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Uremic Retention Solutes

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Abstract

This chapter will address the broad subject of uremic retention solutes (URS), also known as uremic toxins. Some of these solutes had been recognized for decades, and in 1999 when the European Uremic Toxin Work Group was established, a fuller description of URS was presented. The group sought to identify and characterize the solutes in the serum of patients with impaired glomerular filtration, in order to explore their role in the pathogenesis of the uremic syndrome and improve current therapeutic options. This chapter will review the different types of URS, as well as the adverse effects associated with their accumulation. It will also cover current and potential therapeutic approaches to reduce their levels.

Keywords: uremic retention solutes (URS), uremic toxins, CKD, ESRD, indoxyl sulfate, p-cresyl sulfate, kynurenine

1. Introduction

Chronic kidney disease (CKD) is defined by estimated glomerular filtration rate (eGFR). Uremic syndrome occurs as this eGFR declines over time. Uremia is due to the accumulation of uremic retention solutes (URS) that affect multiple organ systems most notably the cardiovascular, neurologic, endocrine, and skeletal systems. These URS become elevated during the course of CKD and reach their peak during end-stage renal disease (ESRD). Organ dysfunction due to URS is seen, at times, long before patients reach the stage of dialysis dependency. Patients with early stages of CKD are much more likely to die from cardiovascular disease than to progress to ESRD [1]. While accelerated cardiovascular disease in patients undergoing chronic hemodialysis has been attributed to traditional cardiovascular risk factors, e.g., hypertension, diabetes, and lipid abnormalities, Lindner identified an accelerated risk of atherosclerosis in

CKD patients without these risk factors [2]. During the past 10 years, there has been growing interest in characterizing the relationship between URS and cardiovascular disease. Since accelerated cardiovascular disease is seen in well-dialyzed patients, attention has been focused on solutes that are poorly dialyzed. Protein-bound URS, specifically indoxyl sulfate and p-cresyl sulfate, have been the focus of many studies over the past several decades. The interest is a result of their strong association with cardiovascular disease, their poor dialyzability, and their propensity to act on receptors (organic anion transporters) on the endothelium. Many different strategies for enhancing their removal and novel methods for reducing their generation have evolved over this period of time. The focus of this chapter will be to describe the classification of URS, describe their physiology, review their negative effects in the setting of uremia, and outline the different strategies currently being investigated to reduce levels of these solutes.

2. Classification of uremic retention solutes

The established classification system for URS is dependent on carrier protein binding and molecular weight [3]. The first class, termed low molecular weight (LMW) solutes, is categorized as less than 500 Da and is efficiently removed via hemodialysis. The next class is known as middle molecular weight (MMW) solutes. These molecules have molecular weights greater than 500 Da and require high-flux dialysis membranes, which have greater transport capacity and larger pore size for removal [4]. Protein-bound solutes comprise the last group, which are typically less than 500 Da though there is no official size demarcation. Their defining feature is their limited dialytic removal due to protein binding that impedes their movement across a dialysis membrane. A brief survey of LMW and MMW solutes will be given before focusing more in depth on the protein-bound solutes.

2.1. Low molecular weight solutes

Some of the most prominent examples of the LMW category are urea, creatinine, asymmetric dimethylarginine (ADMA), trimethylamine-N-oxide (TMAO), and uric acid.

Urea has long been known to be elevated in patients with acute and chronic kidney diseases (**Table 1**). Today, urea levels are used as a surrogate for kidney function and for assessing the adequacy of hemodialysis sessions [5]. However, the data that has been gathered over the past several decades has been conflicting over whether urea is harmful or inert [6]. While research has shown that increasing the plasma levels of urea to ten times the upper limit can produce moderate uremic symptoms (lethargy and headache), there is no evidence of a survival benefit with aggressive reductions in urea during dialysis [7, 8]. In vitro and in vivo studies have linked urea to gut epithelial damage, endothelial dysfunction, and vascular smooth muscle apoptosis [6, 9]. Despite this data, it is difficult to determine the true effect of urea reduction on uremic syndrome and patient survival due to numerous confounding factors [6].

