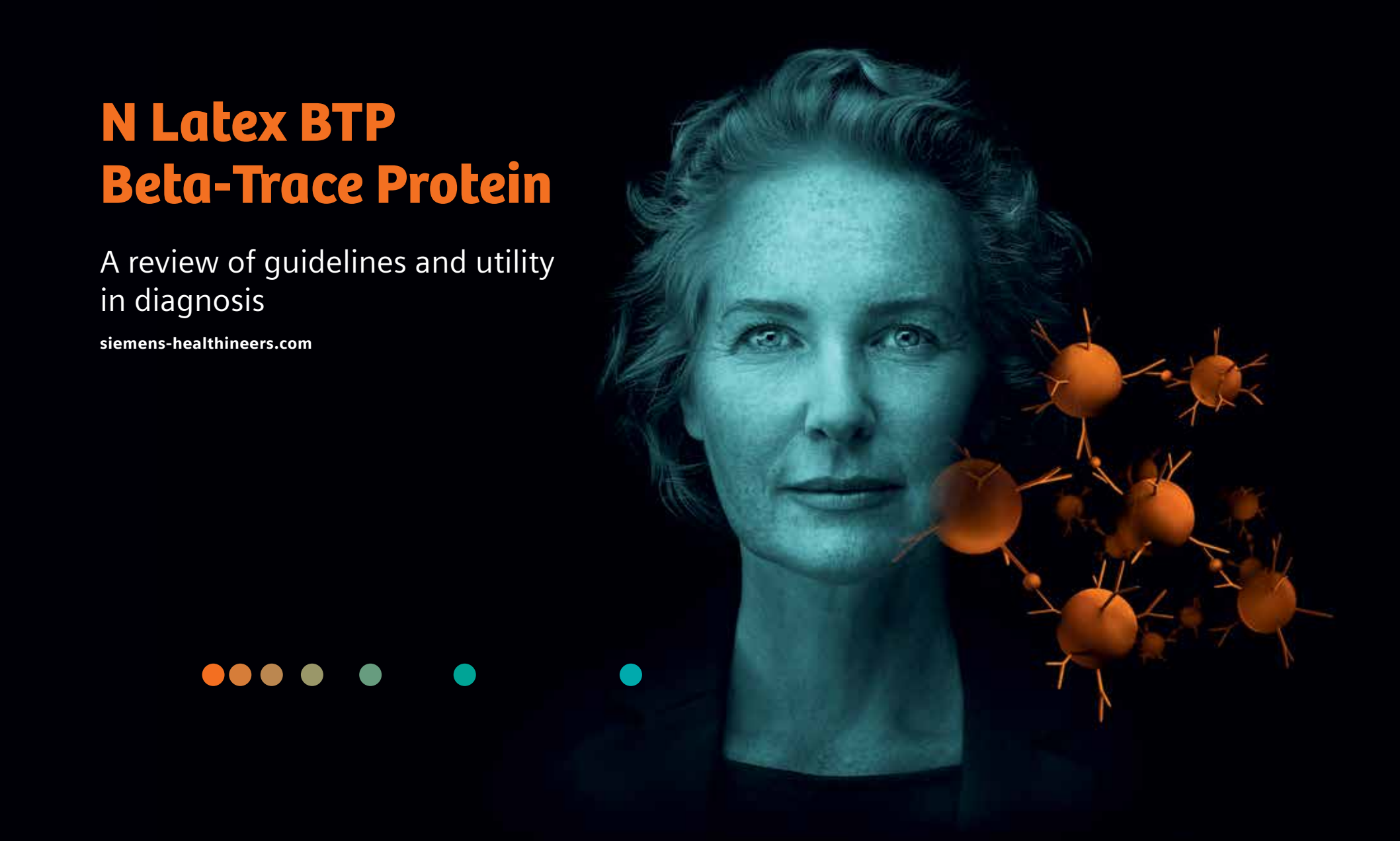
N Latex BTP Beta-Trace Protein

A review of guidelines and utility in diagnosis

siemens-healthineers.com



SIEMENS Healthineers

Contents

ESRD Guidelines and Data Resources

1 National Kidney Foundation. Am J Kidney Dis. 2006; 48(Suppl 1):S2-90. (free)

KDOQI Clinical Practice Guideline for Hemodialysis Adequacy, 2015 Update.

Residual Kidney Function: Given the trends and recommendations for earlier institution of dialysis therapy and perhaps the more successful preservation of RKF in the past several years, a large number of currently dialyzed patients have substantial RKF. A consideration of solute kinetics shows that even low levels of RKF can account for removal of large amounts of solute, including such large-molecular-weight solutes as ß2M, in addition to helping maintain salt and water balance. Survival in patients treated with twice-weekly HD was no worse (and was possibly better) in a USRDS patient sample. Given these data and with earlier initiation of dialysis in patients with higher levels of RKF, the Work Group decided that thrice-weekly HD as a minimum frequency level was no longer appropriate. Based on solute kinetics, the Work Group was comfortable recommending a twice-weekly dialysis schedule, but only for patients with substantial RKF. The minimally adequate dose of dialysis can be reduced in patients with Kr greater than 2 mL/min/1.73 m^2.

2 Tattersall J, Martin-Malo A, Pedrini L, et al. Nephrol Dial Transplant. 2007;22(Suppl 2):ii5-21. (free)

EBPG guidelines on dialysis strategies.

European guideline on dialysis strategies with recommendations for time and frequency, flux and convection, dialysis dose methodology including measurement of RRF every other month, and minimum adequate dialysis dose.

3 Ashby D, Borman N, Burton J, et al. Renal Association Clinical Practice Guideline on Haemodialysis. BMC Nephrol. 2019;20(1):379. Published 2019 Oct 17. (free)

Renal Association Clinical Practice Guideline on Haemodialysis.

This guideline is written primarily for doctors and nurses working in dialysis units and related areas of medicine in the UK. It aims to provide guidance on how to look after patients and how to run dialysis units, and provides standards which units should in general aim to achieve. We would not advise patients to interpret the guideline as a rulebook, but perhaps to answer the question: "what does good quality haemodialysis look like?"

