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Accurate estimation of GFR in children using endogenous serum markers

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Summary

Glomerular filtration rate (GFR) is an important indicator of kidney function and accurate knowledge of a patient's GFR is necessary in identifying and follow-up of renal disease as well as for dosing of renally excreted medication. GFR can be fairly accurately measured by intravenous injection of an exogenous marker and measuring either the rate of decline of serum levels or the rate at which the marker appears in the urine. These measurements are invasive, time consuming and costly and therefore are rarely performed in clinical setting. Usually GFR is estimated using serum levels of endogenous markers.

Chapter one starts by outlining the properties an endogenous marker should adhere to. Subsequently several known endogenous markers for kidney function; creatinine, urea, cystatin C, beta-trace protein and beta-2 microglobulin are discussed in terms of physiology, analytical methods and specifically their use in children. Different strategies for obtaining an estimated GFR from serum levels of the endogenous markers are outlined along with a table summarizing eGFR equations for children published in recent years.

While influence of corticosteroids on serum levels of cystatin C has been researched, little is known about the effects of these very commonly used drugs in pediatric nephrology on the most widely used marker for eGFR, creatinine. **Chapter 2** is a retrospective study using both longitudinal and cross-sectional comparisons of the bias of creatinine based eGFR with and without corticosteroid use. No significant effect of corticosteroid use was found in our population and while the longitudinal analysis showed a trend towards underestimation of GFR in the corticosteroid group, the cross-sectional analysis trended towards dose-dependent overestimation of GFR with steroids, strengthening the conclusion that corticosteroids have no effect on serum creatinine independent from GFR.

Beta-trace protein is a relatively newly discovered marker for kidney function and few beta-trace protein based eGFR equations exist for children. Recently an effort has been made to create creatinine and cystatin C based equations for the full age spectrum (FAS) using rescaled serum levels based on normal values found in healthy populations. In **Chapter 3** we extend this approach to create a new beta-trace protein based eGFR equation for a pediatric population, which we compare to the creatinine and cystatin C based FAS equations. Our new equation is slightly less accurate than particularly the cystatin C based equation in the general population, however in specific populations, such as patients with malignancy the beta-trace protein equation outperforms the other two. Combining any two equations improves accuracy, however combining all three does not further improve performance.

Recently a condition termed “Shrunken Pore Syndrome” (SPS) has been proposed as an explanation for both discrepant GFR estimation based on cystatin C and creatinine as well as the observed link between increased mortality and cystatin C, independent of kidney function in adults. The theory is that smaller glomerular pore size retains cystatin C, along with pro-inflammatory factors, while the smaller creatinine is freely excreted. **Chapter 4** explores this phenomenon in children by comparing discrepant eGFR results between creatinine and cystatin C based equations with beta-trace protein based eGFR, as the latter is similar in size to cystatin C. The results show a link between cystatin C and beta-trace protein which is independent from creatinine and measured GFR, suggesting that SPS exists in children. We also propose an alternate definition of SPS using gold standard measurement of GFR to rule out abnormally low levels of creatinine as reason for patients to fit the original definition of SPS.

Most pediatric eGFR equations based on creatinine require knowledge of a patient's height, which makes it difficult for laboratories to directly report eGFR as is common for adults. As described in chapter 3, studies have shown improvement of accuracy when creatinine and cystatin C-based equations are combined. **Chapter 5** shows that highly accurate eGFR can be reported by using the mean of the height-independent FASage and FAScys equations. This allows for direct eGFR reporting by laboratories as opposed to serum concentrations of the markers.

Building on the previous chapter, **chapter 6** explores ways to increase the accuracy of eGFR based on the mean of a creatinine and cystatin C based equation. One approach is to use the geometric mean i.e. the root of the function between creatinine and cystatin C based eGFR, which showed slightly higher accuracy rates than the arithmetic mean i.e. half of the addition of eGFR based on creatinine and cystatin C. Another is to adjust the weight of the creatinine and cystatin C based equation within the arithmetic or geometric mean. In our general population equal contributions of creatinine and cystatin C are most accurate. However specific groups, such as patients with malignancy, nephritis, spina bifida had higher accuracy rates with different relative contributions of creatinine and cystatin C. Finally, accuracy rates of the geometric are exceedingly high in patients with low level of discrepancy between creatinine and cystatin C based eGFR. These findings prompt the proposition of a strategy for accurate eGFR reporting. If the discrepancy between height-independent eGFR based on creatinine and cystatin C is less than 40%, which was the case in 83% of our population, report the geometric mean between the two. If the discrepancy exceeds 40%, identify a patient characteristic, such as diagnosis of malignancy of spina bifida, that calls for a weighted mean and use the

appropriately weighted mean. If no such patient characteristic is apparent, consider performing a gold standard measurement using an exogenous marker.