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ORIGINAL ARTICLE

Elevation in plasma creatinine and renal failure in premature neonates without major anomalies: terminology, occurrence and factors associated with increased risk

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Objective: The goal of this study was to describe the changes in plasma creatinine levels that occur in prematurely born neonates, to better understand the use of the terms 'renal dysfunction' and 'renal failure' among premature neonates, as well as to evaluate the demographic and outcome characteristics associated with renal problems in preterm neonates who have no major congenital anomalies.

Study Design: Retrospective review of the Pediatrix neonatal intensive care patient clinical data warehouse.

Result: The study cohort consisted of neonates born with an estimated gestational age of $\leqslant 30$ completed weeks in whom there was no report of any major anomalies ($n = 66\,526$). In this group of 66 526 neonates, there were 64 030 (96.2%) with no report of renal dysfunction or failure, 1239 (1.9%) in whom there was a diagnosis of renal dysfunction and 1257 infants (1.9%) with a diagnosis of renal failure. The clinical circumstances most strongly associated with a diagnosis of renal dysfunction and/or renal failures were low gestational age and birth weight. In addition, multivariate analysis showed that the factors associated with an increased risk of renal problems were vasopressor use during the first 7 days after birth, grade 3 or 4 intraventricular hemorrhage, a patent ductus arteriosus, necrotizing enterocolitis, male gender, the use of indomethacin, a positive blood culture during the first 7 days after birth, the use of high-frequency ventilation in the first 2 days after birth, non-White race and prolonged exposure to antibiotics. Mortality was higher in patients with renal problems than in neonates without renal problems (39.1 vs 10.2%, $P<0.01$) and higher in neonates with renal failure than in neonates with renal dysfunction (57.6 vs 20.1%, $P<0.01$).

Conclusion: Renal dysfunction and/or failure are common diagnoses, especially in extremely premature neonates and there are potentially modifiable factors that increase the risk of renal problems.
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Introduction

The assessment of renal function is an important part of the clinical care of prematurely born neonates.[1–5] Unfortunately, there is no consensus on diagnostic criteria of acute renal failure in newborn infants. Some authors have suggested a persistent increase in plasma creatinine concentration >1.5 mg per 100 ml[6,7] but more stringent criteria were proposed by others.[2,8]

The assessment of renal function is critical for the adjustment of medication dosing, and in planning fluid, nutritional and electrolyte support. The measurement and interpretation of renal function in premature neonates is complicated by *in utero* events, maternal drug exposure history, delivery history, gestational age, birth weight, postnatal illness severity, renal development and changing muscle mass.[1,3,5,9,10] Plasma creatinine and blood urea nitrogen measurements are commonly used to assess renal function and protein tolerance in premature neonates. However, data on how these values change over time and how they are influenced by gestational age and birth weight are limited. In addition, there exist very little data on the gestational age-specific occurrence of renal dysfunction and/or renal failure in premature neonates. The goal of this study was to describe the changes in plasma creatinine levels that occur in prematurely born neonates, to correlate the increases in plasma creatinine levels with the reported diagnoses of renal dysfunction and renal failure, as well as to evaluate the demographic characteristics and mortality associated with renal problems in preterm neonates.

Methods

Clinical data warehouse

The Pediatrix Medical Group is a multisite group of health-care professionals (physicians and nurse practitioners) providing care to neonates admitted for intensive care. This group provides intensive care services in 286 hospitals in 32 states and in Puerto Rico.

