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Cystatin C in newborns: a promising renal biomarker in search for standardization and validation

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Abstract

Objective—Neonatologists still commonly use creatinine as a proxy for renal clearance, despite issues related to neonatal (patho)physiology and methodology (assay variability). Cystatin C (CysC) has been suggested to be a more reliable biomarker, but assay related differences have also been reported in children and adults. We are unaware of any review on the assay related impact on CysC reference values in newborns.

Methods—A structured literature search was performed on published CysC values in (pre)term neonates.

Results—The extensive range (>5-fold) in serum CysC observations in neonates in part relates to the fact that CysC concentrations are higher at birth with subsequent decrease and that CysC concentrations are higher in preterm compared to term neonates. The CysC assay matters while disease characteristics also affect CysC values, but not always in the predicted direction.

Conclusions—Similar to creatinine, the extensive CysC range in neonates is only in part explained by renal (patho)physiology. Its applicability in neonatal medicine can be further improved by use of assay specific reference values, adapted to neonatal renal physiology (e.g. weight, age) and should be compared to a gold standard such as inulin clearance.

Keywords

Cystatin C; developmental nephrology; neonatal renal clearance; glomerular filtration rate

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Declaration of interest

None of the authors has to declare any conflict of interest related to the topic discussed in this paper.

Introduction

Glomerular filtration rate (GFR) in early life is very low and can only be maintained due to a delicate balance between both vasodilatory effects at the afferent arterioli (e.g. prostaglandins) as well as vasoconstrictive effects at the efferent glomerular arterioli (e.g. angiotensin II). Despite this low clearance capacity, the GFR variability within this population is extensive (at least 5-fold) and can in part be predicted by covariates like e.g. gestational age, birth weight, postnatal age, drugs, growth restriction or periparturient asphyxia, but also assay (Jaffe or enzymatic) related differences [1–7]. Despite this variability, GFR is a relevant parameter, since renal dysfunction is associated with increased mortality and morbidity (e.g. retinopathy of prematurity, neurodevelopmental impairment) in neonates, and is crucial to tailor pharmacotherapy or fluid exposure to the individual newborn [1–7]. Furthermore, an association of extreme preterm birth and renal dysfunction in later life has been described [1,7].

At present, serum creatinine is commonly measured as a proxy for renal (dys)function. However, before creatinine values can be used to estimate renal elimination capacity, there are some specific aspects related to (patho)physiology and bio-analysis that need to be considered. Creatinine at birth does not yet reflect neonatal but maternal creatinine [1,8]. Moreover, because of passive tubular back leak instead of active secretion, creatinine clearance does not yet fully reflect GFR. Finally, creatinine values also depend on the technique (Jaffe or enzymatic assays) used for its measurement [1,6,7]. The move towards harmonization through isotope dilution mass spectrometry (IDMS) traceability helped to reduce the extent of the between assay differences, but has not fully abolished the problem [1,9,10].

Low molecular weight proteins (e.g. Cystatin C, beta-trace protein, beta-2 microglobulin, alpha-1 microglobulin) have been suggested to be more reliable biomarkers [11–13] to estimate renal elimination capacity and – related to this – risk assessment based on kidney function in adult patients [14]. It is hereby has been assumed that Cystatin C (CysC) is not affected by gender, body muscle mass, age, inflammation or nutritional conditions [14,15] although these assumptions and claims are not yet sufficiently supported by data in early infancy [7].

CysC is a low-molecular mass (13 kDa) basic protein and belongs to the cystatin superfamily of reversible inhibitors of cysteine proteases. It is a proteinase inhibitor involved in normal intracellular protein turnover. Consequently, CysC is produced at a constant rate by any nucleated cell, and is eliminated exclusively through glomerular filtration. After ultrafiltration through the glomerular basal membrane, CysC is metabolized in the proximal renal tubular cell following endocytosis at the apical brush border of the renal tubular cell [7,9,13]. Consequently, serum CysC reflects GFR, while urinary CysC reflects renal tubular dysfunction.

