Neutrophil Gelatinase-associated Lipocalin at ICU Admission Predicts for Acute Kidney Injury in Adult Patients

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Rationale: Measured at intensive care unit admission (ICU), the predictive value of neutrophil gelatinase-associated lipocalin (NGAL) for severe acute kidney injury (AKI) is unclear.

Objectives: To assess the ability of plasma and urine NGAL to predict severe AKI in adult critically ill patients.

Methods: Prospective-cohort study consisting of 632 consecutive patients.

Measurements and Main Results: Samples were analyzed by Triage immunoassay for NGAL expression. The primary outcome measure was occurrence of AKI based on Risk-Injury-Failure (RIFLE) classification during the first week of ICU stay. A total of 171 (27%) patients developed AKI. Of these 67, 48, and 56 were classified as RIFLE R, I, and F, respectively. Plasma and urine NGAL values at ICU admission were significantly related to AKI severity.

Conclusion: NGAL measured at ICU admission predicts the development of severe AKI similarly to serum creatinine–derived eGFR. However, NGAL adds significant accuracy to this prediction in combination with eGFR alone or with other clinical parameters.

Keywords: NGAL; AKI; ICU; eGFR

In critically ill patients, acute kidney injury (AKI) is independently associated with increased costs of medical care and increased risk of morbidity and mortality (1–4). In addition, when AKI develops during hospital admission it results in accelerated progression toward end-stage renal disease (ESRD), especially in elderly patients (5). Recent observational studies have shown a 14% incidence of dialysis dependency at the time of hospital discharge among survivors of critical illness (3). Therefore, early recognition of renal injury is important and may help prevent further renal damage and functional impairment.

Recent experimental (6–8) and clinical (9–11) studies have identified biomarkers that may serve as early indicators of AKI. Of these, neutrophil gelatinase-associated lipocalin (NGAL) seems to be the most promising. NGAL is a 25-kD protein that is covalently bound to gelatinase and is secreted from human neutrophils (12). It is generally expressed at low concentrations in various organs containing epithelial tissues, including the kidney. When acute tubular damage occurs it is rapidly expressed at high concentrations in both plasma and urine (7–9, 13).

The first clinical validation was performed in pediatric cardiac surgery patients (9). In this study NGAL measured 2 hours after surgery was an excellent predictor of AKI, whereas serum creatinine (SCr) did not start to rise until 24 to 72 hours after surgery. However, in settings in which the initiation of renal injury is unclear, such as in cases of sepsis, trauma, and acute and critical illness, the predictive value of plasma NGAL (pNGAL) and urine NGAL (uNGAL) is less certain (13–19). Furthermore, whether NGAL on its own or in combination with clinical parameters can be of additional value for the prediction of severe AKI has yet to be determined.

We therefore conducted a prospective study in a large cohort of adult patients in the intensive care unit (ICU) to assess the predictive value of pNGAL and uNGAL levels at the time of admission with regard to the development of severe AKI during the early days of ICU treatment and their extended contribution in early diagnosis beyond estimated glomerular filtration rate (eGFR). None of the results of this current study have been previously reported in abstract form.

METHODS

A detailed method session is given in the online supplement.

Patients

The institutional review board of Erasmus University Medical Center, Rotterdam, The Netherlands, approved the study. All consecutive
admitted patients between September 2007 and April 2008 were eligible for enrollment. Exclusion criteria included age under 18 years, refusal of consent, nephrectomy, chronic kidney disease (CKD), ESRD, and renal transplantation. Deferred consent was used, and written informed consent was obtained from all participants or their health care proxy (20).

Procedures
After admission, plasma and urine samples were collected (T = 0) and thereafter at 4, 8, 24, 36, 48, 60, and 72 hours. Missing admission (T = 0) samples were replaced by first collection values at either 4 or 8 hours after admission. pNGAL and uNGAL were measured on the Triage NGAL Test point-of-care fluorescence immunosassay in a laboratory, masked to patient clinical data (Biosite, Inc, San Diego, CA). The Triage NGAL test has been validated against an NGAL ELISA assay (see online supplement) (21).

SCr was measured at admission and thereafter daily at 6:00 a.m. The eGFR was calculated using the Modification of Diet in Renal Disease Study Equation (MDRD) (see online supplement) (22). Baseline SCr was defined as the steady state level 4 weeks before admission. If not available, the admission value was used as a surrogate baseline. Other variables included age, sex, body mass index (BMI), temperature, pH, bicarbonate, potassium, blood-urea-nitrogen (BUN) content, white blood cell (WBC) count, C-reactive protein (CRP), and lactate. For disease severity assessment, the Acute Physiology and Chronic Health Evaluation score (APACHE II) and the sequential organ failure assessment score (SOFA) were used. Furthermore, the cumulative urine output, initiation of renal replacement therapy (RRT), ICU days, ICU mortality, and hospital mortality were recorded. The primary outcome variable was AKI occurring within 7 days after ICU admission according to the Risk-Injury-Failure (RIFLE) classification (23). The RIFLE classification is based on the rise in SCr compared with a baseline value. Risk (RIFLE R) represents a 1.5–2 times increase, injury (RIFLE I) a 2–3 times increase, and failure (RIFLE F) a more than 3 times increase.

Statistical Analysis
MATLAB version 7.5.0 and SPSS version 16.0 were used. The relationships between AKI and NGAL levels were assessed using the Mann-Whitney U test and the chi-square test. Continuous variables were described by medians and interquartile ranges. Receiver operating characteristic (ROC) curves with their area under the curve (AUC) with two times its standard error was calculated. Univariable and multivariable logistic regression analyses were used to assess the predictive value of NGAL in combination with clinical parameters. Statistical significance was assessed by estimating the standard error of its coefficient and conducting a Wald test of the null hypothesis. Stepwise forward likelihood ratio regression was used to determine the model’s most efficient predictors. Goodness of fit was assessed using the Hosmer-Lemeshow test. The net reclassification improvement was calculated. All reported P values were two-tailed, and P values less than 0.05 were considered statistically significant.

