# New biomarkers of acute kidney injury

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**Acute kidney injury (AKI) represents a major clinical problem, with rising incidence and high mortality rate. The lack of early biomarkers has resulted in a delay in initiating therapies. Fortunately, the tools of modern science have revealed promising novel biomarkers for AKI, with potentially high sensitivity and specificity. These include a plasma panel (neutrophil gelatinase–associated lipocalin and cystatin C) and a urine panel (neutrophil gelatinase–associated lipocalin, interleukin 18, and kidney injury molecule-1). Because they represent sequential biomarkers, it is likely that the AKI panels will be useful for timing the initial insult and assessing the duration of AKI (analogous to the cardiac panel for evaluating chest pain) and for predicting overall prognosis with respect to dialysis requirement and mortality. It is also likely that the AKI panels will help distinguish between the various types and pathogeneses of AKI. It will be important in future studies to validate the sensitivity and specificity of these biomarker panels in clinical samples from large cohorts and from multiple clinical situations. Such studies will be markedly facilitated by multidisciplinary participation of various specialties (intensivists, cardiologists, surgeons) in AKI clinical studies and by the availability of commercial tools for the reliable and reproducible measurement of biomarkers across different laboratories. (Crit Care Med 2008; 36[Suppl.]:S159–S165)**

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In a recent multinational study of acute kidney injury (AKI) in nearly 30,000 critically ill patients, the overall prevalence of AKI requiring renal replacement therapy was 5.7%, with a mortality of 60.3% (1). An increase in morbidity and mortality associated with AKI has been demonstrated in a wide variety of clinical situations (2–11), including, but not limited to, those exposed to radiocontrast dye (12), cardiopulmonary bypass (13–18), mechanical ventilation (19), and most commonly, sepsis (20, 21). The negative influence of AKI on overall outcomes in critically ill patients is also well documented (22–27). In addition, recent studies have revealed that AKI is a major risk factor for the development of nonrenal complications, and it independently contributes to mortality (12, 28). Furthermore, the treatment of AKI represents an enormous financial burden to society, with annual AKI-associated medical expenses estimated at $8 billion (29, 30).

Tremendous progress has been made in our understanding of the molecular mechanisms of renal diseases such as AKI. However, a translation of these findings to diagnostics and therapeutics used in clinical practice remains challenging (31). Several agents that work remarkably well in animal models of AKI (32–34) have failed in clinical trials (35–38). This disparity in the efficacy of therapies in animal and human studies has been attributed, in part, to the failure to identify suitable physiologic surrogate end points for use in clinical studies testing the efficacy of new interventions. In the field of cardiology, the use of serum cardiac enzyme concentrations has facilitated development of several newer agents for management of coronary insufficiency and has affected the morbidity and mortality of acute myocardial infarction. By contrast, AKI prevention and therapy studies using variables such as urine output and serum and urine chemistries have not yielded interventions proven to decrease the requirement for dialysis and reduce mortality. In fact, very few AKI studies have demonstrated a beneficial effect on the most commonly used physiologic surrogate end points, the serum urea nitrogen and creatinine concentrations (39, 40). Of those interventions that have been successful in smaller, phase 2 efficacy studies of AKI, most prominently exemplified by the experiences with atrial natriuretic peptide (41) and insulin-like growth factor (42), none was successful at improving clinical end points, such as dialysis requirement or mortality, in larger phase 3 trials (36, 37, 43). Possibly, the interventions would have been successful if they could be initiated at the onset of AKI rather than waiting several days for creatinine to rise.

The diagnosis of AKI is based on either the elevation of serum creatinine or the detection of oliguria. Serum creatinine, however, is a poor marker of early renal dysfunction because the serum concentration is greatly influenced by changes in muscle mass and tubular secretion (44). Hence, the normal reference interval is relatively wide, and the use of serum creatinine alone to follow disease progression is fraught with imprecision. There are numerous nonrenal factors influencing the serum creatinine concen-

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tration, such as body weight, race, age, sex, total body volume, drugs, muscle metabolism, and protein intake. In AKI, serum creatinine is an even poorer reflection of kidney function because the patients are not in steady state, and serum creatinine therefore lags far behind renal injury (45). Furthermore, significant renal disease (e.g., fibrosis) can exist with minimal or no change in creatinine because of renal reserve, enhanced tubular secretion of creatinine, or other factors (44, 46). The issues discussed above increase the risk of failure in drug development. These issues also increase the variability in the outcomes and magnify the size and cost of clinical studies. A troponin-like biomarker of AKI that is easily measured, unaffected by other biological variables, and capable both of early detection and risk stratification would be a tremendous advance in clinical medicine.