Unfortunately, before CysC can be considered to be a good biomarker for renal elimination capacity in newborns, similar aspects as related to creatinine should be considered. An important advantage is that – as compared to creatinine – CysC does not cross the placental

barrier [16]. Consequently and in contrast to creatinine, there is no correlation between maternal and umbilical cord blood CysC observations [8,16]. However, the daily caloric needs and metabolic activity are significantly different in early infancy while renal tubular cell transport activity also displays extensive maturation. This may affect CysC production or CysC elimination respectively. Finally and comparable to creatinine, there are different methods reported to quantify CysC with suboptimal diagnostic performance because of imprecision, between assay differences, over-recovery or between laboratory differences [17,18]. Until now, this assay related issue remained unexplored in this specific population.

At present, there are at least three different registered methods for serum CysC analysis. Besides particle-enhanced nephelometric immune-assays (PENIA), the use of particle-enhanced turbidimetric immune-assays (PETIA) and enzyme-linked immune-assays (ELISA) methods have been reported and paired analysis confirmed between assay differences [17]. For both PENIA and PETIA, specific GFR equations have been developed in adults and children [9,13,18]. This resulted in the suggestion of Li et al. to apply assay-specific cystatin C based GFR equations or estimators, until an international calibration for CysC – similar to the above mentioned IDMS approach for creatinine – has been developed [18]. Since we are unaware of any review on assay-specific relevance of CysC reference values in newborns, we performed an extensive literature search to collect information on CysC reference values and its covariates in neonates.

Methods

An electronic bibliographic search was performed, using PubMed and EMBASE as search engines. Keywords were “infant”, “newborn” or “preterm” and “Cystatin C” with a cut-off point in time (August 2014). Retrieved sources were further explored applying both the snowball approach (verifying the references) as well as verifying for citations of these original papers through Isi-knowledge and PubMed. Corresponding authors were contacted for additional information on assay related issues if this was not sufficiently clearly described in the original source document.

CysC reference values were extracted from these source documents based on mean and standard deviation, median and range or reference value as published by the authors and were classified based on the clinical characteristics [healthy term (Table 1), healthy preterm (Table 2), specific disease characteristics (Table 3)] with explicit reference to the assay used to quantify CysC.

Results

Based on the bibliographic search, data in 13 cohorts of healthy term cases (1549 CysC measurements, day 1–30, Table 1) [16,19–30] and in 12 cohorts of healthy preterm cases (1519 CysC measurements, day 1–30, gestational age 24–36 weeks, Table 2) [24,28,30,32–37] were retrieved. In search for specific disease characteristics, we retrieved information on the impact of gentamicin exposure, periparturient asphyxia, umbilical cord pH, congenital renal anomalies, renal dysfunction, respiratory distress with or without acute kidney injury, and sepsis/severe sepsis/septic shock on CysC measurements (Table 3) [25,29,30,33,36,38,39].

Cohorts were reported chronologically. Pooled CysC measurements in preterm and term cases, or in neonates and young infants were not retained in these tables.

Discussion: how to aim for a moving target?

The quality of neonatal care depends on the availability of reference intervals for any specific laboratory test or biomarker to support prognosis, clinical decision making or to tailor therapy [7,40,41]. Since maturational variability is most prominent in early infancy, the crucial issue is how to disentangle the signal from the noise, as illustrated in the extensive variability in CysC reference values. This variability in part is due to physiological changes (e.g. gestational or postnatal age, weight) (Tables 1 and 2) as well as changes related to pathophysiology (e.g. periparturient asphyxia, co-medication, haemoglobin, respiratory distress) (Table 3). Besides these (patho)physiological covariates, we also found arguments on the relevance of assay differences in newborns to explain the range in CysC values reported.