Role of Funding Source
Biosite Incorporated (San Diego, CA) provided biomarker measurements and statistical support. They had no role in study design, data collection, or writing of the manuscript. The first author had full access to all data and had final responsibility to submit for publication.

RESULTS
Patient Characteristics
Of the 700 consecutive patients who were screened for inclusion in the study, 68 (9.8%) were excluded because of refusal of consent (n = 6), nephrectomy (n = 6), CKD, ESRD, kidney transplantation (n = 25), or missing admission data (n = 31). Thus, 632 (90.2%) patients were included in the analysis. Patient characteristics are shown in Table 1.

AKI occurred in 171 patients (27%). Of those patients, 67 developed RIFLE R, 48 patients developed RIFLE I, and 56 patients developed RIFLE F. The time to reach a SCr increase of more than 50% compared with baseline for the first time (= RIFLE R) was T = 0 in 58.5%, T = 24 in 24%, T = 48 in 6.4%, and T = 72 in 5.8% of the patients. Thus, 94.7% of the patients reached “first AKI” within 72 hours after ICU admission. Twenty-eight (50%) of the patients with AKI in the RIFLE F class received RRT (4.4% of the overall patient cohort).

Baseline characteristics in all RIFLE classes were compared with subjects who did not develop AKI. There were no differences with respect to age, sex, or BMI. Patients with AKI had higher APACHE II and SOFA scores than patients without AKI (Table 1). Furthermore, there were positive correlations between the severity of kidney injury and length of stay, ICU mortality, and hospital mortality (Table 1). The incidence of AKI was higher in patients admitted after cardiopulmonary resuscitation was performed, and in patients with sepsis or multiorgan failure syndrome (P < 0.0001) (Table 1).

Association between NGAL and AKI Development
Patients’ pNGAL and uNGAL concentrations at the time of ICU admission were significantly related to their RIFLE scores (P < 0.0001) (Table 1, Figure 1). The pNGAL test performance for predicting the severity of AKI in the entire cohort showed an AUC of 0.77 ± 0.05 for RIFLE R and above, 0.80 ± 0.06 for RIFLE I and above, and 0.86 ± 0.06 for RIFLE F. Similar analysis for uNGAL revealed AUCs of 0.80 ± 0.04 (RIFLE R), 0.85 ± 0.04 (RIFLE I), and 0.88 ± 0.04 (RIFLE F) (Figures 2A and 2B). The differences between the plasma and urine AUCs were not significant. The AUC and ROC curves for eGFR predicting AKI stratified for RIFLE stage are shown in Figure 2C. Comparing the performance of eGFR with pNGAL and uNGAL showed that only pNGAL predicting R and above or I and above were significantly different compared with the corresponding AUCs of eGFR (P = 0.015 and P = 0.039).

Table 2 lists the calculated sensitivities at fixed specificities of 50%, 70%, and 90% (derived by visual inspection of the ROC curves) with the corresponding cut-off concentrations of pNGAL and uNGAL for the prediction of RIFLE F.

Association between NGAL and AKI Development in Patients with eGFR Greater Than 60 ml/min/1.73 m²
To determine the potential additional contribution of NGAL as a biomarker predicting AKI before SCr has started to rise and consequently eGFR has started to decline a subset analyses was performed in patients with apparently normal renal function (n = 498) at the time of ICU admission (i.e., excluding patients with an eGFR <60 ml/min/1.73 m²). ROC analysis demonstrated that in patients who did not show any increase in SCr yet at ICU admission, pNGAL and uNGAL had diagnostic superiority over SCr and eGFR for predicting severe AKI (RIFLE I and F). The AUCs for pNGAL and uNGAL were respectively 0.75 ± 0.10 and 0.79 ± 0.10 compared with 0.65 ± 0.10 and 0.67 ± 0.10 for SCr and eGFR, respectively (Figure 2D).

Relative Contribution of NGAL to the Most Efficient Clinical Prediction Model at Admission for Prediction of RIFLE F
Adding pNGAL and uNGAL to eGFR in a multivariable logistic regression model improved the prediction significantly (P < 0.001). To determine the added contribution of NGAL to eGFR and other available clinical variables at ICU admission for predicting the occurrence of RIFLE F within the first week of patients’ ICU stay, additional logistic regression analysis was performed (Table 3). The available clinical predictors included age, BMI, temperature, diagnosis of sepsis, pH, bicarbonate, potassium, BUN, WBC count, CRP, and lactate. Adding NGAL to
Relative Contribution of Serial NGAL Measurements to the Most Efficient Clinical Prediction Model for Prediction of RIFLE F

The progression of mean pNGAL and uNGAL concentrations stratified by RIFLE classification over time is shown in the online supplement (see Figures E1 and E2). To determine if serial sampling could be of additional value for the prediction of RIFLE F pNGAL and uNGAL values and those of the other predictors at T = 0 and T = 24 (temperature, pH, bicarbonate, potassium, BUN, WBC, CRP, and lactate) were used for multivariable logistic regression analysis. In addition, age, BMI, diagnosis of sepsis, eGFR MDRD T = 0, the 24-hour urine production, the 24-hour cumulative fluid balance, APACHE II, and SOFAscore were added. All subjects with established RIFLE F or missing data in the first 24 hours were excluded, leaving 429 patients for the plasma and 411 for the urine analysis. With stepwise forward likelihood ratio logistic regression the most efficient predictors were pNGAL T = 24 (P = 0.000) and CRP T = 0 (P = 0.024) for the pNGAL model. Adding pNGAL T = 24 changed the model’s AUC from 0.63 ± 0.04 to 0.91 ± 0.03, underlining that pNGAL T = 24 is a very strong predictor for RIFLE F. For urine, the model showed NGAL T = 24 (P = 0.001), temperature T = 0 (P = 0.02), APACHE T = 24 (P = 0.011), urine production T = 24 (P = 0.009), pH T = 24 (P = 0.005), and potassium T = 0 (P = 0.055) as most efficient predictors. Adding uNGAL T = 24 changed the model’s AUC from 0.84 ± 0.01 to 0.93 ± 0.04.

