin-B2 or EphB2. The rising incidence of hypospadias may be related to the effect of various environmental pollutants what act as 'endocrine disrupters' by their antiandrogenic or estrogenic properties. Insecticides utilized in agriculture, natural plant estrogens, pharmaceuticals and coating chemicals of food cans are known to have estrogenic activity. They find their way into the fresh- and sea-water and accumulate at the top of food-chain. In a meta-analysis of 9 studies Rocheleau et al[9] found an odds ratio for the risk of hypospadiac offspring to be 1.4 and 1.2 for maternal and paternal occupational exposure respectively as compared with parents not exposed to pesticides. Yadav and Bajpai[10] have shown higher levels of some organochlorine pesticides to be associated with increased risk of hypospadias. Bisphenol A (BPA), which is commonly found in the plastics packings of food industry, has been implicated in the etiology of hypospadias. Its involvement may be related to the down-regulation of matrix metallopeptidase 11 (MMP11) expression. Fibroblast cells of human skin from hypospadias and cryptorchidism patients showed a significantly lower expression of MMP11 in the hypospadias group than in the cryptorchidism group[11].

In the developing genital tubercle, 5-alpha-reductase type-2 isoenzyme is located in the mesenchyme surrounding the developing urethra where midline fusion of urethral tubularization is destined to occur. In-utero exposure to 'estrogenic' or 'anti-androgenic' pollutants inhibits the binding of testosterone and DHT to the androgen receptors. This results in reduced size of the genital tubercle and shortened anogenital distance (AGD) in hypospadiac boys[12]. Similarly, 5-alpha-reductase inhibitors inhibit the distal development of the urethra resulting in hypospadias. Mutations of the SRD5A2 gene located on chromosome 2 at band p23 inhibits the activity of 5-alpha-reductase type 2 which causes masculinization defects of varying degrees[13-15]. The affected child may have ambiguous genitalia (male pseudohermaphroditism) or isolated hypospadias along with a myriad of other malformation such as micropenis and congenital adrenal hyperplasia.

Although an increase in the incidence of hypospadias was previously attributed to maternal intake of loratidine, recent studies have refuted this hypothesis[16-18]. Carmichael et al[19] found no association of hypospadias with several aspects of the diet. It has been shown that

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boys with isolated hypospadias have longer CAG alleles in their androgen-receptor gene which may affect its transcriptional activity[20].

HYPOSPADIAS AND CRYPTORCHIDISM

Cryptorchidism and hypospadias are common genital birth defects affecting 2 - 9% and 0.2 - 1% of male newborns respectively. Though uncommon, genetic defects in the production or receptor binding of androgen can cause both cryptorchidism and hypospadias. Environmental factors also play a major role in this respect. Qin et al, on studying 334 Japanese and 187 Italian males, found that single nucleotide polymorphisms of genes involved in environment endocrine disrupters (EED) metabolism are associated with increased risk of cryptorchidism and hypospadias[21]. Sathyanarayana et al found that anogenital and anoscrotal distances are influenced by heritable genetic factors associated with hypospadias and cryptorchidism[22].

HYPOSPADIAS AND TESTICULAR DYSGENESIS SYNDROME

The testicular dysgenesis syndrome (TDS) is a hypothetical combination of cryptorchidism, hypospadias, impaired spermatogenesis and testicular malignancy. However, it is not necessary that all the four components be present in all affected men. Various epidemiological, clinical and molecular studies have suggested an interrelation between the different components. The rapid pace with which the prevalence of these reproductive disorders is increasing suggests that environmental or life-style factors are the more likely causes rather than genomic structural defects. Prenatal exposure to endocrine disrupters including phthalates has been implicated in the etiology but for ethical reasons, it is not possible to establish a causal relationship in human beings. The recently developed animal TDS model will be an important tool for investigating the pathogenesis of testicular dysgenesis syndrome[23].

SURGICAL MANAGEMENT OF HYPOSPADIAS

Surgery is the only modality of treatment available for the definitive management of hypospadias. It is usually performed after six months of age. It is done either as an out-patient or in-patient procedure depending upon the severity of malformation, hospital setup, surgeon's outlook and parental preference. The two cardinal aims of hypospadiac surgery are bringing the urethral meatus to the tip and straightening the penile shaft.

VENTRAL CHORDEE

Chordee in hypospadias is due to arrested development [24] and not due to fibrous coalescence of dysplastic dartos and corpus spongiosum. This has been proved histologically in both embryonal and surgical specimens. Snodgrass et al[25] failed to demonstrate any fibrous bands or dysplastic tissue in the urethral plate. All the samples showed well-vascularized connective tissue consisting of smooth muscles and collagen. It has been suggested that pretreatment with human chorionic gonadotropin (HCG) in infancy may cause disproportionate penile enlargement, which advances the meatus distally to decrease the severity of hypospadias and chordee[26].