The quest for AKI biomarkers is an area of intense contemporary research and has been endorsed as an area of research priority by the American Society of Nephrology, the Acute Kidney Injury Network, and the National Institutes of Health (47). Conventional urinary biomarkers, such as casts and fractional excretion of sodium, have been insensitive and nonspecific for the early recognition of AKI. Other traditional urinary biomarkers, such as filtered high molecular weight proteins and tubular proteins or enzymes, have also suffered from lack of specificity and dearth of standardized assays. Fortunately, the application of innovative technologies such as functional genomics and proteomics to human and animal models of AKI has uncovered several novel genes and gene products that are emerging as biomarkers. The most promising of these are listed in Table 1 and detailed in this article.

## Desirable Properties and Roles of AKI Biomarkers

Desirable characteristics of clinically applicable AKI biomarkers are as follows: a) they should be noninvasive and easy to perform at the bedside or in a standard clinical laboratory, using easily accessible samples such as blood or urine; b) they should be rapidly and reliably measurable using a standardized assay platform; c) they should be highly sensitive to facilitate early detection and have a wide dynamic range and cutoff values that allow for risk stratification; and d) they should exhibit strong biomarker performance on statistical analysis.

In addition to aiding in the early diagnosis and prediction, they should be highly specific for AKI and enable the identification of AKI subtypes and pathogeneses. AKI is traditionally diagnosed when the kidney's major function of filtration is affected and indirectly measured by change in serum creatinine. However, prerenal factors, such as volume depletion, decreased effective circulating volume, or alterations in the caliber of afferent arterioles leading to the glomerulus, all cause elevations in serum creatinine. Postrenal factors such as urinary tract obstruction similarly result in elevations in serum creatinine. Finally, a multitude of intrinsic renal diseases may result in an abrupt rise in serum creatinine, particularly in hospitalized patients. Although various other maneuvers are utilized to distinguish these various forms of acute renal dysfunction, such as microscopic urine examination for various casts, determination of fractional excretion of sodium, and renal ultrasound, these tests are often imprecise and have not advanced the field of nephrology significantly (48–51). Availability of accurate biomarkers that can distinguish prerenal and postrenal conditions causing an increase in serum creatinine from intrinsic causes of AKI that affect kidney structure and function would represent a significant advance.

Biomarkers may serve several other purposes in AKI. Thus, biomarkers are also needed for a) identifying the primary location of injury (proximal tubule, distal tubule, interstitium, or vasculature); b) pinpointing the duration of kidney failure (AKI, chronic kidney disease, or "acute-on-chronic"); c) identifying AKI pathogeneses (ischemia, toxins, sepsis, or a combination); d) risk stratification and prognostication (duration and severity of AKI, need for renal replacement therapy, length of hospital stay, mortality); e) defining the course of AKI; and f) monitoring the response to AKI interventions. Furthermore, AKI biomarkers may play a critical role in expediting the drug development process. The Critical Path Initiative issued by the U.S. Food and Drug Administration in 2004 stated that "Additional biomarkers (quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness) and additional surrogate markers (quantitative measures that can predict effectiveness) are needed to guide product development" (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html).

Regarding the sample source, the majority of AKI biomarkers described thus far have been measured in the urine. Urinary diagnostics have several advantages, including the noninvasive nature of sample collection, the reduced number of interfering proteins, and the potential for the development of patient self-testing kits. However, several disadvantages also exist, including the lack of sample from patients with severe oliguria and potential changes in urinary biomarker concentration induced by hydration status

