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Urine Output Monitoring for the Diagnosis of Early-Onset Acute Kidney Injury in Very Preterm Infants

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Abstract

Background and objectives The current threshold used for oliguria in the definition of neonatal AKI has been empirically defined as 1 ml/kg per hour. Urine output criteria are generally poorly documented, resulting in uncertainty in the most accurate threshold to identify AKI in very preterm infants with known tubular immaturity.

Design, setting, participants, & measurements We conducted a bicentric study including 473 very preterm infants ($24^{0/7}$–$29^{6/7}$ weeks of gestation) born between January 2014 and December 2018 with urine output measurements every 3 hours during the first 7 days of life and two serum creatinine measurements during the first 10 days of life. AKI was defined using the neonatal Kidney Disease Improving Global Outcomes (KDIGO) definition. We tested whether higher urine output thresholds (1.5 or 2 ml/kg per hour) in modified AKI definitions may better discriminate neonatal mortality compared with the current definition.

Results Early-onset AKI was developed by 101 of 473 (21%) very preterm infants. AKI was diagnosed on the basis of urine output criteria alone (no rise in creatinine) for 27 of 101 (27%) participants. Early-onset AKI was associated with higher risk of death before discharge (adjusted odds ratio, 3.9; 95% confidence interval, 1.9 to 7.8), and the AKI neonatal KDIGO score showed good discriminative performance for neonatal mortality, with an area under the receiver operating characteristic (ROC) curve of 0.68 (95% confidence interval, 0.61 to 0.75). Modified AKI definitions that included higher urine output thresholds showed significantly improved discriminative performance, with areas under the ROC curve of 0.73 (95% confidence interval, 0.66 to 0.80) for the 1.5-ml/kg per hour threshold and 0.75 (95% confidence interval, 0.68 to 0.81) for the 2-ml/kg per hour threshold.

Conclusions Early-onset AKI was diagnosed on the basis of urine output exclusively for a quarter of the cases. Furthermore, modified AKI definitions that included higher urine output improved the discriminative performance for predicting mortality.

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Introduction

Preterm birth affects nearly 15 million births annually, and the survival rate of very preterm infants has greatly improved over the last few decades (1,2). Attention has been focused on long-term neurodevelopmental outcomes, yet AKI remains an underrecognized morbidity for preterm neonates. Very preterm infants are particularly at risk of AKI (3). Very preterm infants show incomplete nephrogenesis (oligonephronia) and tubular immaturity (4). Newborns are particularly exposed to multiple postnatal kidney insults, such as nephrotoxic medication, hypoxic events, or persistent patent ductus arteriosus (PDA) (5).

Neonatal AKI in preterm infants has been associated with higher neonatal mortality (6). There is also growing evidence of the long-term consequences of hypertension and CKD in adults, as AKI is known to further worsen nephron endowment and lead to inflammation, fibrosis, and maladaptive repair mechanisms (7). These infants consequently need to be considered as a specific subgroup with a higher long-term risk of deleterious consequences (8–10). They should be identified early to ensure preventive measures and specific follow-up.

Currently, neonatal AKI is diagnosed on the basis of an increase in serum creatinine levels and/or low urine output. Although several definitions have been used, the current threshold for oliguria integrated into the neonatal Kidney Disease Improving Global Outcomes (KDIGO) AKI definition has been empirically defined by an expert panel as 1 ml/kg per hour for 24 hours (11).

Oliguria criteria are generally poorly documented in the literature in this population due to measurement-related technical challenges, and the diagnosis of AKI is often made on the basis of creatinine values alone. The relevance of the oliguria cutoff is yet to be studied, and thus, results have been extrapolated from adult data, leading to the misconception that neonatal AKI is kidney failure with preserved diuresis. In 2013, a

retrospective study from Bezerra *et al.* (12) suggested that higher urine thresholds (1.5 and 2 ml/kg per hour) better predicted mortality in preterm infants with AKI. We hypothesize that the 1-ml/kg per hour empirical urine threshold may result in an underestimation of AKI in very preterm infants with known tubular immaturity. This may lead to a poor AKI detection rate in this particularly high-risk population.