The practice group uses a proprietary software system to generate clinical admission, discharge and daily progress notes. Site-specific data are consolidated within the Pediatrix Medical Group data warehouse, de-identified and made compliant with the regulations stipulated in the Health Insurance Portability and Accountability Act of 1996. Data are also configured into tables that can be joined and queried for statistical analyses. Using the de-identified data set, from which several other observations have been reported,[11–13] we performed a retrospective case series review of neonates with a diagnosis of renal problems. Cases were identified by searching the diagnosis table in our database for the terms 'renal failure and/or dysfunction.' These diagnoses are entered by the bedside health-care team (nurse practitioner, resident physician or attending physician). Duplicate entries resulting from transfer between consortium units were excluded. We also searched the diagnosis table for major anomalies (such as congenital heart disease, abdominal wall defects, trisomy 13, 18 or 21, renal anomalies, etc.). Neonates who died in the delivery room or those who were not admitted for neonatal intensive care were not included in the data set. The use of the de-identified data set was approved by the Greenville Hospital System University Medical Center, Greenville SC, Institutional Review Board.

Patient population

This study included patients who were discharged from neonatal intensive care units between 1 January 1997 and 1 March 2009. The gestational age assignment was based on the best obstetrical estimate before delivery and was recorded as completed weeks.

Diagnosis

Our analytical approach to these data was descriptive in nature. Specific database tables within the data warehouse used for this analysis were 'patients,' 'medication results,' 'admissions' and 'diagnoses.' All patients in the Pediatrix Clinical Data Warehouse who had a report of a diagnosis of renal dysfunction or failure were reviewed.

Statistical methods

Neonates with major anomalies were excluded from analysis. We developed three distinctive groups of neonates: (1) those with no diagnosis of renal problems, (2) those with a diagnosis of renal dysfunction and (3) those with a diagnosis of renal failure. If a patient had a report of both renal dysfunction and renal failure, they were assigned to the renal failure group. The use of these diagnoses is not strictly defined, and for this reason, we included data on the occurrence of a creatinine >1.3 mg per 100 ml (the 90th percentile for the study cohort) and 2 mg per 100 ml (the 99th percentile for the study cohort). Differences in the demographic characteristics of patients with renal failure or renal dysfunction were compared with the neonatal intensive care unit population without either renal diagnosis. We compared the three population samples using bivariate analyses. Similar comparisons were made comparing neonates in whom all reported creatinine levels were <1.3 mg per 100 ml and those with any report of a creatinine levels >1.3 mg per 100 ml (data not shown). The results of this analysis are similar to those reported on the basis of diagnosis.

Continuous variables (such as estimated gestational age and birth weight) were evaluated with ANOVA (analysis of variance) and *post hoc* Tukey–Kramer methods. Categorical variables (such as race and gender) were evaluated with two-tailed χ^2 tests. Nonparametric data were assessed with Kruskal–Wallis ANOVA. All statistical analyses were performed using JMP 7 (SAS Institute, Cary, NC, USA). The z-score for birth weight was calculated as ((patient's weight−the mean weight for patients with the same gestational age)/s.d. for patients with the same gestational age). This number is a measure of the degree of intrauterine growth restriction. Analysis of changes over time and within estimated gestational age groups was performed using ANOVA for repeated measures.

After bivariate analyses, multivariate logistic regression was used to calculate the adjusted odds ratio (OR) for renal problems by comparing the neonates with a diagnosis of a renal problem with those who had no diagnosis of a renal problem. We incorporated variables into the model using a forward stepwise approach that included variables associated with renal problems at a probability of <0.1. Birth weight and gestational age were entered into the model as continuous variables. Cases with missing values for any of the independent variables were excluded from the analysis. The same approach was used to compare the risk factors associated with renal failure compared with renal dysfunction. This analysis was performed to evaluate the factors that might be associated with more severe disease (failure>dysfunction).

Results

Description of study cohort

During the study period (1 January 1997 to 1 March 2009), there were 560 227 discharges in the data set; 8325 infants (1.5%) had a report of an anatomical renal anomaly based on postnatal evaluation of the patient. Among the 8325 neonates with a renal anomaly, the most common abnormalities reported were hydronephrosis (6127, 73.6%), multicystic kidney (448, 5.4%), renal agenesis (307, 3.7%), renal dysplasia (304, 3.7%), polycystic kidney (252, 3.0%) and obstructive uropathy (59, 0.7%). A total of 828 (9.9%) patients had a combination of anomalies (for example, ectopic kidney and hydronephrosis).