Creatinine is formed from creatine, as part of the metabolic breakdown of the muscle. Clinically, serum creatinine levels are used to estimate glomerular filtration rate (eGFR) [10]. In CKD, creatinine accumulates as a result of decreased renal clearance, but no compelling evidence has linked it to pathology in kidney disease.

Two other LMW solutes (**Table 1**) with possible links to the pathophysiology of cardiovascular disease in CKD patients are asymmetric dimethylarginine (ADMA) and trimethylamine-N-oxide (TMAO). ADMA has been shown to inhibit nitric oxide synthase causing endothelial dysfunction and has been correlated with vascular damage as evidenced by increased vessel wall thickness [3, 11, 12]. For ADMA, removal strategies (other than dialysis) have focused on the enzyme dimethylaminohydrolase. Inhibition of this enzyme has been linked to ADMA accumulation, whereas enzyme upregulation has shown decreased coronary damage in mice [13, 14]. TMAO is a small amine oxide with a well-documented association with cardiovascular disease [15]. However, the mechanism by which it leads to atherosclerosis remains speculative with research focusing on endothelial adhesion molecule dysfunction [15, 16]. Considering that the removal of TMAO via dialysis is already highly efficient, therapeutic strategies have targeted the generation of TMAO by the gut microbiome [17].

Uric acid is a LMW molecule (**Table 1**) that is generated as a result of purine metabolism. Most animals, with the exception of humans and other primates, break down uric acid utilizing the enzyme uricase. Humans lack this enzyme and therefore excrete uric acid via the gut and kidney. Elevated uric acid levels are implicated in the pathophysiology of gout, but it has been proposed that it also plays a role in cardiovascular disease among the CKD population. Numerous studies have looked at the relationship of uric acid on cardiovascular events and mortality in the setting of early CKD [18–20]. The results have not been consistent, and this topic remains controversial. Hyperuricemia is believed to cause chronic stimulation of the renin angiotensin system leading to hypertension and progressive kidney disease [21]. Numerous randomized controlled trials have been conducted to determine whether the administration of urate-lowering therapy has an effect on CKD progression [22, 23]. There is a trend toward benefit, but it remains controversial due to significant heterogeneity among study groups and a lack of blinded studies.

2.2. Middle molecular weight (MMW) solutes

These solutes range from a MW of 500 to many tens of thousands of Daltons (Da). It is difficult at times to differentiate between solutes that are elevated due to reduced renal excretion (such as β_2 -microglobulin and leptin) versus those that are elevated due to other reasons (such as parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23), and advanced glycation end products (AGEP), among others). This section will focus on the former group.

	MW (Da)	Source	Metabolism	Toxicity
Urea [6]	60.05	Dietary proteins	Hepatic	Vascular disease, insulin resistance (in vivo data)
ADMA [24]	202.25	Protein metabolism	Endogenous enzymes	Vascular disease
TMAO [15]	75.11	Diet	Hepatic	Vascular disease, renal fibrosis
Uric acid [18–20]	168.11	Purine metabolism	Endogenous enzymes	Accelerated CKD, vascular disease, hypertension

URS, uremic retention solutes; MW, molecular weight; ADMA, asymmetric dimethylarginine; TMAO, trimethylamine-N-oxide

Table 1. Low molecular weight URS.

The most prominently studied MMW solute is β_2 -microglobulin (**Table 2**), an important component of the major histocompatibility complex [4]. β_2 -Microglobulin is recognized to be related to the deposition of amyloid in bones and joints. Speculation exists that it is not only a URS marker but additionally plays an active role in cardiovascular damage [25]. The removal of MMW solutes has centered on high-flux membranes containing wider pores to accommodate these larger molecules. However, the survival benefit of high flux versus low flux has not been definitively demonstrated in the dialysis population [26].

The discovery of the obesity gene in 1994 and its subsequent protein product, leptin, was an important step in understanding obesity [27]. Leptin accumulates in CKD/ESRD (**Table 2**). It is produced by white adipose tissue in response to an increase in body fat. It is found in a free form as well as bound to leptin-soluble receptor, which has a molecular weight of >150,000 Da. Exogenous administration of leptin, in an in vitro study, led to a reduction in food intake, increased energy expenditure, and a subsequent decrease in body weight [28]. Leptin is predominantly cleared by the kidneys, and it has been demonstrated that chronic hemodialysis patients have supraphysiological levels of this protein [29]. Using a mouse model, in which uremia was induced via subtotal nephrectomy, it has been demonstrated that the level of malnutrition was lower in leptin-receptor-deficient mice compared to wild-type mice [30].

