Kinetics of Urinary Cell Cycle Arrest Markers for Acute Kidney Injury Following Exposure to Potential Renal Insults

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Objectives: Urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 predict the development of acute kidney injury following renal insults of varied aetiology. To aid clinical interpretation, we describe the kinetics of biomarker elevations around an exposure.

Design: In an ancillary analysis of the multicenter SAPPHIRE study, we examined the kinetics of the urinary [tissue inhibitor of metalloproteinase-2]•[insulin-like growth factor binding protein 7] in association with exposure to common renal insults (major surgery, IV radiocontrast, vancomycin, nonsteroidal anti-inflammatory drugs, and piperacillin/tazobactam).

Setting: Thirty-five sites in North America and Europe between September 2010 and June 2012.

Patients: Seven hundred twenty-three critically ill adult patients admitted to the ICU.

Interventions: None.

Measurements and Main Results: We compared the urinary [tissue metalloproteinase-2]•[insulin growth factor binding protein 7] kinetics from the day prior to exposure up to 5 days after exposure in patients developing acute kidney injury stage 2–3, stage 1, or no acute kidney injury by Kidney Disease Improving Global Outcome criteria. Among the 723 patients, 679 (94%) had at least one, 70% had more than one, and 35% had three or more exposures to a known renal insult. There was a significant association between cumulative number of exposures up to study day 3 and risk of acute kidney injury (p = 0.02) but no association between the specific type of exposure and acute kidney injury (p = 0.22). With the exception of radiocontrast, patients who developed acute kidney injury stage 2–3 after one of the five exposures, had a clear rise and fall of urinary [tissue inhibitor of metalloproteinase-2]•[insulin-like growth...
Acute kidney injury (AKI) is a common complication of critical illness, affecting 50–60% of patients admitted to the ICU (1–5). Both, identification of high risk patients and the early diagnosis of AKI are essential in order to implement renoprotective measures in a timely manner and to prevent harm (6). We have previously shown that the urinary biomarkers tissue inhibition of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) predicted the development of AKI secondarily to a variety of renal insults, including surgery, sepsis, and medications (7–12). However, in order to better interpret biomarker results, the kinetics of biomarker elevations around an exposure are necessary.

The risk of AKI results from the interaction between susceptibility and exposures. During critical illness, patients are exposed to a large number of insults that are potentially harmful to renal function, often simultaneously and/or in succession. For instance, approximately 20% of the drugs prescribed in the ICU are nephrotoxic (13). The adverse impact of drug-induced AKI on patient outcomes can be severe with hospital mortality rates reported between 18% and 50% (14, 15). Exposure to iodinated contrast is also common. A prospective study in three teaching hospitals showed that more than 25% of all ICU patients had at least one CT scan and more than 80% were performed with iodinated contrast (16). The risk of dialysis following contrast is particularly high. A prospective study in two teaching hospitals showed that 37% of patients developing AKI stage 2–3, the kinetics of urinary [TIMP-2]•[IGFBP7] matched the exposure except in the case of radiocontrast. (Crit Care Med 2018; 46:375–383)

**Key Words:** acute kidney injury; biomarker; cell-cycle arrest markers; exposures; nephrotoxicity

**MATERIALS AND METHODS**

**Study Design**

The Sapphire study has been described in detail elsewhere (7). In summary, it was a prospective multicenter study in which TIMP-2 and IGFBP7 were identified as biomarkers of AKI and subsequently validated in an independent validation cohort and compared with existing markers of AKI. Between September 2010 and June 2012, 744 critically ill adults (≥21 yr) were recruited at 35 sites in North America and Europe. Subjects were enrolled within 24 hours of admission to the ICU, had cardiovascular or respiratory dysfunction, and were expected to stay in the ICU for at least 48 hours. AKI was defined according to the Kidney Disease Improving Global Outcome (KDIGO) criteria (20). Subjects were excluded if they had AKI stage 2 or 3 at enrolment. The study showed that urinary [TIMP-2]•[IGFBP7] predicted the development of AKI 2–3 within 12 hours and before a serum creatinine rise. In this follow-up study, we describe the kinetics of urinary [TIMP-2]•[IGFBP7] around the exposure to five common insults and compare patients with and without AKI.