In essence, (i) CysC concentrations are higher at birth, with a subsequent decrease in term as well as preterm neonates, (ii) CysC concentrations are higher in preterm neonates when compared to term neonates, with the highest values in the most immature cases, (iii) CysC assays also matter for neonates. Even if we limit the analysis to blood samples in healthy term neonates in the first 24 h of life to restrict the impact of covariates, there is significant difference in mean values reported following PETIA [16,19,20] or ELISA [26] compared to PENIA assays [21,23,27,28,30], as illustrated in Figure 1. Finally, (iv) disease characteristics like respiratory distress [36], bilateral kidney abnormalities [25], periparturient asphyxia [30,38], aminoglycoside exposure [29], hemoglobin [30,38], renal dysfunction [33,37] or sepsis [39] also affect the CysC values observed, but not always in the expected direction. Aminoglycoside exposure in preterm neonates resulted in slightly *lower* serum CysC values, suggesting higher clearance [29]. Similar, neonates in septic shock had lower CysC values when compared to neonates with (severe) sepsis [39]. This strongly suggests that besides aspects related to the CysC assay, additional clinical research is needed to document the potential add on benefit of more advanced biomarkers like CysC in neonatal medicine.

Different authors described a progressive physiological decrease in CysC values throughout infancy, with subsequent stabilization to age-independent reference values after the first year of life (0.57–1.12 mg/l) [1,9,13,20,21,31]. This means that – similar to creatinine – age-specific reference values in early infancy are needed before we can consider to integrate this biomarker into neonatal practice as a sensitive and specific marker to discriminate between physiology and pathophysiology (i.e. renal dysfunction) [7,40,41]. Moreover, CysC values should be compared to golden standard clearance assessment tools [e.g. inulin clearance, ⁵¹Chromium ethylene diamine tetra acetic acid (EDTA), ^{99m}Technetium diethylene triamine penta acetic acid (DTPA)] to confirm that CysC values can be converted to GFR estimates. At present, we are only aware of one study in 20 preterm infants that linked CysC values to inulin clearance (correlation = 0.766) (Table 3) [33].

Based on the currently retrieved information, an extensive range (5-fold) in serum CysC observations in early infancy has been documented, only in part explained by renal (patho)physiology. This can be further improved by the use of assay specific reference values. Such reference values should be adapted to the clinical characteristics (e.g. weight, gestational or postnatal age) and compared to inulin clearance or similar as golden standard for GFR estimation. Besides the search for new biomarkers, we feel strongly that the efforts made to standardize creatinine assays toward IDMS also hold an unique opportunity to develop serum creatinine reference values and centiles for creatinine in (pre)term neonates [6,7,40,41]. A research effort similar to the CALIPER (Canadian Laboratory Initiative on Pediatric Reference intervals) initiative, but focussed on early infancy reference values is mandatory [7,15,40,41] to really disentangle the signal from the noise.

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Figure 1.

Mean Cystatin C (CysC) values in 9 cohorts of healthy term newborns (<24 h) of life were retrieved in the literature. In 5 of these cohorts, CysC measurement was based on PENIA [21,23,27,28,30], there was one ELISA measurement [26] and 3 PETIA [16,19,20] based measurements. Mean values following PENIA were significantly lower when compared to non-PENIA techniques [PENIA = particle enhanced nephelometric immune-assay; PETIA = particle enhanced turbimetric immune-assay; ELISA = enzyme linked immune-sorbent assay].

Table 1

Cystatin C (CysC) reference values as reported in literature in full term healthy neonates in the first 30 days of postnatal life (PENIA = particle enhanced nephelometric immune-assay; PETIA = particle enhanced turbidimetric immune-assay; ELISA = enzyme linked immune-sorbent assay, SD = standard deviation) [16,19–30].

