Avaliação da estimativa da taxa de filtração glomerular com cistatina C em pacientes pediátricos

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Avaliação da estimativa da taxa de filtração glomerular com cistatina C em pacientes pediátricos

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LUCIANO DA SILVA SELISTRE

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Tese apresentada como requisito para a obtenção do grau de Doutor em Clínica Médica, pelo programa de Pós-Graduação da Faculdade de Medicina da Pontifícia Universidade Católica do Rio Grande do Sul.

Orientador: DAVID SAITOVITCH

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Dedico esta tese

Aos meus pais,

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“Todo efeito tem uma causa. Todo efeito inteligente tem uma causa inteligente. O poder da causa inteligente está na razão da grandeza do efeito.”

Hippolyte Leon Denizard Rivail **(1804, Lyon – 1869, Paris).**

LISTA DE ABREVIATURAS

IMC	Índice de Massa Corporal
SC	Área Superfície Corporal
BUN	Blood Urea Nitrogen
CrP	Creatinina Plasmática
Cys C	Cistatina C Sérica
mGFR	Taxa de Filtração Glomerular medida
eGFR	Taxa de Filtração Glomerular estimada
eGFRCys	Equações para eGFR baseada em Cys C
eGFRPCr	Equações para eGFR baseada em PCr
eGFRCom	Equações para eGFR baseada em PCr e Cys C
CKD	Chronic Kidney Disease
CKiD	Cohort Study of Kidney Disease in Children equation
IQR	Amplitude Interquartil
DP	Desvio Padrão
K/DOQI	Kidney Disease Outcomes Quality Initiative
IDMS	Isotope Dilution Mass Spectrometry

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SUMÁRIO

CONSIDERAÇÕES SOBRE A TESE

O Programa de Pós-Graduação em Medicina e Ciências da Saúde – FAMED/PUCRS não exige um formato específico para apresentação da tese de doutorado. Assim, o formato segue a preferência do autor, sendo a mesma escrita conforme as recomendações de *Spector* (Spector, N. *Manual para Redação de Teses, Dissertações e Projetos de Pesquisa.* Rio de Janeiro: Guanabara Koogan; 1997. 117 p.). As referências bibliográficas na introdução seguem as normas de *Vancouver* e as citações indicadas no texto seguiram o sistema de citações em sequência.

A avaliação da Taxa de Filtração Glomerular (TFG) é considerada o melhor índice para avaliar a função renal. Sua estimativa acurada é necessária para detectar, classificar e acompanhar o estágio da doença renal. Há escassos trabalhos brasileiros na literatura, que avaliem esse parâmetro em crianças. Objetivando à solução desse fato, realizamos pesquisa em França com a produção de um banco de dados a partir da coorte de Lyon do serviço de nefrologia pediátrica.

Incluímos nessa tese, como introdução, o projeto basilar que nos levou a realizar a pesquisa. Após, descrevemos as produções científicas. O autor participou da revisão da literatura, do desenvolvimento da ideia, da preparação do projeto, da seleção dos pacientes, da coleta de dados, da análise e interpretação dos dados e da redação da tese e do artigo. No Laboratório de Fisiologia Renal do Hospital Edouard Herriot de Lyon, a técnica e procedimentos para avaliação das substâncias estudadas foi instruída pela professora Laurence Dubourg.

O primeiro manuscrito foi o artigo original, que deu o escopo para o tema, publicado na revista internacional *Journal of the American Society of Nephrology* (fator de impacto 9,66) sobre avaliação de equações em adolescentes e adultos jovens. Outros dois artigos basearam-se na doença renal policística autossômica dominante e

transplantados renais pediátricos, tendo sido publicados nas revistas *Pediatric Nephrology* (fator de impacto 2,52) e *Transplantation Proceedings* (fator de impacto 1,05).

No momento, estamos com um quarto artigo em vias de encaminhamento para publicação para *Clinical Journal of the American Society of Nephrology* (fator de impacto 5,22). Concomitantemente, participamos da elaboração de capítulo de livro, em francês, e de 5 temas livres apresentados em congressos internacionais, versando sobre o mesmo assunto.