On the basis of rigorous urine quantification in very preterm infants during the first week of life, we aimed to (*1*) determine the incidence of AKI on the basis of the neonatal KDIGO definition in this population and evaluate the contribution of urine output to its diagnosis, (*2*) assess the association of AKI on the basis of the neonatal KDIGO definition and mortality, and (*3*) determine the most accurate oliguria threshold in very preterm infants to define AKI using an outcome-based (death before discharge) threshold determination.

Materials and Methods

Study Design and Population

We performed a bicentric study in two neonatal intensive care units: Robert Debré Children's Hospital, Paris, France and University Children Hospital, Geneva, Switzerland. Our study was approved by the respective pediatric ethics committees (Comité Consultatif d'Ethique Local, Robert Debré Pediatric Hospital and Commission Cantonale d'Ethique de la Recherche).

Any very preterm infant ($24^{0/7}$–$29^{6/7}$ weeks of gestation) born between January 2014 and December 2018 was eligible to participate in the study with written parental consent. Exclusion criteria included death within 24 hours of life. Inclusion criteria included urine output (recorded every 3 hours during the first 7 days of life) and two serum creatinine samples (taken during the first 10 days of life).

Data Collection

Demographic data were obtained from neonatal medical charts. Maternal characteristics included the main cause of premature delivery and antenatal treatment with steroids for fetal lung maturation. Infant characteristics included sex, gestational age, birth weight, intrauterine growth restriction (IUGR; birth weight less than the third percentile), Apgar score at 5 minutes, and the need for postnatal resuscitation. Postnatal data included death before discharge, significant PDA, and exposure to nephrotoxic medications (ibuprofen, indomethacin, gentamicin, or vancomycin) during the first week of life. Early-onset sepsis (before 48 hours of life) was also recorded and diagnosed by the association of positive biologic inflammatory signs and clinical evidence of infection with or without positive bacteriologic culture. Late-onset sepsis (after 48 hours of life) was diagnosed with clinical symptoms associated with positive blood culture and biologic inflammatory signs (C-reactive protein >10 mg/L or procalcitonin >0.5 ng/ml).

Primary Outcome

The primary outcome was defined as death before discharge.

Urine Measurement

Diuresis was recorded between day 1 and day 7, with consideration to oliguria in neonates within the first 24 hours of life. Urine output was measured for 7 days every 3 hours by diaper weight ($8/\text{d} \times 7$ days $= 56$ diapers weighed). Urine output was expressed as milliliters per kilogram per hour and was averaged over 24-hour periods. Finally, the lowest urine output in a 24-hour period was selected.

Creatinine Measurement

Creatinine (milligrams per deciliter) was measured in the serum using the kinetic colorimetric compensated Jaffe method (CREJ2 by Roche/Hitachi on Cobas c systems) in Geneva. An enzymatic method was used in Paris. The Jaffe method used in Geneva is known to be influenced by hyperbilirubinemia. The creatinine value used to diagnose AKI was the percentage rise from baseline, hence the need for two measurements during the first 10 days of life.

Neonatal Kidney Disease Improving Global Outcomes AKI Definition

AKI was defined according to the neonatal KDIGO work group definition modified for neonates (11). Participants were classified as having AKI if they presented an increase in creatinine levels and/or oliguria. The neonatal KDIGO definition proposes three stages of AKI severity. The stage of severity is determined by the more severe criteria between creatinine and urine output (Table 1).

Modified AKI Definition

We aimed to determine the ideal oliguria threshold to define neonatal AKI using an outcome-based threshold determination (death before discharge). The neonatal KDIGO AKI stage 1 definition regarding urine criteria (1 ml/kg per hour) was modified to include a modified very preterm AKI definition with a threshold of 1.5 ml/kg per hour (AKI 1.5) and a modified threshold of 2 ml/kg per hour (AKI 2). Only stage 1 was modified to improve early AKI detection and to evaluate the effect of oliguria on mortality (Table 1).