Paper	Technique	Clinical characteristics	Cys C values (mg/L)
[19]	PETIA, CysC PET kit, DAKO	Day 1, $n = 50$ (cord blood)	2.23 (range 1.17–4.84)
		Day 3, $n = 50$	1.82 (range 0.85–3.09)
		Day 5, $n = 50$	1.63 (range 0.66–1.63)
[20]	PETIA, CysC PET kit, DAKO	<3days, $n = 23$	2.16 (range 1.64–2.59)
[20]	PETIA, CysC PET kit, DAKO	Day 3–30, $n = 14$	2.02 (range 1.52–2.40)
[16]	PETIA, CysC PET kit, DAKO	Day 1, $n = 78$ (cord blood)	2.11 (1.45–2.81)
		Day 3, $n = 78$	1.75 (0.85–2.52)
		Day 5, $n = 78$	1.63 (0.86–2.09)
[21]	PETIA, in house	Day 1–7, $n = 50$	1.70 (SD 0.26)
[22]	PENIA	Day 1, $n = 112$	1.36 (SD 0.35)
	N Latex CysC, Dade Behring	Day 3, $n = 98$	1.35 (SD 0.33)
[23]	PENIA	Day 1, 36 weeks, $n = 24$	1.84 (range 1.32–2.63)
	N Latex CysC, Dade Behring	Day 3, 36 weeks, $n = 21$	1.58 (range 1.16–1.95)
[24]	PENIA	Day 1, $n = 21$ (cord blood)	1.70 (SD 0.26)
	N Latex CysC, Dade Behring	Day 3, $n = 21$	1.51 (SD 0.19)
		Day 7, $n = 21$	1.54 (SD 0.15)
		Day 28, $n = 21$	1.51 (SD 0.15)
[25]	PENIA, DAKO Cytomation	Day 1, $n = 100$ (cord blood)	2.02 (range 1.40–2.70)
[26]	ELISA	Day 1, $n = 22$	2.23 (range 1.75–2.62)
	Quantikine Human CysC	Day 3, $n = 22$	2.14 (range 1.55–2.54)
		Day 10, $n = 22$	2.48 (range 2.35–2.99)
[27]	PENIA, CysC Dade Behring	Day 1, $n = 33$ (cord blood)	1.21 (SD 0.30)
[28]	Latex agglutinin immuno-assay	Day 0–3, $n = 119$	1.64 (SD 0.32)
	(not further defined)	Day 4–6, $n = 99$	1.42 (SD 0.26)
		Day 7–10, $n = 97$	1.51 (SD 0.23)
		Day 11–15, $n = 44$	1.55 (SD 0.29)
		Day 16–21, $n = 27$	1.55 (SD 0.34)
		Day 22–30, $n = 14$	1.56 (SD 0.39)
[29]	PENIA	Day 3–7, $n = 40$	1.33 (SD 0.18)
	N Latex CysC, Dade Behring		
[30]	PENIA	Day 1, $n = 50$ (cord blood)	1.39 (SD 0.19)
	N Latex CysC, Dade Behring	Day 3, $n = 50$	1.34 (SD 0.21)

Table 2

Cystatin C (CysC) reference values as reported in literature in preterm healthy neonates in the first 30 days of postnatal life.