Summary of clinical practice guidelines:
Dialysis dose in thrice weekly dialysis schedules:
We recommend targeting dialysis dose to achieve consistently a minimum eKt/V of 1.2 for thrice weekly patients, in the absence of a measured contribution from residual function.

Non-standard/incremental schedules: We suggest that lower haemodialysis dose targets may be optimal in patients with significant residual renal function. We recommend that residual renal function should be quantified intermittently in patients on incremental dialysis schedules.

4 United States Renal Data System. 2019 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2019. (free)

US Renal Data System 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States.

The mission of the United States Renal Data System is to characterize the kidney disease population in the country and serve as a comprehensive, regularly updated, online resource for the descriptive epidemiology of kidney disease in the United States. In addition, supporting investigator initiated research by data provisioning to the community of researchers is one of the key functions of the USRDS.

Importance of Residual Renal Function in Dialysis Patients

5 Bargman JM, Golper TA. Nephrol Dial Transplant. 2005;20:671-3. (free)

The importance of residual renal function for patients on dialysis.

It is the goal of every practitioner involved in the care of dialysis patients to maximize survival and quality of life. The last two decades have seen a plethora of investigations that have sought to determine how this goal can be achieved. The bulk of the studies have, unfortunately, concentrated on small solute clearance and outcome (measured principally as mortality. Residual renal function is a valuable asset to those on dialysis, best demonstrated in PD. It is crucial to try to preserve this asset for as long as possible by re-educating ourselves, and our medical colleagues, that we still have to continue to think about protection of renal function, even in the dialysis patient.

6 Brener ZZ, Kotanko P, Thijssen S, Winchester JF, Bergman M. Am J Med Sci. 2010;339(5):453-456.

Clinical benefit of preserving residual renal function in dialysis patients: an update for clinicians.

Residual renal function (RRF) remains important even after beginning of dialysis. RRF contributes significantly to the overall health and well-being of patients on dialysis. It plays an important role in maintaining fluid balance, phosphorus control, nutrition, and removal of middle molecular uremic toxins and shows inverse relationships with valvular calcification and cardiac hypertrophy in patients on dialysis. RRF may allow for a reduction in the duration of hemodialysis sessions and the need for dietary and fluid restrictions in both patients on peritoneal dialysis and hemodialysis. More importantly, the loss of RRF is a powerful predictor of mortality. This article will review the evidence supporting the importance of RRF on outcome and outline potential strategies that may better preserve RRF in patients on dialysis.

7 Termorshuizen F, Dekker FW, Van Manen JG, et al. J Am Soc Nephrol. 2004;15(4):1061-70. (free)

Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2.

A high delivered Kt/V(urea) (dKt/V(urea)) is advocated in the U.S. National Kidney Foundation Dialysis Outcomes Quality Initiative guidelines on presence of residual renal function. The contribution of treatment adequacy and residual renal function to patient survival was investigated. The Netherlands Cooperative Study on the Adequacy of Dialysis is a prospective multicenter study that includes incident ESRD patients older than 18 yr. The longitudinal data on residual renal function and dialysis adequacy of patients who were treated with HD 3 mo after the initiation of dialysis (n = 740) were analyzed. The mean renal Kt/V(urea) (rKt/V(urea)) at 3 mo was 0.7/wk (SD 0.6) and the dKt/V(urea) at 3 mo was 2.7/wk (SD 0.8). Both components of urea clearance were associated with a better survival (for each increase of 1/wk in rKt/V(urea), relative risk of death = 0.44 [$P < 0.0001$]; dKt/V(urea), relative risk of death = 0.76 [$P < 0.01$]). However, the effect of dKt/V(urea) on mortality was strongly dependent on the presence of rKt/V(urea), low values for dKt/V(urea) of <2.9/wk being associated with a significantly higher mortality in anuric patients only. Furthermore, an excess of ultrafiltration in relation to interdialytic weight gain was associated with an increase in mortality independent of dKt/V(urea). In conclusion, residual renal clearance

seems to be an important predictor of survival in HD patients, and the dKt/V(urea) should be tuned appropriately to the presence of renal function. Further studies are required to substantiate the important role of fluid balance in HD adequacy.

8 Liu FX, et al. Brener ZZ, Kotanko P, et al. Perit Dial Int. 2015 Jul-Aug;35(4):406-20. (free)

A global overview of the impact of peritoneal dialysis first or favored policies: an opinion.

Given the ever-increasing burden of end-stage renal disease (ESRD) in a global milieu of limited financial and health resources, interested parties continue to search for ways to optimize dialysis access. Government and payer initiatives to increase access to renal replacement therapies (RRTs), particularly peritoneal dialysis (PD) and hemodialysis (HD), may have meaningful impacts from clinical and health-economic perspectives; and despite similar clinical and humanistic outcomes between the two dialysis modalities, PD may be the more convenient and resource conscious option. This review assessed country-specific PD-First/Favored policies and their associated background, implementation, and outcomes. It was found that barriers to policy implementation are broadly associated with government policy, economics, provider or healthcare professional education, modality related factors, and patient-related factors. Notably, the success of a given country's PD-Favored policy was inversely associated with the extent of HD infrastructure. It is hoped that this review will provide a foundation across countries to share lessons learned during the development and implementation of PD-First/Favored policies.

9 Shafi T, Jaar BG, Plantinga LC, et al. Am J Kidney Dis. 2010;56(2):348–58. (free)

Association of residual urine output with mortality, quality of life and inflammation in incident hemodialysis patients: the CHOICE (Choices for healthy outcomes in caring for end-stage renal disease) Study.

Residual kidney function (RKF) is associated with improved survival in peritoneal dialysis patients, but its role in hemodialysis patients is less well known. Urine output may provide an estimate of RKF. The aim of our study is to determine the association of urine output with mortality, quality of life (QOL), and inflammation in incident hemodialysis patients. 734 incident hemodialysis participants treated in 81 clinics; enrollment, 1995–1998; follow-up until December 2004. 617 of 734 (84%) participants reported urine output at baseline, and 163 of 579 (28%), at year 1. Baseline urine output was not associated with survival. Urine output at year 1, indicating preserved RKF, was independently associated with lower all-cause mortality (HR, 0.70; 95% CI, 0.52–0.93; P = 0.02) and a trend toward lower cardiovascular mortality (HR, 0.69; 95% CI, 0.45–1.05; P = 0.09). Participants with urine output at baseline reported better QOL and had lower C-reactive protein (P = 0.02) and interleukin 6 (P = 0.03) levels. Importantly, EPO dose was 12,000 U/wk lower in those with urine output at year 1 compared with those without (P = 0.001). Urine volume was measured in only a subset of patients (42%), but agreed with self-report (P < 0.001). RKF in hemodialysis patients is associated with better survival and QOL, lower inflammation, and significantly less EPO use. RKF should be monitored routinely in hemodialysis patients. The development of methods to assess and preserve RKF is important and may improve dialysis care.