Assessment of both pNGAL and uNGAL values’ difference scores in the logistic regression analysis showed that the temporal

eGFR and clinical variables improved the prediction significantly for pNGAL (P = 0.014) and almost significantly for uNGAL (P = 0.092).

Using a stepwise forward likelihood ratio logistic regression NGAL, eGFR, diagnosis of sepsis, WBC count, and temperature on admission made the most efficient clinical model for the prediction of RIFLE F for plasma out of the available variables in this study. For urine the most efficient model comprised NGAL, eGFR, diagnosis of sepsis, and WBC count (Table 4). Adding NGAL changed the model’s AUCs from 0.95 ± 0.02 to 0.96 ± 0.02 for pNGAL and from 0.94 ± 0.02 to 0.95 ± 0.01 for uNGAL. Furthermore, we assessed the ability of pNGAL and uNGAL to “reclassify” the degree of risk for RIFLE F within 7 days as assessed by the model. Subjects were categorized into prespecified “low-risk,” “medium-risk,” and “high-risk” groups using cut-offs of less than 30%, 30–60%, and greater than 60%, respectively. We compared the proportions of reclassified subjects across these three risk groups when NGAL was added to the clinical model for plasma and urine (see online supplement for detailed reclassification table). For five patients with RIFLE F reclassification was more accurate when the model with all four variables for pNGAL was used and for two patients it became less accurate. Among the subjects without RIFLE F, nine were correctly reclassified in a lower risk category, whereas three were incorrectly reclassified to be at higher risk. The same analysis was performed for uNGAL (see online supplement). The generated net reclassification improvement for pNGAL and uNGAL added to the clinical prediction model was 8.5% (P = 0.087) and 2.3% (P = 0.570), respectively.

### TABLE 1. PATIENTS’ CHARACTERISTICS AND CLINICAL OUTCOME

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-AKI (n = 461)</th>
<th>RIFLE R (n = 67)</th>
<th>RIFLE I (n = 48)</th>
<th>RIFLE F (n = 56)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>58 (43,68)</td>
<td>59 (45,70)</td>
<td>61.5 (53,75)</td>
<td>62 (50,68)</td>
<td>NS</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>264 (57)</td>
<td>46 (69)</td>
<td>29 (60)</td>
<td>30 (54)</td>
<td>NS</td>
</tr>
<tr>
<td>BML, kg/m²</td>
<td>24.5 (22.5, 27.2)</td>
<td>25.5 (22.5, 27.4)</td>
<td>25.5 (22.9, 28.6)</td>
<td>25.3 (22.1, 28.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Temperature</td>
<td>36.9 (36.2, 37.6)</td>
<td>37 (36.2, 37.6)</td>
<td>36.6 (35.8, 37.7)</td>
<td>34.9 (36.3, 37.8)</td>
<td>NS</td>
</tr>
<tr>
<td>SOFA score</td>
<td>37 (18, 72)</td>
<td>41.3 (18, 61)</td>
<td>41.8 (18, 64)</td>
<td>41.2 (18, 66)</td>
<td>NS</td>
</tr>
<tr>
<td>White blood cell count, 10⁹/ml</td>
<td>41.2 (18, 61)</td>
<td>41.8 (18, 64)</td>
<td>41.2 (18, 66)</td>
<td>41.2 (18, 66)</td>
<td>NS</td>
</tr>
<tr>
<td>RRT, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>28 (50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU mortality, n (%)</td>
<td>49 (8)</td>
<td>10 (16)</td>
<td>6 (9)</td>
<td>26 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital mortality, n (%)</td>
<td>71 (11)</td>
<td>20 (30)</td>
<td>16 (33)</td>
<td>30 (54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnostic group, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>166 (36)</td>
<td>15 (22)</td>
<td>6 (13)</td>
<td>5 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical</td>
<td>99 (22)</td>
<td>13 (19)</td>
<td>15 (31)</td>
<td>11 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>Neurologic</td>
<td>88 (19)</td>
<td>5 (8)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neurotrauma</td>
<td>27 (6)</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Multitrauma</td>
<td>26 (6)</td>
<td>6 (9)</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LTX</td>
<td>19 (4)</td>
<td>8 (12)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Sepsis</td>
<td>14 (3)</td>
<td>6 (9)</td>
<td>8 (17)</td>
<td>15 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP</td>
<td>11 (2)</td>
<td>6 (9)</td>
<td>7 (15)</td>
<td>3 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemorrhagic shock</td>
<td>9 (2)</td>
<td>4 (6)</td>
<td>3 (6)</td>
<td>3 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>MOF</td>
<td>1 (0)</td>
<td>2 (3)</td>
<td>3 (6)</td>
<td>15 (27)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** AKI = acute lung injury; APACHE II = Acute Physiology and Chronic Health Evaluation score at T = 24; BMI = body mass index; BUN = blood urea nitrogen; CRP = cardiaopulmonary resuscitation; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate according to the Modification of Diet in Renal Disease Study Equation (MDRD); ICU = intensive care unit; HCO₃⁻ = bicarbonate; K = potassium; LTX = liver transplant surgery; MOF = multiorgan failure; NGAL = neutrophil gelatinase-associated lipocalin; NS = nonsignificant; OR = odds ratio; RC = regression coefficient; RIFLE = Risk-Injury-Failure; RRT = renal replacement therapy; Scr = serum creatinine; SOFA = sequential organ failure assessment score at T = 24; UP = urine production first 24 hours after admission.

**Relative Contribution of Serial NGAL Measurements to the Most Efficient Clinical Prediction Model for Prediction of RIFLE F**

**Definition of abbreviations:** RIFLE = Risk-Injury-Failure; NGAL = neutrophil gelatinase-associated lipocalin; NS = nonsignificant; OR = odds ratio; RC = regression coefficient; RIFLE = Risk-Injury-Failure; RRT = renal replacement therapy; Scr = serum creatinine; SOFA = sequential organ failure assessment score at T = 24; UP = urine production first 24 hours after admission.
Changes were not relevant, pointing out that the NGAL value measured closer to the end point "RIFLE F" was the strongest predictor.