**Sample and Data Collection**

Following informed consent, urine and blood samples were taken at enrolment and at 12-hour intervals for 4 days and daily for another 3 days (7). Serum and urine supernatants were frozen within approximately 1 hour of collection, stored at –70°C or lower, and thawed immediately before analysis.

All clinical data, including patient demographics, reason for ICU admission, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) III score, serum creatinine, and hourly urine output, were collected and stored in a password-protected dataset residing on servers at independent sites (Medidata Solutions, New York, NY).

**Biomarker Assays**

Urinary TIMP-2 and IGFBP7 concentrations were measured by technicians who were blinded to the clinical data using a clinical immunoassay (NephroCheck Test and Astute140 Meter; Astute Medical, San Diego, CA). The Astute140 Meter automatically multiplies the concentrations of both biomarkers and divides the product by 1,000 to report a single numeric result in (ng/ml)/1,000. Creatinine was measured in study-specific serum samples at a central laboratory (LabCorp, San Diego, CA).

**Exposure and Biomarker Analysis**

We identified and described the proportion of patients who were exposed to at least one dose of vancomycin, NSAIDs, piperacillin/tazobactam, or IV iodinated radiocontrast or
underwent major surgery within 5 days prior to enrollment through 7 days after enrollment. Major surgery was defined as in-patient surgery under general anesthesia involving opening of a major body cavity (21). These exposures were chosen because they are frequent, definable, potentially modifiable, and have a well-defined onset. We evaluated serial urinary [TIMP-2]•[IGFBP7] concentrations from the day prior to exposure up to 5 days later and compared the biomarker kinetics of patients according to their maximum AKI stage (no AKI, stage 1, stage 2–3) within 3 days following exposure.

Serum creatinine data from 6 months prior to enrollment through hospital discharge (truncated at 30 days after enrollment) and urine output data from the day prior to enrollment through 7 days after enrollment were collected to determine maximum AKI stage (20).

Ethics
According to the Declaration of Helsinki, the Sapphire study was approved by the Western Institutional Review Board (Olympia, WA) and individual investigational review boards/research ethics committees of each participating institution. All subjects or their legal representatives provided written informed consent prior to enrollment.

Statistical Analysis
We investigated the effect of cumulative exposures by counting the number of exposures each subject received up to each study day and calculating the maximum AKI stage according to KDIGO criteria from enrollment up to each study day. We examined if there was an association between the cumulative number of exposures up to each day and the maximum AKI stage up to that day using test for linear-by-linear association. We also examined the association between specific types of exposure and the development of any AKI or AKI stage 2–3. For this analysis, we only included patients who 1) did not have AKI stage 2–3 prior to the exposure; 2) had biomarker data between −1 and 5 days from the start of exposure; and 3) had serum creatinine and/or urine output data available within 3 days of exposure. Supplemental Table S1 (Supplemental Digital Content 1, http://links.lww.com/CCM/D36) lists the exclusions for each exposure. A generalized linear mixed model analysis was performed to test the significance of the association.

In patients who did not have AKI prior to any of the five selected exposures, we studied the kinetics of urinary [TIMP-2]•[IGFBP7] concentrations relative to each of the exposures separately. The null hypothesis for each exposure was that on each day up to 5 days after the first exposure, the median urinary [TIMP-2]•[IGFBP7] value within each AKI group (stage 0, 1, and 2–3) was less than 0.3 (ng/ml)²/1,000 (i.e., low risk for progression). For an individual subject, multiple [TIMP-2]•[IGFBP7] values may be determined within the same time interval (such as within 12, 24, or 36 hours from exposure, or on a calendar day following exposure). To account for repeated measurements of [TIMP-2]•[IGFBP7] results from the same subject within a time interval, the estimates of median and its interquartile range (IQR) were obtained by stratified bootstrap (stratified by AKI groups) (22). The p values for the tests of the null hypothesis that the median [TIMP-2]•[IGFBP7] values were below 0.3 (ng/ml)²/1,000, versus the alternative hypothesis of median above 0.3, were calculated using bootstrap stratified by AKI status.