10 Rosansky S, Glassock RJ, Clark WF. Clin J Am Soc Nephrol. 2011;6:1222-8. (free)

Early start of dialysis: a critical review.

In the US, patients who initiate dialysis "early" (at Modification of Diet in Renal Disease estimated GFR [eGFR]> 10 ml/min per 1.73m^2) account for over 50 percent of new dialysis starts. This trend to an early start is based on conventional wisdoms regarding benefits of dialytic clearance, that albumin levels are nutritional markers, and early dialytic therapy is justified to improve nutrition especially in diabetics and that waiting until low levels of eGFR (i.e., <6 ml/min per 1.73 m^2) may be dangerous. In order to justify early dialysis treatment, the therapy must provide a morbidity, mortality, or quality of life benefit. The current review examines whether early dialysis initiation provides any of these benefits and whether the conventional wisdoms that have promoted this early dialysis trend are valid. Utilizing this information and the results of recent large observational studies and the randomized controlled Initiating Dialysis Early and Late (IDEAL) study, we suggest that dialysis initiation is justified at GFR levels of 5–9 ml/min/1.73 m^2, if accompanied by uremia symptoms or fluid management issues.

11 Tattersall J. Residual renal function in incremental dialysis. Clin Kidney J. 2018;11(6):853-856.

Residual renal function in incremental dialysis.

Incremental haemodialysis has the potential to allow better preservation of renal function, is less invasive to the patient and has lower cost. Despite these advantages, it is not commonly applied. This may be due to uncertainty about how to account for renal function in the prescription of dialysis and measurement of dose. In this issue, Vartia describes the practical basis for including the effect of renal function in the prescription and quantification of dialysis. He uses a well-known and validated urea kinetic model to calculate time average urea concentrations and the equivalent renal clearance (EKR) from dialysis. The effect of renal function is amplified by a weighting factor to account for the relatively greater effect of renal function compared with dialysis with the same urea clearance. In that way, patients on differing dialysis regimens can be dialysed with the same target dose. A further step would be to use a downward adjusting factor for dialysis to convert the urea clearance by dialysis (as EKR) to a glomerular filtration rate (GFR) equivalent. A factor of 0.75 is suggested. In that way, dialysis dose can be reported as GFR equivalent in mL/min/1.73 m^2, comparable between different types of dialysis and also to renal function without dialysis.

Reviews: Beta-trace protein and other filtration markers

12 Li T, Wilcox CS, Lipkowitz MS, Gordon-Cappitelli J, Dragoi S. Am J Nephrol. 2019;50(6):411-421.

Rationale and Strategies for Preserving Residual Kidney Function in Dialysis Patients.

Residual kidney function (RKF) conveys a survival benefit among dialysis patients, but the mechanism remains unclear. Improved volume control, clearance of protein-bound and middle molecules, reduced inflammation and preserved erythropoietin and vitamin D production are among the proposed mechanisms. Preservation of RKF requires techniques to measure it accurately to be able to uncover factors that accelerate its loss and interventions that preserve it and ultimately to individualize therapy. The average of renal creatinine and urea clearance provides a superior estimate of RKF in dialysis patients, when compared with daily urine volume. However, both involve the difficult task of obtaining an accurate 24-h urine sample.

In this article, we first review the definition and measurement of RKF, including newly proposed markers such as serum levels of beta2-microglobulin, cystatin C and beta-trace protein. We then discuss the predictors of RKF loss in new dialysis patients. We review several strategies to preserve RKF such as renin-angiotensin-aldosterone system blockade, incremental dialysis, use of biocompatible membranes and ultrapure dialysate in hemodialysis (HD) patients, and use of biocompatible solutions in peritoneal dialysis (PD) patients. Despite their generally adverse effects on renal function, aminoglycoside antibiotics have not been shown to have adverse effects on RKF in well-hydrated patients with end-stage renal disease (ESRD). Presently, the roles of better blood pressure control, diuretic usage, diet, and dialysis modality on RKF remain to be clearly established. Key Messages: RKF is an important and favorable prognostic indicator of reduced morbidity, mortality, and higher quality of life in both PD an HD patients. Further investigation is warranted to uncover factors that protect or impair RKF. This should lead to improved quality of life and prolonged lifespan in patients with ESRD and cost-reduction through patient centeredness, individualized therapy, and precision medicine approaches.

Serum BTP may be the most reliable marker for assessing RKF and recently a commercial assay has been launched but presently is available only in Europe.

13 Castro, I., Rodrigues, A. SN Compr. Clin. Med. 2, 140–148 (2020).

Estimating Residual Kidney Function: Present and Future Challenge.

Residual kidney function is a major prognosis factor in patients with end-stage renal disease under hemodialysis or peritoneal dialysis. Advances in later years promoted residual kidney function protection as an adequacy target and the advocacy of incremental dialysis, utilizing its assessment as a parameter of individualized dialysis schedules. Glomerular filtration rate measurement is only a dimension of kidney function neglecting the share of tubular function, with several dialytic limitations. The need for interdialytic urine collections to quantify residual kidney function, by the mean of urea and creatinine clearances, is cumbersome and prone to errors in dialysis patients. This review will approach residual kidney function estimation without urine collection, mainly with biomarkers such as cystatin C, beta-2 microglobulin, and beta-trace protein, as well as the behavior of these molecules on various dialysis modalities, their non-renal determinants, and its potential use for patient risk stratification. Multi-frequency bioimpedance analysis is also described as a promising approach to estimate residual kidney function, being an opportunity to highlight the relevant link between volume balance and diuresis. We conclude that standard glomerular filtration rate estimation formulas are not sufficiently accurate for residual kidney function assessment. There is a need for innovative tools that consider glomerular and interstitial function to be implement in clinical practice, therefore the new equations already developed and approached in this review should be validated in larger cohorts.