Paper	Technique	Clinical characteristics	Cys C values (mg/L)
[31]	PENIA, CysC Dade Behring	Day 8–30, $n = 12$	1.63 (SD 0.26)
[32]	PETIA, in house	Day 1, 24–28 weeks ($n = 16$)	1.48 (range 0.65–3.37)
		Day 1, 29–36 weeks ($n = 14$)	1.65 (range 0.62–4.42)
[21]	PETIA, in house	Day 1–7, 32 (range 25–37) weeks ($n = 58$)	1.88 (SD 0.36)
[33]	PETIA, CysC PET kit, DAKO	Day 4–7, 33 (range 28–34) weeks ($n = 20$)	1.88 (range 1.20–2.30)
[34]	PENIA, CysC Dade Behring	Day 1, 32.5 (SD 2.6) weeks ($n = 108$, cord blood)	1.8 (SD 0.30)
		Day 3, 32.5 (SD 2.6) weeks, ($n = 108$)	1.65 (SD 0.30)
[23]	PENIA N Latex CysC	Day 1, 24–28 weeks ($n = 22$)	1.63 (range 1.17–2.24)
		Day 3, 24–28 weeks ($n = 23$)	1.47 (range 1.14–2.08)
		Day 1, 28–32 weeks ($n = 33$)	1.79 (range 1.05–2.41)
		Day 3, 28–32 weeks ($n = 33$)	1.60 (range 1.07–2.17)
		Day 1, 32–36 weeks ($n = 29$)	1.89 (range 0.58–2.93)
		Day 3, 32–36 weeks ($n = 37$)	1.64 (range 1.17–2.19)
[27]	PENIA, N Latex CysC, Dade Behring	Day 1, 33–36 weeks ($n = 30$, cord blood)	1.21 (SD 0.31)
		Day 1, 28–32 weeks ($n = 35$, cord blood)	1.41 (SD 0.27)
[35]	<i>not defined</i>	Day 1, 24–26 weeks ($n = 17$)	1.80 (range 0.80–2.20)
		Day 3, 24–26 weeks ($n = 17$)	1.52 (range 0.54–2.00)
		Day 1, 26–28 weeks ($n = 19$)	1.80 (range 1.51–3.19)
		Day 3, 26–28 weeks ($n = 19$)	1.61 (range 1.10–3.41)
		Day 1, 28–30 weeks ($n = 32$)	1.80 (range 0.65–2.48)
		Day 3, 28–30 weeks ($n = 32$)	1.70 (range 0.56–2.31)
		Day 1, 30–32 weeks ($n = 45$)	1.79 (range 0.68–2.31)
		Day 3, 30–32 weeks ($n = 45$)	1.61 (range 0.92–2.21)
[36]	PENIA, N Latex CysC, Dade Behring	Day 3, 27–29 weeks ($n = 11$)	1.34 (SD 0.10)
		Day 30, 27–29 weeks ($n = 11$)	1.32 (SD 0.20)
		Day 3, 30–32 weeks ($n = 23$)	1.28 (SD 0.20)
		Day 30, 30–32 weeks ($n = 23$)	1.27 (range 0.68–1.58)
[37]	PENIA, N Latex CysC, Dade Behring	Day 3, 28–29 weeks ($n = 11$)	1.34 (SD 0.1)
		Day 3, 30–32 weeks ($n = 23$)	1.28 (SD 0.2)
		Day 3, 33–34 weeks ($n = 18$)	1.24 (SD 0.2)
		Day 30, 28–29 weeks ($n = 11$)	1.32 (SD 0.2)
		Day 30, 30–32 weeks ($n = 23$)	1.25 (SD 0.1)
		Day 30, 33–34 weeks ($n = 18$)	1.22 (SD 0.2)
[28]	Latex agglutinin immuno-assay <i>not further defined</i>	Day 0–3, 28 weeks ($n = 15$)	1.60 (SD 0.21)
		Day 0–3, 29–32 weeks ($n = 40$)	1.56 (SD 0.28)
		Day 0–3, 33–36 weeks ($n = 72$)	1.67 (SD 0.25)
		Day 4–6, 28 weeks ($n = 12$)	1.55 (SD 0.28)
		Day 4–6, 29–32 weeks ($n = 21$)	1.53 (SD 0.21)