There were 5187 infants without renal anomalies who had a diagnosis of renal dysfunction ($n=2597$) or renal failure ($n=2590$). Of these 5187, 1510 (29%) had other major anatomical or genetic abnormalities (such as heart defects, trisomy 21, diaphragmatic hernia and gastroschisis). Thus, in our data set of 560 227 neonatal intensive care unit discharges, there were 3677

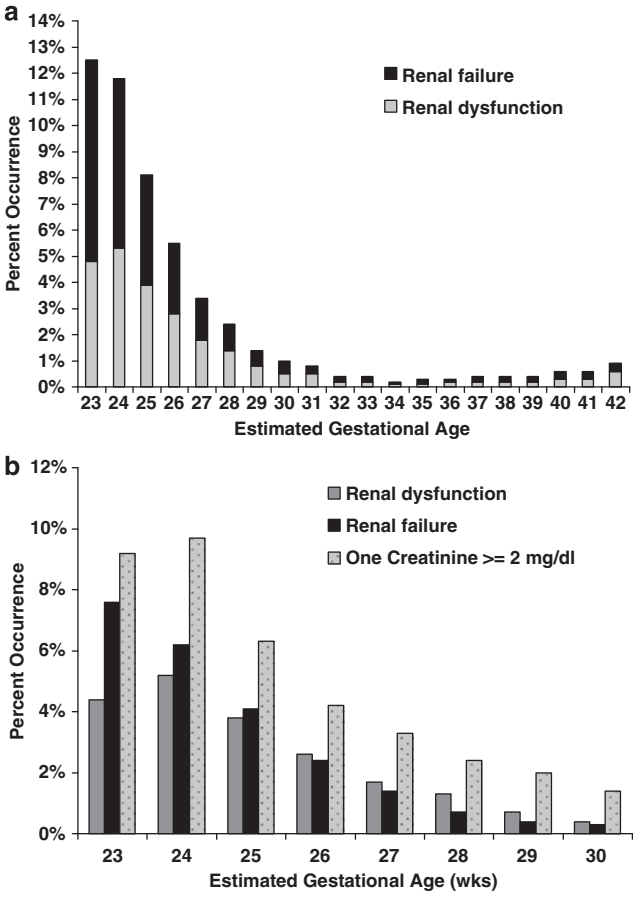

Figure 1 (**a**) The diagnosis of renal failure or dysfunction by estimated gestational age in all neonates reported as discharged from the Pediatrix Medical Group Clinical Data Warehouse. (**b**) The incidence of these two diagnoses and the occurrence of a plasma creatinine value $\geqslant 2$ mg per 100 ml by estimated gestational age decreased with increasing gestational age (panel **b**) in neonates without any major anomalies. The estimated gestational age is 23 to 30 weeks.

(0.6%) neonates with a diagnosis of renal dysfunction or renal failure who did not have a report of other major anomalies in the diagnostic table. The incidence of renal failure and/or renal dysfunction decreased with increasing gestational age (Figure 1a); therefore, we elected to focus our study on premature neonates $\leqslant 30$ completed weeks of gestation.

Our study cohort consisted of neonates born with an estimated gestational age of $\leqslant 30$ completed weeks in whom there was no report of any major anomalies ($n = 66\,526$). In this group of 66 526 neonates, there were 64 030 neonates (96.2%) in whom there was no diagnosis of renal problems, 1239 (1.9%) in whom there was a diagnosis of renal dysfunction and 1257 (1.9%) in whom there was a diagnosis of renal failure. In 69 patients, there was a report of both renal dysfunction and renal failure; all of these patients were assigned to the renal failure group. The incidence of these two diagnoses and the occurrence of a plasma creatinine value of $\geqslant 2$ mg per 100 ml by estimated gestational age decreased with increasing gestational age (Figure 1b).

