Early Diagnosis of Acute Kidney Injury: The Promise of Novel Biomarkers

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\section*{Introduction}

Acute kidney injury (AKI) formerly referred to as acute renal failure (ARF) is a common clinical problem. The term ARF was first coined by Homer W. Smith [1] in his textbook in which he referred to kidney dysfunction related to traumatic injuries. Since then this term has been commonly used in clinical practice and medical literature. ARF is the generic term for an abrupt and sustained decrease in renal function resulting in retention of nitrogenous (urea and creatinine) and non-nitrogenous waste products [2]. Until recently there was no clear definition of ARF. In 2002, the Acute Dialysis Quality Initiative (ADQI) workgroup found that over 30 definitions for ARF were used in the literature. The definitions varied from a 25\% increase over baseline serum creatinine to the need for dialysis [3]. The development of consensus definition of AKI was an important priority [3, 4]. The term AKI has been proposed to replace ARF, as acute decline in renal function is generally secondary to an injury which leads to functional and structural changes in the kidneys. The term AKI is also intended to reflect the entire spectrum of ARF.

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In order to meet the need for uniform definition, early detection and grading of severity of AKI, RIFLE classification [Risk-Injury-Failure-Loss-End-stage kidney disease (ESKD)] (table 1) was developed by ADQI [5]. The first three represent the level of severity and last two are outcome criteria. This definition has been validated in various studies. Worse RIFLE class is found to correlate with increased mortality in many studies [6–8]. For further refinement of the definition of AKI, the Acute Kidney Injury Network (AKIN) was created, which proposed a modified version of the RIFLE classification, also known as the AKIN criteria [9]. The important modifications in RIFLE criteria over the RIFLE classification include: (a) the outcome criteria are removed and severity criteria are designated as stage 1, 2 and 3; (b) the ‘risk’ category of RIFLE is broadened to include an increase in serum creatinine of at least 0.3 mg/dl even if this does not reach the 50% threshold; (c) a 48-hour window is set for the first documentation of any stage, and (d) any patient treated with renal replacement therapy is categorized as stage 3 regardless of serum creatinine or urine output. The AKIN criteria were found to improve sensitivity of detection of AKI compared to the RIFLE classification by Lopes et al. [10]. However, a retrospective evaluation of Australia and New Zealand Intensive Care Society (ANZICS) database did not reveal any significant difference [11].

### Epidemiology of AKI

The reported incidence of AKI varies from 5% in hospitalized patients to 30–50% in intensive care units (ICUs) [12]. The incidence varies with the definition employed and the study setting. The incidence of community-acquired severe AKI (defined as serum creatinine >5.68 mg/dl) was found to be 172 cases per million adults per year, of which 22 per million received renal replacement therapy (RRT) in a British study [13]. In another study, in a community setting, the incidence of non-dialysis requiring AKI was found to be 384.1 per 100,000 person-years and that of dialysis requiring AKI was 24.4 per 100,000 person-years [14]. In ICUs, 4.9% patients required RRT in a study reported by Metnitz et al. [15] while AKI was reported to occur in around 19% patients with moderate sepsis, in 23% with severe sepsis, and in 51% of those with septic shock and positive blood cultures [16]. In a prospective multinational observational study involving critically ill patients from 54 hospitals in 23 countries, 5.7% patients developed AKI with the majority requiring RRT [17].

Recent studies have reported AKI epidemiology using RIFLE criteria. In a population-based study from Scotland, the incidence of AKI and acute over CKD was found to be 1,811 and 336 per million population, respectively [18]. In a study from north-east Italy, AKI occurred in 10.8% of all ICU patients when RIFLE criteria were applied at the time of admission [8], while it occurred in 67.2% of ICU patients when RIFLE criteria were applied at peak creatinine during an ICU stay in another study [7].
**Etiology of AKI**