Statistical Analyses

Premature infant characteristics were described as counts and percentages for qualitative variables and means and SDs for quantitative variables. Our analysis aims to determine the best urine output threshold among the neonatal KDIGO definition and the modified very preterm AKI 1.5 and AKI 2 definitions using an outcome-based approach. We assessed the capacity of each definition to discriminate between death before discharge and survival using the area under the receiver operating characteristic curves (AUCs). Uncertainty of the AUCs was estimated according to the DeLong method. The AUCs for the modified very preterm AKI 1.5 and 2 definitions were compared with the neonatal KDIGO AUC using the DeLong test for two correlated receiver operating characteristic curves. The effect of AKI (neonatal KDIGO and modified very preterm AKI definitions) on mortality was assessed using multivariable logistic models. A restricted list of potential confounding factors was defined *a priori* and included gestational age,

Table 1. Neonatal Kidney Disease Improving Global Outcomes AKI definition and modified very preterm AKI definitions

Stage	Neonatal Kidney Disease Improving Global Outcomes AKI Definition (Neonatal Modification 2016)	Very Preterm AKI 1.5	Very Preterm AKI 2
1	Urine <1 ml/kg per hour for 24 h; creatinine =0.3-mg/dl rise within 48 h or >1.5×–1.9× baseline	Urine <1.5 for 24 h; creatinine = 0.3-mg/dl rise within 48 h or >1.5×–1.9× baseline	Urine <2 for 24 h; creatinine = 0.3-mg/dl rise within 48 h or >1.5×–1.9× baseline
2	Urine <0.5 ml/kg per hour for 24 h; creatinine = 1.5×–1.9× baseline	Same as neonatal KDIGO AKI definition	Same as neonatal KDIGO AKI definition
3	Urine <0.3 ml/kg per hour for 24 h; creatinine =3× baseline or >2.5 mg/dl	Same as neonatal KDIGO AKI definition	Same as neonatal KDIGO AKI definition

We modified the oliguria threshold for stage 1 to improve early AKI detection. For the creatinine criterion, stages 2 and 3 were not modified. Very preterm AKI 1.5 indicates the modified definition with a threshold of urine of 1.5 ml/kg per hour for stage 1. Very preterm AKI 2 indicates the modified definition with a threshold of urine of 2 ml/kg per hour for stage 1. KDIGO, Kidney Disease Improving Global Outcomes.

sex, IUGR, absence or incomplete antenatal corticosteroid course, and center effects. The restriction on the number of factors to include in the model (n=6 including AKI) was on the basis of statistical considerations (one factor for ten events), whereas the selection of variables was on the basis of clinical considerations (known predictive factors of death) (13–15). Missing data were not replaced; we performed a complete case analysis with no subgroup or interaction examinations. We performed no sensitivity analysis. Potential selection bias owing to urine output or creatinine data not being available was examined by comparing included and excluded very preterm infants' characteristics. Statistical significance was set at the two-sided 0.05 level for all analyses. All analyses were performed using R software version R-4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Population Characteristics

In total, 568 very preterm infants were admitted between January 2014 and December 2018 to the neonatal intensive care units of Paris and Geneva. Among them, 27 were excluded due to death within 24 hours of birth, nine were excluded due to missing urine output data, and 59 were excluded due to missing creatinine measurements (Figure 1). Finally, 473 participants were included (161 in Geneva and 312 in Paris). The mean gestational age was 27.4±1.6 weeks, and the mean birth weight was 993±256 g. The study population is described in Table 2.

Participant characteristics—distinguished by units—are available in Supplemental Table 1A. Characteristics of participants excluded for missing data characteristics are available in Supplemental Table 1B.

