BMJ Open

Early urine output monitoring in very preterm infants to predict in-hospital neonatal outcomes: a bicentric retrospective cohort study

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ABSTRACT

Objective To evaluate whether urine output (UO), rarely assessed in the literature, is associated with relevant neonatal outcomes in very preterm infants, and which UO threshold may be the most clinically relevant.

Design Retrospective cohort study.

Setting Two Level IV neonatal intensive care units.

Patients Very preterm infants born between $24^{0/7}$ and $29^{6/7}$ weeks of gestation documented with eight UO measurements per day between postnatal day 1 and day 7.

Main outcome measures Composite outcome defined as death before discharge, or moderate to severe bronchopulmonary dysplasia, or severe brain lesions. The association between this outcome and UO was studied using several UO thresholds.

Results Among 532 infants studied, UO <1.0 mL/kg/hour for at least 24 consecutive hours was measured in 55/532 (10%) infants and the primary outcome was recorded in 25 patients. The association between a UO threshold <1.0 mL/kg/hour and the primary outcome was found marginally significant (crude OR 1.80, 95% CI 1.02 to 3.16, p=0.04). The primary outcome was recorded in 112/242 (46%) patients with a UO <2.0 mL/kg/hour and only 64/290 (22%) patients with a UO ≥2.0 mL/kg/hour (p<0.001). This UO threshold was found significantly associated with the primary outcome (crude OR 3.1, 95% CI 2.1 to 4.7, p<0.001), an association confirmed using a multivariate logistic regression model including baseline covariates (adjusted OR 3.7, 95% CI 2.2 to 6.4, p<0.001).

Conclusion A UO <2 mL/kg/hour over 24 hours between postnatal day 1 and day 7 strongly predicts neonatal mortality or severe morbidities in very preterm infants.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Large sample size of very and extremely preterm infants.
⇒ Exhaustive urine output (UO) data collection during the first postnatal week of life.
⇒ The retrospective study design is the main limitation of this study.
⇒ UO measure by the weighing of diapers may not be entirely accurate in case of mixed stools.
⇒ We acknowledge the lack of an online a priori registered protocol.

INTRODUCTION

Every year, 2.25 million infants worldwide are born very preterm and at risk of adverse neonatal outcomes.[1] [2] Due to remarkable advances in neonatal intensive care, most survive into adulthood, raising the issue of minimising long-term morbidity. Aside from brain and lung complications, preterm infants are particularly at risk of reduced urine output (UO) due to a reduced number of nephrons combined with tubuloglomerular immaturity.[3] Furthermore, this population is exposed to multiple postnatal renal insults, including exposure to nephrotoxic medications, repeated hypoxic events and haemodynamic effects of patent ductus arteriosus (PDA).[4] Kidney dysfunction has been associated with mortality and other adverse outcomes, including hypertension and chronic kidney disease, in various paediatric and adult populations.[5–8] Acute kidney injury (AKI) leading to kidney dysfunction is the consequence of the underlying severity of illness and can itself induce the dysfunction of other organs by modifying the inflammatory cascade, oxidative stress or apoptosis.[9]

According to the Neonatal Kidney Disease Improving Global Outcome (NKDIGO) criteria, the definition of neonatal AKI is currently based on two markers: serum creatinine (SCr) levels increase from a baseline steady state or reduced UO.[10 11] Some limitation exists to use SCr in neonates due to the lack of baseline steady-state SCr in critically ill preterm neonates. Because of measurement-related technical challenges, longitudinal UO has also rarely been assessed as an AKI criterion in the literature, leading to uncertainty in the accurate classification of patients with AKI. The current threshold for oliguria

integrated in the NKDIGO AKI definition has been empirically defined as a UO below 1.0 mL/kg/hour. However, it does not consider the tubular immaturity of very preterm infants, leading to the failure to concentrate urine. Hence, the UO threshold defined by the NKDIGO criteria may not be appropriate for this population of very preterm infants. Furthermore, it has not been evaluated as a marker of relevant clinical outcomes in this very specific population.