We analyzed the urinary [TIMP-2]•[IGFBP7] kinetics in association with a specific exposure without taking into account other concomitant or sequential exposures. We identified the earliest time a patient was exposed to each insult and defined the maximum AKI stage from the earliest time to 3 days after the first exposure.

Statistical analyses were performed using SAS 9.3 and R3.0 (23). Two-sided p-values less than 0.05 and one-sided p-values less than 0.025 were considered statistically significant.

RESULTS
Patient Population
The Sapphire cohort consisted of 723 patients (Fig. 1); their median age was 64 years (Table 1). During the study period, 679 patients (94%) had at least one of the selected exposures (vancomycin, NSAIDs, piperacillin/tazobactam, IV contrast or major surgery), either alone or in combination. More than one exposure occurred in 503 patients (70%), three or more exposures in 250 (35%), and 74 patients (10%) were exposed to four. Six patients (0.8%) were actually exposed to all five renal insults.

Forty-four patients were not exposed to any of the five insults of interest (Fig. 1 and Table 1). They were nonsurgical patients who were predominantly admitted from the Emergency Department or general ward. Their primary reason for admission to the ICU was respiratory failure (61%). Overall, patients with or without exposures had similar baseline characteristics (Table 1).

Prevalence of Exposures With Renal Injury Potential
Exposure to substances or events that may be harmful to the kidney was very common (Tables 2 and 3). In total, 659 patients (91.1%) had at least one exposure up to the first study day, and 666 patients (92.1%) had one or more exposures up to study day 2 (Table 2). The median time of exposure relative to ICU admission was 0 days (IQR, −0.3 to 1.0). There was a significant association between cumulative number of exposures up to study day 3 and risk of AKI (p = 0.02) but not beyond day 3 (Table 2). After exclusion of patients who had AKI before any of the five exposures, we found that 325 (51%) had had major surgery, 270 (42%) had received IV radiocontrast, 258 (40%) had vancomycin, 220 (34%) had received at least one dose of a NSAID, and 209 patients (33%) had had piperacillin/tazobactam (Table 3). There was no statistically significant association between type of exposure and AKI stage 2–3 (p = 0.20) or any stage of AKI (p = 0.22).

Biomarker Kinetics
Analysis of biomarker kinetics was performed in 642 patients together with corresponding serum creatinine kinetics (Figs. 1 and 2A-E; and Supplemental Fig. S1a-e, Supplemental Digital Content 1, http://links.lww.com/CCM/D36).
Three hundred twenty-five patients had major surgery (Fig. 2A; and Supplemental Table S2a, Supplemental Digital Content 1, http://links.lww.com/CCM/D36). Urinary [TIMP-2]•[IGFBP7] in those who developed AKI stage 2–3 (n = 74 [23%]) were significantly elevated from the day of surgery to 48 hours later. The median serum creatinine results during this period were between 1.0–1.1 mg/dL (Supplemental Fig. S1a, Supplemental Digital Content 1, http://links.lww.com/CCM/D36). In addition, for patients with AKI stage 1, urinary [TIMP-2]•[IGFBP7] was significantly elevated at 24–48 hours postoperatively (Fig. 2A). By contrast, there was no significant elevation in urinary [TIMP-2]•[IGFBP7] for patients who did not develop AKI.

**Biomarker Kinetics Following IV Radiocontrast Exposure**

Among 270 patients exposed to IV radiocontrast, 48 patients (18%) developed AKI stage 2–3 (Table 3). They had significantly higher urinary [TIMP-2]•[IGFBP7] from the day of contrast administration up to 72 hours later (Fig. 2B; and Supplemental Table S2b, Supplemental Digital Content 1, http://links.lww.com/CCM/D36). Unlike the biomarker kinetics described following the four other exposures, there was no typical rise and fall of urinary [TIMP-2]•[IGFBP7] around radiocontrast exposure. Median serum creatinine results were not significantly elevated from their baseline values (Supplemental Fig. S1b, Supplemental Digital Content 1, http://links.lww.com/CCM/D36). In patients who did not develop AKI, there was no significant elevation in urinary [TIMP-2]•[IGFBP7].