RESUMO

RESUMO

Introdução: As recomendações internacionais e nacionais recomendam a aferição da taxa de filtração glomerular como preditor de doença renal na população geral, com uso de creatinina plasmática. Entretanto, na pediatria existe uma alta prevalência de fatores que interferem na creatinina plasmática, dentre os quais a taxa de crescimento. As equações mais empregadas são derivadas da fórmula de Schwartz abreviada (*bedside*). A cistatina C sérica, uma proteína não glicosilada de baixo peso molecular que é produzida por todas as células nucleadas, tem sido apontada como um marcador de filtração glomerular. Nesse contexto, há dúvidas em relação à cistatina C na pediatria, devido à escassez de estudos com delineamento adequado no Brasil.

Objetivo: Avaliar transversalmente a acurácia diagnóstica da cistatina C, creatinina plasmática, ou ambas em estimar mudanças na TFG comparados à inulina numa coorte prospectiva de crianças com doença renal.

Pacientes e Métodos: Em uma fase inicial, adquirimos a estratégia metodológica para a realização da TFG por depuração plasmática de inulina, em pediatria e na população de adultos jovens, com respectiva publicação. Após, utilizou-se de medidas simultâneas e repetidas de depuração renal de inulina em pacientes pediátricos. A análise foi realizada por modelo linear misto, devido ao número repetido de medidas no mesmo paciente. Para avaliar a concordância entre os métodos foram utilizados gráficos de Bland Altman e teste de correlação de concordância. Em uma segunda fase, foram realizadas medidas de cistatina C e de creatinina plasmática em pacientes renais pediátricos, inclusive transplantados, com subsequente publicação de um artigo e submissão de outro para análise.

Resultados: Essa tese gerou 4 apresentações em congressos científicos internacionais, 4 artigos e 1 capítulo de livro em francês (em anexo).

Conclusões: A aferição adequada da TFG é de fundamental importância na prática clínica em todas as fases da vida do indivíduo. A TFG declina progressivamente, com o tempo, na maioria das enfermidades renais, o que resulta em complicações como hipertensão arterial, anemia, desnutrição, enfermidade óssea, neuropatias.

Descritores: Cistatinas. Taxa de Filtração Glomerular. Inulina. Pediatria.

ABSTRACT

ABSTRACT

Introduction: There have been national and international recommendations to estimate glomerular filtration rate as a predictor of kidney disease, in the general population, measuring plasma creatinine concentration. In pediatrics, however, there is a high incidence of factors that affect plasma creatinine concentration, such as growth rate and the equations most commonly used to estimate GFR are derivative from Bedside Schwartz formula. The serum cystatin C, an unglycosylated protein of low molecular weight, produced by all nucleated cells, has been proposed as a marker of glomerular filtration. In this context in Brazil, there have been doubts among professionals about using cystatin C in pediatrics, due to the lack of appropriate studies about it. **Objective**: We sought to investigate the transversal diagnostic accuracy, either related to cystatin C or plasma creatinine or both in comparison with inulin, for estimating changes in GFR in a prospective cohort of children with kidney disease. **Patients and Methods**: Firstly, we have chosen as methodological strategy for the estimation of GFR the measurement by inulin clearance, in pediatrics and in a young adult population, followed by a respective publication. Secondly, we have used repeated and simultaneous measurements of renal clearance by inulin in pediatric patients. The analysis has been performed by linear mixed model due to the number of repeated measurements from the same patient. In order to assess the equivalence between methods, we applied Bland & Altman graphics, as well as concordance correlation tests. In a second phase, we had cystatin C and serum creatinine measured in pediatric renal patients, including those patients who had undergone a transplant. Consequently, an article was submitted to publication and another one was submitted to analysis. **Results**: This thesis has generated four presentations at international scientific congresses, 4 articles and 1 book chapter in French (attached). **Conclusions**: The adequate measurement of GFR is of fundamental importance in clinical practice in all phases of one's life. The GFR progressively declines with time, in most renal diseases, which results in complications such as hypertension, anemia, malnutrition, bone disease, neuropathies.

Keywords: Glomerular Filtration Rate. Inulin. Pediatrics. Cystatins.