Based on an exhaustive quantification of neonatal UO, we hypothesised that UO, a marker of AKI, is associated with neonatal mortality and morbidities in infants born very preterm and that a higher UO threshold may be more relevant in clinical practice in this population.

PATIENTS AND METHODS
Study population
We performed a retrospective study in two neonatal intensive care units (NICUs) at University Hospitals of Geneva (centre A) and Robert Debré Children's Hospital in Paris (centre B). The screened population included infants born between January 2014 and December 2018 delivered between $24^{0/7}$ and $29^{6/7}$ weeks of gestation (n=568). Gestational age (GA) was calculated based on the date of the last menstrual period and ultrasonographic screening performed within the first trimester of pregnancy (crown-rump length). Eligible population was preterm infants with UO values between postnatal day 1 and day 7. Exclusion criteria were infants with missing UO measurements (n=9) and death before 24 hours of life (n=27). A written parental formular has been collected from parents of all patients at admission for further use of health-related data.

Data collection
Data on maternal characteristics and pregnancy events were extracted from the clinical database of each maternity ward and NICU. Maternal characteristics included the main cause of preterm delivery and antenatal steroid treatment. Perinatal characteristics included the sex, GA at birth, birth weight, intrauterine growth restriction (IUGR) as birth weight below the 10th percentile, Apgar score at 5 min and the need for delivery room resuscitation.

Neonatal outcomes included neonatal mortality before discharge and major neonatal morbidities associated with very preterm birth, including severe respiratory distress syndrome requiring surfactant therapy, bronchopulmonary dysplasia (BPD) at 36 weeks of postmenstrual age (according to the physiological definition[12]), PDA, necrotising enterocolitis (grades >IIA according to Bell's classification), severe brain lesions, including grade 3–4 intraventricular haemorrhage (IVH; according to Papile's classification) and cystic white matter damage (cWMD). Early-onset sepsis (EOS) was defined, before 48 hours of life, as the association of biological signs and clinical deterioration, with or without bacteriological documentation,

but treated by antibiotics for at least 5 days. Late-onset sepsis was confirmed when altered clinical conditions were associated with positive standard blood cultures and elevated levels of standard inflammatory blood markers (C-reactive protein >10 mg/L, and/or procalcitonin >0.5 ng/mL), leading to antibiotic treatment for more than 5 days. Exposure to nephrotoxic medications (ibuprofen, indomethacin, gentamicin and vancomycin) during the first week was also studied. In particular, ibuprofen and indomethacin were used similarly in both centres for selective treatment of hemodynamically significant PDA.

UO measurement
Diuresis was recorded between day 1 and day 7 with consideration to oliguria in neonates within the first 24 hours of life. UO was measured every 3 hours by weighing diapers (8/day×7 days=56 diapers weighed in total) and these eight UO measurements per day were averaged over 24 hours. Hence, we obtained seven mean UO values. We selected the lowest mean UO value between day 1 and day 7 to study its association with the outcomes. We considered several UO thresholds when UO was <2.0 mL/kg/hour.

Primary outcome
The primary outcome was defined as a composite outcome defined as death before discharge, or moderate to severe BPD, or severe brain lesions (grade 3–4 IVH and/or cWMD).