14 White CA, Ghazan-Shahi S, Adams MA. Am J Kidney Dis. 2015;65(1):131-46.

ß-trace protein: a marker of GFR and other biological pathways.

ß-trace protein (BTP), also known as lipocalin prostaglandin D2 synthase (L-PGDS; encoded by the PTGDS gene), is a low-molecular-weight glycoprotein and an emerging novel marker of glomerular filtration rate. BTP is an important constituent of cerebral spinal fluid and is found in much lower concentrations in blood. Its serum origin and renal handling remain poorly understood. Unlike serum creatinine, BTP is not physiologically inert. It possesses both ligandbinding and enzymatic properties. BTP catalyzes the conversion of prostaglandin H2 (PGH2) to PGD2. PGD2 is an eicosanoid involved in a variety of important physiologic processes, including platelet aggregation, vasodilation, inflammation, adipogenesis, and bone remodeling. Several studies now have documented BTP's strong association with glomerular filtration rate, end-stage renal disease, cardiovascular disease, and death in a variety of different patient populations. This review provides an overview of the biochemistry, physiology and metabolism, biological functions, and measurement of BTP; summarizes the evidence for BTP as a marker of both kidney function and cardiovascular disease; and then considers the interplay between its biological properties, serum concentration, and patient outcomes. The nephrology community should use the lessons learned from the analytical difficulties it has experienced with creatinine and cystatin C before the marker becomes more widely applied. Improved understanding of the clinical utility of BTP will require significant collaboration between basic scientists, clinical chemists, clinical researchers, and renal epidemiologists.

15 Filler G, Kusserow C, Lopes L, Kobrzyński M. Clin Biochem. 2014 Sep;47(13-14):1188-94.

Beta-trace protein as a marker of GFR—history, indications, and future research.

Recent findings suggest that ß-trace protein (BTP), a small molecular weight protein, is at least equal if not superior to serum creatinine as a marker of glomerular filtration rate (GFR), particularly since it is independent from height, gender, age and muscle mass. In an effort to summarize knowledge on BTP and its use as a marker of GFR, the authors compiled key articles and all relevant recent literature on this topic. Physical and chemical features of the molecule are described, as well as factors that may affect its expression. The use of BTP in estimating GFR as a whole and in specific patient groups, including pregnant women, neonates and infants, children and adolescents, and patients who have undergone renal transplantation is discussed. The use of BTP as a marker for cardiovascular risk factors is also briefly addressed. Although its performance in the general population is marginally inferior to cystatin C, studies have suggested that it may be superior in accurately estimating GFR in select patient groups such as pregnant women and neonates. This novel marker shows promise, but further research is required to clarify findings from available data.

16 Karger AB, Inker LA, Coresh J, Levey AS, Eckfeldt JH. EJIFCC. 2017;28(4):277-288. (free)

Novel filtration markers for GFR estimation.

Creatinine-based glomerular filtration rate estimation (eGFRcr) has been improved and refined since the 1970s through both the Modification of Diet in Renal Disease (MDRD) Study equation in 1999 and the CKD Epidemiology Collaboration (CKD-EPI) equation in 2009, with current clinical practice dependent primarily on eGFR for accurate assessment of GFR. However, researchers and clinicians have recognized limitations of relying on creatinine as the only filtration marker, which can lead to inaccurate GFR estimates in certain populations due to the influence of non-GFR determinants of serum or plasma creatinine. Therefore, recent literature has proposed incorporation of multiple serum or plasma filtration markers into GFR estimation to improve precision and accuracy and decrease the impact of non-GFR determinants for any individual biomarker. To this end, the CKD-EPI combined creatinine-cystatin C equation (eGFRcr-cys) was developed in 2012 and demonstrated superior accuracy to equations relying on creatinine or cystatin C alone (eGFRcr or eGFRcys). Now, the focus has broadened to include additional novel filtration markers to further refine and improve GFR estimation. Beta-2-microglobulin (B2M) and beta-trace-protein (BTP) are two filtration markers with established assays that have been proposed as candidates for improving both GFR estimation and risk prediction. GFR estimating equations based on B2M and BTP have been developed and validated, with the CKD-EPI combined BTP-B2M equation (eGFRBTP-B2M)

demonstrating similar performance to eGFR and eGFR. Additionally, several studies have demonstrated that both B2M and BTP are associated with outcomes in CKD patients, including cardiovascular events, ESRD and mortality.

This study found that both BTP and B2M were associated with ESRD, with BTP having the stronger association. These findings support prior studies that have shown that B2M or BTP have prognostic value beyond measured GFR.

17 Inker LA, Tighiouart H, Coresh J, et al. Am J Kidney Dis. 2016;67(1):40-48. (free)

GFR estimation using ß-trace protein and ß-microglobulin in CKD.

ß-trace protein (BTP) and s2-microglobulin (B2M) are novel glomerular filtration markers that have stronger associations with adverse outcomes than creatinine. Comparisons of BTP and B2M to creatinine and cystatin C are limited by the absence of rigorously developed glomerular filtration rate (GFR) estimating equations for the novel markers. Pooled database of 3 populations with chronic kidney disease (CKD) with mean measured GFR of 48 mL/min/1.73 m^2 (N=3551; MDRD [Modification of Diet in Renal Disease] Study, AASK [African American Study of Kidney Disease and Hypertension], and CRIC [Chronic Renal Insufficiency Cohort] Study). GFR estimated using creatinine, cystatin C, BTP, or B2M level. Reference Test: GFR measured as the urinary clearance of iothalamate.