**Biomarker Kinetics in Association With Exposure to Vancomycin**

Urinary [TIMP-2]•[IGFBP7] for the 57 of 258 patients (22%) who developed AKI stage 2–3 were significantly elevated on the day of first dose of vancomycin and the following 2 days with a peak on day 1 (Fig. 2C; and Supplemental Table S2c, Supplemental Digital Content 1, http://links.lww.com/CCM/D36). There was no significant elevation in urinary [TIMP-2]•[IGFBP7] results in patients without AKI or those with AKI stage 1 (Fig. 2C).

**Biomarker Kinetics in Association With NSAIDs**

Among 220 patients who received at least one dose of NSAID, urinary [TIMP-2]•[IGFBP7] concentrations were significantly elevated on day 1 and 2 around the first dose in those who developed AKI stage 2–3 (n = 38 [17%]) (Fig. 2D; and Supplemental Table S2d, Supplemental Digital Content 1, http://links.lww.com/CCM/D36). On both days, the median serum creatinine results were not significantly different from their baseline values (Supplemental Fig. S1d, Supplemental Digital Content 1, http://links.lww.com/CCM/D36). In patients with AKI stage 1, urinary [TIMP-2]•[IGFBP7] were also significantly elevated around NSAID exposure but only on day 1 (Fig. 2D). There was no significant elevation in urinary [TIMP-2]•[IGFBP7] in patients who did not develop AKI.

**Biomarker Kinetics in Association With Piperacillin/Tazobactam Administration**

Of 209 patients who received at least one dose of piperacillin/tazobactam, 37 patients (18%) developed AKI stage 2–3. They
TABLE 1. Baseline Demographics of Patients With or Without At least One of Five Selected Exposures

| Baseline Characteristics       | Patients With ≥ 1 of the 5 Selected Exposures (n = 679) | Patients With None of the 5 Selected Exposures (n = 44) | p     |
|-------------------------------|--------------------------------------------------------|-----------------------------------------------------|-------|
| Age (yr)                      | 64 (54–74)                                             | 63 (48–71)                                          | 0.18  |
| Male gender, n (%)            | 422 (62.2)                                             | 22 (50.0)                                           | 0.11  |
| Race, n (%)                   |                                                        |                                                    | 0.20  |
| Black or African American     | 80 (11.8)                                              | 7 (15.9)                                            |       |
| White or Caucasian            | 532 (78.4)                                             | 36 (81.8)                                           |       |
| Other/unknown/missing         | 67 (9.9)                                               | 1 (2.3)                                             |       |
| Body mass index (kg/m²)       | 27 (23–32)                                             | 26 (23–31)                                          | 0.29  |
| Admitted to ICU from, n (%)   |                                                        |                                                    | <0.001|
| Emergency department          | 235 (34.6)                                             | 26 (59.1)                                           |       |
| General ward                  | 138 (20.3)                                             | 10 (22.7)                                           |       |
| Operating room                | 201 (29.6)                                             | 0 (0.0)                                             |       |
| Other hospital                | 90 (13.3)                                              | 4 (9.1)                                             |       |
| Other ICU                     | 3 (0.4)                                                | 2 (4.5)                                             |       |
| Unknown                       | 12 (1.8)                                               | 2 (4.5)                                             |       |
| Reason for ICU admission, n (%)|                                                      |                                                    |       |
| Respiratory                   | 281 (41.4)                                             | 27 (61.4)                                           | 0.009 |
| Surgery                       | 247 (36.4)                                             | 0 (0.0)                                             | <0.001|
| Cardiovascular                | 230 (33.9)                                             | 8 (18.2)                                            | 0.03  |
| Sepsis                        | 126 (18.6)                                             | 9 (20.5)                                            | 0.75  |
| Cerebrovascular               | 67 (9.9)                                               | 3 (6.8)                                             | 0.51  |
| Trauma                        | 52 (7.7)                                               | 3 (6.8)                                             | 0.84  |
| Burn                          | 14 (2.1)                                               | 0 (0.0)                                             | 0.34  |
| Other                         | 115 (16.9)                                             | 12 (27.3)                                           | 0.08  |
| Medical history, n (%)        |                                                        |                                                    |       |
| Chronic kidney disease        | 62 (9.1)                                               | 3 (6.8)                                             | 0.64  |
| Diabetes mellitus             | 199 (29.3)                                             | 11 (25.0)                                           | 0.60  |
| Congestive heart failure      | 114 (16.8)                                             | 7 (15.9)                                            | 0.45  |
| Coronary artery disease       | 211 (31.1)                                             | 4 (9.1)                                             | 0.004 |
| Hypertension                  | 406 (59.8)                                             | 23 (52.3)                                           | 0.35  |
| Chronic obstructive pulmonary disease | 146 (21.5)                                             | 15 (34.1)                                           | 0.12  |
| Cancer                        | 178 (26.2)                                             | 9 (20.5)                                            | <0.001|
| Liver disease                 | 33 (4.9)                                               | 1 (2.3)                                             | 0.43  |
| Acute Physiology and Chronic Health Evaluation III score | 68 (51–92)                                             | 67 (54–97)                                          | 0.65  |
| Baseline serum creatinine (mg/dL) | 0.8 (0.7–1.1)                                         | 0.8 (0.6–1.1)                                       | 0.46  |