Statistical analysis
Preterm infant characteristics are described as counts and percentages for qualitative variables and as means and SDs or medians and IQRs (Q1; Q3) for quantitative variables. The lowest mean UO (averaged over 24 hours) between postnatal days 1–7 was categorised as <0.5, 0.5 to <1.0, 1.0 to <1.5, 1.5 to <2.0 and ≥2.0 mL/kg/hour. The composite primary outcome and each of its components (neonatal death, BPD and severe brain injury) are described according to UO as counts and percentages. The main objective of the study was to assess the effect of UO on the primary outcome. Thus, we used a multivariable logistic regression model. A restricted list of potential confounding factors based on clinical relevance was defined a priori: sex, GA at birth, Apgar score at 5 min (≤5 vs >5), IUGR, absence of or incomplete antenatal corticosteroid therapy and EOS. The restriction on the number of factors to include in the model was on the basis of statistical considerations (one factor for 10 events), whereas the selection of variables was on the basis of clinical considerations (known predictive factors of death). As this was a bicentric study, a centre effect was included in the model. Estimation of the coefficients of the regression models was based on a complete case analysis and no multiple imputation methods were used. For GA at birth, the assumption of log linearity was graphically assessed. Secondary analyses consisted of assessing

the effect of UO based on several thresholds. Statistical significance was assessed at the two-sided 0.05 level for all analyses. All analyses were performed using R software V.4.0.2 (R Foundation for Statistical Computing, Vienna, http://www.R-project.org).

Patient and public involvement
The development of the research question and outcome measures was driven by patients' priorities, experience and preferences. It was not possible to involve patients in the retrospective design of this study. Patients were not involved in the recruitment to and conduct of the study. The results of the study will be disseminated to study participants through social media.

RESULTS
Population characteristics
Among the 568 preterm infants born between $24^{0/7}$ and $29^{6/7}$ weeks of gestation and admitted to either centre A or B, nine were not included in the study due to the absence of UO data and 27 were excluded due to death within 24 hours of birth. Congenital anomalies of kidney and urinary tract (renal hypodysplasia or agenesis, multicystic dysplastic kidney, hydronephrosis, duplex kidney or duplicated collecting system, megaureter, posterior urethral valve) were not reported in this cohort.

In total, 532 patients were included (217 from centre A and 315 from centre B). Population characteristics of the entire cohort and according to the occurrence of the primary outcome are presented in table 1.

Overall, we observed the primary outcome, defined as death, moderate to severe BPD or severe brain lesions, for 176/532 (33%) patients: 55 deaths (10%), 112 cases of BPD (21%) and 66 severe brain lesions (12%).

Incidence of the primary outcome according to UO threshold
UO threshold distributions either in the entire population or according to the primary outcome and its components are described in table 2.

UO <1.0 mL/kg/hour for at least 24 consecutive hours, defining oliguria according to the NKDIGO criteria, was measured in only 55/532 (10%) infants, among them the primary outcome was recorded in 25 patients. The association between a UO threshold <1.0 mL/kg/hour and the primary outcome was found marginally significant (crude OR 1.80, 95% CI 1.02 to 3.16, p=0.04). In contrast, 242/532 (45%) infants were recorded with a more liberal UO threshold of <2.0 mL/kg/hour. This UO threshold corresponding to the closest median value of the variable was further tested to predict neonatal outcomes in multivariate analyses.

Table 2 also summarises the primary outcome and its components according to the lowest mean UO between postnatal days 1–7. The primary outcome was observed for 112/242 (46%) patients with a UO <2.0 mL/kg/hour compared with 64/290 (22%) patients when UO was ≥2.0 mL/kg/hour (p<0.001). This between-group

difference for a UO threshold of 2 mL/kg/hour was also observed among the components of the composite outcome (5% vs 19% for death, 14% vs 30% for BPD and 8% vs 17% for brain injury). Our data did not show significant differences in mortality (p=0.28), BPD (p=0.36) or severe brain injury (p=0.66) among subgroups according to UO thresholds <2.0 mL/kg/hour. In contrast, comparison by centre found statistically significant differences in the incidence of the primary outcome (p=0.01) and severe brain lesions (p=0.02). Centre effect will be addressed in the multivariate logistic regression.