The penile curvature is assessed intraoperatively by producing artificial erection using intracorporal saline perfusion (Gittes Test). Pharmacological erection by intracorporal injection of a vasodilator (prostaglandin or papaverine) did not gain popularity due to lack of accurate dosing regimens in children, lack of response or prolonged erections lasting more than 6 hours (priapism), additional cost and the need for a reversal agent[27]. The lateral and dorsal tilting of the glans can be corrected by releasing the skin bridge or the frenulum responsible for ventral deflection. Dorsal plication technique is useful for mild to moderate penile curvature and in patients with previous failed repairs[28]. However, the efficacy of midline dorsal plication is poor when used in older boys probably because the placating sutures will not hold up to rigid erections[29].

In 1975, Devine and Horton described dermal grafts for the correction of chordee associated with hypospadias and epispadias. Dermal grafts are associated with better cosmesis. They can also prevent penile shortening which is seen in plication technique. However, there has been some reluctance to use dermal grafts for augmenting the tunica albuginea. By violating the integrity of the tunica, venous leakage may ensue and result in erectile dysfunction. This hypothetical view has been refuted by Badawy et al who reported 88% preservation of erectile function in 16 post-pubertal patients 10 years after penile dermal grafts. Two patients had mild residual curvature and one of them needed phosphodiesterase inhibitors to achieve rigid erections[30].Other materials such as tunica vaginalis, dura, pericardium and small intestinal submucosa[31, 32] have also been tried but with inferior results and without long-term follow-up. Leslie et al also reported successful chordee correction using 1-ply small intestinal submucosa, tunica vaginalis flap and dermal grafts[33].

URETHROPLASTY

Surgical repair of hypospadias can be broadly categorized as urethral plate tubularization, urethral plate supplementation or substitution with skin flaps and urethral plate substitution with grafts. The choice of surgery depends upon many factors including "*personal taste, upbringing, situational preference, training, experience and personal success*"[34]. Table 1 summarizes the findings of 2 independent surveys of pediatric urologists as to the optimal surgical technique of hypospadias repair[34, 35].

TUBULARIZATION OF THE URETHRAL PLATE: ORIGINAL CONCEPT AND ITS MODIFICATIONS

Tubularized incised-plate urethroplasty of Snodgrass (TIPS or 'Snodgrass' urethroplasty) is the most commonly used technique of distal hypospadias repair. It incorporates primary tubularization of the urethral plate with a 'relaxing incision' in the posterior wall of it allowing its forward hinge. The incision also circumvents the limitation imposed by the width of the urethral plate in Thiersch-Duplay procedure. The technique has also been successfully employed in the correction of proximal hypospadias and in 'hypospadiac cripples'.

Urethrocutaneous fistula and meatal stenosis remain the most common complications of TIPS. Braga et al[36], on reviewing 4554 children from 62 published reports, found overall complication rate of TIPS was 33%; the mean frequency of fistula and meatal stenosis were 5.9% and 2.1% respectively. Jayanthi et al[37] recommended modified Barcat repair in patients with a narrow urethral plate (less than 8 Fr) or a 'flat glans'. The repair incorporates several modifications including 1) urethral plate incision extending from the meatus to the tip of the glans, 2) urethral tubularization from the meatus proximally, and 3) meatal calibration such that even before tubularization, it would accept a 10 or 12Fr bougie. He reviewed his results on 110 patients retrospectively and found that the incidence of meatal stenosis and fistula formation was 0% and 1% respectively.

Table 1: *Survey of Pediatric Urologists regarding optimal technique of hypospadias repair*