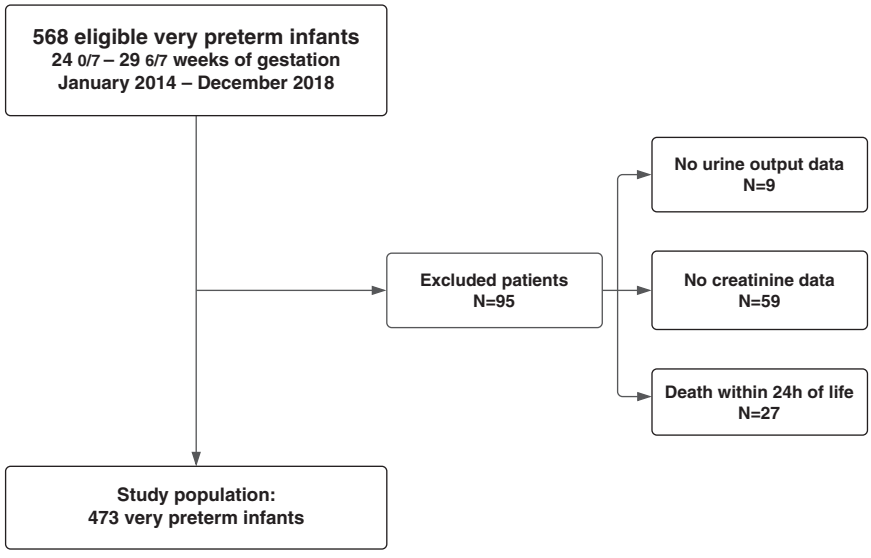

Figure 1. | Study cohort flow chart.

Table 2. Characteristics of neonates admitted to two neonatal intensive care units in France and Switzerland, with a comparison of mortality at discharge

Population Characteristics	n=473	Mortality: No, n=421	Mortality: Yes, n=52
Girls, n (%)	226 (48)	202 (48)	24 (46)
Gestational age, wk, mean (SD)	27.4 (1.6)	27.6 (1.5)	26.2 (1.6)
Birth weight, g, mean (SD)	993 (256)	1019 (249)	778 (210)
Main cause of preterm delivery, *n* (%)			
Preterm labor	207 (44)	188 (45)	19 (37)
Premature rupture of membranes	81 (17)	72 (17)	9 (17)
Hypertensive disorders of pregnancy	71 (15)	62 (15)	9 (17)
Chorioamnionitis	59 (12)	50 (12)	9 (17)
Antepartum hemorrhage	30 (6)	27 (6)	3 (6)
Other	25 (6)	22 (5)	3 (5)
Antenatal corticosteroid therapy, *n* (%)			
No or incomplete course	112 (24)	94 (22)	18 (35)
Full course	361 (76)	327 (78)	34 (65)
Intrauterine growth restriction, n (%)	48 (10)	37 (9)	11 (21)
Apgar score at 5 min,[a] mean (SD)	7.5 (2.3)	7.7 (2.2)	6.5 (2.8)
Cardiac resuscitation at birth, n (%)	35 (7)	26 (6)	9 (17)
Fluid expansion, n (%)	44 (9)	32 (8)	12 (23)
Vasoactive drugs exposure, n (%)	140 (30)	106 (25)	34 (65)
Intubation, n (%)	313 (66)	276 (66)	37 (71)
Surfactant administration,[c] n (%)	307 (65)	259 (62)	50 (92)
Weight loss,[c] %, mean (SD)	8.6 (5.1)	8.7 (5)	7.9 (5.4)
Sepsis, *n* (%)	283 (60)	246 (58)	37 (71)
Early onset	118 (25)	96 (23)	22 (42)
Late onset	222 (47)	192 (46)	30 (58)
Vancomycin exposure, n (%)	257 (54)	219 (52)	38 (73)
Gentamicin exposure, n (%)	349 (74)	304 (72)	45 (87)
Hemodynamically significant PDA,[b] n (%)	227 (48)	182 (43)	45 (88)
Indomethacin exposure, n (%)	53 (11)	46 (11)	7 (13)
Ibuprofen exposure, n (%)	153 (32)	127 (30)	26 (50)
PDA ligation, n (%)	35 (7)	33 (8)	2 (4)

Very preterm infants who died before discharge were more premature with lower birth weight. They had a more complicated clinical course (worse immediate neonatal adaptation, more early-onset sepsis, and significant PDA). PDA, patent ductus arteriosus.
[a]Four with missing data.
[b]One with missing data.
[c]Thirty-eight with missing data.