INTRODUÇÃO – PROJETO INICIAL

1 INTRODUÇÃO

1.1 ASPECTOS GERAIS

A Taxa de Filtração Glomerular (TFG) é considerada o melhor índice de função renal, e a técnica mais utilizada para a sua avaliação é a medida da depuração plasmática de certos compostos endógenos ou exógenos pelos rins[1-38]. A taxa de depuração (clearance) é definida como a quantidade de plasma que é eliminada de uma substância na unidade de tempo. A determinação estrita da TFG requer a medida da depuração de um marcador que não seja reabsorvido e nem secretado pelo túbulo, sendo excretado na urina apenas por filtração glomerular[1-38].

A TFG poder ser aferida pelo método de infusão endovenosa contínua de substâncias exógenas (exemplo: inulina), com coletas de urina e sangue a intervalos regulares, sendo esta a técnica padrão de depuração renal[1-8].

A TFG pode ser medida por meio da determinação da concentração plasmática de proteínas endógenas, como ureia, creatinina e cistatina C.

A dosagem plasmática de ureia foi introduzida como índice de função renal, em 1903, por Strauss. A ureia conserva-se como um teste de baixa precisão por ter poucos caracteres de um marcador ideal, visto que não tem uma produção constante, variando na ingestão e no catabolismo proteico e apresentando uma grande reabsorção tubular[1, 2].

A avaliação precisa da TFG é uma importante chave para a identificação e tratamento da doença renal crônica (DRC), cujas primeiras etapas são silenciosas e não são detectadas com exames de rotina. A função renal declina progressivamente com o tempo, na maioria das enfermidades renais, o que resulta em complicações como hipertensão arterial, anemia, desnutrição, enfermidade óssea, neuropatia e baixa qualidade de vida[2].

1.2 INULINA

Em 1935, Shannon e Smith propuseram como substância ideal para a medida da taxa de filtração glomerular, a inulina[3, 22]. A depuração renal da inulina é o padrão ouro de medida da TFG, tanto para animais como para o homem; e, desde que foi descrito em 1951, poucas mudanças foram feitas na técnica original[1-2,22-23]. A inulina é um polímero de frutose com peso molecular de aproximadamente 5.200 daltons, sendo encontrada na natureza em poucas espécies de plantas, como a alcachofra de Jerusalém, a dália e a chicória. Possui todos os atributos de um marcador ideal de extracelular, é livremente filtrada pelos glomérulos, não sofre reabsorção nem secreção pela célula tubular renal[22-23].

A técnica de injeção única de inulina é outra forma de se medir a TFG, através do cálculo da dose injetada dividida pela área sob a curva de decaimento plasmático[27,38]. Para calcular a área sob a curva de maneira acurada, são necessárias várias amostras da concentração ou da atividade do marcador no plasma. A estimativa dessa área fundamenta-se na estimativa da inclinação na curva, denominado como método da inclinação-intercepto.

Na prática clínica, a TFG é estimada, preferencialmente, pela creatinina plasmática (CrP)[4]. A cistatina C (Cys C) tornou-se mais frequente como novo marcador da TGF, visto que a CrP possui variação importante na sua medida em pacientes com doença renal[1,2,4-38].

1.3 CREATININA PLASMÁTICA

As determinações da CrP e da sua depuração em urina de 24 horas são os procedimentos mais utilizados para a avaliação da função de filtração glomerular na rotina laboratorial[1,2,23,38]. A CrP é formada a partir da hidrólise não-enzimática da creatina e da fosfocreatina musculares, com um peso molecular de 113 daltons e sem ligação a proteínas plasmáticas. Noventa e oito por cento da creatina é estocada no músculo após ter sido sintetizada no fígado a partir dos aminoácidos glicina e arginina. A outra fonte de creatina é a ingestão de proteína animal[5,23].

Um percentual próximo a 2% da creatina muscular é convertido em creatinina a cada dia. Entretanto, apresentam alguns inconvenientes. Variáveis pré-analíticas, como a perda de urina durante a coleta e a hidratação do paciente, — bem como a

interferência analítica o método de Jaffé dependente decorrente da presença de bilirrubina, glicose, ascorbato e hemólise, ou substâncias exógenas como as ciclosporinas e cefalosporinas e outros medicamentos e seus metabólitos —– podem prejudicar o uso da CrP[1,4-38]. A desproteinização de amostras e o uso de métodos enzimáticos, a creatinina iminoidrolase ou amidoidrolase, foram implantados na prática laboratorial para extrair esses interferentes[6,22-23].