	Cook 2005 [21]	**Springer 2011** [22]
Respondents	101/121 (83%)	377/438 (91.3%)
Pre-treatment with Androgen		Topical dihydrotesterone (39.4%) Intramuscular testosterone (43.8%) Topical Testosterone cream (15.7%) β-HCG Injections (1.1%)
Distal Penile Hypospadias sans chordee	TIPS (91%), Mathieu UP (4%), TVIF onlay UP (3%), MAGPI (2%)	**Glandular hypospadias**: TIPS (39.0%), MAGPI (34.1%), Other UP (15%), None (12%) **Coronal hypospadias:** TIPS (71%), Duckett onlay UP (0.8%), Other UP (27.7%), Two stage UP (0.5%) **Subcoronal hypospadias**: TIPS (62.1%), Duckett onlay UP (0.5%), Two stage UP (0.8%), Other UP (36.7%)
Mid Penile Hypospadias sans chordee	TIPS (82%), TVIF onlay UP (16%)	TIPS (52.9%), Duckett onlay UP (14%), Two staged UP (12.9%), Other UP (20.2%)
Proximal Penile Hypospadias sans Chordee	TIPS (43%), TVIF onlay UP (43%), TVIF tube UP (10%)	Staged UP (43.6 -76.6%), TIPS (0.9-16.7%), Onlay flaps and tubes (11.3-29.5%)
Proximal Penile Hypospadias + Moderate Chordee (30° to 40°)	**Chordee Correction** Dorsal Plication (82%), Ventral Approach (12%) **Urethroplasty** TVIF Onlay UP (35%), TIPS (24%), TVIF tube UP (19%)	**Chordee Correction** Simple Plication & Nesbitt Procedure **Urethroplasty** Staged UP (43.6 -76.6%), TIPS (0.9-16.7%), Onlay flaps and tubes (11.3-29.5%)
Proximal Penile Hypospadias + Severe Chordee (> 50°)	**Chordee Correction** Dorsal Plication (31%) Ventral repair (68%) **Urethroplasty** Staged Urethroplasty (37%), TVIF tube (40%), TVIF onlay (11%), TIPS (3%)	**Chordee Correction** Urethral division + ventral Incision **Urethroplasty** Staged UP (43.6 -76.6%), TIPS (0.9-16.7%), Onlay flaps and tubes (11.3-29.5%)

TIPS - Tubularized incised plate urethroplasty of Snodgrass; MAGPI - Meatal advancement and glanuloplasty incorporated; TVIF - Tunica vaginalis interposition flap

Kiss et al[38] reported reduced complications and improved cosmesis when midline urethral plate incision is combined with a perimeatal-based flap (Mathieu).

The most creative modification of the Snodgrass procedure is the 'Snodgraft' procedure wherein an inlay preputial graft is used to cover the raw surface of the incised urethral plate. The technique was initially described by Kolon and Gonzales[39] when they used dorsal inlay-graft urethroplasty for re-do cases. The modification incorporates harvesting a graft from the inner prepuce, defattening it and suturing onto the incised urethral plate. Several authors found the technique useful for salvage hypospadias repair[40, 41]. In the series of Asanuma et al[42] involving 28 patients with shallow urethral groove and minimal chordee, Snodgraft procedure was complicated by urethrocutaneous fistula in only 3.6% while meatal stenosis, neourethral stricture and urethral diverticulum were nil. Tavakkoli et al[43], using the buccal mucosa Snodgraft, achieved 0% urethrocutaneous fistula and 4.8% meatal stenosis.

The problem of urethrocutaneous fistula formation gave birth to the concept of interposition flaps. Singh et al[44] advocated the use of partially de-epithelialized preputial flap (triangular soft tissue flap) to cover the neourethra in the region of the glans, corona and subcorona. Baccala et al[45] suggested the use of local de-epithelialized skin flap to cover the urethroplasty. Al-Hunayan et al[46] also reported a lower incidence of urethrocutaneous fistulae with use of lateral skin flap to cover the repair rather than a flap harvested from preputial skin. Corpus spongiosum - either from the normal native urethra as a turnover perimeatal flap or from the diverging spongiosa - has also been used[47]. A scrotal dartos flap or a tunica vaginalis flap have also

been described[48-50]. Dartos flap has been used in various ways such as a ventral based vascular dartos pedicle[51,52], longitudinal dorsal dartos flap transposed ventrally by button-hole manoeuvre[53,54], "limited" double dorsal dartos flap[55] or a vascularised overlapping double layered dorsal dartos flap[56]. Superiority of double dartos flap over single flap coverage in preventing urethrocutaneous fistulae and glanular torsion after TIPS has been documented in several studies[57, 58, 59]. TIPS protected by double dartos flap is associated with a low complication rate (fistula in 1%, stenosis in 0.3%, mild stenosis in 2.5%, dehiscence of ventral skin in 0.5% and penile torsion in 1.3%). Moreover, all urethrocutaneous fistulae resolved spontaneously[59].

Ardelt[60] developed a novel technique of glandular resection and central embedding of the neourethra. In a series of 112 procedures (including 7 cases of secondary hypospadias repair) they found urethrocutaneous fistulas in 4% and meatal or urethral stricture in 4%. The neomeatus was located at the tip of the glans in 98%; cosmetically impeccable slit-like meatus was achieved in 84%. Both maximum and average urinary flow rates were within the standard ranges in 93.7% and 96% respectively.