**Table 1.** Current status of new biomarkers for early detection of acute kidney injury (AKI) in various clinical settings

| Biomarker Name | Sample Source | Cardiopulmonary Bypass (CPB) | Contrast Nephropathy | Sepsis or ICU Setting | Kidney Transplant (tx) | Commercial Assay |
|---|---|---|---|---|---|---|
| NGAL | Urine | 2 hrs post-CPB | 4 hrs postcontrast | 48 hrs before AKI | 12–24 hrs post-tx | ELISA, Abbott[a] |
| IL-18 | Urine | 4–6 hrs post-CPB | Not tested | 48 hrs before AKI | 12–24 hrs post-tx | ELISA |
| KIM-1 | Urine | 12–24 hrs post-CPB | Not tested | Not tested | Not tested | ELISA |
| NGAL | Plasma | 2 hrs post-CPB | 2 hrs postcontrast | 48 hrs before AKI | Not tested | ELISA, Biosite[a] |
| Cystatin C | Plasma | 12 hrs post-CPB[b] | 8 hrs postcontrast | 48 hrs before AKI | Variable | Nephelometry; Dade-Behring |

ICU, intensive care unit; NGAL, neutrophil gelatinase–associated lipocalin; ELISA, enzyme-linked immunosorbent assay; IL-18, interleukin-18; KIM-1, kidney injury molecule-1.

[a]In development; [b]unpublished data. Times indicated are the earliest time points when the biomarker values become significantly elevated from baseline values. The ELISA assays are research based, although clinical platforms for NGAL measurement are nearing completion.

and diuretic therapy. Plasma-based diagnostics have revolutionized many facets of critical care medicine, as exemplified by the use of troponins for the early diagnosis of acute myocardial infarction and the value of B-type natriuretic peptide for prognostication in acute coronary syndrome. Thus, in the case of AKI, it is important to develop both urinary and plasma biomarkers.

## Phases of Biomarker Development

In developing new biomarkers for diagnostic purposes, five phases of research and development have been identified. These were developed by Pepe et al. (52) for cancer-related biomarkers, but the principles can be applied for development of biomarkers for other pathophysiologic states such as AKI. These phases are akin to the drug development stages, such that with each advancing stage, the study design gets more rigorous, requiring more subjects, time, and resources.

The first is the preclinical phase or the discovery phase in which research identifies promising molecules or markers that require further exploration. In this regard, some of the newer biomarkers of AKI, such as interleukin (IL)-18, kidney injury molecule (KIM)-1, and neutrophil gelatinase–associated lipocalin (NGAL, discussed in detail below), were initially discovered and described to play a role in the pathophysiology of AKI in animal models (53–55). The second and third phases of development are translational phases in which a robust clinical assay (typically an enzyme-linked immunosorbent assay test) is developed for the biomarker and the potential biomarker is tested in a limited clinical setting to determine whether it detects established disease. In this regard, IL-18 and NGAL have been shown to be increased in patients with established AKI compared with controls (56). It is most efficient to design this phase as a retrospective study using samples available from bio-repositories of well-annotated clinical trials. Such studies have demonstrated that IL-18, NGAL, and cystatin C perform very well as early markers of AKI (57–60). The fourth phase is the validation phase, in which the biomarker undergoes large-scale prospective studies or clinical trials to determine performance characteristics of the test, after which a biomarker can be made available for clinical use.

Unfortunately, many promising biomarkers never make it into clinical practice or even broad application in clinical or laboratory research. The development process is complex, and investigators need a complete development plan with access to sufficient, well-characterized samples. An understanding of the complex biomarker development process and the incorporation of a team approach are required for successful development of the biomarkers. As detailed below, AKI biomarkers, such as IL-18, NGAL, KIM-1, and cystatin C, have systematically advanced through the development process and are now ready for further clinical development.

## Novel AKI Biomarkers Under Evaluation in Humans

*Neutrophil Gelatinase–Associated Lipocalin.* Human NGAL was originally identified as a 25-kDa protein covalently bound to gelatinase from neutrophils. NGAL is normally expressed at very low levels in several human tissues, including kidney, lungs, stomach, and colon. NGAL expression is markedly induced in injured epithelia. For example, NGAL concentrations are elevated in the serum of patients with acute bacterial infections, the sputum of subjects with asthma or chronic obstructive pulmonary disease, and the bronchial fluid from the emphysematous lung (53, 61–63). NGAL was recently identified by micro-array analysis as one of the earliest and most robustly induced genes and proteins in the kidney after ischemic or nephrotoxic injury in animal models, and NGAL protein was easily detected in the blood and urine soon after AKI (53, 62). These findings have generated a number of translational studies to evaluate NGAL as a novel biomarker of human AKI.