Nas situações em que a função renal está discretamente alterada, a correlação entre a CrP e a filtração glomerular é menor, levando a uma estimativa imprecisa da filtração glomerular, devido à alta variabilidade interindividual e a secreção tubular da mesma[5,23].

Nos consensos, recomenda-se a aplicação de fórmulas para avaliar a TFG em vez da depuração da CrP. Essas equações propõem-se a minimizar os fatores que interferem na CrP, tais como peso, altura, idade, sexo, raça, dieta e o método analítico laboratorial[1,2].

1.4.1 CREATININA PLASMÁTICA NA PEDIATRIA

Notoriamente, a CrP é a substância mais utilizada para aferição da TFG, seja por fórmulas ou por coleta de 24 horas. Entretanto, como descrito anteriormente possui as mesmas dificuldades, seja na aferição laboratorial, seja na variabilidade interindividual que varia com o crescimento da criança[22-23,33].

A depuração de creatinina também traz limitações pela necessidade de armazenar urina por um período de 24 horas, pois fica sujeita a erros de coleta e ao esvaziamento incompleto da bexiga, além do efeito de secreção tubular da creatinina.

Assim, a estimativa do clearance de creatinina pode ser realizada, com confiabilidade razoável, por fórmulas que relacionam a estatura, ou altura em centímetros, com o valor da CrP em mmol/litro. A equação mais difundida na pediatria é a de Schwartz simplificada[2,11,19-20,23]. Essa fórmula foi proposta pela primeira vez, em 1976, por Schwartz[2], tendo sido revisada em 2009. A equação derivou-se da relação, por regressão linear, entre a CrP e altura de 349 crianças portadoras de doença renal crônica, com idade mediana de 10,8 anos e com retardo de crescimento[20,23,33]. Após análise por regressão multivariada, demonstrou-se que a razão entre a CrP e estatura possui a melhor correlação com TFG (R^2=0.65),

indicando essa associação (altura e CrP) como essencial para avaliar a filtração glomerular em população pediátrica[2,20].

1.4 CISTATINA C

A cistatina C (Cys C) é uma proteína não glicosilada, de baixo peso molecular de 13,35 daltons, constituída por uma cadeia polipeptídica de 120 aminoácidos, com uma ponte de enxofre entre os resíduos 73 e 83 e uma entre os resíduos 97 e 117[14]. O ponto isoelétrico é de 9,3 e ela tem carga positiva, inibidora da proteinase da cistina, que é produzida pela maioria das células nucleadas, e está presente em todos os líquidos biológicos em concentrações fisiologicamente relevantes[6-7].

A Cyst C é produzida em taxa uniforme pelas células nucleadas, sendo um inibidor das proteinases cisteínicas. O seu gene é localizado no cromossoma 20. A Cyst C faz parte de uma superfamília com 12 membros, subdividida em: Família 1, ou estefinas, na qual estão incluídas as cistatinas A e B; Família 2, ou cistatinas, que compreende as cistatinas C, D, E, F, G, S, AS e SN; e a Família 3, formada por duas glicoproteínas nomeadas kininogênios[6-7].

A determinação plasmática da Cys C possui alta sensibilidade na avaliação do índice de filtração glomerular[8-14,16-37]. A concentração média normal dessa proteína é de 0,7 mg/dL e aumenta proporcionalmente com a diminuição da taxa de filtração glomerular (TFG). Esta alta sensibilidade deve-se ao fato de a Cys C ser produzida de forma constante, de sua produção não ser influenciada por processos inflamatórios, dieta ou massa muscular e de não ocorrerem variações no sexo do paciente[8,7-14,25].

Estudos mostram que os níveis séricos de Cys C começam a aumentar quando a TFG está em torno de 88 ml/min, enquanto a concentração sérica de creatinina somente aumenta quando a TFG está abaixo de 75 ml/min[9-10,22].

Os principais atributos da Cys C, como marcador de função renal, são o peso molecular baixo e a característica isoelétrica, os quais permitem que essa proteína seja facilmente filtrada através da membrana glomerular, sendo reabsorvida no túbulo proximal em uma proporção significativa e, então, catabolizada de forma quase total neste sítio[9]. Não estão descritas rotas extrarrenais de eliminação da Cys C, e fatores como processos inflamatórios e infecciosos não alteram os níveis dessa proteína, que são essencialmente dependentes da filtração glomerular. Portanto, os

níveis séricos de Cyst C não seriam afetados pela massa muscular nem pela idade, nítidas vantagens sobre a CrP[9, 11-13].