For BTP and B2M, coefficients for age, sex, and race were smaller than for creatinine and were similar or smaller than for cystatin C. For B2M, coefficients for sex, age, and race were smaller than for creatinine and were similar (age and race) or smaller (sex) than for cystatin C. The final equations with BTP (BTP, age, and sex) or B2M (B2M alone) were less accurate than either the CKD-EPI (CKD Epidemiology Collaboration) creatinine or cystatin C equations. The combined BTP-B2M equation (BTP and B2M alone) had similar accuracy to the CKD-EPI creatinine or cystatin C equation. The average of the BTP-B2M equation and the CKD-EPI creatinine-cystatin C equation was not more accurate than the CKD-EPI creatinine-cystatin C equation. Limitations: No external validation population, study population was restricted to CKD (not under dialysis), few participants older than 65 years, or nonblack nonwhite race. BTP and B2M are less influenced by age, sex, and race than creatinine and less influenced by race than cystatin C, but provide less accurate GFR estimates than the CKD-EPI creatinine and cystatin C equations. The CKD-EPI BTP and B2M equation provides a methodological advance for their study as filtration markers and in their associations with risk and adverse outcomes, but further study is required before clinical use.

Introduction of CKD-EPI equations for GFR estimation from BTP, B2M and the combination: $GFR_{BTP} = 55 \times BTP^{-0.695} \times 0.998^{age}$ (x 0.900 if female).

18 White CA, Akbari A, Doucette S, et al. Clin Chem. 2007;53(11):1965-8. (free)

A novel equation to estimate glomerular filtration rate using beta-trace protein.

Beta-trace protein (BTP) is a low molecular weight glycoprotein that is a more sensitive marker of glomerular filtration rate (GFR) than serum creatinine. The utility of BTP has been limited by the lack of an equation to translate BTP into an estimate of GFR. The objectives of this study were to develop a BTP-based GFR estimation equation. We measured BTP and GFR by 99mTc-DTPA acid in 163 stable adult renal transplant recipients. Stepwise multiple regression models were created to predict GFR corrected for body surface area. The following variables were considered for entry into the model: BTP, urea, sex, albumin, creatinine, age, and race. BTP alone accounted for 75.6% of variability in GFR. The model that included all the predictor variables had the largest coefficient of determination R^2 at 0.821.

The model with only BTP, urea, and sex had only a slightly lower R^2 of 0.81 and yielded the following equation: GFR mL min^{-1} $(1.73\ m^2)^{-1} = 112.1 \times BTP^{(-0.662)} \times Urea^{(-0.280)}$ x (0.88 if female). A 2nd equation ($R^2 = 0.79$) using creatinine instead of urea was also developed: GFR mL min^{-1}. $(1.73\ m^2)^{-1} = 1.678 \times BTP^{(-0.758)} \times creatinine^{(-0.204)}$ x (0.871 if female). We have shown that BTP can be used in a simple equation to estimate GFR. Further study is needed in other populations to determine accuracy and clinical utility of this equation.

N Latex BTP assay for determination of RRF in dialysis patients

19 Shafi T, Michels WM, Levey AS, Inker LA, et al. Kidney Int. 2016 May;89(5):1099-1110. (free)

Estimating residual kidney function in dialysis patients without urine collection.

Residual kidney function contributes substantially to solute clearance in dialysis patients but cannot be assessed without urine collection. We used serum filtration markers to develop dialysis specific equations to estimate urinary urea clearance without the need for urine collection. In our development cohort, we measured 24-hour urine clearances under close supervision in 44 patients and validated these equations in 826 patients from the Netherlands Cooperative Study on the Adequacy of Dialysis. For the development and validation cohorts, median urinary urea clearance was 2.6 and 2.4 ml/min, respectively. During the 24-hour visit in the development cohort, serum ß-trace protein concentrations remained in steady state but concentrations of all other markers increased. In the validation cohort, bias (median measured minus estimated clearance) was low for all equations. Precision was significantly better for ß-trace protein and ß2-microglobulin equations and the accuracy was significantly greater for ß-trace protein, ß2-microglobulin, and cystatin C equations, compared with the urea plus creatinine equation. Area under the receiver operator characteristic curve for detecting measured urinary urea clearance by equation-estimated urinary urea clearance (both 2 ml/min or more) were 0.821, 0.850, and 0.796 for ß-trace protein, ß2-microglobulin, and cystatin C equations, respectively; significantly greater than the 0.663 for the urea plus creatinine equation. Thus, residual renal function can be estimated in dialysis patients without urine collections. The RKF Study equations will allow estimation of CL_{UREA} from serum markers without urine collection. Low molecular weight proteins, and in particular BTP, may then be used for more reliable RKF estimation and clinical decision making.

RKF Study equation for estimating urea/creatinine clearance: $CL_{UREA,CREAT}$ (mL/min/1.73 m^2) = 95 x $BTP^{-2.16}$ (x 1.652 if male).

20 Gerhardt T, Pöge U, Stoffel-Wagner B, et al. Nephrol Dial Transplant. 2008;23(1):309-314. (free)

Serum levels of beta-trace protein and its association to diuresis in haemodialysis patients.

Beta-trace protein (BTP) has been proposed as an alternative endogenous marker of the glomerular filtration rate. However, possible determinants of BTP in ESRD patients undergoing regular renal replacement therapy have not been evaluated. Serum levels of BTP, beta-2-microglobulin, creatinine and urea were analysed before and after dialysis treatment in 73 patients [haemodialysis (HD) n = 52; haemodiafiltration (HDF) n = 21]. Patients were categorized into four groups with residual diuresis (RD) <0.5 l/day (group 1; n = 24), 0.5–1 l/day (group 2; n = 18), 1.1–1.5 l/day (group 3; n = 12) and >1.5 l/day (group 4; n = 19).

Subsequently RD was compared to pre-treatment levels of BTP. HD treatment did not affect BTP serum levels [pre-treatment 8.1 ± 4.1 mg/L (mean+SD) vs. post-treatment 7.7 ± 4.1 mg/L; –0.6 ± 16.1%; ns]. However, in 6 out of 21 patients undergoing HDF BTP levels were reduced by more than 20%.

Overall, the resulting decrease in serum concentration was minuscule (9.6 ± 6.2 vs. 8.3 ± 4.9 mg/L; –14 ± 21.9%; P = 0.03). BTP serum levels were tightly associated to RD of the four groups. Comparison of BTP levels showed significant differences between patients of groups 1 vs. 3 and 4 as well as 2 vs. 4.