Analyzing further contribution of serial measurements over the succeeding time points was not possible because of the significant reduction in sample size with the diminished availability of equal measurements. Furthermore, because the difference in serial measurements in the first 24 hours did not add to the prediction of RIFLE F, it is not expected that the results will be different when analyzing subsequent time points.

Association of NGAL and Sepsis in Patients without AKI

In patients with sepsis (n = 14) who did not develop AKI, uNGAL levels were significantly higher than those of patients in the other diagnostic groups. The median NGAL value was 1,264.1 ng/ml (650.3, 4,124) (Figure 3). In the group of 14 patients with septic non-AKI, one received renal drainage because of obstructive hydronephrosis, one had a positive urine culture with *Acinetobacter* species, one had a positive WBC and nitrite count in the urine sediment without a positive culture already under antibiotic treatment, and one patient had a proved renal abscess with *Escherichia coli*. After we adjusted the uNGAL analysis removing those patients and patients who died within 48 hours after admission to the ICU, uNGAL levels were still significantly higher among patients with a diagnosis of sepsis than among patients in the other diagnostic groups (P = 0.0005).

**Figure 1.** Admission plasma (A) and urine (B) neutrophil gelatinase-associated lipocalin (NGAL) concentrations stratified by Risk-Injury-Failure (RIFLE) classification. An exploratory Mann-Whitney U test of adjacent categories, including nonacute kidney injury versus R, R versus I, and I versus F, resulted in P values of < 0.0001, 0.10, and 0.0005, respectively, for plasma NGAL and < 0.0001, 0.028, and 0.001, respectively, for urine NGAL. AKI = acute lung injury.

**Figure 2.** Receiver operating characteristic curve analysis for the ability of admission plasma (A) and urine (B) neutrophil gelatinase-associated lipocalin, estimated glomerular filtration rate (C) to predict acute kidney injury, stratified by Risk-Injury-Failure (RIFLE) classification. (D) Both plasma and urine neutrophil gelatinase-associated lipocalin’s predictive properties for RIFLE I or worse in patients with estimated glomerular filtration rate above 60 ml/min/1.73 m² are presented parenthetically after the RIFLE classification. eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease Study Equation; NGAL = neutrophil gelatinase-associated lipocalin; SENS = sensitivity; SPEC = specificity.

Association between NGAL and RRT or Mortality

In the entire cohort both NGAL plasma and urine values were predictive of RRT initiation within the first week of ICU admission (respectively, AUC 0.88 ± 0.06 and AUC 0.89 ± 0.04). However, Scr and eGFR reached similar performances (respectively, AUC 0.90 ± 0.05 and 0.91 ± 0.05). Both pNGAL and uNGAL have a minor role in predicting hospital mortality with very modest performances (AUC 0.63 ± 0.06 and AUC 0.64 ± 0.06).

**DISCUSSION**

The present study shows that pNGAL and uNGAL levels at time of ICU admission predict the development of severe AKI and the initiation of RRT in critically ill patients within the first 7 days of their ICU stay. Furthermore, adding NGAL values to a model with eGFR alone or to the most efficient clinical model with available parameters improves the prediction significantly. Using serial NGAL measurements did not provide additional accuracy in the prediction of RIFLE F. Finally, patients with sepsis but no AKI have significantly higher urinary NGAL values compared with other patients without AKI.

NGAL fulfills a central role in regulating epithelial neo genesis, and in iron chelation and delivery after ischemic or toxic insults to the renal tubular epithelium (24, 25). After kidney injury, NGAL is rapidly expressed on the apical epithelial membranes of the distal nephron. NGAL is excreted in the urine through exocytosis and has local bacteriostatic and proapoptotic effects (26, 27). PNGAL is easily filtered by the glomerulus and...
TABLE 2. NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN TEST CHARACTERISTICS AT DIFFERENT CUTOFF VALUES FOR THE PREDICTION OF RISK-INJURY-FAILURE F

<table>
<thead>
<tr>
<th>Cutoffs for pNGAL</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>168 ng/ml</td>
<td>0.91</td>
<td>0.50</td>
<td>0.15</td>
<td>0.98</td>
</tr>
<tr>
<td>245 ng/ml</td>
<td>0.82</td>
<td>0.70</td>
<td>0.21</td>
<td>0.98</td>
</tr>
<tr>
<td>417 ng/ml</td>
<td>0.70</td>
<td>0.90</td>
<td>0.40</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Cutoffs for uNGAL

<table>
<thead>
<tr>
<th>Cutoffs for uNGAL</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>94 ng/ml</td>
<td>0.98</td>
<td>0.50</td>
<td>0.16</td>
<td>1.00</td>
</tr>
<tr>
<td>247 ng/ml</td>
<td>0.89</td>
<td>0.70</td>
<td>0.22</td>
<td>0.98</td>
</tr>
<tr>
<td>1,310 ng/ml</td>
<td>0.55</td>
<td>0.90</td>
<td>0.35</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Definition of abbreviations: NGAL = neutrophil gelatinase-associated lipocalin; pNGAL = plasma NGAL; uNGAL = urine NGAL.

Reabsorption is mediated by megalin-cubulin dependent endocytosis with a very high affinity. The delivered iron is needed in the regeneration processes that occur after damage is inflicted to these cells. Under normal circumstances the estimated half life of pNGAL is approximately 10 minutes, with urinary loss less than 0.2% (28, 29). PNGAL and uNGAL concentrations increase by 10- to 100-fold during the 2 hours that follow tubular injury (7–9), whereas SCr does not start to rise until 24 to 72 hours after the initial renal insult (9, 16, 30).

Because we are interested in the possible prevention of (further) kidney injury in patients who are critically ill, AKI was assessed only during the first week of each ICU patient’s stay to link the condition of the patient at the time of admission and the initial resuscitation efforts to the development of AKI.

In this study, we found that pNGAL and uNGAL measured at the time of admission were good predictors of AKI. The test performance of both pNGAL and uNGAL increased as the severity of the functional damage to the kidney’s increased; the AUCs ranged from 0.77 (RIFLE R) to 0.95 (RIFLE F) for pNGAL and from 0.80 (RIFLE R) to 0.88 (RIFLE F) for uNGAL.