The causes of AKI are traditionally divided into three categories: prerenal, intrinsic renal and postrenal. The prerenal azotemia indicates physiological response of the kidney to hypoperfusion [19] which could be a result of an absolute decrease in circulating volume or reduction in the effective circulating volume. The postrenal category refers to the conditions causing obstruction to urine outflow. The major pathological correlate of intrinsic AKI is acute tubular necrosis (ATN). It is a common clinical practice to use the terms intrinsic AKI and ATN interchangeably. Prerenal azotemia and ATN are considered to represent the continuum of the same pathophysiological process and together account for three-quarters of AKI cases [20]. The etiology of AKI is variable across the world. In developing countries, AKI is the disease of younger subjects and community-acquired cases are common. Acute diarrheal diseases, acute glomerulonephritis, tropical infections (mainly malaria and leptospirosis), environmental agents and snake bite are the common causes of AKI in developing countries [21, 22]. In developed countries AKI is common in the elderly and hospital-acquired causes dominate [21]. In the multinational study of AKI in critically ill patients [17], septic shock was the most common etiology (47.5%) followed by postsurgical AKI (34%), cardiogenic shock (27%), hypovolemia (26%) and drugs (19%), with more than one factor involved in many cases. Acute radiocontrast nephropathy is an important cause of AKI in hospitalized patients undergoing contrast-based procedures [20].

**Pathophysiology of Intrinsic AKI**

Pathophysiologically, intrinsic AKI can be due to ischemia, toxins or sepsis with more than one factor playing its part concomitantly. Derangements of vascular and tubular compartments of the kidneys are proposed to contribute to the marked decrease in glomerular filtration rate in AKI [2]. The vascular events include severe and persistent renal vasoconstriction and congestion in the outer medullary compartment. Renal vasoconstriction decreases the renal blood flow to approximately 50% of normal. The outer medullary congestion decreases tissue oxygen delivery to the already hypoxic S3 segment of proximal collecting tubule (PCT) and the medullary thick ascending limb of the loop of Henle [23]. The tubular events include tubular obstruction, backleak and increased tubuloglomerular feedback. In sepsis, renal vasoconstriction in the presence of systemic vasodilation is considered to be the hallmark, although this viewpoint has been challenged recently. Wan et al. [24] have proposed that renal vasodilation and hyperemia could be more pivotal to septic AKI than renal vasoconstriction and ischemia and pathologically tubular cell apoptosis or tubular cell dysfunction could be more common than tubular necrosis. The reader is referred to recent publications for detailed mechanisms of AKI in ischemia [23], toxins [16] and sepsis [25].

**Complications of AKI**

**Increased Length of Hospital Stay**

Development of AKI is associated with a longer ICU and hospital stay. Even patients with mild AKI (RIFLE class R) have a longer hospital stay than those without AKI and this trend continues in a stepwise manner with the worse RIFLE class having longer hospital stay [26, 27]. In a study by Hoste et al. [6], patients with AKI had a longer hospital stay (RIFLE class R 8 days, Injury 10 days, Failure 16 days) compared to the patients without AKI (6 days).

**Increased Mortality and Morbidity**

Despite impressive advances in treatment, mortality in critically ill patients with AKI continues to remain very high. The mortality rate of AKI was around 91% during the Second World War [28]. In a systematic review of the literature from 1970 to 2004, Ympa et al. [29] observed an unchanged mortality of around 50% from 80 studies. A recent study has reported a hospital mortality rate of 60.3% [17]. A multicenter evaluation of RIFLE criteria showed a crude hospital mortality of 17.9% for Risk, 27.7% for Injury and 33.2% for Failure criteria of the RIFLE classification [30]. In a systematic review of the studies reporting mortality data for non-AKI patients and separately for patients in the Risk, Injury and Failure categories of the RIFLE classification, Ricci et al. [31] have found a stepwise increase in relative risk for death with increasing AKI severity (Risk 2.40, Injury 4.15, Failure 6.37) compared with non-AKI patients. Increasing severity of AKI is also associated with increased 1-month and 1-year mortality compared with non-AKI patients [32]. In addition, some survivors do not regain renal function and progress to ESKD. In the BEST Kidney Study, 13.8% of survivors progressed to ESKD [17]. The risk of ESKD is higher in elderly patients [33]. Reports on childhood AKI also suggest a higher risk of progressive renal disease by adolescence or adulthood [34].
Increased Cost