Incidence of Early-Onset AKI on the Basis of Different Definitions

Urine Output and Creatinine Distribution. The joint urine and creatinine distribution is shown in Figure 2. Urine output was reported in categories; 276 of 473 (58%) preterm infants had diuresis above 2 ml/kg per hour, and 425 of 473 (90%) preterm infants had diuresis above 1 ml/kg per hour. Creatinine was stable (no increase of >1.5 from baseline) in 399 of 473 (75%) participants.

Incidence of Early-Onset AKI on the Basis of the Neonatal Kidney Disease Improving Global Outcomes Definition. Among the 473 preterm infants, 101 (21%) developed AKI during the first week of life. From these, 27 infants showed low urine output only, 53 increased creatinine only, and 21 had both criteria. The incidence was different between the two neonatal intensive care units: 57 of 161 infants (35%) in Geneva and 44 of 312 (14%) in Paris (P<0.001). Population characteristics comparing very preterm infants with or without a neonatal KDIGO-diagnosed AKI are in Supplemental Table 2.

Incidence of AKI Using the Modified Definitions. Urine output <1.5 ml/kg per hour on a 24-hour period was measured for 116 of 473 (24%) infants. On the basis of this modified 1.5-ml/kg per hour threshold, 150 of 473 (32%) infants developed AKI (*i.e.*, 49 additional diagnoses compared with the diagnoses using the conventional definition).

Urine output <2 ml/kg per hour was measured for 197 of 473 (42%) infants. On the basis of this modified threshold, 217 of 473 (46%) infants developed AKI (*i.e.*, 116 additional diagnoses compared with the diagnosis using the conventional definition).

Among the infants developing AKI, regardless of the definition, 52 exhibited moderate to severe disease (34 in stage 2 and 18 in stage 3).

AKI and Mortality

AKI on Basis of the Neonatal Kidney Disease Improving Global Outcomes Definition and Mortality. Overall, 52 infants (11%) died before discharge. AKI according to the neonatal KDIGO definition was associated with a higher risk of in-hospital death, with 27 of 101 deaths for infants with neonatal KDIGO AKI and 25 of 372 deaths for those without (odds ratio [OR], 5.1; 95% confidence interval [95% CI], 2.8 to 9.3; P<0.001) (Table 3). In multivariable analysis, AKI according to the neonatal KDIGO definition remained independently associated with a higher risk of