Demographic and outcome differences between the diagnostic groups

Bivariate analysis. We compared neonates with no report of renal problems ($n = 64\,030$) with those with a report of a renal problem (dysfunction or failure, $n = 2496$). We also compared neonates with a diagnosis of renal dysfunction with those with renal failure using both bivariate and multivariate techniques. The goal of this second analysis was to understand the factors associated with the clinical diagnosis of more severe renal disease.

The results of the bivariate analysis are summarized in Table 1. Neonates with renal dysfunction presented earlier compared with neonates with a diagnosis of renal failure (7 vs 11 days after birth) and less often had creatinines >2 mg per 100 ml (25.3 vs 39.5%) The factors most strongly associated with renal dysfunction and/or renal failure were gestational age (Figure 1b) and birth weight. Mortality was higher in patients with renal problems than in neonates without renal problems (39.1 vs 10.2%, $P<0.01$) and higher in neonates with renal failure than in neonates with renal dysfunction (57.6 vs 20.1%, $P<0.01$). Acquired bowel disease and severe intraventricular hemorrhages were more common in neonates with renal problems compared with those with no renal problems (Table 1).

Multivariate analysis

Using multivariate analysis, we found that the factors associated with an increased risk of renal dysfunction/failure were the use of vasopressors during the first 7 days after birth (adjusted OR = 1.7 (1.5 to 1.9), $P<0.001$), a grade 3 or 4 intraventricular hemorrhage (adjusted OR = 1.5 (1.3 to 1.7), $P<0.0001$), a patent ductus arteriosus (adjusted OR = 1.5 (1.3 to 1.7), $P<0.001$), necrotizing enterocolitis (adjusted OR = 1.5 (1.4 to 1.7), $P<0.001$), male gender (adjusted OR = 1.4 (1.2 to 1.5), $P<0.001$), the use of indomethacin (adjusted OR = 1.2 (1.1 to 1.3), $P = 0.002$), a positive blood culture during the first 7 days after birth (adjusted OR = 1.2 (1 to 1.4), $P = 0.02$), the use of high-frequency ventilation in the first 2 days after birth (adjusted OR = 1.1 (1 to 1.2), $P = 0.02$), non-White race (adjusted OR = 1.1 (1 to 1.2), $P = 0.01$) and each additional day of treatment with antibiotics (adjusted OR = 1.04 (1.03 to 1.05), $P<0.001$). Increasing gestational age and birth weight were both associated with a decrease in the risk of renal problems ($P<0.001$, adjusted OR for each week of increase in gestation = 0.8 (0.78 to 0.85)).

Using multivariate analysis, we found that the factors associated with an increased risk of renal failure compared with renal dysfunction were necrotizing enterocolitis (adjusted OR = 1.7 (1.4 to 2.1), $P<0.001$) and the use of vasopressors during the first 7 days after birth (adjusted OR = 1.4 (1.1 to 1.6), $P = <0.001$). Increasing birth weight was associated with a decreased risk of renal failure compared with renal dysfunction ($P<0.001$).