As discussed earlier, development of AKI is associated with an increased length of ICU and hospital stay. In addition, many of these patients require RRT. Not surprisingly, AKI increases the cost of patient care. Even a slight increase in creatinine increases the cost manifold. Himmelfarb and Ikizler [35] have reported that an increase in creatinine by 0.3 mg/dl increases the cost by USD 4,886, an increase by 0.5 mg/dl by USD 7,499, an increase by 1 mg/dl by USD 13,200, and an increase by 2 mg/dl by USD 22,023 per patient in hospital-acquired AKI. In patients with cardiac surgery-associated AKI, Dasta et al. [27] concluded that AKI accounted for a large chunk of postoperative costs which was incremental with the increasing severity of AKI. In patients with RIFLE class R, 73.3% of postoperative expenditure was related to treatment of AKI, while Class I accounted for 74.2% and Class F accounted for 93.7% of postoperative cost of care.

Concept of Biomarker

As is the case with any cellular insult, in AKI too, the injury begins by inducing molecular modifications later evolving into cellular damage. The cells start producing markers of injury and the clinical syndrome develops subsequently. It is postulated that the biological clock (biomarker expression) always precedes the clinical clock. The biological clock represents an earlier stage in progression to clinical syndrome [40]. Thus, detection of biomarker may provide the much needed window of opportunity for early intervention.

Possible newer biomarkers of AKI can be components of serum or urine or can be imaging studies or any other quantifiable parameter. New biomarkers are likely to be useful in facilitating early diagnosis, guiding targeted intervention and monitoring disease progression and resolution [12, 41]. Desirable characteristics and expectations from an ideal biomarker for AKI are listed in table 2.

Emerging Biomarkers

Cystatin C

Cystatin C is a cysteine protease inhibitor synthesized by all nucleated cells. It is freely filtered by the glomerulus, reabsorbed completely by PCT, and not secreted [42]. Unlike serum creatinine, the levels of cystatin C are not affected by gender, age, race or muscle mass. It has been found useful both as serum or urinary biomarker. In 85 critically ill patients at high risk for developing AKI, serum cystatin C was found to detect AKI almost 2 days earlier compared to detecting AKI by the RIFLE Classification using serum creatinine [43]. Many other studies have confirmed utility of serum cystatin C as a useful early biomarker [44, 45]. Koyner et al. [46] found urinary cystatin C a very promising early (within 6 h after surgery) biomarker of AKI in adult cardiac surgery patients.

Interleukin-18 (IL-18)

IL-18 is a proinflammatory cytokine which is induced in PCT and is detected in urine following AKI. It was found to be an early predictor of AKI in patients with adult respiratory distress syndrome with an area under the curve (AUC) of 0.73. It was also found to be an inde-
pendent predictor of mortality in this study [47]. In another study on patients undergoing cardiac surgery, urinary IL-18 levels increased 6 h after cardiopulmonary bypass (CPB) and peaked at 12 h in patients who were diagnosed to have AKI 2 days later by creatinine criteria [48]. Elevated urinary IL-18 is more specific for ischemic AKI and its levels are not deranged in CKD, urinary tract infections or nephrotoxic AKI [49]. However, a study by Haase et al. [50] did not find IL-18 to be a useful early predictor of AKI in a group of 100 adult patients undergoing cardiac surgery. 

**Kidney Injury Molecule-1 (KIM-1)**

KIM-1 is a transmembrane protein which is markedly overexpressed in PCT in response to ischemic or toxic AKI in animal models [51, 52]. In a cross-sectional study of 6 patients with ATN, KIM-1 was found to be highly expressed in proximal tubule cells in renal biopsies from

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**Table 3. Major studies reporting use of NGAL as an early biomarker in AKI**