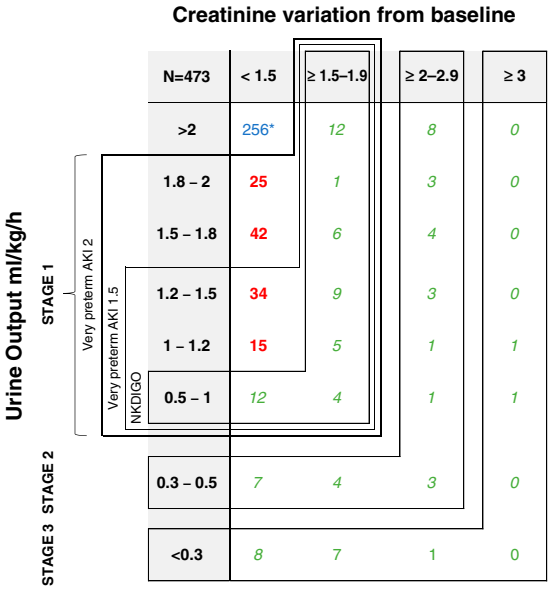

Figure 2. | Urine output and creatinine distribution among 473 very preterm infants and AKI incidence using different definitions: neonatal Kidney Disease Improving Global Outcomes (NKDIGO) versus very preterm AKI 1.5 versus very preterm AKI 2. Italic green numbers indicate patients diagnosed with the NKDIGO AKI definition. Bold red numbers indicate patients newly diagnosed with AKI using the modified definition: very preterm AKI 1.5 and 2. Stages 2 and 3 are not modified; 101 of 473 (21%) very preterm infants developed AKI according the NKDIGO definition. By raising the oliguria threshold for stage 1, 150 of 473 infants (32%) developed AKI using the very preterm AKI 1.5 definition, and 217 of 473 infants (46%) developed AKI using the very preterm AKI 2 definition. *The blue number indicates patients without AKI even using the modified definition.

mortality (adjusted OR, 3.9; 95% CI, 1.9 to 7.8) (Table 3). Low gestational age at birth and IUGR were also associated with a higher risk of mortality. Of note, a center effect was shown and was accounted for in the multivariable analysis.

Modified AKI Definitions and Mortality. AKI according to the neonatal KDIGO definition showed good discrimination for mortality before discharge, with an AUC of 0.68 (95% CI, 0.61 to 0.75). The discriminative performance on the basis of the modified very preterm AKI definitions resulted in an AUC of 0.73 (95% CI, 0.66 to 0.80) for the 1.5-ml/kg per hour threshold and 0.75 (95% CI, 0.68 to 0.81) for the 2-ml/kg per hour threshold. The discriminative performance was statistically significantly higher using the modified AKI definitions than the neonatal KDIGO definition: very preterm AKI 1.5 versus neonatal KDIGO, $P=0.04$; very preterm AKI 2 versus neonatal KDIGO, $P=0.02$.

As already mentioned, AKI according to the neonatal KDIGO definition was significantly associated with four-fold higher odds of mortality in multivariable analysis (adjusted OR, 3.9; 95% CI, 1.9 to 7.8). The increased discriminative performance of the modified AKI definitions translated into a five-fold higher risk of mortality: very preterm AKI 1.5 adjusted OR, 5.0; 95% CI, 2.4 to 11.0 and very preterm AKI 2 adjusted OR, 5.0; 95% CI, 2.2 to 12.3 (Table 4, Supplemental Table 3).

Discussion

In this study of 473 very preterm infants from two centers, AKI was diagnosed on the basis of the urine criteria alone in a quarter of cases, highlighting the importance of this measurement. Early-onset AKI was associated with a higher risk of mortality. Furthermore, the modified AKI definition for very preterm infants on the basis of a higher urine output threshold showed significantly higher discriminative performance for mortality than that on the basis of the conventional definition.

Data from the literature on AKI incidence in the very preterm infant population are limited, and only a few articles have reported urine output.

Single-center studies have reported rates of AKI from 12% to 40%, and only the creatinine criterion was used in most of the series, which is in contradiction with the methodology behind the neonatal KDIGO AKI definition (16–18). In the recently published multicentric Extremely Low Gestational Age Newborns study, which included 923 extreme preterm neonates (<28 weeks), the prevalence of early-onset AKI was low (12%) (19). However, urine data were not available in this large study. The multicentric retrospective Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates study is the largest study performed to date on neonatal AKI, with >2000 critically ill neonates from 24

Table 3. Multivariable models assessing neonatal Kidney Disease Improving Global Outcomes AKI association with mortality (*n*=473)

Model's Variables	Mortality: No, *n*=421	Mortality: Yes, *n*=52	Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)	*P* Value
AKI neonatal KDIGO, *n* (%)	74 (18)	27 (52)	5.1 (2.8 to 9.3)	3.9 (1.9 to 7.8)	<0.001
Boys, *n* (%)	219 (52)	28 (54)	1.1 (0.6 to 1.9)	0.8 (0.4 to 1.5)	0.45
Gestational age, wk, mean (SD)	27.6 (1.5)	26.2 (1.6)	0.6 (0.5 to 0.7)	0.6 (0.5 to 0.7)	<0.001
Intrauterine growth retardation, *n* (%)	37 (9)	11 (21)	2.8 (1.3 to 5.7)	4.2 (1.7 to 9.9)	0.001
Corticosteroids,[a] *n* (%)	94 (22)	18 (35)	1.8 (1.0 to 3.4)	1.6 (0.8 to 3.1)	0.22
Centre RDP, *n* (%)	275 (65)	37 (71)	1.3 (0.7 to 2.5)	2.2 (1.1 to 4.7)	0.02