BTP serum levels may serve as a surrogate marker for residual renal function since HD and HDF do not exert clinical relevant alterations on them. Furthermore, BTP serum concentrations appear strongly associated to RD.

21 van Craenenbroeck AH, et al. Kidney Blood Press Res. 2017;42(5):877-885. (free)

Plasma beta-trace protein as a marker of residual renal function: the effect of different hemodialysis modalities and intra-individual variability over time.

Beta-trace protein (BTP) is a low-molecular-weight molecule, which may be used to assess residual renal function (RRF) in dialysis patients. Here we evaluated the influence of hemodialysis (HD) and hemodiafiltration (HDF) on plasma BTP, and analyzed the inter- and intra-individual variability of plasma BTP over time in HD and peritoneal dialysis (PD) patients. Plasma BTP was measured using a nephelometric method. No significant decrease in plasma BTP was seen following a session of low-flux HD. A significant reduction of the molecule persisted only in HDF and a significant decrease (-15%) was still found immediately before the start of the next dialysis session. In both HD and PD patients, the reproducibility over time was excellent. In a small cohort of 12 PD patients, fair agreement existed between mGFR (average of renal urea and creatinine clearance from a 24 hours urine collection) and the BTP-based GFR estimation. BTP is a stable marker and a promising tool for RRF estimations in PD and HD patients. In patients receiving HDF, plasma levels of BTP should be interpreted with caution.

22 Bargnoux AS, Buthiau D, Morena M, et al. Artif Organs. 2020;44(6):647-654.

Estimation of residual renal function using beta-trace protein: Impact of dialysis procedures.

Beta-trace protein (BTP), a low molecular weight protein of 23–29 kDa, has been proposed as a promising biomarker to estimate residual renal function (RRF) in patients on maintenance hemodialysis (HD). Indeed, BTP is cleared by native kidney but not during conventional HD session. By contrast, the removal rate of BTP using convective processes (mainly hemodiafiltration [HDF]) and peritoneal dialysis (PD) has been little or not investigated. Therefore, an aim of this study was to evaluate the impact of dialysis procedures (high-flux HD, on-line post-dilution HDF and PD) on BTP removal in comparison with beta-2 microglobulin (B2M) and cystatin C (CYSC) removals after a single session. In addition, the ability of BTP to predict RRF in PD was assessed. This observational cross-sectional study included a total of 82 stable chronic kidney disease patients, 53 patients were on maintenance dialysis (with n = 26 in HD and n = 27 in HDF) and 29 were on PD. Serum concentrations of BTP, B2M, and CYSC were measured (a) before and after a single dialysis session in HD and HDF anuric patients to calculate reduction percentages, (b) in serum, 24-hour-dialysate and 24-hour-urine in PD patients to compute total, peritoneal, and urinary clearance. RRF was estimated using four equations developed for dialysis patients without urine collection and compared to the mean of the urea and creatinine clearances in PD.
The concentrations of the three studied molecules were significantly reduced ($P < .001$) after dialysis session with significantly higher reduction ratio using HDF compared to HD modality ($P < .001$): BTP 49.3% vs 17.5%; B2M 82.3% vs 69.7%; CYSC 77.4% vs 66% in HDF and HD, respectively. In non-anuric PD patients, B2M and CYSC were partly removed by peritoneal clearance (72.3% and 57.6% for B2M and CYSC, respectively). By contrast, BTP removal by the peritoneum was negligible and a low bias for the BTP-based equation to estimate RRF (-1.4 mL/min/1.73 m^2) was calculated. BTP is significantly removed by high-flux HD or HDF, thereby compromising its use to estimate RRF. By contrast, BTP appears as a promising biomarker to estimate RRF in PD patients since it is not affected by peritoneal clearance, unlike B2M and CYSC, and it is well correlated to RRF.

23 Lindström V, Grubb A, Alquist Hegbrant M, Christensson A. Scand J Clin Lab Invest. 2008;68(8):685-691.

Different elimination patterns of beta-trace protein, beta2-microglobulin and cystatin C in haemodialysis, haemodiafiltration and haemofiltration.

Low molecular mass proteins (LMMP) are putative uraemic toxins, but their elimination is negligible in standard haemodialysis (HD). In this study, we used beta(2)-microglobulin, cystatin C and beta-trace protein, which differ in molecular mass and charge, to characterize the elimination patterns of three different dialysis modalities. Plasma samples were obtained at the start, 30 min after the start, at the end of the dialysis treatment and 30 min after termination of the dialysis session. Seventeen patients were treated with lowflux HD, 13 with post-dilution haemodiafiltration (HDF) and 8 with pre-dilution haemofiltration (HF). The changes in concentrations of the three LMMPs were monitored and expressed as percentages of the concentrations at the start of treatments. Conventional HD with low-flux membranes showed a high elimination of small molecules (urea and creatinine), but did not reduce the levels of the three LMMPs studied. During HDF and HF, there was a significant decrease in the plasma levels of cystatin C (to 28% and 44%, respectively) ($p < 0.001$) and of beta(2)-microglobulin (to 23% and 33%, respectively) ($p < 0.001$). However, the level of beta-trace protein was significantly reduced (to 65%) only after HDF.

The three dialysis modalities showed significantly different elimination patterns for the LMMPs studied. Elimination of beta-trace protein was lower than those of cystatin C and beta(2)-microglobulin both in HDF and HF. Beta-trace protein was only moderately eliminated by HDF and not at all by HF, and may be a useful marker in the evaluation of different convective therapies.

24 Foster MC, Coresh J, Hsu CY, et al. Am J Kidney Dis. 2016;68(1):68-76.

Serum ß-trace protein and ß2-microglobulin as predictors of ESRD, mortality, and cardiovascular disease in adults with CKD in the Chronic Renal Insufficiency Cohort (CRIC) Study.