<table>
<thead>
<tr>
<th>Group (first author)</th>
<th>Year</th>
<th>Patients</th>
<th>Known timing of insult</th>
<th>Specimen</th>
<th>Assay</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mishra [65]</td>
<td>2005</td>
<td>71 children</td>
<td>Yes</td>
<td>Plasma and urine</td>
<td>Western blot and research ELISA</td>
<td>2 h postoperative uNGAL and pNGAL had high sensitivity and specificity for predicting AKI. AUC 0.998 for uNGAL and 0.91 for plasma</td>
</tr>
<tr>
<td>Dent [71]</td>
<td>2007</td>
<td>120 children</td>
<td>Yes</td>
<td>Plasma</td>
<td>Triage® NGAL device</td>
<td>2 h pNGAL had high sensitivity (0.84) and specificity (0.94) for predicting AKI</td>
</tr>
<tr>
<td>Bennett [79]</td>
<td>2008</td>
<td>196 children</td>
<td>Yes</td>
<td>Urine</td>
<td>Architect®</td>
<td>2 h uNGAL had high sensitivity (0.82) and specificity (0.90) for predicting AKI</td>
</tr>
<tr>
<td>Wagener [73]</td>
<td>2006</td>
<td>81 adults</td>
<td>Yes</td>
<td>Urine</td>
<td>Immunoblotting</td>
<td>uNGAL levels were significantly increased in AKI patients early (at 1 h) after surgery</td>
</tr>
<tr>
<td>Xin [74]</td>
<td>2008</td>
<td>33 adults</td>
<td>Yes</td>
<td>Serum and urine</td>
<td>ELISA</td>
<td>2 h uNGAL and IL-18 had high sensitivity and specificity for predicting AKI. Postoperative serum NGAL levels were not increased significantly</td>
</tr>
<tr>
<td>Tuladhar [75]</td>
<td>2009</td>
<td>50 adults</td>
<td>Yes</td>
<td>Plasma and urine</td>
<td>ELISA</td>
<td>2 h postoperative uNGAL and pNGAL had high sensitivity and specificity for predicting AKI</td>
</tr>
<tr>
<td>Hirsch [66]</td>
<td>2007</td>
<td>91 children</td>
<td>Yes</td>
<td>Plasma and urine</td>
<td>ELISA</td>
<td>2 h uNGAL and pNGAL had high specificity (1) and sensitivity (0.73) for predicting AKI</td>
</tr>
<tr>
<td>Bachorzewska-Gajewska [76]</td>
<td>2007</td>
<td>100 adults</td>
<td>Yes</td>
<td>Serum and urine</td>
<td>ELISA</td>
<td>Significant elevation of serum NGAL at 2, 4 and 8 h and uNGAL at 4, 8 and 24 h after percutaneous coronary intervention</td>
</tr>
<tr>
<td>Zappitelli [68]</td>
<td>2007</td>
<td>140 children</td>
<td>No</td>
<td>Urine</td>
<td>ELISA</td>
<td>uNGAL within 24–48 h of mechanical ventilation was early predictor of AKI</td>
</tr>
<tr>
<td>Wheeler [67]</td>
<td>2008</td>
<td>143 children</td>
<td>No</td>
<td>Serum</td>
<td>ELISA</td>
<td>Serum NGAL measured within 24 h of ICU admission was found to be a highly sensitive (0.84) but less specific (0.39) predictor of AKI</td>
</tr>
<tr>
<td>Makris [70]</td>
<td>2009</td>
<td>31 adult</td>
<td>No</td>
<td>Urine</td>
<td>ELISA</td>
<td>uNGAL at admission to ICU was a highly sensitive (0.91) and specific (0.96) predictor of AKI</td>
</tr>
<tr>
<td>Nickolas [69]</td>
<td>2008</td>
<td>635 adults</td>
<td>No</td>
<td>Urine</td>
<td>Immunoblotting</td>
<td>Single ED uNGAL measurement was predictive of AKI and clinical outcomes. It helped to distinguish AKI from prerenal azotemia and chronic kidney disease</td>
</tr>
</tbody>
</table>

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**Early Diagnosis of Acute Kidney Injury: The Promise of Novel Biomarkers**

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL is the most promising among all emerging biomarkers for AKI (table 3) [56]. It is a protein of the lipocalin family and is composed of 8 β-strands that form a β-barrel enclosing a calyx [57]. The calyx binds and transports low-molecular-weight substances. NGAL is expressed by neutrophils and other epithelial cells including PCT [58]. NGAL gene expression is demonstrated in various human tissues like uterus, prostate, salivary gland, lung, trachea, stomach, colon, and kidney [59]. Understanding its role in human physiology and disease is rapidly increasing. Recent findings suggest its role in binding siderophores (small iron-carrying molecules) and its expression in various pathological states like AKI have prompted a large number of studies [60]. Human NGAL consists of a polypeptide chain of 178 amino acids with a molecular mass to 25 kDa. It occurs predominantly in a monomeric form with a small percentage occurring as a dimer or trimer.