AKI according to the neonatal KDIGO definition remained independently associated with a higher risk of mortality after adjustment. KDIGO, Kidney Disease Improving Global Outcomes; RDB, Robert Debré Children's Hospital, Paris, France.
[a]Absent or incomplete antenatal corticosteroid course.

Table 4. Multivariable models assessing AKI association with mortality using different urine thresholds for the AKI definition

Multivariable Models	n=473	Mortality: No, n (%), n=421	Mortality: Yes, n (%), n=52	Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)	P Value
Model 1	AKI KDIGO	74 (18)	27 (52)	5.1 (2.8 to 9.3)	3.9 (1.9 to 7.8)	<0.001
Model 2	Very preterm AKI 1.5	114 (27)	36 (69)	6.1 (3.3 to 12.0)	5.0 (2.4 to 11.0)	<0.001
Model 3	Very preterm AKI 2	174 (41)	43 (83)	6.8 (3.4 to 15.0)	5.0 (2.2 to 12.3)	<0.001

All models were adjusted on sex, gestational age, intrauterine growth restriction, corticosteroids, and center. KDIGO, Kidney Disease Improving Global Outcomes.

centers (6), including a cohort of 265 very preterm infants (22–28 weeks of gestation) for whom 24-hour urine data were requested. The incidence of early-onset AKI was higher (28%) than that reported in the Extremely Low Gestational Age Newborns study (12%) (20).

In our study, 21% of very preterm infants ($24^{0/7}$–$29^{6/7}$ weeks of gestation) were diagnosed with AKI during the first week of life (36% in Geneva and 14% in Paris). Urine output was rigorously measured. All included participants had their diapers weighed every 3 hours for 7 consecutive days (8/d ×7 days =56 diapers weighed), and 27 of 101 (27%) cases were diagnosed solely on the basis of this criterion. Measurement of urine output only in "at-risk situations" may lead to the underdiagnosis of AKI. This study highlights the importance of considering regular urine output follow-up as the standard of care for very preterm infants during the first week of life, a vulnerable period associated with increased insults to the kidney, to diagnose early-onset AKI.

AKI has been shown to be significantly associated with an independent higher risk of mortality in various pediatric and adult populations (21,22). In the neonatal population, AKI should also be recognized as a major risk factor for mortality, as for other well-known and well-studied parameters, such as gestational age and IUGR. In the AWAKEN study, the diagnosis of neonatal AKI was associated with higher mortality (adjusted OR, 4.6; 95% CI, 2.5 to 8.3; P<0.001) (6). In a secondary analysis of this study on early-onset AKI, the number of very preterm participants (n=265) was insufficient to demonstrate a significantly higher neonatal mortality (20). In our larger population of very preterm infants, early-onset AKI was associated with a four-fold higher risk of mortality (OR, 3.9; 95% CI, 1.9 to 7.8) and should be considered a red flag for poor clinical evolution.