Serum s-trace protein (BTP) and s2-microglobulin (B2M) are independently associated with end-stage renal disease (ESRD) and mortality in the general population and high-risk groups with diabetes or advanced chronic kidney disease (CKD). Less is known about their associations with outcomes and predictive ability in adults with moderate CKD. 3613 adults from the Chronic Renal Insufficiency Cohort (CRIC) Study (45% women; mean age, 57.9 years; 41.0% non-Hispanic black; 51.9% with diabetes). BTP and B2M with a reciprocal transformation to reflect their associations with filtration, creatinine-based estimated glomerular filtration rate (eGFRcr), measured GFR (mGFR) and a 4-marker composite score combining BTP, B2M, creatinine, and cystatin C were used. Over a six year median follow-up, 755 (21%) participants developed ESRD, 653 died, and 292 developed new onset cardiovascular disease. BTP, B2M, and the 4-marker composite were independent predictors of ESRD and all-cause mortality, and B2M and the 4-marker composite of cardiovascular events, after multivariable adjustment. These associations were stronger than those observed for eGFRcr (p vs. eGFRcr ≤ 0.02). The 4-marker composite led to improvements in the statistic and 2.5 year risk reclassification beyond eGFRcr for all outcomes.

25 Teo BW, Xu H, Koh YY, et al. Am J Kidney Dis. 2012;60(3):500-502.

Estimating kidney function in a multiethnic Asian population with multiple filtration markers.

Our study shows that ethnicity is not a significant factor in GFR estimation in a multiethnic Asian population when multiple markers of filtration are used, particularly if they exclude SCr and include serum BTP. SCr is an important biomarker in predicting GFR because models with SCr perform much better than non-SCr models. Also, serum BTP alone is not a good marker, but only contributes to improving prediction when used in combination with other markers. Further research into combinations of biomarkers in other populations would be required to confirm our findings.

This is the first study of a fairly large multiethnic Asian population including individuals with normal kidney function and those with CKD that also examines serum BTP as a kidney function biomarker over a wide range of GFRs. Predictive performance is improved when at least 2 biomarkers are incorporated in the equation, either SCysC or serum BTP plus standardized SCr.

Our study is limited by the absence of a validation sample and a small number of participants in each ethnic group. Although the idea of using a multiple marker panel for more accurate GFR estimation is attractive for clinical practice, this may be limited by the cost of assays.

In summary, equations incorporating multiple serum biomarkers improve the accuracy of GFR estimation. Ethnicity is rendered a less significant factor in GFR estimation in a multiethnic Asian population when multiple markers are used. Further studies are required to confirm our findings and develop definitive equations.

26 El-Sayed HM, et al. Egyptian Journal of Hospital Medicine. 2017 Oct;69(1):1589-94. (free)

Using serum beta trace protein to estimate residual kidney function in hemodialysis patients.

Residual kidney function (RKF) in end stage kidney disease (ESKD) patients contributes significantly to solute clearance. This improves survival as well quality of life in these patients. Kidney Diseases Outcomes Quality Initiative (KDOQI) guidelines suggest that hemodialysis (HD) dose can be safely reduced in those with RKF in the form of residual urea clearance (KRU) of 2 ml/min/1.73 m^2 or more. However, measurement of RKU is difficult as it requires regular inter-dialytic urine collections.

Simpler methods for measuring KRU and thus RKF are needed. Beta trace protein (BTP) has been proposed as an alternative marker of RKF and RKU. Dialysis specific equations to estimate KRU based on serum BTP were recently developed. This study aimed to compare measured KRU using inter-dialytic urine collection and estimated KRU using serum BTP.

Conclusion: KRU and thus RKF can be better estimated using serum BTP in patients with urine output >500 mL (a strong positive correlation was found between the estimated and measured KRU), than in patients with daily urine output 200–500 mL.

27 Bhavsar NA, Appel LJ, Kusek JW, et al. Am J Kidney Dis. 2011;58(6):886-893. (free)

Comparison of measured GFR, serum creatinine, cystatin C, and beta-trace protein to predict ESRD in African Americans with hypertensive CKD.

Identification of persons with chronic kidney disease (CKD) who are at highest risk to progress to end-stage renal disease (ESRD) is necessary to reduce the burden of kidney failure. The relative utility of traditional markers of kidney function, including estimated glomerular filtration rate (eGFR) and serum creatinine level, and emerging markers of kidney function, including cystatin C and beta-trace protein (BTP) levels, to predict ESRD and mortality has yet to be established. 865 African American individuals with hypertensive CKD enrolled in a clinical trial of 2 levels of blood pressure control and 3 different antihypertensive drugs as initial therapy and subsequently followed by an observational cohort study. 246 participants reached ESRD during a median follow-up of 102 months. The incidence rate of ESRD was higher with higher quintiles of each marker. The association between higher BTP level and ESRD was stronger than those for the other markers, including mGFR. All markers remained significantly associated with ESRD after adjustment for mGFR and relevant covariates (all $P < 0.05$), with BTP level retaining the strongest association (HR for highest vs lowest quintile, 5.7; 95% CI, 2.2–14.9). Associations with the combined end point of ESRD or mortality (n = 390) were weaker, but remained significant for cystatin C ($P = 0.05$) and BTP levels ($P = 0.004$). The ability of these markers to predict ESRD and mortality in other racial and ethnic groups and in individuals with CKD due to other causes is unknown. Plasma BTP and cystatin C levels may be useful adjuncts to serum creatinine level and mGFR in evaluating risk of progression of kidney disease.

N Latex BTP assay in children and transplant patients

28 Benlamri A, Nadarajah R, Yasin A, Lepage N, Sharma AP, Filler G. Pediatr Nephrol. 2010;25(3):485-490.

Development of a beta-trace protein based formula for estimation of glomerular filtration rate.

Beta-trace protein (BTP) is a novel marker of glomerular filtration rate (GFR). To date, no pediatric formula for calculating GFR based on BTP has been developed. We measured GFR, serum creatinine and BTP in 387 children who underwent 474 99mTc-DTPA acid renal scans. A BTP-based formula for estimating GFR was derived using stepwise linear regression analysis. A separate control group of 116 measurements in 99 children was used to validate the novel formula. A formula was also developed for each gender. The novel formula is: [formula: see text]. The Spearman rank correlation coefficient between the BTP-derived GFR estimate and the measured GFR was 0.80 [95% confidence interval (CI) 0.76–0.83], which is substantially better than that derived with the Schwartz formula (r = 0.70, 95% CI 0.65–0.74). The Bland-Altman analysis revealed a mean bias of 1.21% [standard deviation (SD) 28%] in the formula development dataset, which was virtually identical to the 1.03% mean bias (29.5% SD) in the validation group and no different from the Schwartz formula bias. The percentage of values within 10% (33.0 vs. 28.3%) and 30% deviation (76.8 vs. 72.6%) were better for BTP-based formula than for the Schwartz formula. Separate formulas according to gender did not perform better than that for the pediatric population.