NGAL as a Biomarker in AKI

Early Detection of AKI

As discussed earlier, early detection of AKI is of paramount importance. Improvement in clinical outcomes of the patients with acute coronary syndrome in the last few decades is aided by the availability of a panel of biomarkers. Absence of a similar panel in AKI is a major impediment in improving clinical outcomes. NGAL shows a promise of becoming the equivalent of troponin in AKI and is likely to be an important component of the ‘AKI panel’ [12]. In a study by Mishra et al. [61], NGAL was found to be one of the seven genes which were highly upregulated in mouse models of renal ischemia reperfusion injury. NGAL was detected in the very first urine sample within 2 h following ischemia. Its levels correlated to the duration of ischemia. Later it was identified as a marker of cisplatin nephrotoxicity in an animal model [62]. Further experiments [63, 64] validated NGAL as one of the earliest and most robustly induced proteins in kidneys following ischemic and nephrotoxic insults. Many clinical studies followed this novel observation. In a study of 71 children undergoing CPB, urinary NGAL (uNGAL) and plasma NGAL (pNGAL) at 2 h after CPB were found to be powerful independent predictors of AKI with extraordinary AUC of 0.998 for uNGAL and 0.91 for pNGAL [65]. In a prospective study of 91 children with congenital heart disease undergoing elective cardiac catheterization with contrast administration, both uNGAL and pNGAL predicted contrast-induced nephropathy within 2 h of contrast administration [66]. The AUC for prediction of contrast nephropathy (at 2 h) was found to be 0.92 for uNGAL and 0.91 for pNGAL.

After initial encouraging results, NGAL has been tested as an early biomarker in a variety of clinical settings. Wheeler et al. [67] studied serum NGAL in 143 critically ill children with systemic inflammatory response syndrome (SIRS) or septic shock within 24 h of admission to an ICU. Serum NGAL was found to be highly sensitive but non-specific (sensitivity 84%, specificity 39%) biomarker of AKI. It was also found to correlate with the severity of systemic disease with higher values in patients with septic shock than with SIRS and healthy controls. Zappitelli et al. [68] studied uNGAL in 140 critically ill mechanically ventilated patients. A significant rise (>6 times) in levels of uNGAL occurred 2 days earlier than a 50% increase in serum creatinine levels. uNGAL levels increased in a stepwise fashion with worsening RIFLE class.

In a recently published study [69], a single measurement of uNGAL in the emergency department in 635 patients was found to be highly sensitive and specific (sensitivity 90%, specificity 99%) in diagnosing AKI. Additionally, uNGAL level helped to distinguish patients with AKI from other morbid conditions with elevated creatinine like prerenal azotemia and CKD. Makris et al. [70] have found uNGAL as an early marker of AKI in critically ill polytrauma patients. Many other studies have found NGAL to be a reliable early biomarker for AKI [71–76].

Correlation with Risk Factors for AKI

In a large prospective study, Wagener et al. [77] studied 426 adult patients undergoing cardiac surgery and found elevation of uNGAL to correlate with CPB time and aortic cross-clamp time (AXT). CPB time and AXT are indices of renal hypoperfusion and are established risk factors for development of AKI [78]. Serum creatinine did not show any correlation with CPB time or AXT.
NGAL as a Protective Agent in AKI

By virtue of its ability to act as a growth factor, NGAL has also been found to have a renoprotective effect in acute ischemic renal injury in an animal model [81]. In mouse models of ischemia reperfusion injury, purified NGAL was injected intravenously at doses of 50, 100 or 250 μg of NGAL or an equal amount of normal saline for comparison. The animals receiving 250 μg NGAL showed best protection from tubular damage and azotemia. This novel observation needs to be validated in a clinical study.

Measurement of NGAL

Methods of Measurement

In the initial phase, NGAL estimation was carried out by Western blot technique. Subsequent clinical studies have utilized ELISA-based techniques using the commercially available kit from Antibodyshop, Gentofte, Denmark [72, 77].