had significantly elevated urinary [TIMP-2]•[IGFBP7] on the first day of exposure and the following day (Fig. 2E; and Supplemental Table S2e, Supplemental Digital Content 1, http://links.lww.com/CCM/D36). There was no significant elevation in [TIMP-2]•[IGFBP7] in patients with AKI stage 1 or no AKI.

Association Between Biomarker Rise and Severity of Illness on the Day of Exposure
In patients who developed AKI 2–3, urinary [TIMP-2]•[IGFBP7] concentration was already elevated on the day of exposure to vancomycin, piperacillin/tazobactam, and contrast. However, the exact
time of vancomycin and piperacillin/tazobactam administration was not recorded, and therefore, it was not possible to determine whether the increase in urinary [TIMP-2]•[IGFBP7] occurred after the exposure or was already present at time of exposure. To further investigate any potential causes of [TIMP-2]•[IGFBP7] elevations prior to exposures, as seen with IV contrast, we compared the frequency of concomitant exposures and severity of illness by AKI stage. There were no

| Cumulative No. Different Exposures | No. Subjects | No AKI, n (%) | AKI Stage 1, n (%) | AKI Stage 2, n (%) | AKI Stage 3, n (%) | p     |
|-----------------------------------|-------------|--------------|-------------------|-------------------|-------------------|-------|
| Up to study day 1                 |             |              |                   |                   |                   |       |
| 0                                 | 64          | 34 (53)      | 21 (33)           | 7 (11)            | 2 (3)             | <0.001|
| 1                                 | 225         | 145 (64)     | 59 (26)           | 16 (7)            | 5 (2)             |       |
| 2                                 | 262         | 142 (54)     | 77 (29)           | 34 (13)           | 9 (3)             |       |
| 3                                 | 117         | 52 (44)      | 43 (37)           | 20 (17)           | 2 (2)             |       |
| 4                                 | 50          | 24 (48)      | 15 (30)           | 7 (14)            | 4 (8)             |       |
| 5                                 | 5           | 1 (20)       | 1 (20)            | 2 (40)            | 1 (20)            |       |
| Up to study day 2                 |             |              |                   |                   |                   |       |
| 0                                 | 57          | 25 (44)      | 17 (30)           | 12 (21)           | 3 (5)             | 0.001 |
| 1                                 | 203         | 106 (52)     | 62 (31)           | 27 (13)           | 8 (4)             |       |
| 2                                 | 260         | 126 (48)     | 84 (32)           | 39 (15)           | 11 (4)            |       |
| 3                                 | 139         | 54 (39)      | 54 (39)           | 25 (18)           | 6 (4)             |       |
| 4                                 | 58          | 20 (34)      | 16 (28)           | 15 (26)           | 7 (12)            |       |
| 5                                 | 6           | 1 (17)       | 2 (33)            | 2 (33)            | 1 (17)            |       |
| Up to study day 3                 |             |              |                   |                   |                   |       |
| 0                                 | 51          | 22 (43)      | 17 (33)           | 9 (18)            | 3 (6)             | 0.02  |
| 1                                 | 185         | 85 (46)      | 61 (33)           | 29 (16)           | 10 (5)            |       |
| 2                                 | 267         | 124 (46)     | 81 (30)           | 50 (19)           | 12 (4)            |       |
| 3                                 | 148         | 56 (38)      | 58 (39)           | 27 (18)           | 7 (5)             |       |