GRAFT SUBSTITUTION OF THE URETHRAL PLATE

In mid 1980s, Aivar Bracka[61,62] introduced a modern two-staged "terminalising" repair that could produce an even-calibre neo-urethra free of hair and with a natural slit-like meatus. Since then, the use of free grafts for substitution of the urethral plate has gained widespread acceptance. Technically speaking, the first stage is creation of a neo-urethral plate. The existing plate is excised; the glans clefted; chordee released and the resulting defect is covered with a Wolfe graft (inner layer of prepuce, buccal mucosa (Fig.1) or posterior auricular skin). The reconstructed urethral plate is tubularized in the second stage[63]. In Bracka's own words; "*Almost any hypospadias can now be corrected to optimum standard using a simple protocol consisting only of the popular one-stage TIP ('Snodgrass'), the graft-augmented TIP ('Snod-graft') and the Bracka two-stage repair. These three methods form a natural progression*".

Alsikafi et al[64] found comparable success rate with both the penile skin and oral mucosa in substitution urethroplasty. Barbagli et al[65, 66] found the success rate of oral mucosa be superior to skin in one-stage bulbar urethroplasty (82.8% vs 59.6%) and in one-stage penile urethroplasty (80% vs. 67%). Mixed interposition of inner preputial skin[67] or dorsal shaft skin[68] (Fig.2) are other technically viable options. Gill et al[69] recommended two-staged Bracka's technique for hypospadias cripples.

Mokhless et al[70] studied histological changes in the buccal mucosa before grafting and at six months after graft uptake and exposure to air. Buccal mucosa displayed epithelial hyperplasia with mild focal keratinisation. The lamina propria was slightly edematous and minimally infiltrated by mononuclear inflammatory cells. The lamina propria papillae were elongated, extended to 75% of the mucosal thickness. The buccal mucosal graft displayed good vascularisation, similar to that of normal mucosa.

FISTULA CLOSURE AFTER HYPOSPADIAS SURGERY

Urethrocutaneous fistula (UCF) is the most common complication of hypospadias repair. Despite the development of several techniques targeting interposition of 'waterproof' layer between the neourethra and the skin, the development of UCF has not been eliminated.

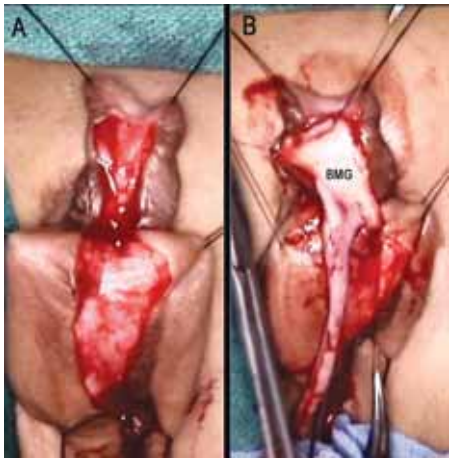

Figure 1a & 1b: *Buccal mucosal graft being apposed to the under surface of penis*

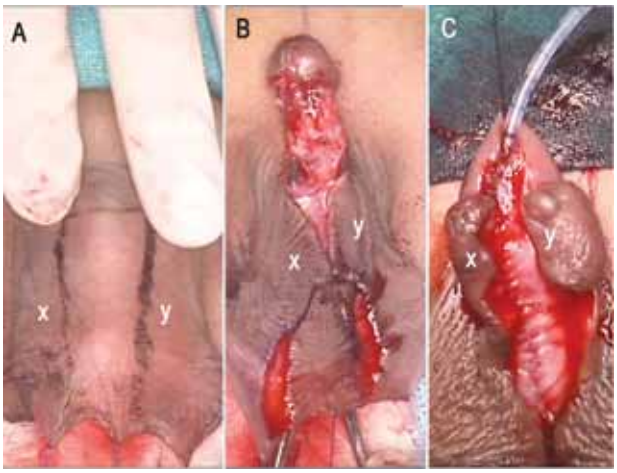

Figure 2a-c: *Dorsal shaft skin transposed ventrally (2a) using 'button hole' technique (2b) & tubularized (2c). 'X' & 'Y' represent the lateral wings of the dorsal skin.*

Numerous techniques have been used for fistula closure.