Previous studies in pediatric patients in the ICU with sepsis and septic shock (14) and in a group of adult critically ill patients (17) have studied the predictive accuracy of pNGAL and uNGAL reporting AUCs of 0.68 and 0.64 for sustained AKI. Both Zappitelli and coworkers (16) (pediatric population) and Cruz and coworkers (19) (adult population) observed AUC’s for prediction of RIFLE R or worse AKI by NGAL that were comparable with those observed in the present study. Constant and coworkers (18) and Nickolas and coworkers (13) reported very high AUCs for the ability of pNGAL and uNGAL to predict AKI in critically ill adult and emergency department patients (0.92 and 0.95, respectively). Several explanations exist for the observed variability of NGAL's test performance in these studies, in which the timing of renal insult was not strictly identified.

First, in the current study NGAL measurement was performed immediately after ICU admission and patients were monitored for the occurrence of AKI for the next 7 days. The timing of NGAL measurement in the previously mentioned studies ranged from 48 hours after the initiation of mechanical ventilation (up to 3 d after admission) to within 24 hours of ICU admission to the first possible moment on ICU admission. With the rapid changes in pNGAL and uNGAL concentrations, the slow changes in SCr concentrations, the reversibility of the early phases in the continuum of AKI, and the effects of intensive resuscitation in the golden hours after ICU admittance, timing of measurement

### TABLE 3. MULTIVARIABLE LOGISTIC REGRESSION FOR THE PREDICTION OF RIFLE F COMBINING NGAL WITH EGFR AND OTHER CLINICAL PREDICTORS

<table>
<thead>
<tr>
<th>Plasma NGAL</th>
<th>Urine NGAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
<td><strong>OR (B) (SE) P Value</strong></td>
</tr>
<tr>
<td>NGAL, ng/ml</td>
<td>1.83 (0.6) (0.25) 0.017</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>0.95 (0.05) (0.01) 0.000</td>
</tr>
<tr>
<td>Age, yr</td>
<td>0.98 (0.02) (0.02) 0.240</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.93 (0.07) (0.06) 0.240</td>
</tr>
<tr>
<td>Temp, °C</td>
<td>0.68 (0.39) (0.16) 0.016</td>
</tr>
<tr>
<td>Sepsis</td>
<td>10.52 (2.35) (0.70) 0.001</td>
</tr>
<tr>
<td>PH</td>
<td>2.07 (0.73) (3.35) 0.828</td>
</tr>
<tr>
<td>HCO₃⁻, mmol/L</td>
<td>1.01 (0.01) (0.06) 0.822</td>
</tr>
<tr>
<td>K, mmol/L</td>
<td>2.10 (0.74) (0.34) 0.028</td>
</tr>
<tr>
<td>BUN, mmol/L</td>
<td>0.99 (0.01) (0.04) 0.816</td>
</tr>
<tr>
<td>WBC, 10⁹/ml</td>
<td>0.93 (0.07) (0.03) 0.025</td>
</tr>
<tr>
<td>CRP, mmol/L</td>
<td>1.00 (0.00) (0.00) 0.259</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>0.87 (0.14) (0.11) 0.224</td>
</tr>
<tr>
<td>Total</td>
<td>0.014</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** B = beta; BMI = body mass index; BUN = blood urea nitrogen; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate according to the Modification of Diet in Renal Disease Study Equation (MDRD); HCO₃⁻ = bicarbonate; K = potassium; NGAL = neutrophil gelatinase-associated lipocalin; OR = odds ratio; RC = regression coefficient; Temp = temperature; WBC = white blood cell.

### TABLE 4. STEPWISE FORWARD LIKELIHOOD RATIO LOGISTIC REGRESSION FOR DETERMINATION OF MOST EFFICIENT CLINICAL MODEL FOR THE PREDICTION OF RISK-INJURY-FAILURE F

<table>
<thead>
<tr>
<th>Plasma NGAL</th>
<th>Urine NGAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
<td><strong>OR (B) (SE) P Value</strong></td>
</tr>
<tr>
<td>NGAL, ng/ml</td>
<td>1.71 (0.54) (0.21) 0.010</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>0.95 (0.05) (0.01) 0.000</td>
</tr>
<tr>
<td>Sepsis</td>
<td>9.94 (2.30) (0.59) 0.000</td>
</tr>
<tr>
<td>WBC, 10⁹/ml</td>
<td>0.95 (0.06) (0.03) 0.057</td>
</tr>
<tr>
<td>Temp, °C</td>
<td>0.78 (0.25) (0.13) 0.061</td>
</tr>
<tr>
<td>Total</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** B = beta; eGFR = estimated glomerular filtration rate according to the Modification of Diet in Renal Disease Study Equation (MDRD); NGAL = neutrophil gelatinase-associated lipocalin; OR = odds ratio; RC = regression coefficient; Temp = temperature; WBC = white blood cell count.
has effects on the NGAL concentrations measured in relation to the changes in SCr (31). Therefore the time at which NGAL levels are measured clearly influences their test performance.

Second, the number of patients with AKI in a given study and their RIFLE class distribution also influences test results (32). Because of the large sample size in this study and the fairly equal patient distribution between RIFLE categories, we were able to analyze the ability of NGAL to predict more severe AKI end points, such as RIFLE F. In contrast, Wheeler and coworkers (14) used very unusual criteria for AKI, making it impossible to compare their results with those of other studies. The AKI cohort in the study performed by Siew and coworkers (15) was comprised of patients with less severe stages of AKI (median uNGAL 127 ng/ml interquartile range [IQR]: 32–623 and median SCr 1.5 mg/dl IQR: 1–2.2 at enrollment) resulting in low performance characteristics of NGAL (AUC = 0.71; 95% confidence interval, 0.63–0.78). Nickolas and coworkers (13) reported that NGAL was an excellent predictor of AKI (AUC = 0.95; 95% confidence interval, 0.88–1) in an emergency department setting. However, the mean SCr and fractional sodium excretion of this entire AKI subgroup at the time of study inclusion were 5.6 mg/dl (SD = 5.5) and 69% (SD 9.1), respectively, indicating that severe loss of renal function had already occurred in most of these patients. Accordingly, test results generated in patients with established AKI should not be used for the comparison with those in a cohort of developing AKI.