1.4.1 CISTATINA C - dosagem laboratorial.

Ensaios automatizados baseados em nefelometria e turbidimetria possibilitaram a ampliação do uso da Cyst C na rotina. O primeiro ensaio laboratorial por turbidimetria (PETIA – *Particle-enhanced immunoturbidimetry assay*) para a dosagem de Cyst C em amostras de soro e plasma foi comercializado em 1994. Em 1997, se propôs o primeiro ensaio laboratorial baseado na técnica de nefelometria[9,14,36].

A nefelometria é uma técnica para medir as concentrações de imunoglobulinas e outras proteínas plasmáticas de uma amostra. É utilizado, para isso, um aparelho específico que mede a turbidez e mede a difração (desvio) da luz ao passar por uma solução contendo complexos imunológicos[34].

Já a imunoturbidimetria mede a diminuição da luz ao passar por um complexo antígeno-anticorpo. Em outras palavras, a turbidimetria mede o quanto a solução antígeno-anticorpo absorve da luz e o quanto ela deixa passar. Essa técnica, assim como a nefelometria, é usada para medir a concentração plasmática de diversas proteínas[34].

A principal diferença entre nefelometria e a turbidimetria é que na nefelometria a luz é difundida, ou seja, atravessa a solução, enquanto que na turbidimetria a luz não difundida (a absorvida) é medida.

Em princípio, a dosagem sérica de Cyst C não apresenta interferências laboratoriais com bilirrubinas, paraproteínas, hemoglobina, triglicérides, processos inflamatórios, proteinúria, massa muscular, sexo, etnia ou superfície corpórea[7,9,12,14,32].

O uso de doses elevadas de corticoides tem sido associado ao aumento da produção de Cyst C e à elevação dos seus níveis séricos[15,22,36]. A terapia com corticoides resulta em subestimativa do TFG dose-dependente, devido à elevação da cistatina C. A disfunção da tireoide, mesmo sendo leve, altera os seus níveis[36]. A Cyst C possui valores influenciados pela ação dos hormônios na sua produção celular, sendo eles inferiores no hipotireoidismo e elevados no hipertireoidismo[9,36].

1.4.2 CISTATINA C EM PEDIATRIA

A determinação de Cys C apresentaria vantagens em relação à CrP em populações pediátricas[7,13,17-19,21-22]. Por estar relacionada com a massa muscular, a CrP poderia não detectar alterações na TFG em crianças menores de 4 anos.[16-17] Por outro lado, a Cys C seria constante em crianças a partir do primeiro ano de vida até a fase adulta[18]. Bokenkamp e colaboradores descreveram uma acurácia melhor para Cys C em relação à CrP para aferição da TFG em crianças, quando comparado à inulina[6].

Filler e colaboradores definiram os intervalos adequados para Cys C em crianças, sendo eles mais elevados em neonatologia, com redução gradativa no decorrer do primeiro ano de vida, e permanecendo constantes entre o primeiro ano de vida até os 17 anos[19].

Finney H *et al*.[5] definiram, pela primeira vez, os intervalos de referência para a concentração sérica de Cyst C na população pediátrica, notando que a sua concentração não se alterava por influência de variantes antropométricas, como peso e massa muscular, no desenvolvimento das crianças. A Cyst C é mais elevada em prematuros (0,43 à 2,77 mg/dL), neonatos (0,81 à 2,32 mg/dL) e gradativamente cai no primeiro ano de vida. Em crianças com idade entre 1 e 17 anos, a Cyst C foi constante entre 0,50 a 1,27 mg/dL. Já a CrP tem comportamento semelhante nos primeiros meses de vida, porém os níveis séricos crescem gradualmente na infância e na adolescência, independente da filtração glomerular.

Como não há trabalhos no Sul do Brasil que avaliem a Cys C como marcador de TFG em pacientes pediátricos, decidiu-se avaliar este marcador, utilizando-o como componente em fórmulas para medida de TFG. Para isso, seria de fundamental importância a utilização de inulina, que é o padrão ouro para avaliação de TFG, como controle das medidas que incluíssem Cys C, técnica não disponível para uso rotineiro no Rio Grande do Sul. Assim, a possibilidade de concretizar este estudo com um número suficiente de indivíduos seria conduzindo a pesquisa em um Centro que realizasse rotineiramente a avaliação da TFG através da inulina em pacientes pediátricos.