Simple fistula can be repaired primarily; the skin and urethral layers must be separated from each other and each layer must be closed separately with absorbable sutures (reported success rate 80 - 82.6%)[48]. Fistula closure in three layers as well as use of dermal subcutaneous flaps has been described for larger fistulas. The interposition of a vascular intermediate layer between the neourethra and the skin is mandatory in patients with lack of prepuce and excessive scarring consequent to prior surgeries. Snow et al[71] used the tunica vaginalis to wrap the neourethra during primary repair and subsequently for fistula closure. Tunica vaginalis wrap has gained worldwide acceptance due to its inherent advantages[72 -74]; it is thin, elastic, expandable, highly vascular, easy to harvest and anatomically close to penile shaft. Tunica vaginalis, scrotal dartos and external spermatic fascia have been used with appreciable success rates[75, 76].

Muruganandham et al[77] divided urethrocutaneous fistulas into three groups based on size. Those less than 2 mm were managed with excision and simple closure (failure 25.4%). Fistulae of 2 - 4 mm were managed with flip-flap technique along with dartos flap wrap (failure 9.5%). Fistulae >4mm were managed with flip-flap technique along with tunneled tunica vaginalis flap (Fig. 3) (failure 0%).

In patients with multiple failures excessive scarring and compromised vascularity preclude the use of local tissues. In such cases buccal mucosa grafts are useful in fistula repair[78]. This technique, originally described by Nahas' in 1994, is reported to have a success rate of more than 80%[78 - 81] Gopal et al[82] successfully used fibrin glue as sealent of suture-line during primary surgery to reduce fistula rate from 32% (controls) to 10% (study cohort). Kajbafzadeh et al[83] suggested the application of single-donor fibrin glue Soyer et al[84] have tried the use of autologous platelet-rich fibrin (PRF) in a 3-year-old boy with hypospadiac fistula. PRF is an autologous source of growth factors obtained from the serum of the patients. It supports collagen synthesis and tissue repair and accelerates wound healing. It is very difficult to designate any particular technique of fistula closure as 'the best' or 'universally applicable'; the surgeon has to individualize the choices.

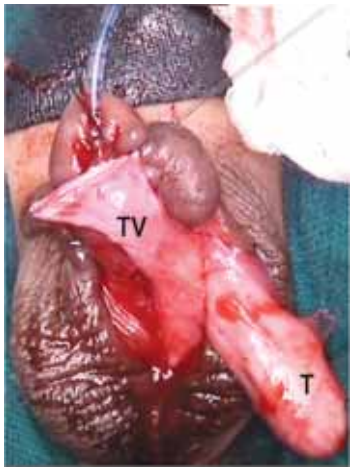

Figure 3: *Tunica vaginalis flap raised from the left side and applied over the suture line of urethral tube.*

ROLE OF TISSUE EXPANDERS IN HYPOSPADIAS REPAIR

A hypospadias cripple will have minimal residual skin available for additional reconstructive procedures. Tissue expansion is argued to be superior to grafts because of pigment and texture-matching of the penile skin. Mir et al[85] reviewed their experience with tissue expanders in 6 patients of hypospadias after multiple failures. The injection port was positioned in the suprapubic region and the tissue expander under the skin of dorsal penile shaft. Inflations were made at intervals of 2 weeks up to 12-16 weeks. After maximum tissue expansion, the expander was removed and urethral reconstruction was attempted. Successful phallus resurfacing could be achieved in all the 6 patients; UCF and meatal stenosis were seen in 1 patient each which were successfully managed. Mathews et al[86], in a group of 18 patients (including 7 hypospadiac cripples), reported successful placement and inflation of tissue expander in 17 patients, replantation of expander in 2 and extrusion of expander requiring graft replacement in 3. Eight of them had good outcome without the need of additional surgical procedures and one patient could be salvaged by repeat expansion followed by supplemental pedicle grafting. The graft was removed for malfunction, erosion and infection in 1 patient each.

LONG TERM RESULTS OF HYPOSPADIAS REPAIR

Vallasciani et al[87], on following-up 770 patients for a mean of 16 years, reported overall complication rate of 36% for tubularized preputial island flap (TIF) repair, 33% for on-lay island-flap (OIF) repair, 25% for Belt-Fuqua staged repair and 7.5% for Bracka procedure. The most common complication encountered was neo-urethral fistula. Acquired megalourethra occurred in 5 cases, none with associated distal urethral stenosis, all in the TIF and OIF groups. All cases were successfully treated by reduction redo-urethroplasty. Ratan et al[14] noted significantly higher follicular stimulating hormone (FSH), lower estrogen and lower dehydro epiandrosterone sulphate (DHEA-S) levels in hypospadias patients as compared to controls. High FSH among hypospadiacs hints at the possibility of Sertoli cell dysfunction and impaired reproductive functions during adulthood.

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