Table 1 Characteristics of neonates with renal problems

	No problem	*Renal problem*	*No problem vs problem*	*Renal dysfunction*	*Renal failure*	*Dysfunction vs failure*
Number in each group	64 030	2496		1239	1257	
Demographics						
Age diagnosis reported, median (10–90th percentile)				7 (2–27)	11 (1–35)	<0.001
Duration of problem, median (10–90th percentile)				8 (2–26)	6 (1–21)	<0.001
Any creatinine ⩾1.3 (90th percentile)	9645 (15.1)	1731 (69.4)	<0.001	847 (68.4)	884 (70.3)	0.3
Any creatinine ⩾2 (99th percentile)	1613 (2.5)	810 (32.5)	<0.001	313 (25.3)	497 (39.5)	<0.001
Maternal age, median (10–90th percentile)	27 (19–36)	27 (19–36)	0.6	27 (19–37)	26 (19–36)	0.5
Born at an outside hospital (Outborn), *N* (%)	10 834 (16.9)	509 (20.4)	<0.001	264 (21.3)	245 (19.5)	0.5
Male gender, *N* (%)	33 792 (52.8)	1467 (58.8)	<0.001	712 (57.5)	755 (60.1)	0.2
Gestational age, median (10–90th percentile)	28 (24–30)	25 (23–28)	<0.001	25 (24–29)	25 (23–28)	<0.001
Birth weight, median (10–90th percentile)	1.06 (0.6–1.5)	0.74 (0.5–1.2)	<0.001	0.77 (0.6–1.2)	0.7 (0.5–1.1)	0.01
z-Score, median (10–90th percentile)	0 (−1.1 – 1)	−0.1 (−1.3–0.8)	<0.001	−0.1 (−1.2–0.8)	−0.2 (−1.5–0.7)	<0.001
Percentage change in weight						
Birth to 7 days after birth, median (10–90th percentile)	−5 (−13–6)	−1 (−15–17)	<0.001	−2 (−15–14)	−0.7 (−14–21)	0.02
Birth to 14 days after birth, median (10–90th)	6 (−4–19)	9 (−7–34)	<0.001	8 (−7–28)	11 (−7–41)	<0.001
Race/Ethnicity, N (%)						
American/Alaska native	514 (0.8)	16 (0.6)	0.4	7 (0.6)	9 (0.7)	0.8
Asian	1491 (2.3)	61 (2.4)	0.6	23 (1.9)	38 (3)	0.07
Black	15 195 (23.7)	643 (25.8)	0.02	326 (26.3)	317 (25.2)	0.5
Hispanic	12 845 (20.1)	636 (25.5)	<0.001	335 (27)	301 (23.9)	0.08
Other	3523 (5.5)	124 (5)	0.3	55 (4.4)	69 (5.5)	0.2
White	30 462 (47.6)	1016 (40.7)	<0.001	493 (39.8)	523 (41.6)	0.4
Cesarean section, *N* (%)	42 485 (66.4)	1638 (65.6)	0.3	834 (67.3)	804 (64)	0.2
Apgar 1 min, median (10–90th percentile)	6 (2–8)	4 (1–8)	<0.001	5 (1–8)	4 (1–8)	0.01
Apgar 5 min, median (10–90th percentile)	8 (5–9)	7 (3–9)	<0.001	7 (4–9)	7 (3–9)	0.1
Multiples, *N* (%)	16 371 (25.6)	588 (23.6)	0.03	283 (22.8)	305 (24.3)	0.4
Treatments						
Antibiotic exposure in first 7 days, *N* (%)	54 587 (85.3)	2285 (91.5)	<0.001	1129 (91.1)	1156 (92)	0.8
Duration of antibiotics (start ⩽7days), *N*	51 031	2228		1111	1117	
⩽2	16 214 (25.3)	374 (15)	<0.001	181 (14.6)	193 (15.4)	0.5
3–6	18 261 (28.5)	684 (27.4)	0.2	340 (27.4)	344 (27.4)	0.9
7–10	14 136 (22.1)	916 (36.7)	<0.001	459 (37)	457 (36.4)	0.8
>10	2395 (3.7)	254 (10.2)	<0.001	131 (10.6)	123 (9.8)	0.2
Median (10–90th percentile)	3 (2–10)	7 (2–11)	<0.001	7 (2–12)	7 (2–11)	0.3
Respiratory support during 48 h after birth						
On a ventilator	42 686 (66.7)	2150 (86.1)	<0.001	1025 (82.7)	1125 (89.4)	<0.001
On high-frequency ventilation	9498 (14.8)	787 (31.5)	<0.001	378 (30.5)	409 (32.5)	0.3
Oxygen support (Fio_2), median (10–90th percentile)	0.35 (0.21–1)	0.4 (0.21–1)	<0.001	0.4 (0.21–1)	0.41 (0.21–1)	<0.001
Surfactant, *N* (%)	41 161 (64.3)	2008 (80.4)	<0.001	980 (79.1)	1028 (81.8)	0.1
Patent ductus arteriosus, *N* (%)	29 589 (46.2)	1922 (77)	<0.001	989 (79.8)	933 (74.2)	0.01
Ibuprofen, *N* (%)	1148 (1.8)	100 (4)	<0.001	54 (4.4)	46 (3.7)	0.1
Indomethacin, *N* (%)	18 972 (29.6)	1295 (51.9)	<0.001	688 (55.5)	607 (48.3)	<0.001
Any report of vasopressors, *N* (%)	14 790 (23.1)	1361 (54.5)	<0.001	617 (49.8)	744 (59.2)	<0.001