Several neonatal AKI definitions have been proposed in the past, resulting in the consensual neonatal KDIGO definition in 2016. This neonatal AKI definition includes a 1-ml/kg per hour threshold for 24 hours defined by an expert panel (11). In 2013, Bezerra *et al.* (12) used a 1.5-ml/kg per hour oliguria threshold for AKI diagnosis in a retrospective study (n=384 preterm). Their study showed better performance in predicting mortality than the neonatal RIFLE AKI definition. In the low–birth weight subgroup (<1500 g, n=151), a 2-ml/kg per hour threshold was shown to be the best cutoff to predict mortality in participants with AKI. In our population, we tested modified AKI definitions for very preterm infants that included a higher oliguria threshold for stage 1: modified very preterm AKI definition 1.5 or 2 ml/kg per hour. We increased the AKI detection up to 32% and 46% of the patients, respectively. AKI was diagnosed solely on urine output in 35% and 65% of the participants, respectively. These definitions resulted in significantly greater performance (AUCs of 0.73 and 0.75 versus 0.68) in discriminating neonatal mortality than the conventional neonatal KDIGO definition. These results raise questions about the optimal threshold for oliguria to detect AKI in this population, especially in the context of tubular immaturity.

The major strength of this study was the sample size, consisting of a large bicentric population of very preterm infants with few missing data. The collection of diuresis was extensive for all participants during the first 7 days of life (8/d ×7 days =56 diapers weighed).

This study also had several limitations. Urine was measured by diaper weight, which is a common and pragmatic technique in the neonatal intensive care unit but not completely accurate in the event of mixed stools (23). Catheterization, which may have resulted in more accurate urine measurements, remains risky, is resource intensive, and is often unethical considering the sensitivity of our population. AKI rates were different between centers. Highly variable AKI rates between neonatal centers have already been described (from 3% to 74% in the AWAKEN study) and are likely related to differences in the local standard of care and varying practices in kidney function monitoring, such as the frequency of creatinine monitoring (6). In our population, the observed differences between the proportions of AKI cases can also be partially explained by the use of indomethacin in Geneva for PDA treatment, which is known to be associated with more frequent episodes of oliguria than ibuprofen. We introduced a center effect in our multivariable analysis to account for these differences. Finally, the number of events is also a limitation in our analysis. We cannot exclude that confounding factors have been omitted, particularly clinical variables measuring the severity of illness in participants. However, a sensitivity analysis including either early sepsis or cardiac resuscitation in the model did not change the association between neonatal KDIGO AKI and death.

Our data emphasize the need to refine the neonatal AKI definition by accounting for tubular immaturity and using specific gestational age groups. An adapted definition that integrates a higher urine threshold for very preterm infants

will allow for earlier detection in at-risk poor outcome patients, leading to timely intervention and ensuring specific follow-up. Future studies are needed to re-evaluate this new AKI definition for very preterm infants and to determine whether it also shows better discriminative performance in identifying very preterm infants with poorer long-term outcomes, such as CKD and hypertension.

Early-onset AKI, developed by a fifth of very preterm infants, is diagnosed exclusively on the basis of oliguria for a quarter of cases. Furthermore, a modified AKI definition that includes a higher threshold value for urine output improved the discriminative performance for neonatal mortality. A higher urine threshold should probably be integrated into future neonatal AKI definitions, especially for very preterm infants with tubular immaturity, to ensure specific follow-up.

Disclosures

All authors have nothing to disclose.

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Author Contributions

O. Baud, V. Biran, A. De Mul, A. Héneau, P. Parvex, A. Poncet, M. Saint-Faust, and A. Wilhelm-Bals conceptualized the study; A. De Mul and A. Héneau were responsible for data curation; O. Baud, V. Biran, A. De Mul, A. Héneau, P. Parvex, A. Poncet, M. Saint-Faust, and A. Wilhelm-Bals were responsible for formal analysis; A. De Mul and A. Wilhelm-Bals wrote the original draft; and O. Baud, V. Biran, A. De Mul, A. Héneau, P. Parvex, A. Poncet, M. Saint-Faust, and A. Wilhelm-Bals reviewed and edited the manuscript.

Data Sharing Statement

All data used in this study are available in this article.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.15231121/-/DCSupplemental.

Supplemental Table 1. Population characteristics by center and population characteristics when comparing included and excluded patients for missing data.

Supplemental Table 2. Population characteristics comparing very preterm infants with or without neonatal KDIGO AKI.

Supplemental Table 3. Multivariable logistic model describing the effect of the different very preterm AKI definitions on mortality.

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