2 OBJETIVOS

2 OBJETIVOS

GERAL

Comparar o desempenho preditivo de fórmulas para estimativa de TFG utilizando Cys C, com equações que utilizam CrP, em pacientes pediátricos, tendo como padrão ouro a medida da TFG com a inulina.

ESPECÍFICOS

1. Colacionar quatro fórmulas para medida da TFG utilizando Cys C isoladamente (Filler[19] e Bricon[12]) ou associada à CrP (CKID[20] e Zappitelli[21]) com duas equações (Schwartz bedside[20] e Schwartz Lyon[22]) que utilizam exclusivamente CrP, em pacientes pediátricos;

2. Confrontar o desempenho preditivo de quatro fórmulas para medida da TFG utilizando Cys C, isoladamente (Filler e Bricon) ou associada à CrP (CKiD e Zappitelli), com duas equações (Schwartz bedside e Schwartz Lyon) que utilizam exclusivamente CrP, utilizando-se como padrão ouro de controle a TFG estimada com inulina como marcador, em pacientes pediátricos.

3 PACIENTES E MÉTODOS

3 PACIENTES E MÉTODOS

3.1 Definição de Termos

Variáveis de confusão: aquelas cujas modificações durante o período do estudo poderiam interferir na taxa de filtração glomerular. As variáveis de confusão cujas modificações poderiam interferir nos valores de inulina, creatinina e cistatina C são: índice de massa corporal (IMC), dose diária de prednisona, inulina, bexiga neurogênica, uso de diuréticos.

Insuficiência Renal Crônica: consiste em lesão renal e perda progressiva e irreversível da função dos rins (glomerular, tubular e endócrina).

Estadiamento da Insuficiência Renal Crônica: definido pela taxa de filtração glomerular pela inulina em grupo 1 (>90 ml/min /1,73m^2), grupo 2 (60-89), grupo 3 (30-59), grupo 4 (15-29) e grupo 5 (<15).

Síndrome nefrótica: presença de proteinúria ≥ 3,5 g/1,73m² em 24 h ou 50 mg/ Kg de peso, acompanhada de hipoalbuminemia, dislipidemia e edema.

Índice de massa corporal: IMC (kg/m²) = Peso/Altura².

Percentil altura e peso: Os resultados dos percentis de crescimento são comparados com as medidas normais ou padrão para meninos ou meninas da mesma idade e sexo. Os resultados foram interpretados como médias de percentis.

Classificação do estado nutricional, como se segue:

- Acima do percentil 97: classificar como sobrepeso;

- Entre os percentis 97 e 10: faixa de normalidade nutricional;
- Entre os percentis 10 e 3: classificar como risco nutricional;
- Entre os percentis 3 e 0,1: classificar como peso baixo;
- Abaixo do percentil 0,1: classificar como peso muito baixo.

3.2 Delineamento do Estudo

Estudo transversal com medidas repetidas da coorte da população pediátrica do Serviço de Nefrologia Pediátrica da região Rhône-Alpes, França.

Fase 1

Lyon – França

- ❖ Aquisição da metodologia da aferição da TFG através da inulina.
- ❖ Comparar a TFG através da inulina e a TFG estimada por Cyst C e CrP.
- ❖ Estágio no serviço de bioestatística do *Hôpital Edouard Herriot.*

Fase 2

Brasil

Análise de dados, redação da tese, confecção e submissão do artigo a uma revista de impacto internacional e defesa pública do doutorado.

3.3 Amostra

A amostra é composta de 259 crianças com 695 medidas, média de 3 medidas, por indivíduo, de clearance de inulina da coorte do Serviço de Nefrologia do *Hôpital Mére et Enfants* e *Hôpital Edouard Herriot.*

3.4 Período de Realização do Estudo

1. Contato e aceite do serviço de Lyon para estágio prático-teórico (anexo1)

2. Estágio prático-teórico no serviço de transplantes renais e laboratório de fisiologia renal do *Hôpital Femme Mère et Enfants* (Lyon-França) com submissão dos dados em artigos científicos: julho/2010 a dezembro/2011 (anexo 2).
3. Execução do projeto no Brasil com coleta de cistatina C em pacientes pediátricos: foi abortado por falta de recursos financeiros e técnicos no país.
4. Aprovação no teste de qualificação em abril de 2012.
5. Análise dos dados coletados na França: maio/2011 a junho/2012.
6. Confecção da tese de doutorado e artigo para publicação: julho/2012 a outubro/2012.
7. Apresentação da tese: 18 de dezembro de 2012.