Statistical association between UO and the primary outcome
The UO threshold of 2 mL/kg/hour was found significantly associated with the primary outcome (crude OR 3.1 95% CI 2.1 to 4.7, p<0.001) (table 3). This association was further confirmed in a multivariate logistic regression model including sex, GA at birth, Apgar score at 5 min, IUGR, antenatal steroids, EOS and centre as baseline covariates (adjusted OR 3.7, 95% CI 2.2 to 6.4, p<0.001). Other variables significantly associated with the primary outcome were IUGR, low GA at birth, low Apgar score and EOS.

DISCUSSION
This cohort study of 532 very preterm infants investigated the clinical relevance of UO monitoring during the first postnatal week to predict neonatal outcomes of infants born very preterm. We found an association between a UO threshold <2.0 mL/kg/hour and a composite outcome defined as death before discharge, or moderate to severe BPD, or severe brain lesions.

Data from literature on UO monitoring in very preterm infants
There have been very few studies of early UO in the neonatal population. The multicentre retrospective Assessment of Worldwide Acute Kidney Epidemiology in Neonates (AWAKEN) study is currently the largest study to investigate AKI in the NICU (2022 critically ill neonates from 24 centres), but only 274 infants born very preterm were included.[6] Among very preterm infants, a 28% rate of early-onset AKI within the first postnatal week was reported based on changes in creatinine levels or UO.[13] An AKI diagnosis was rarely only based on low UO (<10% of the diagnoses) for very preterm infants compared with more mature infants (>50% of the diagnoses), raising questions about the empirical 1 mL/kg/hour UO threshold in this population. Consistently, 10% of our population was considered to be oliguric (UO <1.0 mL/kg/hour), as currently defined in the NKDIGO AKI definition. In contrast, UO <2.0 mL/kg/hour was observed for 45% of the population. Hence, our study was designed to challenge the relevance of the current oliguria threshold, and to provide more exhaustive UO data in a large population of infants delivered before 30 weeks at risk of tubular immaturity.

Table 1 Characteristics of the population according to the primary outcome (death, moderate to severe BPD or severe brain lesions)

Population characteristics	Entire population	Primary outcome	
	(N=532)	No (n=356)	Yes (n=176)
Sex (male)	272 (51)	175 (49)	97 (55)
Mean (SD) gestational age at birth (weeks)	27.5 (1.6)	28.0 (1.4)	26.5 (1.6)
Mean (SD) birth weight (g)	1009 (273)	1090 (257)	847 (229)
Cause of preterm delivery			
Preterm labour	226 (42)	147 (41)	79 (45)
PPROM	92 (17)	69 (19)	23 (13)
Hypertensive disorders of pregnancy	78 (15)	49 (14)	29 (16)
Chorioamnionitis	67 (13)	40 (11)	27 (15)
Antepartum haemorrhage	39 (7)	32 (9)	7 (4)
Antenatal steroids			
No or incomplete course	127 (24)	80 (22)	47 (27)
Complete course	405 (76)	276 (78)	129 (73)
Intrauterine growth restriction <10th percentile	51 (10)	18 (5)	33 (19)
Mean (SD) Apgar score at 5 min*	7.6 (2.3)	7.9 (2.0)	6.8 (2.6)
Cardiac resuscitation at birth	35 (7)	13 (4)	22 (12)
Volume expansion	52 (10)	22 (6)	30 (17)
Vasoactive drug exposure	147 (28)	54 (15)	93 (53)
Intubation	355 (67)	242 (68)	113 (64)
Exogenous surfactant†	320 (60)	173 (49)	147 (84)
Mean % (SD) weight loss‡	8.7 (5.0)	9.0 (4.9)	7.9 (5.1)
Sepsis			
Any	301 (57)	162 (46)	139 (79)
Early onset (before 48 hours)	133 (25)	65 (18)	68 (39)
Late onset (after 48 hours)	226 (42)	113 (32)	113 (64)
Vancomycin exposure	261 (49)	135 (38)	126 (72)
Gentamicin exposure	390 (73)	243 (68)	147 (84)
Haemodynamically significant PDA†	234 (44)	99 (28)	135 (77)
Indomethacin exposure	57 (11)	28 (8)	29 (16)
Ibuprofen exposure	155 (29)	67 (19)	88 (50)
PDA ligation	45 (8)	36 (10)	9 (5)
Necrotising enterocolitis grade ≥2	47 (9)	35 (10)	12 (7)

Unless otherwise specified, all data are presented as n (%).
*Missing data for 4 patients.
†Missing data for 1 patient.
‡Missing data for 38 patients.
BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus; PPROM, prolonged premature rupture of the membranes >24 hours.