Third, AKI and its severity defined by RIFLE are dependent on how baseline SCr values are determined and will contribute to different outcomes between studies. In our study the first available SCr value was used as a surrogate baseline when a patient’s historical data were not available. This undoubtedly has resulted in an underestimation of attained RIFLE stage in some of these patients. Furthermore, with the artificial definition of AKI using three set severity stages the issue of timing may simply be definitional.

This study adds to the current literature because it showed that NGAL significantly improves the diagnostic accuracy for severe AKI adding it to MDRD eGFR calculated at ICU admission, even in patients having an apparently normal eGFR at admission. Especially in these patients this could be of value because their AKI is not yet reflected in an increase in SCr. Patients in the ICU are typically diagnosed with AKI several days after the onset of their illness or injury, resulting in a delay in the discontinuation or dose adjustment of nephrotoxic medications or continued use of procedures that could cause further renal damage. Whether NGAL levels have the potential to influence clinical decision making in the ICU should be the topic for further randomized studies that should be performed before using NGAL measurements in clinical practice.

These studies may include applying more intensive resuscitation, avoiding nephrotoxic drugs, or implementation of a more timely initiation of RRT in patients with elevated NGAL levels (33). In addition, recent animal studies examining interventions to reverse AKI have been promising, implying that it may be possible to reverse AKI in humans if it is treated early (29, 34–39). Second, this study adds to current knowledge because we defined a most efficient clinical model in the prediction of AKI using available data at the time of ICU admission, improving the predictive accuracy for RIFLE F significantly with NGAL above eGFR and clinical predictors. The predictive accuracy of eGFR on its own was roughly comparable with that of pNGAL or uNGAL. However, we should take into account that SCr is used to define the end point RIFLE F and is likewise used to calculate eGFR, which is incorporation bias. Therefore, it is somewhat biased to compare NGAL’s performance with the ability of SCr to predict itself. Furthermore, in this study, the point of first AKI was satisfied in many patients at the time of ICU admission (58.5%). As such, it is to be expected that in many of the AKI cases, SCr would already be elevated at the time of admission. AKI that was present at the time of ICU admission was determined by retrospective collection of baseline SCr values from the patient records before admission. However, in clinical practice, a prior baseline SCr is more often not available at ICU admission and as such it is not possible to correctly determine the end point of AKI compared with CKD. Furthermore, we should also take into account that NGAL is a direct injury marker that is unfortunately compared with a gold standard AKI diagnosis that is based on a functional marker (SCr), which has major imperfections on its own (40). In this context it is indispensable to emphasize the importance of (injury) biomarker combinations to achieve more accurate predictions irrespective of SCr.

Third, we showed that temporal changes in NGAL measurements do not provide additional information for the prediction of RIFLE F. And finally, we found that patients with sepsis without AKI had markedly increased uNGAL concentrations, whereas there were no significant differences between groups with regard to the pNGAL values. A possible explanation for our results lies in the two-compartment model theory of NGAL (which applies to an animal model under relatively normal conditions) (27) and the fact that AKI is an inflammatory disease (41). In patients with AKI, human Toll-like receptor 2 (TLR2) stimulates tubular epithelial apoptosis (42) and NGAL expression (43). Bacterial pathogens produce lipoproteins and activate cytokine networks by inducing the expression of multiple proinflammatory genes.
Lipopolysaccharides also have strong affinity for TLRs that trigger an innate immune response. Therefore, it could be postulated that these circulating ligands that are linked to tubular epithelial TLR activation are responsible for the increased uNGAL concentrations that we observed in patients who had sepsis but showed no increases in their SCr levels (44). However, a very recent study in patients with sepsis, septic shock, and systemic inflammatory response syndrome has reported contradictory findings (45). A possible explanation for this difference is the variability of the subject inclusion time (up to 48 h after ICU admission). Intensive resuscitation and the administration of antibiotics may have already occurred before study inclusion, therefore most likely inducing rapid changes of uNGAL values.

In conclusion, the present study shows that both pNGAL and uNGAL levels at ICU admission are good predictors of severe AKI and significantly add to the prediction of AKI using eGFR and to a model with clinical parameters. Because the study population reflects a mixed group of diagnoses that are present in most ICUs these findings could have major clinical implications regarding optimization of therapy in patients at risk for AKI. Our findings could also facilitate studies of the effectiveness of early therapeutic and supportive interventions in patients with established AKI.

Author Disclosure: H.R.H.D.G. received $1,001–$5,000 from Inverness Medical in lecture fees. J.B. received up to $1,000 from Hutchinson Technology in advisory board fees; up to $1,000 from GlaxoSmithKline and up to $1,000 from Hutchinson Technology in lecture fees; and $10,001–$50,000 from Pulsion in industry-sponsored grants. E.M.E.H.L. received $5,001–$10,000 from Novartis in nonpromotional lecture fees. J.B. received up to $1,000 from Hutchinson Technology in advisory board fees; up to $1,000 from Biosite/Inverness in nonpromotional lecture fees.

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References


Online Data Supplement

Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients.

Hilde RH de Geus, Jan Bakker, Emmanuel MEH Lesaffre, Jos LML le Noble

ODS-1 Patients and Methods

Laboratory sample processing

Following admission, plasma and urine samples were collected (T=0) and thereafter at 4, 8, 24, 36, 48, 60 and 72 hours. Missing admission (T=0) samples were replaced by first draw values at either 4 or 8 hours after admission. This occurred for 40 plasma samples and 61 urine samples.

Arterial blood was sampled in EDTA tubes from an arterial line and freshly voided urine was collected from an indwelling catheter. Both blood and urine samples were sent immediately to the hospital’s general laboratory and centrifuged at 3,000 rpm at 4°C for 10 minutes with a relative centrifugal force of 1700-g. The supernatants were aliquotted equally into 3 cryovials and stored at -80°C. After study completion all samples were shipped by air transportation on dry ice to San Diego.