Paper	Technique	Clinical characteristics	Cys C values (mg/L)
		Day 4–6, 33–36 weeks ($n = 46$)	1.68 (SD 0.27)
		Day 7–10, 28 weeks ($n = 11$)	1.73 (SD 0.41)
		Day 7–10, 29–32 weeks ($n = 30$)	1.75 (SD 0.29)
		Day 7–10, 33–36 weeks ($n = 61$)	1.69 (SD 0.32)
		Day 11–15, 28 weeks ($n = 14$)	1.87 (SD 0.26)
		Day 11–15, 29–32 weeks ($n = 22$)	1.87 (SD 0.31)
		Day 11–15, 33–36 weeks ($n = 25$)	1.72 (SD 0.24)
		Day 16–21, 28 weeks ($n = 8$)	1.80 (SD 0.28)
		Day 16–21, 29–32 weeks ($n = 26$)	1.68 (SD 0.31)
		Day 16–21, 33–36 weeks ($n = 26$)	1.81 (SD 0.22)
		Day 22–30, 28 weeks ($n = 11$)	2.02 (SD 0.42)
		Day 22–30, 29–32 weeks ($n = 23$)	1.84 (SD 0.27)
		Day 22–30, 33–36 weeks ($n = 20$)	1.64 (SD 0.23)
[29]	PENIA, N-latex CysC Dade–Behring	Day 3–7, 34 (SD 3) weeks ($n = 60$)	1.42 (SD 0.21).

PENIA = particle enhanced nephelometric immune-assay; PETIA = particle enhanced turbimetric immune-assay; ELISA = enzyme linked immune-sorbent assay, SD = standard deviation [24,28,30,32–37].

Table 3

Plasma cystatin C (CysC) values in neonates with specific perinatal disease characteristics.

Reference	Assay	Clinical characteristics	CysC values
[33]	PETIA	Preterms ($n = 20$), Postnatal 4–7 days 28–34 weeks, birth weight 910–2250 g Raised CysC in cases with lower inulin clearance	1.88 (1.2–2.3) mg/L
[38]	PENIA	$n = 75$, umbilical blood at birth (34–41 weeks) Raised CysC with pH57.2 at birth Correlation ($r = 0.28$) with hemoglobin	1.97 (SD 0.60) mg/l
[25]	PENIA	100 controls (term), all umbilical cord blood 13 congenital renal anomaly cases, bilateral	2.02 (1.54–2.64) mg/l 2.52 (1.80–3.50) (+24.5%)mg/l
[39]	ELISA	32 neonates, 34–40 weeks, 0 and 48 h Sepsis Severe sepsis Septic shock	1.47 (1.01–1.9) to 1.43 (1.05–1.81) mg/l 1.5 (1.12–1.87) to 1.31 (1.05–1.58) mg/l 1.23 (0.92–1.54) to 1.21 (0.95–1.47) mg/l
[36]	PENIA	34 cases without respiratory distress, day 3 28 cases with respiratory distress, day 3 No acute kidney injury (22/28) Acute kidney injury (6/28) 34 cases without respiratory distress, day 30 28 cases with respiratory distress, day 30 No acute kidney injury (22/28) Acute kidney injury (6/28)	1.30 (SD 0.2) mg/l 1.14 (SD 0.1) mg/l 1.49 (SD 0.09) mg/l 1.29 (0.68–1.67) mg/l 1.40 (1.01–1.89) mg/l 1.51 (1.16–1.70) mg/l
[29]	PENIA	Preterm, 34 (SD 3) weeks Second part of first week of life 26/60 exposed to gentamicin (<i>CysC lower</i>)	1.35 (SD 0.19) to 1.47 (SD 0.21) mg/l
[30]	PENIA	50 term cases perinatal asphyxia/controls At birth (umbilical cord blood) On day 3 of life (venous blood)	2.12 (SD 0.53) to 1.39 (SD 0.19) mg/l 1.56 (SD 0.32) to 1.34 (SD 0.21) mg/l

PENIA = particle-enhanced nephelometric immune-assay; PETIA = particle-enhanced turbimetric immune-assay; ELISA = enzyme linked immune-sorbent assay, SD = standard deviation [25,29,30,33,36,38,39].