Table 1 Continued

	No problem	*Renal problem*	*No problem vs problem*	*Renal dysfunction*	*Renal failure*	*Dysfunction vs failure*
Morbidities						
Blood culture positive ⩽7 days	2377 (3.7)	229 (9.2)	<0.001	111 (9)	118 (9.4)	0.7
Acquired bowel disease						
Isolated perforation only	897 (1.4)	146 (5.8)	<0.001	45 (3.6)	101 (8)	<0.001
Medically treated necrotizing enterocolitis	2780 (4.3)	154 (6.2)	<0.001	75 (6.1)	79 (6.3)	0.5
Necrotizing enterocolitis requiring surgery	1354 (2.1)	246 (9.9)	<0.001	81 (6.5)	165 (13.1)	<0.001
Intraventricular hemorrhage grade reported	51 876 (81)	2269 (90.9)	<0.001	1149 (92.7)	1120 (89.1)	0.1
Intraventricular hemorrhage (Grades 3 Or 4)	4883 (7.6)	603 (24.2)	<0.001	268 (21.6)	335 (26.7)	0.004
Retinopathy grade reported	38 676 (60.4)	1293 (51.8)	<0.001	804 (64.9)	489 (38.9)	<0.001
Retinopathy that was treated	2307 (3.6)	271 (10.8)	<0.001	145 (11.7)	126 (10)	0.5
Discharge status						
Acute transfer	5848 (9.1)	228 (9.1)	0.9	127 (10.3)	101 (8)	0.06
Convalescent transfer	3324 (5.2)	89 (3.6)	0.002	55 (4.4)	34 (2.7)	0.03
Died	6530 (10.2)	975 (39.1)	<0.001	251 (20.3)	724 (57.6)	<0.001
Discharged home	45 495 (71.1)	1102 (44.2)	<0.001	735 (59.3)	367 (29.2)	<0.001
Missing data	356 (0.6)	9 (0.4)	0.2	5 (0.4)	4 (0.3)	0.8
Transfer of service	2477 (3.9)	93 (3.7)	0.8	66 (5.3)	27 (2.1)	<0.001
Dialysis reported	2 (0.003)	5 (0.2)	<0.01	0	5 (0.4)	<0.01
Median creatinine within 7 days of discharge						
Patients who died						
Number of reported values	2588	553		152	401	
Median (10–90th percentile)	1.1 (0.6–1.7)	1.8 (0.7–3)	<0.001	1.4 (0.5–2.4)	1.9 (0.8–3.2)	<0.001
Patients who were discharged home						
Number of reported values, *N*	9498	369		260	109	
Median (10–90th percentile)	0.4 (0.2–0.7)	0.4 (0.2–0.7)	0.6	0.4 (0.2–0.6)	0.4 (0.2–0.8)	0.6

Unless otherwise labeled the data are presented as *n* (%).