| 4                                 | 66          | 23 (35)      | 19 (29)           | 16 (24)           | 8 (12)            |       |
| 5                                 | 6           | 1 (17)       | 2 (33)            | 2 (33)            | 1 (17)            |       |
| Up to study day 4                 |             |              |                   |                   |                   |       |
| 0                                 | 48          | 19 (40)      | 15 (31)           | 11 (23)           | 3 (6)             | 0.10  |
| 1                                 | 177         | 73 (41)      | 62 (35)           | 31 (18)           | 11 (6)            |       |
| 2                                 | 256         | 109 (43)     | 80 (31)           | 54 (21)           | 13 (5)            |       |
| 3                                 | 166         | 66 (40)      | 61 (37)           | 31 (19)           | 8 (5)             |       |
| 4                                 | 70          | 21 (30)      | 23 (33)           | 17 (24)           | 9 (13)            |       |
| 5                                 | 6           | 1 (17)       | 2 (33)            | 2 (33)            | 1 (17)            |       |
| Up to study day 5                 |             |              |                   |                   |                   |       |
| 0                                 | 44          | 16 (36)      | 14 (32)           | 11 (25)           | 3 (7)             | 0.10  |
| 1                                 | 176         | 69 (39)      | 65 (37)           | 30 (17)           | 12 (7)            |       |
| 2                                 | 253         | 95 (38)      | 86 (34)           | 58 (23)           | 14 (6)            |       |
| 3                                 | 170         | 65 (38)      | 64 (38)           | 32 (19)           | 9 (5)             |       |
| 4                                 | 74          | 21 (28)      | 24 (32)           | 19 (26)           | 10 (14)           |       |
| 5                                 | 6           | 1 (17)       | 2 (33)            | 2 (33)            | 1 (17)            |       |

AKI = acute kidney injury.
Table 3. Development of New Acute Kidney Injury in Association With Different Types of Exposures

| Type of Exposure | No. Subjects, n (%) | No AKI, n (%) | AKI Stage 1, n (%) | AKI Stage 2, n (%) | AKI Stage 3, n (%) |
|------------------|---------------------|--------------|-------------------|-------------------|-------------------|
| Major surgery    | 325 (51)           | 134 (41)     | 117 (36)          | 57 (18)           | 17 (5)            |
| IV contrast      | 270 (42)           | 131 (49)     | 91 (34)           | 40 (15)           | 8 (3)             |
| Vancomycin       | 258 (40)           | 114 (44)     | 87 (34)           | 45 (17)           | 12 (5)            |
| Nonsteroidal anti-inflammatory drugs | 220 (34) | 111 (50) | 71 (32) | 30 (14) | 8 (4) |
| Piperacillin/tazobactam | 209 (33) | 97 (46) | 75 (36) | 29 (14) | 8 (4) |

AKI = acute kidney injury.

*p* Values for the association of exposure type with AKI stage 2–3 and with any AKI are 0.20 and 0.22, respectively (likelihood ratio test).

clinically significant differences in concomitant exposures or APACHE III scores between patients with different stages of AKI. However, although not reaching statistical significance (*p* = 0.06), higher APACHE III scores were observed in patients with AKI stage 2–3 in the context of IV contrast administration (median APACHE III score, 95.5 [IQR, 56.5–108.2]) compared with those with AKI stage 1 (median 51 [IQR, 46.5–65.5]) and patients without AKI (median 60 [IQR, 46.25–73.7]), which may have contributed to the release of biomarkers.