Early UO monitoring and clinical outcomes

UO <2.0 mL/kg/hour was found independently associated with a fourfold increase in neonatal mortality or severe morbidities before discharge. No other study has assessed the impact of reduced UO itself on short-term clinical outcomes in this population. Our findings are consistent and complement another recent report showing that early-onset AKI-modified definition with UO >1 mL/kg/hour improved its discriminative performance for predicting only mortality in very preterm neonates.[14] Several single-centre studies also described an increased risk of mortality in the event of AKI in preterm infants based solely on changes in SCr levels.[15–18] In the AWAKEN study, AKI was associated with a fourfold higher risk of death.[6] Secondary analysis of this cohort revealed a significant and independent association between AKI and moderate to severe BPD or grade ≥2 IVH.[19 20] These morbidities may be more frequently observed in cases

Table 2 Primary outcome according to urine output and centre

Variable	N	Primary outcome*	Death	BPD	Brain injury
UO (mL/kg/hour)					
Any	532	176 (33)	55 (10)	112 (21)	66 (12)
≥2.0	290 (55)	64 (22)	15 (5)	40 (14)	24 (8)
(1.5–2.0)	96 (18)	41 (42)	14 (15)	28 (29)	16 (17)
(1.0–1.5)	91 (17)	46 (51)	15 (16)	31 (34)	18 (20)
(0.5–1.0)	22 (4)	9 (41)	3 (14)	7 (32)	4 (18)
<0.5	33 (6)	16 (48)	8 (24)	6 (18)	4 (12)
Centre					
A	217 (41)	58 (27)	16 (7)	38 (18)	18 (8)
B	315 (59)	118 (37)	39 (12)	74 (23)	48 (15)

Data are presented as n (%).
*Composite outcome including death before discharge, or moderate to severe BPD, or severe brain injury (grade 3–4 intraventricular haemorrhage or cystic white matter damage).
BPD, bronchopulmonary dysplasia; UO, urine output.

of AKI due to its related systemic consequences, such as fluid overload, abnormal blood pressure regulation, electrolyte and acid-base disturbances, systemic inflammatory response, impaired immunity and the modification of medication metabolism.[9] In our population, the UO cut-off of 2.0 mL/kg/hour is higher than the current oliguria threshold integrated in the NKDIGO definition, probably due to the tubular immaturity of this specific population. Interestingly, a Brazilian retrospective study including 151 low birthweight patients (<2500 g) also investigated these UO thresholds.[21] In this study, the prognostic value of UO to predict mortality was found better with a 2.0 mL/kg/hour cut-off when using a modified pRIFLE (Pediatric Modified Risk, Injury, Failure, Loss and End-stage definition) AKI definition.

Perspectives
The identification of early risk factors/markers in neonatal practice can lead to improve outcome prediction

of infants born very preterm. For example, patients with systematic ultrasound screening of PDA before postnatal day 3 were associated with a lower in-hospital mortality, independent of PDA treatment in extremely preterm infants.[22] Our data suggest that UO monitoring can also be considered as a key variable to predict neonatal mortality and major morbidities, similar to other risk factors, including GA, IUGR, PDA or sepsis. In particular, EOS and IUGR were revealed as strong predictors of the primary outcome, an observation explained, at least in part by their putative effect on reduced UO. Indeed, IUGR late in nephrogenesis can lead to a marked reduction in nephron endowment.[23] EOS can induce haemodynamic instability and systemic inflammation, risk factors for neonatal kidney injury.[24]