2.3. Protein-bound solutes

Protein-bound URS are generally <500 Da. As mentioned earlier, protein-bound URS are poorly dialyzable due to their high affinity for carrier proteins such as albumin. Albumin binding is complex and determined by numerous factors that are not fully understood. This section will focus on two binding sites found on albumin, Sudlow’s sites I and II, which were first described in 1975 [31]. Sudlow’s site I is also known as the warfarin site, and Sudlow’s site II is the diazepam site. But there are numerous drugs and URS that bind to these sites. Sudlow’s site I is the binding site of 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF), indomethacin, salicylates, and many others. 3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) is considered to be one of the most potent inhibitors of drug binding to albumin compared to other URS [32, 33]. Sudlow’s site II is the binding site of IS, PCS, hippuric acid, and ibuprofen. Observational studies have demonstrated a link between indoxyl sulfate (IS) and p-cresyl sulfate (PCS) concentrations and increased cardiovascular morbidity and mortality in CKD/ESRD. Both of these compounds have a shared quality of possessing high affinity to Sudlow’s site II [34]. As such, they both exist primarily in the bound form (**Table 3**).

	MW (Da)	Source	Toxicity
β_2 -Microglobulin [25]	11,729	Major histocompatibility complex	Amyloid bone and joint disease, vascular wall infiltration
Leptin [28]	16,000	Endogenous	Malnutrition

URS, uremic retention solutes; MW, molecular weight

Table 2. Middle molecular weight URS.

	MW (Da)	Source	Metabolism	Toxicity	Percent unbound
Indoxyl sulfate [37, 38, 45–48]	251.30	Tryptophan	Gut microbiome, hepatic	Cardiovascular	~10%
p-Cresyl sulfate [37, 38, 45, 46]	188.19	Tyrosine	Gut microbiome, hepatic	Cardiovascular	5–10%
Kynurenine [41–43]	208.21	Tryptophan	Primarily hepatic, also immune cells	CNS	N/A
Kynurenic acid [41–43, 52]	189.17	Tryptophan	CNS	CNS	14%
Quinolinic acid [41, 44]	167.12	Tryptophan	Brain microglia	Bone marrow, CNS	N/A
CMPF [38]	240.25	Furanoid fatty acids	Endogenous enzymes	Bone marrow, thyroid, albumin drug binding	<1%

URS, uremic retention solutes; MW, molecular weight; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid

Table 3. Protein-bound URS.

There are known differences in the rate of production of protein-bound URS, and this likely explains why their plasma levels do not correlate well with creatinine, urea levels, or estimated GFR [3]. Organic anion transporters (OAT1 and OAT3) on the basolateral membrane of the proximal tubule are responsible for URS entry into the cell, and subsequent secretion into the tubular lumen appears to be mediated by OAT4 [35–37]. This important physiological process is hindered by nephron loss in advanced CKD and almost nonexistent in ESRD leading to significant elevation of protein-bound URS.

CMPF is a highly protein-bound URS (see **Table 3**). It is very poorly dialyzable, and there is in vitro data that it leads to radical oxygen species (ROS) production in endothelial cells. Unlike other protein-bound URS, CMPF does not demonstrate any significant removal during dialysis, but dialysate effluent levels were not measured to determine whether there is filtration [38]. The probable explanation, offered by the authors, for the paradoxical rise of CMPF levels after dialysis is hemoconcentration. CMPF has significant effects on drug binding to albumin. CMPF has also been implicated in numerous pathological pathways including anemia, hypothyroidism, and others [39, 40].

Tryptophan metabolism via the kynurenine pathway produces several solutes (including kynurenine and quinolinic acid) relevant to renal failure. In ESRD patients, elevated levels of kynurenine and quinolinic acid have been associated with endothelial dysfunction, inflammation, and carotid artery thickening [41]. Metabolic products of kynurenine, specifically kynurenic acid, are also known to have neural activity at several neurotransmitter receptors, and alterations in kynurenine removal are thought to be sufficient to produce CNS effects [42, 43]. Researchers have demonstrated that quinolinic acid inhibits erythropoietin release in vitro, possibly contributing to the anemia seen in ESRD patients [44].