This BTP-based formula was found to estimate GFR with reasonable precision and provided improved accuracy over the Schwartz GFR formula.

29 den Bakker E, Gemke R, Pottel H, et al. Clin Chim Acta. 2018;486:259-264.

Estimation of GFR in children using rescaled beta-trace protein.

Beta-trace protein (BTP) is a low molecular weight protein, produced mainly in the cerebrospinal fluid. It has been proposed as a marker for kidney function. Recently, a new method for GFR estimation using mean normal values to rescale GFR marker concentrations has been described for creatinine and cystatin C, two commonly used endogenous markers for kidney function. The aim of this study is to apply this approach to BTP in children. 322 inulin clearance tests were studied. Overall, our novel equation performed comparably to the creatinine-based FASage and the BTP-based Benlamri equations but was less accurate than FAScys (P30: 79.2 vs 86.3%, p = .008). Combining markers significantly enhanced performance compared to the single marker equations, with the exception of FAScys. Rescaled BTP concentrations are a simple method for estimating GFR in children. However, the additional value of BTP for the estimation of GFR compared to rescaled creatinine and cystatin C still remains to be demonstrated.

30 Zwiers AJ, Cransberg K, de Rijke YB, et al. Clin Chem Lab Med. 2014;52(12):1815-1821.

Reference ranges for serum ß-trace protein in neonates and children younger than 1 year of age.

Reliable reference values of enzymatically assayed serum creatinine categorized in small age intervals are lacking in young children. The aim of this study was to determine reference values for serum creatinine during the first year of life and study the influence of gender, weight and height on these values. Serum creatinine determinations between 2003 and 2008 were retrieved from the hospital database. Strict exclusion criteria ensured the selection of patients without kidney damage.

Correlation analysis was performed to evaluate the relation between height, weight and serum creatinine; the Mann-Whitney test was used to evaluate the relation between gender and serum creatinine. A broken stick model was designed to predict normal serum creatinine values. Mean serum creatinine values were found to decrease rapidly from 55 µmol/L on day 1 to 22 µmol/L in the second month of life; they then stabilized at 20 µmol/L until the seventh month, followed by a slight increase. No significant relation was found between serum creatinine and gender, weight and height. We present here reference values of serum creatinine in infants not at risk of decreased renal function. The absence of a relationship with gender, weight and height confirms that heightbased equations to estimate glomerular filtration rate are less useful in patients of this age group.

BTP was determined in 95 samples from healthy children <12 months of age by N Latex BTP. BTP was normally distributed (mean concentration 0.84± standard deviation 0.35 mg/L). Considering all children, the 50th centile BTP reference concentration was 0.82 mg/L (5th–95th centiles; 0.27–1.38). BTP concentrations were the highest in neonates and steadily declined with increasing age. No gender differences were found.

31 Pöge U, Gerhardt T, Stoffel-Wagner B, et al. Am J Transplant. 2008;8(3):608-615. (free)

Beta-trace protein-based equations for calculation of GFR in renal transplant recipients.

Recently, we showed that serum beta-trace protein (BTP) is an alternative marker of glomerular filtration rate (GFR) in renal transplant recipients (RTR). We have now developed three BTP-based GFR formulae derived by multiple regression analyses from the patients who had participated in that study. Currently, we validated the diagnostic performance of these BTP-formulae in 102 consecutive RTR who underwent a technetium diethylenetriamine pentaacetic acid (DTPA) clearance for GFR measurement in comparison to the re-expressed Modification of Diet in Renal Disease (MDRD) equation and a recently proposed BTP-based equation (referred to as 'White equation'). The best-performing BTP formula was found to be: GFR = 89.85 x BTP$^{-0.5541}$ x urea$^{-0.3018}$. This equation estimated true GFR virtually without bias (+0.43 mL/min/1.73 m^2, not significant [NS]), while a small, but significant, overestimation was seen for the MDRD formula (+3.43 mL/min/1.73 m^2, p = 0.003). Precision and accuracies within 50% of true GFR (93.1% and 88.2%, respectively) tended to be higher for the BTP formula, but the differences did not reach significance. The White equation overestimated the true GFR by 9.43 mL/min/1.73 m^2 (p = 0.001), and was inferior with respect to precision and 50% accuracy (79.4%).

BTP-based GFR calculations are reliable, and may serve as an alternative to the re-expressed MDRD equation.

Glossary:

99mTc-DTPA: 99m technetium diethylenetriaminepentaacetic acid

ESRD: end-stage renal disease

GFR: glomerular filtration rate

RRF/RKF: residual renal function/residual kidney function

free: Article with free online access.

At Siemens Healthineers, our purpose is to enable healthcare providers to increase value by empowering them on their journey toward expanding precision medicine, transforming care delivery, and improving patient experience, all made possible by digitalizing healthcare.

An estimated 5 million patients globally benefit every day from our innovative technologies and services in the areas of diagnostic and therapeutic imaging, laboratory diagnostics, and molecular medicine, as well as digital health and enterprise services.

We are a leading medical technology company with over 120 years of experience and 18,000 patents globally. Through the dedication of more than 50,000 colleagues in 75 countries, we will continue to innovate and shape the future of healthcare.

Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

This brochure is intended for use outside U.S. only (OUS). Display or promotion to U.S. audience is prohibited.

Siemens Healthineers Headquarters
Siemens Healthcare GmbH
Henkestr. 127
91052 Erlangen, Germany
Phone: +49 9131 84-0
siemens-healthineers.com

Published by
Siemens Healthcare Diagnostics Products GmbH
Laboratory Diagnostics
Emil-von-Behring-Strasse 76
35041 Marburg, Germany

Published by Siemens Healthcare Diagnostics Inc. · Order No. 30-20-DX-198-76 · 10-2020 · ©Siemens Healthcare Diagnostics Inc., 2020