3.5 Critérios de Inclusão

1. Idade inferior a 18 anos.
2. Ambos os sexos.
3. Função renal medida pela inulina.
4. Consentimento informado assinado pelo responsável (em anexo).

3.6 Critérios de Exclusão

- Pacientes portadores de hipotireoidismo.
- Alta doses de corticoterapia, acima de 0,5 mg/kg de peso

3.7 Desfechos de Interesse

- Taxa de filtração glomerular.

3.8 Variáveis Analisadas

Foram avaliados os seguintes parâmetros: idade, índice de massa corporal, doença básica, faixa etária, TFG por inulina e estimadas pelas fórmulas.

Fórmulas utilizadas para estimar a taxa de filtração glomerular.

	Formula (mL/min per 1,73 m²)
Creatinina plasmática	
Schwartz Lyon	eGFR = *k* × altura (cm)/CrP
	*k**= 35,5 meninos >13 anos
	*k**= 32,5 todas as outras crianças
	*k***= 0,401 meninos >13 anos
	*k***= 0,368 todas as outras crianças
2009 Schwartz bedside	eGFR* = 36,5 × altura (cm)/CrP
	eGFR** = 0,413 × altura (cm)/CrP
Cistatina C	
Bricon	eGFR** = (78/Cys C**) + 4
Filler	log(eGFR)**= 1,962 + [1,123 × log (1/Cys C**)
Combinadas	
CKID	eGFR** = 39,1 × [altura (m)/(CrP**)]^{0,516} × [1,8/Cys C] ^{0,294} × [30/BUN (mg/dl)]^{0,169} × [1,099]^{masculino} × [altura(m)/1,4] ^{0,188}
Zappitelli	
	eGFR* = [507,76 × e$^{0,003\times altura\ (m)}$]/[Cys C**^{0,635}] × [CrP*^{0,547}]
	Se transplante renal, × 1,165
	Se espinha bífida, × [CrP*^{0,547}])/40,45

µmol/L*, mg/dL**

CrP(µmol/L) = CrP (mg/dL) ×88,4

3.8.1 Determinação da Depuração Renal de Inulina

As medidas de depuração foram feitas no laboratório da Unidade de *Éxploration Functionelle Rénale de Lyon* - França. Os pacientes foram mantidos em repouso absoluto no leito, em decúbito dorsal, após período de jejum de 12 horas e dieta pobre em proteínas nas 18 horas que antecederam ao exame.

A apresentação farmacêutica da inulina utilizada foi o polyfructosan, uma forma sintética de inulina (sinistrin, INUTEST 25*%, Fresenius Kabi Austria GmbH,* Linz, Austria). Esse polímero de frutose tem elevada solubilidade e conveniência para administração endovenosa, com equivalente permeabilidade na membrana basal glomerular. A inulina foi administrada com técnica de infusão contínua, em veia periférica e com Bomba de Infusão após dose em *bolus* de 30 mg/kg de peso diluída em 100ml de SF 0,9%. O tempo de infusão foi de 05h30min, dando início às 07h30min e término às 13h. Os pacientes receberam aporte hídrico de 5 ml/kg antes da infusão do *bolus*, seguidos por 3 ml/kg de água a cada 30 minutos e solução de cloreto de sódio à 0,9%, até o final do exame. Após 90 minutos de infusão, tempo necessário para a estabilização da inulina no sangue, foi feita coleta de sangue e solicitado ao paciente esvaziamento espontâneo da bexiga, dando início ao 1º período de depuração. Para cada paciente foram feitos 04 períodos de clearance, e o resultado final dado como a média dos 04 períodos.

O esvaziamento vesical se deu de modo espontâneo. A decisão por não cateterização foi baseada em estudos já publicados de validação de métodos de depuração que utilizaram a depuração renal de inulina como método padrão-ouro e com esvaziamento espontâneo da bexiga.