In a cross-sectional study, human adults in the intensive care unit with established ARF (defined as a doubling of the serum creatinine in $<5$ days) secondary to sepsis, ischemia, or nephrotoxins displayed a greater than ten-fold increase in plasma NGAL and more than a 100-fold increase in urine NGAL by Western blot when compared with normal controls (61). Both plasma and urine NGAL correlated highly with serum creatinine levels. Kidney biopsies in these patients showed intense accumulation of immunoreactive NGAL in 50% of the cortical tubules. These results identified NGAL as a widespread and sensitive response to established AKI in humans.

In a prospective study of children undergoing cardiopulmonary bypass, AKI (defined as a 50% increase in serum creatinine) occurred in 28% of the subjects, but the diagnosis using serum creatinine was only possible 1–3 days after surgery (58). In marked contrast, NGAL measurements by Western blot and by enzyme-linked immunosorbent assay revealed a robust ten-fold or greater increase in the urine and plasma within 2–6 hrs of the surgery in patients who subsequently developed AKI. Both urine and plasma NGAL were powerful independent predictors of AKI, with an outstanding area under the curve (AUC) of 0.998 for the 2-hr urine NGAL measurement and 0.91 for the 2-hr plasma NGAL measurement (58). Thus, plasma and urine NGAL emerged as sensitive, specific, and highly predictive early biomarkers of AKI after cardiac surgery in children. It should be emphasized that the patients in this study were primarily children with congenital heart disease, who lacked many of the common comorbid conditions (such as diabetes, hypertension, and atherosclerosis) that are frequently encountered in adults. Nevertheless, these findings have now been confirmed in a prospective study of adults who developed AKI after cardiac surgery, in whom urinary NGAL was significantly elevated by 1–3 hrs after the operation (64). AKI, defined as a 50% increase in serum creatinine, did not occur until the third postoperative day. However, patients who did not encounter AKI also displayed a significant increase in urine NGAL in the early postoperative period, although to a much lesser degree than in those who subsequently developed AKI. The AUC reported in the adult study was 0.74 for the 3-hr NGAL and 0.80 for the 18-hr NGAL, which is perhaps reflective of the confounding variables one typically accumulates with age.

NGAL has also been evaluated as a biomarker of AKI in kidney transplantation. Biopsies of kidneys obtained 1 hr after vascular anastomosis revealed a significant correlation between NGAL staining intensity and the subsequent development of delayed graft function (65). In a prospective multicenter study of children and adults, urine NGAL levels in samples collected on the day of transplant clearly identified cadaveric kidney recipients who subsequently developed delayed graft function and dialysis requirement (which typically occurred 2–4 days later). The

receiver operating characteristic curve for prediction of delayed graft function based on urine NGAL at day 0 showed an AUC of 0.9, indicative of an excellent predictive biomarker (66). Urine NGAL has also been shown to predict the severity of AKI and dialysis requirement in a multicenter study of children with diarrhea-associated hemolytic uremic syndrome (67). Preliminary results also suggest that plasma and urine NGAL measurements represent predictive biomarkers of AKI after contrast administration (68) and in the pediatric intensive care setting (69).

In summary, NGAL is emerging as an important biomarker in AKI, with tremendous potential for early diagnosis. However, it is acknowledged that the studies published thus far are small, in which NGAL seems to be most sensitive and specific in relatively uncomplicated patient populations with AKI. NGAL measurements may be influenced by a number of coexisting variables, such as preexisting renal disease and systemic or urinary tract infections. Robust clinical assays for NGAL that are accurate and report results in minutes have now been developed and are currently undergoing large-scale clinical testing.