3. The gut-kidney axis

Over the last few decades, microbial metabolism in the human gut has been recognized as offering beneficial effects to the host. These effects include fermentation of carbohydrates resistant to our own enzymatic processes, formation of several vitamins, and unique contributions to the mammalian metabolome [49, 50]. Important to the current discussion of uremic retention solutes is that a significant amount of protein-bound solutes (IS and PCS included) are formed by dietary protein metabolism in the large intestine [51]. In fact, a 2011 study with dialysis patients comparing the URS levels of individuals with a total colectomy versus those with an intact colon showed IS and PCS to be nearly absent in those patients without colons [52]. Similarly, IS and PCS levels are very low in germ-free rodents.

Protein metabolism in the large intestine generates IS and PCS along parallel pathways (**Figure 1**). For IS the process starts with dietary tryptophan being acted upon by bacterial tryptophanase enzymes that convert tryptophan to indole. Indole is then absorbed in the large intestine and travels to the liver where it is oxidized and sulfated to form indoxyl sulfate [53]. Similarly, bacterial metabolism of tyrosine generates p-cresyl, which is absorbed and converted to p-cresyl sulfate by the liver. Both IS and PCS become bound to albumin and circulate in the plasma until they are secreted by the kidneys via OATs found on the basolateral and luminal membranes of proximal renal tubular cells. The relationship between gut bacterial metabolites, normal human metabolism, and renal excretion has been termed the gut-kidney axis [51, 54–56]. In fact, an additional classification of URS has been proposed, organizing solutes based on their origin (human metabolism, microbial metabolism, or diet) as opposed to their behavior during dialysis [49].

In addition to the colon microbiota species, the main determinants of gut microbial metabolism are diet and transit time [56]. With diet, the ratio of carbohydrate catabolism to protein catabolism by the microbiota determines the extent to which protein metabolism (and therefore URS generation) takes place. In the case of carbohydrate excess such as with a high-fiber diet, there is a large amount of energy available for bacterial growth and cell division. The nitrogen sources in the gut are consequently utilized for the bacteria’s own growth and replication as

Figure 1. The gut-kidney axis of indoxyl sulfate (IS) and p-cresyl sulfate (PCS). Adapted from [55] with permission.

opposed to being fermented for energy [49]. However, in carbohydrate deficiency, the nitrogen sources are predominantly metabolized to phenols, indoles, and amines, thereby contributing to URS generation [51].

Another modifiable determinant of microbial metabolism is the colonic transit time. In vivo human data has demonstrated that the majority of the variance seen in the urinary phenol excretion rate was due to colonic transit time and dietary protein intake. In fact, a doubling of the colonic transit time corresponded to a 60% increase in urinary excretion of phenols [57]. It is thought that longer transit times induce the development of large populations of many proteolytic bacteria. This, in addition to the relative carbohydrate deficit in the colon, contributes to greater protein metabolism and URS generation [51, 56]. The role of the gut-kidney axis when considering possible therapeutics to lower URS will be discussed in a later section.

4. Effects on the cardiovascular system

Patients with CKD or ESRD have high morbidity and mortality from cardiovascular disease. Unfortunately, a patient with CKD is much more likely to die of cardiovascular disease than to reach the stage of dialysis dependency [1]. Due to their possible contribution to cardiovascular disease, indoxyl sulfate and p-cresyl sulfate have attracted a lot of research attention.

4.1. Indoxyl sulfate

A number of human studies have shown a clinical association between high indoxyl sulfate levels and various adverse outcomes. Especially in the early stages of CKD, there have been associations of higher IS levels with left ventricular dysfunction, coronary atherosclerosis, coronary stent restenosis, and cardiac death [58–61]. However, with more advanced CKD (such as with hemodialysis patients), the associations of higher IS levels with cardiovascular events and cardiac death are mixed [62–65]. Several studies specifically show no association between higher IS levels and cardiovascular morbidity and mortality [64, 65]. This might be related to the fact that with advanced CKD, there is already end organ damage, and so the levels of URS are not as significant.

