EDITORIAL COMMENTARY

A step forward towards accurately assessing glomerular filtration rate in newborns

Guido Filler

Abstract In this edition of *Pediatric Nephrology*, Milena Treiber and colleagues have published a study on cystatin C (CysC) concentrations in relation to renal volumetry in 50 small-for-gestational age (SGA) and 50 appropriate-for-gestational age (AGA) neonates, deriving a new formula for estimating neonatal glomerular filtration rate (GFR). The study builds on previous work which established that renal volumetry together with CysC blood levels is a superior method for establishing GFR in term and pre-term newborns [The Journal of Pediatrics (2014) 164:1026–1031.e2]. Treiber et al. use the expected difference between SGA and AGA renal volumes to document the superiority of their new formula, which is based on total renal volume, CysC and body surface area, but does not incorporate gold-standard inulin clearance. Treiber et al.'s study adds new knowledge to the field that will hopefully improve the safety of renally excreted critical dose drugs in the newborn period. This editorial discusses the strengths and limitations of the current study.

G. Filler
Department of Pediatrics, Schulich School of Medicine & Dentistry, Western University, London, ON, Canada N6A 5 W9

G. Filler
Department of Pathology and Laboratory Medicine, Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada N5A 5A5

G. Filler
Department of Medicine, Schulich School of Medicine & Dentistry, Western University, London, ON, Canada N6A 5 W9

G. Filler (✉)
Department of Pediatrics, Children's Hospital, London Health Sciences Centre, Western University, 800 Commissioners Road East, London, ON, Canada N6A 5 W9
e-mail: guido.filler@lhsc.on.ca

Introduction

Newborns are a particularly vulnerable population, especially when born prematurely. Accurately measuring renal function in neonates is important for properly dosing most drugs, since nearly all are renally excreted. Glomerular filtration rate (GFR) is typically representative of renal function [1]. Drug removal, however, occurs primarily through the active secretion of acids and bases (mainly in the proximal tubule), and to a lesser extent through glomerular filtration. Cationic drugs are secreted into the urine through two main transporter molecules, human organic cation transporters (OCTs) and multidrug and toxin extrusion proteins (MATEs) [2]. Less is known about organic anion transporters (OATs). OATs are remarkable for their broad substrate specificity and their ability to exchange extracellular anions against intracellular organic anions [3], although many have not yet been identified. OATs are also important for determining renal prognosis. This is especially true in children with congenital renal anomalies [4] who may have a reduced nephron endowment due to apoptosis triggered by high pressure in the urinary collecting system [5].

Many developmental changes occur over the course of childhood, changes which are particularly marked in the newborn period. Kearns et al. [6] summarized these well as: (1) changes in the integumentary development, (2) changes in the volume of distribution (newborns have the highest total body water volume), (3) changes in gastrointestinal function, hydrochloric acid production and bile acid excretion, (4) changes in the metabolic capacity of key enzymes and, of course, (5) the acquisition of renal function. The effect of these changes

can be so profound that an infant may metabolize a drug tenfold faster than an adult and may form completely different metabolites.

In utero and postnatal renal blood flow also markedly differs from that in older children and adults. In fetuses and newborns, only 3 % of cardiac output accounts for renal blood flow and GFR is low, whereas an adult distributes 25 % of his or her cardiac output to the kidneys [7]. Although all nephrons are terminally differentiated at birth, they are recruited in a similar sequence as they were formed after birth through branching of the ureteric bud [8–10]. Both term and preterm infants have a low GFR and effective renal plasma flow (ERPF) at birth [11]. The low GFR of a newborn is attributable to a delicate balance between vasoconstrictive and vasodilatory renal forces, which results in ongoing high vascular resistance and limits the postnatal adaptation of renal function to endogenous and exogenous stress [12]. Premature infants may have an even lower GFR. The considerable decrease in systemic vascular resistance after birth may redistribute blood flow and immediately contribute to the low blood flow to the kidneys in neonates. Low ERPF and GFR and significant tubular reabsorption in the distal nephron all contribute to the altered pharmacokinetics of renally excreted drugs in the newborn [13], the latter blunting the newborn's ability to excrete an acute saline load [14].

It is important to review the physiology behind the renal excretion of drugs. First, the mechanism of excretion favors using ERPF rather than GFR as a marker of nephron endowment, and, by proxy, the patient's ability to excrete drugs. Nonetheless, we use GFR because ERPF is difficult to measure [15]. Hyperfiltration may also result in the overestimation of renal function [16].

There are additional problems in neonates. Serum creatinine (Cr), the most widely used surrogate of GFR, is largely affected by maternal GFR. Cr crosses the placenta, and neonatal Cr has been shown to still strongly correlate with maternal creatinine 72 h after birth [17, 18]. Cystatin C (CysC), a low-molecular-weight cysteine protease perpetually produced by all nucleated cells [19], has emerged as a promising alternative to serum Cr: it has been shown to have better diagnostic sensitivity [20] and to be independent of muscle mass [21] and body composition [22]. Currently, the most reliable eGFR formulae in children use CysC alone or in combination with Cr and/or urea [23]. Je-Hyan Lee et al. [24] recently made a significant contribution to advancing our knowledge of CysC concentrations in the first month of life [25]. A suitable formula for calculating eGFR based on neonatal CysC has, however, been elusive. With the above in mind, it is encouraging to see Milena Treiber et al.'s study of 50 full-term small-for-gestational age and 50 appropriate-for-gestational age newborns in whom kidney volume was measured to assess nephron endowment, and CysC and Cr measurements were used to develop a new formula for calculating eGFR [26].