Influence of gestational age and time on creatinine

Both time and gestational age independently influence the measures of plasma creatinine values (Figure 2, median values). The creatinine values increased over the first 2 to 5 days after birth and then decreased. The increase in creatinine was most dramatic in the most premature neonates (23 and 24 week estimated gestational age). There were also time- and gestational age-related changes in serum electrolytes, blood urea nitrogen, calcium, phosphorus and glucose (Supplementary Table 1a; Supplementary Table 2; data not shown). Patients with a diagnosis of renal problems (failure or dysfunction) had higher plasma creatinine values than did those with no report of renal problems (Figure 3). The differences in creatinine were apparent by day 3 after birth and persisted for the first month after birth.

Discussion

Defining renal dysfunction and renal failure in prematurely born neonates is complex.[1–8] This complexity is highlighted by how the terms 'renal dysfunction' and 'renal failure' are used in our data set. Only 15% of infants with any creatinine ⩾1.3 mg per 100 ml and 33% of infants with any creatinine ⩾2.0 mg per 100 ml were identified as having 'renal problems.' This suggests that the use of the terms 'renal dysfunction and renal failure' is imprecise and based on the clinical impression of caregivers rather than a carefully defined clinical criteria. Thus, the actual incidence of renal disease in very preterm neonates may be higher if it was defined by a specific level of serum creatinine levels (Figure 1b). Nevertheless, the first step in defining abnormal is better defining the variability in a 'normal' population, and that is why we choose our study population to be neonates without major anomalies and to create a table of renal function values for neonates without a report of abnormal renal function.

Similar to the results reported by Miall *et al*.,[10] we found that plasma creatinine levels increased significantly over the first 48 h after birth and then began to decrease.[10] Figure 2 demonstrates the time- and gestational age-specific changes in the median creatinine values (similar changes occur in the 90th percentile;

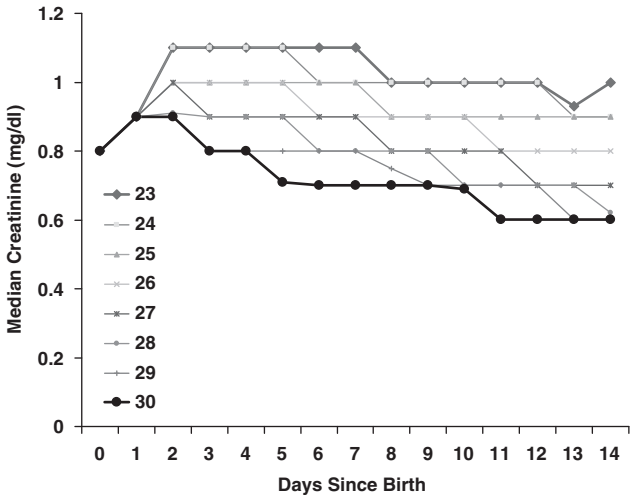

Figure 2 Changes over time in the median serum creatinine values within gestational age-specific groups. The influence of both time and gestational age on the median values must be noted.

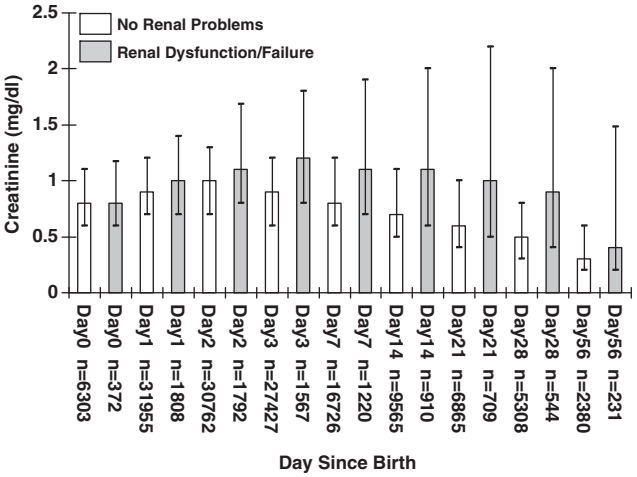

Figure 3 Changes over time in the creatinine values for premature neonates with no report of renal problems compared with those with renal problems. The *x* axis represents changes over time with respect to age (days since birth). The bar is the confidence interval 10th to 90th percentile.