Studies with isolated cells or tissues have demonstrated a number of mechanisms by which IS could possibly lead to cardiovascular disease. One of these mechanisms is via increased tissue factor expression. Multiple studies examining this feature have found evidence that IS acts as an agonist for the aryl hydrocarbon receptor (AHR) in vascular smooth muscle cells. The AHR-IS complex is translocated to the nucleus where it dysregulates a host of genes leading to inhibition of the degradation of tissue factor [66]. This concept was further demonstrated by showing that AHR antagonists reduce tissue factor expression [67]. Additionally, AHR activation has been linked to increased progression of atherosclerosis in a mouse model [68]. Another mechanism might be via leukocyte endothelial adhesion. Studies have demonstrated increased leukocyte recruitment with IS exposure, as well as increased leukocyte adhesion to endothelial cells which is accompanied by increased expression of NF- κ B, TNF α , and E-selectin. IS pretreatment of endothelial cells significantly increased IL-1 β -induced E-selectin expression, monocyte adhesion, and phosphorylation of various MAP kinases and

transcription factors such as NF- κ B [69]. These findings support the hypothesis that altered E-selectin shedding may play a central role in the cardiovascular disease that complicates the course of many CKD patients [70].

Additionally, increased vascular calcifications seem to accompany increased IS levels. In vivo rodent studies demonstrated that uremic-level IS administration resulted in vascular calcifications [71]. The mechanism by which IS leads to vascular calcification is unknown, but it may be related to altered osteoblast signaling [72]. Additional evidence regarding the effects of IS includes disrupted adherens junctions on endothelial cells, impaired proliferation and self-repair of endothelial cells, endothelial microparticle release, free radical production, and increased advanced glycation end products [73–77].

4.2. p-Cresyl sulfate

Clinical studies have identified an association between elevated PCS levels (total and unbound) and cardiovascular complications in CKD patients. These cardiovascular complications include an increased rate of coronary artery disease, vascular calcifications, and cardiovascular and all-cause mortality [78–82].

Cell culture and isolated tissue studies have demonstrated a variety of effects of increased levels of PCS. Several studies have focused on the oxidative stress that results from PCS exposure. Elevated PCS levels have been demonstrated to induce leukocyte-free radical production, oxidative stress in both human umbilical vein endothelial cells and vascular smooth muscle cells, as well as increase NADPH oxidase activity and ROS production in cardiomyocytes leading to cardiac cell apoptosis [83–86]. Other effects include the release of endothelial microparticles, vascular remodeling, and the observation that an increase in PCS appears to stimulate leukocyte rolling along the vascular endothelium, suggesting there is cross talk between leukocytes and endothelial cells [85, 87, 88]. The mechanisms behind these findings are not yet clear.

5. Potential therapeutic interventions

In response to the mounting evidence that supraphysiological levels of URS likely contribute to the morbidity and mortality of CKD/ESRD, there has been significant interest in developing methods to lower URS levels. Two major approaches have substantial research behind them—increasing removal via dialysis and decreasing production by gastrointestinal flora. Broadly speaking, both have shown the ability to lower URS levels, but no method has definitively shown a mortality benefit as of yet.

5.1. Dialysis

There have been several investigational strategies that have proven successful in removing protein-bound URS during hemodialysis. The method with the fewest obstacles to being incorporated into clinical practice is the addition of a pressure gradient across the dialysis membrane (otherwise known as convection). Despite data indicating that it can effectively remove more protein-bound solutes than traditional dialysis, the clinical benefits have yet to

be proven [4, 89, 90]. Another area of research concerns altering the dialysis milieu in order to affect the binding of URS to plasma proteins. Examples of this effort which have data supporting their use include using hypertonic solution, the use of albumin-binding site competitors such as tryptophan and docosahexaenoic acid, increasing temperature, plasma dilutions, and pH manipulation of the dialysate [47, 90–94].