NGAL quantification with Triage® point-of-care immunoassay

Plasma NGAL levels were measured with the Triage® NGAL Test point-of-care fluorescence immunoassay on a Triage MeterPlus (Biosite Inc, San Diego USA) using a commercially available NGAL cartridge. The assay device is a single-use plastic cartridge that contains an NGAL-specific monoclonal antibody conjugated to a fluorescent nanoparticle, NGAL antigen
immobilized on a solid phase, and stabilizers. In addition, the device was engineered with integrated control features including positive and negative control immunoassays. After the device containing the sample is inserted into the Triage® MeterPlus, quantitative measurements of NGAL concentration are displayed on the meter’s screen within 15 minutes. The devices used in this investigation reported plasma NGAL concentrations between 46 ng/ml and 1300 ng/ml. The device was able to measure the NGAL concentrations of almost all (89.7%) samples. However, 7.9% of the T=0 samples had NGAL concentrations that were below the lower limit of the detection range and 2.4% had concentrations above the upper limit of the detection range. The assay variability for plasma NGAL was 15.8%.

Urinary NGAL levels were measured using a non-commercial Triage® immunoassay cartridge with a sandwich format immunoassay in order to provide an appropriate detection range for urine samples. Before application to the cartridge, the urine samples that had NGAL concentrations exceeding the assay’s upper limit of detection were diluted with an equal volume of 200 mM BES buffer, pH 7.2. The effective concentration range of the urine NGAL assay was 2.6 ng/ml to 4100 ng/ml; none of the T=0 urine samples had NGAL concentrations that were below the lower limit of detection and 8.5% of the T=0 samples had NGAL concentrations that were above the upper limit of detection. The assay variability for urine NGAL was 13.9%. 
**ODS-2 Triage® NGAL Test point-of-care standard curves**

The Triage® NGAL Test point-of-care fluorescence immunoassay standard curves for plasma (Fig. E1) and urine (Fig. E2) samples. The curves plot NGAL concentrations vs. the absorbance response (AU). The dots represent the integrated fluorescence signal averaged over 10 individual devices for a series of known NGAL calibration samples.

**Figure E1 and E2:**
**ODS-3 MDRD formula**

The estimated glomerular filtration rate (eGFR) was calculated for each patient at ICU admission using the Modification of Diet in Renal Disease Study Equation (MDRD) [22].

MDRD Formula: $eGFR = 186 \times (sCr \text{ in } \mu g/L \times 0.0113)^{-1.154} \times (\text{Age in years})^{-0.203}$.

The result is multiplied by 0.742 if the patient is female, assuming ethnicity as non-Black.
ODS-5 E1

ODS-5 E2
Defining the optimal management of acute kidney injury or insufficiency (AKI) is a major challenge. Many epidemiological studies found a strong negative impact of AKI on patient outcomes, particularly in the ICU (1–3). Many preventive and therapeutic measures, ranging from low-dose dopamine to early hemofiltration, have been tested, often with disappointing results (4, 5). Today, the management of AKI centers on restoring renal perfusion, avoiding nephrotoxic drugs, and starting renal replacement therapy (RRT) “sufficiently early” (6). Improvements are needed in the detection, prevention, and management of AKI, not only because AKI may influence the risk/benefit assessment at the bedside and aid therapeutic decisions. Distinguishing transient from persistent AKI may help physicians to optimize the fluid balance and to determine the best time for initiating RRT.

Several emerging biomarkers for AKI are available for clinical use. In addition to benefitting epidemiological research and the development of interventional studies on AKI, these new biomarkers may have a place in the management of patients in the ICU. Early AKI detection may improve the risk/benefit assessment at the bedside and aid therapeutic decisions. Distinguishing transient from persistent AKI may help physicians to optimize the fluid balance and to determine the best time for initiating RRT.

Neutrophil gelatinase–associated lipocalin (NGAL) is among the most extensively evaluated biomarkers, although the studies were done in limited and selected patient populations (10). NGAL is up-regulated in AKI, particularly in patients with hypoxia. NGAL was recently found to be not only a marker for tubular damage, but also an active contributor to the progression of kidney damage (11). The complexity of the pathophysiologic mechanisms leading to AKI in ICU patients requires the specific validation of biomarkers in this population. In this issue of the Journal, de Geus and colleagues (pp. 907–914) report data from the largest cohort of heterogeneous ICU
patients in a single-center study (12). AKI was defined using the Risk, Injury, Failure, and Loss (RIFLE) classification, although it is unclear whether urine output criteria were used (9). Plasma and urine NGAL (pNGAL and uNGAL, respectively) were measured in 632 consecutive patients at ICU admission to determine whether these biomarkers predicted severe AKI (Injury and Failure classes) within the first week in the ICU. AKI developed in 171 patients and was severe in 56. Many of these patients already had some degree of AKI at ICU admission. As expected, pNGAL and uNGAL concentrations increased from each AKI severity stage to the next. However, testing the accuracy of a biomarker for predicting the occurrence or severity of AKI in patients with obvious renal dysfunction already present at baseline is of limited clinical relevance. The ROC curves suggest that neither pNGAL nor uNGAL was a better predictor of AKI severity, of the need for RRT, or of death than the estimated glomerular filtration rate or SCr at admission. Using logistic regression, the authors appropriately constructed several models for predicting severe AKI (Failure), an analysis not performed in previous studies. The best predictive model based on patient characteristics was improved by including pNGAL or uNGAL. Unfortunately, the accuracy of the model is questionable: 13 clinical and laboratory characteristics were included, while only 56 patients developed severe AKI, and pNGAL values were lacking in 28% of patients and uNGAL values in 8%. Despite the use of the net reclassification method, which was limited by the large number of missing pNGAL values, a validation cohort would have been helpful.

That NGAL accurately predicted severe AKI in the subgroup of 498 patients with apparently normal renal function at ICU admission is an interesting finding. The proportion of patients who developed AKI is not indicated, but was probably less than 10%. Both pNGAL and uNGAL were better predictors of AKI than SCr or glomerular filtration rate. However, the significance of the difference is not reported, and the area under the ROC curves indicates only acceptable discrimination.