data not shown) Figure 2 shows that a definition of normal is a moving target and is influenced by both time and gestational age. The degree of fluid and protein load influences both electrolyte balance and blood urea nitrogen.[14] The values we report in the Supplementary Table 1a for neonates with no report of renal problems offer the clinician an estimate of the 'normal' gestational age-specific and time-related changes in renal function and may allow the clinician to better identify those premature neonates who have evolving renal failure. Understanding normal should allow the clinician to more optimally provide nutritional support, avoid protein overload and adjust medication dosing.

Beyond gestational age and birth weight, factors associated with renal dysfunction and/or renal failure are also surrogates for severity of illness (namely the use of vasopressors, the use of high-frequency ventilation, more frequent severe intraventricular hemorrhage, more frequent report of a patent ductus arteriosus). These results restate the obvious—immature, small and critically ill neonates are at increased risk of renal dysfunction/renal failure.

We identified some potentially modifiable factors. Prolonged exposure to antibiotics and the use of indomethacin were independent factors associated with an increased risk of renal dysfunction/failure. The risk factors we identified that are associated with renal dysfunction are similar to those previously reported,[1,3,5] and some of these risk factors are potentially modifiable. Cataldi *et al*.[5] showed that low birth weight, maternal exposure to more drugs during pregnancy and delivery (mainly antibiotics and nonsteroidal anti-inflammatory drugs), low Apgar scores and patent ductus arteriosus were the risk factors for renal failure in low-birth-weight infants. In addition, neonates with renal failure received more drugs (antibiotics, nonsteroidal anti-inflammatory drugs and diuretics) and for a longer time. Cuzzolin *et al*.[3] identified five factors that were independently associated with an increased risk of renal failure: maternal consumption of nonsteroidal anti-inflammatory drugs during pregnancy, intubation at birth, respiratory distress syndrome, a low Apgar score and ibuprofen treatment of the neonate. Iacobelli *et al*.[1] showed that the main independent risk factor associated with a high serum creatinine at day 1 after birth was hypertensive disease of pregnancy. During the first week after birth, lower gestational age and ibuprofen-treated patent ductus arteriosus were the main factors independently associated with higher serum creatinine values.[1] Our data in combination with previous reports highlight the importance of carefully considering the medications and the duration of therapy we choose in providing care to the premature neonate.

We realize the limitations of evaluating risk factors associated with abnormal renal function based on a retrospective review of an administrative data set. Proxies for selection bias may not adequately reflect the true severity of illness or therapeutic approach. There may be variations in the process of care or terminology use other than those we chose to evaluate that influence the differences in renal dysfunction/failure that we report. Retrospective studies are also limited by incomplete data, and the evaluation of interactions between drugs is better performed prospectively. Time-related changes are also influenced by censoring of the data and selection bias. Only prospectively captured data can be used to precisely define 'normal' laboratory values (or the range of values that are observed over time within specific gestational age groups).

Conclusion

Although the characterization of renal dysfunction and renal failure in preterm infants is poorly defined, they are commonly

used diagnoses in the smallest and most immature of infants free of other organ anomalies. Renal dysfunction and renal failure diagnoses are performed most frequently in the first 2 weeks of postnatal life and are associated with significant subsequent mortality. The possible risk factors associated with these diagnoses include genetic predisposition, concomitant disease processes, medication side effects and other adverse clinical management strategies. Careful prospective re-examination of clinical care practices and medication choices and dosing strategies may help decrease the prevalence renal failure in premature neonates.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Journal of Perinatology website (http://www.nature.com/jp)