Other techniques have been proposed and studied, but they involve technologies which would profoundly alter the way dialysis is delivered, therefore making their incorporation into clinical practice more difficult. Given the importance of renal tubular secretion in protein-bound URS removal, there has been interest in incorporating bioengineered renal tubules in the dialysis membrane. In vitro data has demonstrated that secretion of protein-bound URS (indoxyl sulfate and kynurenic acid) can be achieved in immortalized proximal tubule epithelial cells by integrating transport proteins such as organic anion transporters (OAT) [95]. The use of sorbent containing extracorporeal devices (SCED) uses an additional circuit within the hemodialysis setup to cleanse albumin of URS before returning them to circulation. The use of SCEDs has even demonstrated effective removal of these solutes from post-dialysis patient plasma. However, this strategy has been limited due to biocompatibility problems with the sorbent, although the development of newer sorbents may circumnavigate this obstacle [96, 97].

5.2. The gut-kidney axis

There is growing interest in affecting URS levels by intervening at the level of the gut-kidney axis. This approach has significant potential because URS accumulate in all stages of CKD, not just in dialysis-dependent ESRD. By intervening upstream in the gut-kidney axis, clinicians could empirically inhibit the production and absorption of URS and their potential cardiovascular effects. The major strategies being investigated in this area include those that affect URS generation and those that act as gastrointestinal adsorbents. Altering URS generation involves using either probiotics or prebiotics to theoretically shift microbial metabolism toward carbohydrate metabolism and away from the generation of proteolytic fermentation end products such as URS.

The administration of live microorganisms in order to alter an individual's microbiome (otherwise known as probiotics) has been utilized as a treatment for various illnesses. While some initial studies utilizing probiotics showed a promise in decreasing URS, these studies were performed in patients with healthy kidneys. Only a few studies were performed which looked at URS in CKD patients, and the results for *Lactobacillus* and *Bifidobacterium* genera have been promising [98–102]. As opposed to introducing a living organism, prebiotics are selectively fermented molecules that result in changes to the composition or activity of the gut microbiota, conferring a benefit to the host. The limited studies that exist in utilizing prebiotics have used ingredients belonging to either the inulin-type fructans or the galacto-oligosaccharides [99, 103].

Due to the advancement of DNA sequencing technology, research on the gut microbiome has accelerated and includes many different conditions. The effect of the gut microbiome on URS production has been studied. Nazzari et al. demonstrated the effect of oral vancomycin on the gut microbiome [104]. They demonstrated that plasma levels of protein-bound indoxyl sulfate

and p-cresyl sulfate were reduced in an ESRD population after a single dose of oral vancomycin, but the effect was transient and reversed itself by the end of the follow-up period. The diversity of the gut microbiome was significantly reduced, and the effect did not resolve by the end of the study period.

Limiting the uptake of colonic solutes by using an oral adsorbent, such as the spherical carbon adsorbent AST-120, has been an additional approach to lowering URS levels. AST-120 binds to a number of URS precursor molecules, and some of the initial studies were very promising, showing a decrease in the levels of several URS, including IS and PCS [105–107]. A randomized controlled trial was performed in CKD patients, which sought to evaluate the effect of AST-120 on intima-media thickness and carotid artery stiffness. The results were encouraging, finding that the AST-120 group had reduced intima-media thickness along with less arterial stiffness compared to the non-AST-120 group [108]. However, EPICC (a large randomized, placebo-controlled, double-blind study) failed to show a benefit of AST-120 for clinical outcomes such as CKD progression and mortality, thereby failing to support the widespread use of AST-120 in advanced CKD [109].

6. Future directions

To this day, our understanding of URS is limited. One major limitation of uremia research is that URS accumulate in synchrony. This makes it difficult to establish a causal relationship. Ideally, URS research should be performed in the early CKD population and should include long follow-up. Another limitation is the lack of targeted methods to decrease the level of a specific URS. Once specific URS can be targeted, prospective randomized control trials will be able to elucidate each URS' true effects.

In addition, it is becoming clear that interventions outside of the realm of hemodialysis could have great potential. As described above, URS accumulate in all stages of CKD, not just in dialysis-dependent ESRD. Considering the prevalence of early CKD and its significant mortality, this would be the ideal population for further research on therapeutic options. By focusing on the gut-kidney axis, we could learn how to halt the production of URS. There is a need for randomized control trials to evaluate the effectiveness of prebiotics, probiotics, dietary alterations, adsorbents, and antibiotics in leading to better outcomes for this patient population.

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