Finally, this study adds to previous doubts about the clinical usefulness of NGAL in patients with sepsis, one of the leading causes of AKI in ICU patients (13, 14). In the absence of AKI, pNGAL and uNGAL were increased in patients with sepsis. Also, pNGAL and uNGAL were higher in patients with AKI and sepsis than in patients with AKI and no sepsis. NGAL is released by activated neutrophils and may be a biomarker for sepsis. Thus, pNGAL predicted severe sepsis in patients admitted to an emergency department for suspected infection (15).

While the study by de Geus and colleagues provides interesting information about the accuracy of NGAL for predicting AKI in patients with apparently normal renal function on ICU admission, the quest for good biomarkers for AKI must go on. Evaluations of new potential biomarkers will continue to be imperfect, however, given the inadequacies of the current reference standard—namely, SCr. Thus, errors in SCr-based patient classification between “no AKI,” “AKI,” and “severe AKI” may influence the results of biomarker evaluations. The poor performance of NGAL for predicting AKI in patients with sepsis illustrates this problem. Patients with sepsis and high NGAL values who are classified as “no AKI” may constitute either false positives for NGAL or false negatives for SCr as markers for AKI. A recent study on renal histopathology in patients who died in the ICU shows that renal tubular damage is common even in patients classified as “no AKI” (16). Biomarkers are usually tested as surrogate markers for survival. Although AKI is clearly associated with mortality (3), de Geus and colleagues found that both pNGAL and uNGAL played only a minor role in predicting hospital mortality. The absence of association between NGAL and ICU death has been reported previously (13, 17). However, NGAL assays may allow the early detection of AKI, at a stage where there is no impact on survival.

As is often the case in critical care, we do not know how good we are at defining AKI. This uncertainty complicates the identification of the ideal biomarker. Thus, research is necessary to better define the principles of a multidisciplinary and individualized AKI management (6). The place of biomarkers in this decision-making process is still uncertain.

**References**


**Shared Decision-Making in the ICU**

**Value, Challenges, and Limitations**

The concept of shared decision-making—sharing the responsibility for and control over medical decisions between clinicians and patients—has been in existence for at least 30 years (1). In the past few years, however, this concept has emerged as a predominant approach to medical decision-making. Shared decision-making has been described as the most ethical and appropriate approach across the full range of medical decisions, from the outpatient clinic to the ICU (2, 3). In the ICU, decision-making often involves surrogate decision-makers, since patients frequently lack decision-making capacity due to their severity of illness. The concept of shared decision-making in decisions about withdrawing life-sustaining treatments has received strong support from critical care societies, including a consensus conference of five international critical care societies (4). Despite this strong endorsement, there is evidence that critical care clinicians frequently do not accomplish the basic steps of shared decision-making during family conferences concerning withdrawal of life-sustaining treatments (5).

In this issue of the Journal (pp. 915–921), Johnson and colleagues report the results of an important study of surrogate decision-makers’ perspectives on the locus of control for decision-making in the ICU (6). This study highlights the value as well as the challenges and limitations of shared decision-making in the ICU. In terms of the value of shared decision-making, this study confirms that the vast majority of family members of critically ill patients want both themselves and physicians to participate in decision-making, especially with regard to decisions about withdrawing life-sustaining treatments. This finding supports what has been found by others in the United States, Canada, and France (7–10). The exact proportion of family members choosing specific decision-making roles varies across these studies. The clinically important finding in these studies, however, is not the proportion of surrogates choosing to play a specific decision-making role. Rather, it is the observation—in all of these studies—that there are some family members who endorse each possible role on the spectrum of decision-making roles, ranging from desiring total control to deferring completely to clinicians. One could question whether family members’ responses on these surveys actually capture their true preferences and needs during actual ICU decision-making, but this diversity of family preferences is likely an important reflection of true diversity. This raises an important challenge of adequate decision-making in the ICU: how and when should we attempt to match our decision-making approach to fit the preference of the surrogate decision-maker?

There have been a number of calls for ICU clinicians to match their decision-making approach to the preferences of surrogate decision-makers (11–13). However, there is little empirical evidence to guide clinicians in the best way to accomplish this goal. While there is evidence that ICU clinicians use the full spectrum for the locus of control in decision-making, clinicians seem to choose their place on this spectrum based on their own preferences, rather than the preferences of surrogate decision-makers (14). Since the prevalence of symptoms of depression and post-traumatic stress disorder are higher when the surrogates’ preferred role in decision-making is different from the role they actually played (8), there is a compelling rationale to take surrogates’ preferences into account. However, simply asking family of critically ill patients what role they want to play in decision-making during an ICU family conference may not be an effective method to uncover these preferences. Furthermore, surrogate preferences alone do not determine the ethical obligations of physicians.

This distinction between surrogate preferences and the ethical obligation of physicians is highlighted by Johnson and colleagues’ observation that a substantial minority of family members report they want control over technical biomedical decisions, such as choice of antibiotics. This finding raises the issue of the appropriate limits of shared decision-making. There are many practical decisions made in the care of critically ill patients, such as which antibiotic to use or the timing for transfer of the improving patient from the ICU, where family members may prefer control over decision-making, but where such control may not be appropriate because of other competing issues such as the best interests of the patient, the practicality of making timely critical care decisions, or the impact of these decisions on the care of other patients. In addition, how decisions about the most appropriate use of healthcare resources enter this calculus is an important issue about which there is little consensus currently, but which we must address as we strive to control healthcare expenditures. Finally, a physician who would act in contradiction to their professional judgment, simply because family members wish them to do so, would be abrogating his or her professional duty. There is an imperative for professional involvement—at some level—in all clinical decision-making. This includes even the most value-laden clinical decisions, such as withdrawal of life-sustaining therapy. To have families make these decisions without input and support is to abandon our professional responsibility.

Johnson and colleagues identified several factors associated with surrogates’ preferences for more control over decisions,