A standardized point-of-care Triage® NGAL device (Biosite, Inc., San Diego, Calif., USA) has been devised for the measurement of pNGAL. It was found to correlate well with research ELISA in a pilot study of 40 plasma samples and 12 calibrations. Its usage was subsequently validated in a study of 120 patients undergoing CPB of which 45 patients developed AKI [71]. Mean pNGAL concentrations increased 3-fold within 2 h, while the diagnosis of AKI using serum creatinine concentration was delayed by 2–3 days. Using a cut-off value of 150 ng/ml for the 2-hour pNGAL concentration, the AUC was 0.96, sensitivity 84% and specificity 94% for prediction of AKI. The assay needs only microliter quantities of whole blood or plasma and quantitative results are available within 15 min, thus making bedside testing of pNGAL feasible.

Similarly, an uNGAL assay Architect® analyzer (Abbott Diagnostics, Ill., USA) is available for clinical application. In a pilot study with 136 urine samples and 6 calibration standards, NGAL concentrations by the Architect® analyzer correlated with research ELISA. Its usage was subsequently validated in a study of 196 patients undergoing CPB [79]. Mean uNGAL concentrations increased 15-fold within 2 h, and by 25-fold at 4 and 6 h after CPB. The diagnosis of AKI using serum creatinine concentration was delayed by 2–3 days after CPB. Using a cut-off value of 100 g/l for the 2-hour uNGAL concentration, the AUC was 0.95, sensitivity 82% and specificity 90% for prediction of AKI [79]. The assay is found to be easy to perform with no manual pretreatment steps [38]. The assay needs only 150 μl of urine and quantitative results are available within 35 min, thus making it an easily deployable tool in testing uNGAL for early diagnosis of AKI.

Indications for Measurement of NGAL

Results from recent clinical studies suggest that NGAL measurement (both urine and plasma) might be useful in early detection of AKI. Measurement of NGAL may present an unique opportunity for timely diagnosis and intervention in order to protect kidney from further insults in numerous clinical situations like critical illness, sepsis and septic shock [67], oliguria [82], contrast procedures [66, 72], CPB [65, 73], especially if CPB and AXT time is prolonged [77], polytrauma [70], complex cardiovascular surgeries and deep hypothermia [83]. Measurement of NGAL might be useful in randomized control trials assessing efficacy of early intervention for AKI. Diagnosis of AKI at an early stage might improve patient selection for such trials. NGAL has also been found to be a useful tool in disease monitoring in other renal diseases, delayed graft function [84], lupus nephritis [85, 86], IgA nephropathy [87] and polycystic kidney disease [88]. In addition, it has been found to be a biomarker in many other non-renal conditions like brain tumor [89], inflammatory bowel disease [90] and pre-eclampsia [91].
Factors Influencing NGAL Measurement

In a study from 426 adults undergoing CPB [77], uNGAL levels were significantly elevated in all patients (with or without AKI), raising a concern whether CPB initiates inflammation and activation of neutrophils leading to increased NGAL levels. In a recent in vitro study by Bobek et al. [92], NGAL was found to be ultra-filtered and adsorbed by polysulfone membranes, reducing its blood levels. As many patients with AKI undergo RRT, this finding if confirmed in vivo, can be potentially confounding in monitoring the clinical course of AKI using NGAL.

Limitations of NGAL as a Biomarker for AKI

Although NGAL appears to be a promising biomarker for predicting AKI and its outcome, most of the literature has emerged from single centers and from homogenous patient populations [93]. Large multicenter studies are required for further validation of its use in heterogenous patient populations and for defining cut-off values for diagnosis and outcomes of AKI. Various other factors like RRT, underlying CKD, and CPB might influence its measurement as discussed earlier.

Conclusions

Recent studies in the field of early detection of AKI have proposed many biomarkers for early detection of AKI. NGAL appears to be the most promising of all biomarkers. It can be used in tandem with other newer biomarkers like cystatin C, KIM-1 or IL-18, and together they may represent a ‘kidney panel’ in the future. Differential expression of these markers may potentially help to distinguish between various types of insults, provide information about duration of injury, predict clinical outcome and help to monitor treatment response. However, until now these markers have been tested in small studies and specific clinical situations. Future studies in large cohorts with multiple clinical situations might substantiate the utility of these markers.

References

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