*Interleukin-18.* IL-18 is a proinflammatory cytokine that is induced and cleaved in the proximal tubule after AKI. The intracellular cysteine protease, capsase-1, converts the pro-form of the cytokines IL-1β and IL-18 to their active forms (54, 70). The active form of IL-18 exits the cell and may enter the urine after being activated in proximal tubules. In mice, urinary IL-18 concentration was increased in ischemic AKI compared with sham-surgery controls (54). In a subsequent cross-sectional study, urine IL-18 levels were markedly increased in patients with established AKI but not in subjects with urinary tract infection, chronic kidney disease, nephritic syndrome, or prerenal failure (56). Urinary IL-18 levels displayed sensitivity and specificity of >90%, with an AUC of 95% for the diagnosis of established AKI. Thus, IL-18 seems to be an excellent tool to differentiate acute tubular necrosis from other types of acute renal diseases.

A subsequent study in acute respiratory distress syndrome patients in 2005 first investigated the potential of urinary IL-18 as an early marker of AKI (57). Urine samples from 52 patients with AKI and 86 control patients were tested for urinary IL-18 using samples previously collected as part of a National Institutes of Health–sponsored Acute Respiratory Distress Syndrome Network trial. AKI was defined as a 50% increase in serum creatinine. On multivariate analysis, urine IL-18 levels of >100 pg/mg predicted the development of AKI 24 hrs before the serum creatinine, with an adjusted odds ratio of 6.5 and AUC of 73%. Importantly, urine IL-18 on day of initiation of mechanical ventilation was also predictive of mortality in acute respiratory distress syndrome patients, independent of severity of illness scores, serum creatinine, and urine output. Similarly, in a pediatric cohort of 137 critically ill patients, urine IL-18 increased as much as 48 hrs before AKI and is a predictor of mortality.

In addition, in a single-center study and in a prospective multicenter study of children and adults, urine IL-18 levels in samples collected at the day of transplant clearly identified cadaveric kidney recipients who subsequently developed delayed graft function and dialysis requirement (which typically occurred 2–4 days later). The receiver operating characteristic curve for prediction of delayed graft function based on urine IL-18 levels at day 0 showed an AUC of 0.9 in both studies, indicative of an excellent predictive biomarker (56, 66).

Urinary NGAL and IL-18 were recently shown to represent early, predictive, sequential AKI biomarkers in children undergoing cardiac surgery (71). In patients who developed AKI 2–3 days after surgery, urinary NGAL was induced within 2 hrs and peaked at 6 hrs, whereas urine IL-18 levels increased around 6 hrs and peaked at >25-fold at 12 hrs after surgery (AUC, 0.75). Both NGAL and IL-18 were independently associated with duration of AKI among cases.

Thus, IL-18 also represents a promising candidate for inclusion in the putative urinary "AKI panel." It has the potential for being a marker for differential diagnosis, early diagnosis, and risk stratification in AKI. IL-18 is more specific to ischemic AKI and other forms of acute tubular necrosis and does not seem to be affected by prerenal azotemia, chronic kidney disease, or urinary tract infections. IL-18 also offers prognostic information regarding severity and mortality at the time of AKI diagnosis.

*Cystatin C.* Cystatin C is a cysteine protease inhibitor that is synthesized and released into the blood at a relatively constant rate by all nucleated cells (72). It is freely filtered by the glomerulus, completely reabsorbed by the proximal tubule, and not secreted. Because blood levels of cystatin C are not significantly affected by age, sex, race, or muscle mass, it is a better predictor of glomerular function than serum creatinine in patients with chronic kidney disease. Urinary excretion of cystatin C has been shown to predict the requirement for renal replacement therapy in patients with established AKI about 1 day earlier, with an AUC of 0.75 (73). In the intensive care setting, a 50% increase in serum cystatin C predicted AKI 1–2 days before the rise in serum creatinine, with an AUC of 0.97 and 0.82, respectively (59).

A recent prospective study compared the ability of serum cystatin C and NGAL in the prediction of AKI after cardiac surgery in children (Devarajan et al., unpublished data). Of 129 patients, 41 developed AKI (defined as a 50% increase in serum creatinine) 1–3 days after cardiopulmonary bypass. In AKI cases, serum NGAL levels were elevated at 2 hrs after surgery, whereas serum cystatin C levels increased only after 12 hrs. Both NGAL and cystatin C levels at 12 hrs were strong independent predictors of AKI, but NGAL outperformed cystatin C at earlier time points. In contrast, in a previously published study, serum cystatin C did not outperform serum creatinine in the early diagnosis of AKI and did not predict clinical outcomes (74).