Using renal volume as a surrogate for renal function

Many researchers have asked the question of whether renal cortex volume, easily measured using by ultrasonography, can be used to assess nephron endowment. A recent study of 1,748 healthy children aged >6 months found a close correlation between renal length and thickness and serum Cr level [27]. Still, the number of published studies on the use of kidney volume as a marker of kidney function in neonates remains limited [28, 29], and it may in fact be more accurate to use renal parenchymal thickness instead [30]. Carolyn Abitbol and co-workers recently measured total kidney volume in relation to serum Cr and CysC levels and a validated formula (through either inulin, iohexol or iothalamate studies) in 60 preterm and 40 term infants to calculate eGFR and GA [31]. Total kidney volume was estimated using the ellipsoid formula: volume = length × width × depth × 0.523 [32]. Since patients with congenital renal anomalies, such as reflux and obstructive uropathy, were excluded from the study, the ellipsoid provided a reasonable estimate of nephron endowment. Hyper-filtering would be negligible in this population since renally excreted toxins are eliminated through the placenta in utero. This research team found renal length to correlate with GA, and term babies had a significantly better eGFR than preterm babies. The results of Abitbol et al.'s study suggest that CysC is superior to Cr as a marker of GFR in neonates [31]. In contrast, a Swedish study examining 61 newborn infants of a similar post-conceptual age found neither CysC nor Cr to correlate with gentamycin clearance [33]. Milena Treiber's research group augmented the typical two-dimensional (2D) approach with three-dimensional (3D) volumetry using a Kretz Voluson 530/730 (Kretztechnik AG/GE Healthcare, Zipf, Austria/Little Chalfont, UK) platform and found excellent agreement between both methods. These researchers compared previous CysC eGFR formulae with a new formula derived from both the total volume of both kidneys and the newborn's body surface area (BSA). Their formula reads eGFR = [(Vol-T/BSA)/cysC]/1.73, where Vol-T is the result of the 3D volumetry, BSA is the body surface area, and cysC is the cystatin C concentration.

Is CysC the best marker of neonatal renal function?

There is ongoing debate as to whether small amounts of CysC cross the placenta. Several authors suggest that CysC does not cross the placenta [34–36], but recent evidence supporting the diaplacental transport of CysC has emerged [4, 18], although the transport found was much less pronounced than that of serum Cr. Another potential low-molecular-weight protein marker is beta-trace protein (BTP) [37]. BTP may be a superior marker for neonates as it does not seem to cross the placenta [38]. However, BTP measurement as a surrogate for eGFR is not widely available, and the modification of

CysC by maternal function is modest. CysC is becoming more widely available all over the world.

Limitations of the proposed approach

As outlined above, neonatal renal function evolves every day with the ongoing recruitment of nephrons. Milena Treiber's approach must be validated against inulin clearance and currently only applies to the first few days of life. 3D volumetry is not widely available, but the proposed 2D approach with renal length and anterior–posterior and transverse measurements is widely available [32]. The feasibility of the proposed method beyond the first days of life must still be determined. Serial volumetry of the kidneys may also pose a challenge. Another challenge can arise when a newborn has a congenital anomaly of the kidneys or urinary tract (CAKUT). Inclusion of the entire kidney in patients with CAKUT and congenital hydronephrosis would lead to a significant overestimation of the renal volume, both with a 2D as well as with a 3D approach. Only the renal cortex would contribute to GFR. One could subtract two eliptoids (the total kidney volume minus the volume of the renal pelvis), but this approach has not been validated.

Percentile curves for CysC would be preferable, or better still, CysC z-scores based on postconceptional age. In clinical pediatrics, we use growth curves and calculate age-independent z-scores or percentiles to take these changes into account [39]. Similar to the U.S. Centers for Disease Control and Prevention or tje World Health Organization, we could use Box-Cox transformations to calculate age-independent z-scores for CysC eGFR and base drug dosing on CysC eGFR z-scores, as suggested in our recent editorial on the challenges of identifying acute kidney injury in young infants [10].

Finally, tubular handling is more important for clearing gentamycin, debekacin, tobramycin, netilmycin and amikacin in humans [40]. It stands to reason that tubular secretion should be a function of nephron endowment, and it may be useful to study the relationship between either vancomycin and aminoglycoside clearance and total kidney volume or parenchymal thickness. We lack a good understanding of how tubular function evolves after birth. For example, the continuous recruitment of additional nephrons with each day of life presumably augments tubular capacity.

Conclusion

Despite its limitations, Milena Treiber's important study [26] adds new knowledge and builds on Carolyn Abitbol's landmark study [31]. This study also revives the debate on whether GFR should be normalized to either height or BSA or to extracellular volume. Future prospective studies are needed to determine whether the new formula will better predict the clearance of both critical dose drugs and renally excreted drugs such as aminoglycosides or vancomycin. Dr. Treiber and her group should be congratulated on this important study, which will hopefully facilitate safer drug dosing in neonates.

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