**DISCUSSION**

Our analysis confirms that critically ill patients are frequently exposed to insults that may be harmful to the kidney. More than 90% of patients had at least one potential renal insult immediately before admission or up to the first study day. Cumulative exposures posed a significant additive risk for AKI. In patients who developed AKI stage 2–3, urinary [TIMP-2]•[IGFBP7] concentrations increased on the day of exposure and exhibited a characteristic rise and fall around most exposures. The exception appeared to be radiocontrast where the characteristic biomarker rise was not seen but instead high levels were already present on the day of exposure in those with AKI. Importantly, in patients who did not develop AKI, there was no significant biomarker rise.

Drug-induced nephrotoxicity is a major problem. Drugs contribute to 20% of community-acquired AKI episodes that result in hospitalization (13, 15, 19, 24). In the ICU, drug-associated AKI affects approximately 15–25% of patients (1, 14, 25). The consequences are potentially serious, with reports of dialysis dependence and/or mortality similar to other types of AKI (40–50%) (13–15).

It has been suggested that the decision to initiate a potentially nephrotoxic compound should be guided by personalized clinical decision making and close monitoring of renal function (20, 26, 27). However, serum creatinine as a marker of glomerular function is not well suited for this purpose, especially since potentially nephrotoxic drugs often exert considerable tubular damage before a significant serum creatinine rise is observed (28, 29). Novel biomarkers of renal tubular injury have been shown to predict both short- and long-term outcomes after AKI (29, 30). The U.S. Food and Drug Administration approved the use of urinary [TIMP-2]•[IGFBP7] to assess the risk for AKI in clinical practice. Our results clearly show that AKI biomarkers are dynamic and change in association with exposures to potentially nephrotoxic insults. Understanding the kinetics of AKI biomarkers is important for interpreting their changing levels over time. Our analysis represents the first such information on the kinetics of urinary [TIMP-2]•[IGFBP7]. Although not directly examined, we hypothesize that the early use of appropriate biomarkers could potentially help clinicians to identify patients with renal stress who may benefit from early interventions to prevent progression (31). The molecules IGFBP7 and TIMP-2 are known to be associated with mechanisms implicated in the pathogenesis of AKI (7, 32, 33). It has been shown that renal tubular cells enter a short period of G1 cell cycle arrest during the early phases of cell injury. It is believed that this prevents them from dividing until the damage is repaired. Markers of cell cycle arrest, such as IGFBP7 and TIMP-2, may signal that the renal epithelium has been stressed and has shut down function (7). Emlet et al (32) showed that TIMP-2 was both expressed and secreted preferentially by cells of distal tubule origin while IGFBP7 was preferentially secreted by cells of proximal tubule origin. Despite significant progress in this area, much remains unknown and work is ongoing.

Our study has certain limitations as expected from retrospective analyses. First, we evaluated only five selected insults while acknowledging that a proportion of patients may have been exposed to many other nephrotoxins. Second, we did not analyze the biomarker kinetics of patients without any of the five chosen exposures, mainly because the majority was exposed to other less frequently used nephrotoxins and therefore could not be considered as true controls. Third, we only knew the day that vancomycin, NSAIDs, and piperacillin/tazobactam were first administered but not the precise time. Our results describe the biomarker kinetics around administration of the first dose. This reflects clinical practice where patients are often exposed to different potentially nephrotoxic insults simultaneously without the exact timing of all exposures being known. Fourth, we included “major surgery” as a separate potentially injurious insult but did not differentiate between different types of surgery and specific perioperative factors. Finally, we analyzed different exposures as binary variables.
and did not evaluate their intensity, number of doses, mode of administration, and duration.

In conclusion, exposure to multiple nephrotoxic insults is common during critical illness and associated with an increased risk of AKI. Urinary [TIMP-2][IGFBP7] exhibit a characteristic rise and fall around various exposures but importantly, only in patients who ultimately develop AKI. By contrast, serum creatinine is not altered during the early hours after exposure to a renal insult. Further studies are necessary to explore whether serial biomarker measurement has a role in selecting and monitoring medications and preventing drug-induced AKI.

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