Thus, cystatin C may represent a promising biomarker candidate for inclusion in the blood AKI panel. It is primarily a sensitive marker of reduction in glomerular filtration and not a marker of kidney injury. Thus, it is an early marker of injury when filtration is affected but cannot differentiate between different types of AKI. An advantage of cystatin C is the commercial availability of a standardized immunonephelometric assay, which is automated and provides results in minutes. In addition, routine clinical storage conditions, freeze/thaw cycles, the presence of interfering substances, and the pathogenesis of the AKI do not affect serum cystatin C measurements.

*Kidney Injury Molecule-1.* KIM-1 is a transmembrane protein that is highly overexpressed in dedifferentiated proximal tubule cells after ischemic or nephrotoxic AKI in animal models (75), and a proteolytically processed domain is easily detected in the urine (76). In a small, human, cross-sectional study, KIM-1 was found to be markedly induced in proxi-

mal tubules in kidney biopsies from patients with established AKI (primarily ischemic), and urinary KIM-1 distinguished ischemic AKI from prerenal azotemia and chronic renal disease (77). Patients with AKI induced by contrast did not have increased urinary KIM-1.

Recent preliminary studies have expanded the potential clinical utility of KIM-1 as a predictive AKI biomarker. In a cohort of 103 adults undergoing cardiopulmonary bypass, AKI (defined as an increase in serum creatinine of 0.3 mg/dL) developed in 31%, in whom the urinary KIM-1 levels increased by about 40% at 2 hrs after surgery and by >100% at the 24-hr time point. In a small case-control study of 40 children undergoing cardiac surgery, 20 with AKI (defined as a 50% increase in serum creatinine) and 20 without AKI, urinary KIM-1 levels were markedly enhanced, with an AUC of 0.83 at the 12-hr time point (78).

A recent study (79) examined the relationship between KIM-1 and the composite end point (dialysis or death) in hospitalized patients. Urinary KIM-1 level possessed an AUC of 0.61 for the prediction of the composite end point. The Acute Physiology and Chronic Health Evaluation II score possessed an AUC of 0.78, which was increased to 0.80 when KIM-1 was added to the model. The association between the KIM-1 quartiles and composite outcome revealed modest odds ratios of 1.4, 1.4, and 3.2 for patients with increasing quartiles as compared with the lowest quartile. These associations were no longer significant after adjusting for covariates; thus, the independent value of KIM-1 for predicting severe AKI is unclear.

However, KIM-1 also clearly represents a promising candidate for inclusion in the urinary AKI panel. An advantage of KIM-1 is that it seems to be more specific to ischemic or nephrotoxic kidney injury and is not significantly affected by chronic kidney disease or urinary tract infections. Thus, it may be an important biomarker for differentiating between various subtypes of AKI. The potential of its use as an early biomarker seems limited because the increase in urinary KIM-1 seems to be delayed by 12–24 hrs after the insult. However, in conjunction with other sensitive biomarkers, such as NGAL and IL-18, KIM-1 may add specificity to early AKI diagnosis.

## Conclusions

The tools of modern science have provided us with promising novel biomarkers for AKI, with potentially high sensitivity and specificity. These include a plasma panel (NGAL and cystatin C) and a urine panel (NGAL, IL-18, and KIM-1). At least two large multicenter studies to confirm the validity of these biomarkers are underway—one is sponsored by the National Institutes of Health and the other is being carried out by industry. Because they represent sequential biomarkers, it is likely that the AKI panels will be useful for timing the initial insult and assessing the duration of AKI (analogous to the cardiac panel for evaluating chest pain) and for predicting overall prognosis with respect to dialysis requirement and mortality. Based on the differential expression of the biomarkers, it is also likely that the AKI panels will help distinguish between the various types and pathogeneses of AKI. However, they have hitherto been tested only in small studies and in a limited number of clinical situations. It will be important in future studies to validate the sensitivity and specificity of these biomarker panels in clinical samples from large cohorts and from multiple clinical situations. Such studies will be markedly facilitated by multidisciplinary participation of various specialties (intensivists, cardiologists, surgeons) in AKI clinical studies and by the availability of commercial tools for the reliable and reproducible measurement of biomarkers across different laboratories.

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