Whereas UO assessment is a low-cost and non-invasive procedure, it unfortunately remains an understudied and inconstantly monitored parameter in NICUs. Our study

Table 3 Multivariate logistic regression analysis for predicting the primary outcome

	Primary outcome*				
	No (n=353)	Yes (n=175)	Crude OR (95% CI)	Adjusted OR (95% CI)	P value
UO (<2.0 mL/kg/hour)	129 (37)	112 (64)	3.1 (2.1 to 4.7)	3.7 (2.2 to 6.4)	<0.001
Male sex	174 (49)	97 (55)	1.3 (0.9 to 1.9)	1.3 (0.8 to 2.1)	0.225
GA (per week)	28 (1.4)	26.5 (1.6)	0.53 (0.46 to 0.61)	0.56 (0.48 to 0.65)	<0.001
Apgar 5 min (≤5)	50 (14)	46 (26)	2.2 (1.3 to 3.5)	1.8 (1.1 to 3.2)	0.030
IUGR	18 (5)	33 (19)	4.3 (2.3 to 8.4)	6.3 (3.1 to 13)	<0.001
No or incomplete antenatal steroids	79 (22)	46 (26)	1.2 (0.8 to 1.9)	1.2 (0.7 to 2.1)	0.447
EOS	64 (18)	68 (39)	2.9 (1.9 to 4.4)	2.6 (1.6 to 4.3)	<0.001
Centre	194 (55)	117 (67)	1.7 (1.1 to 2.5)	4.0 (2.3 to 7.1)	<0.001

Data are presented as n (%), except for GA, for which the data are presented as the mean (SD).
*Composite outcome including death before discharge, or moderate to severe bronchopulmonary dysplasia (BPD), or severe brain injury.
EOS, early-onset sepsis; GA, gestational age at birth; IUGR, intrauterine growth restriction; UO, urine output.

supports the clinical relevance of (1) monitoring UO for at least 1 week after birth in very preterm infants and (2) considering the threshold of 2.0 mL/kg/hour as a red flag for the early detection of at-risk patients. Identifying a subgroup of high-risk patients can lead to timely interventions to avoid additional renal insults by optimising fluid balance, improving renal perfusion and avoiding nephrotoxicity.

Strengths and limitations

The two main strengths of this study are the large sample size and exhaustive UO data collection during the first postnatal week of life.

Nevertheless, this study has several limitations, mostly inherent to its observational design. In addition, UO was measured by the weighing of diapers, which may not be entirely accurate in case of mixed stools.[25] However, it is a real-life and pragmatic practice in the neonatal population. We observed a statistically significant difference in the incidence of the primary outcome between the two participating centres. However, centre effect was considered in the final model of multivariate logistic regression with no impact on the association between UO and the primary outcome. Based on statistical considerations, we restricted the number of factors included in the model due to the limited number of events, but we cannot rule out that few important other ones may be of interest, including volume expansion, haemodynamically significant PDA and vasoactive drug exposure. However, with consideration that a confounder should not be on the causal chain, we decided to focus on baseline variables only for the final adjustment model. These baseline variables were selected a priori based on known confounding variables described in the literature. Finally, UO only cannot be considered as a surrogate of AKI without considering other individual evidence of kidney injury or dysfunction.

CONCLUSION

UO measurement appears to be highly relevant to predict the outcome of very preterm infants. UO <2.0 mL/kg/hour over 24 hours during the first postnatal week is associated with fourfold higher independent odds of neonatal mortality, BPD or severe brain lesions. This UO threshold, higher than that in the current NKDIGO definition, may be considered to refine the definition of neonatal AKI and to guide daily clinical practice. Our data highlight the need for multicentre prospective studies to further confirm the relevance of UO measurements for the population of very preterm infants.

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