O método empregado foi espectrofotometria, utilizando o reagente de antrona 117.

3.8.2 Dosagem de Inulina no plasma

Os plasmas foram desproteinizados por meio da diluição 1:11 do plasma (50 µl) em ácido perclórico a 5% (500 µl) e centrifugação de 06 min; em tubo de ensaio, aos 250 µl do sobrenadante se adicionava 3,0ml do reagente de antrona. Para o tubo branco, adicionava-se 3,0ml de reagente de antrona a 250 µl de ácido perclórico a 5%.

Os tubos foram agitados antes e depois da adição do reagente de antrona e colocados em banho-maria por 10 minutos. Após esse período cronometrado, os tubos foram resfriados em água corrente; a leitura da amostra foi feita por espectrofotometria em 620nm e a concentração plasmática dada pela equação: Concentração plasmática de inulina (mg/dL)= (Absorbância da amostra x Fc x11)/5.

3.8.3 Dosagem de Inulina na urina

Em tubo de ensaio, 100 µl da amostra de urina diluída foi adicionada a 150µl de ácido perclórico a 5%, seguido por 03ml do reagente de antrona. Os tubos foram agitados antes e após a adição do reagente de antrona. Para o tubo branco (blank), 100 µl de água destilada era adicionada a 150 µl de ácido perclórico a 5%, seguido por 03ml do reagente de antrona.

O tubo foi agitado antes e após a adição do reagente de antrona. Os tubos de ensaio (amostras e blank) foram colocados em banho-maria a 52ºC por 10 minutos, depois resfriados em água corrente; por fim, foi feita a leitura da absorbância em espectrofotômetro a 620nm.

A concentração em mg/dL foi calculada pela fórmula baixo: Concentração Urinária de inulina (mg/dL)= (Absorbância x Fc x 11 x 3)/2.

3.8.4 Dosagem de Creatinina Plasmática

A medida da CrP foi determinada pelo método colorimétrico de Jaffé modificado. O método tem como princípio a reação, em solução alcalina, da creatinina com o ácido pícrico, formando um complexo amarelo avermelhado. A leitura espectrofotométrica foi medida em comprimento de onda de 512 nm; a intensidade da cor é diretamente proporcional à CS de creatinina.

Os insumos empregados foram produzidos pela empresa Roche da França. A sensibilidade e a linearidade para o ensaio de creatinina sérica são, respectivamente, 0,2 e 25 mg/dL. O coeficiente de variação intraensaio foi de 0,7% e o interensaio é de 4% em concentrações mais baixas de CrP (45-50 µmol/l) e 1,5% na mais alta concentração (580 µmol/l), respectivamente. Os valores de referência foram estabelecidos para homens em 62-106 µmol/l e, para mulheres, em 44-80 µmol/l. Os resultados foram estandardizados por regressão linear, ajustadas pela

espectrometria cromatográfica de massa (LCMS). LCMS foi calibrada por três laboratórios europeus e 2 americanos, com as concentrações variando entre 66,5 e 404 µmol/l. Os parâmetros da regressão linear eram adquiridas de 54 amostras com creatinina sérica variando de 41 a 220 µmol/l. 94,2% das amostras do nosso grupo estavam dentro desse nível. A calibração respeitava a seguinte equação: creatinina sérica estandardizada= 0,9395* (Jaffé compensada creatinina sérica em µmol/l) + 4.6964. Intercept (4.6964; 95% IC [-2.4619 to 11.8656]) e slope (0.9395; 95% CI [0.8719 to 1.0072]), não sendo significativamente diferente de zero e 1, respectivamente. O coeficiente de correlação foi de 0,97.

3.8.5 Dosagem de Cistatina C Plasmática

A medida da CS de cistatina C foi realizada em amostras de soro por técnica de Nefelometria. As amostras foram dosadas em nefelômetro BN II Dade Behring (Sistema BN), empregando-se insumos da mesma procedência do equipamento (*kit N Latex Cystatin C*)[22].

O método de imunonefelometria utiliza partículas de poliestireno carregadas com anticorpo de coelho específico contra a cistatina C humana, que, na presença de amostras de soro contendo cistatina C, sofrem aglutinação, gerando luminescência. A intensidade de luz dispersa no equipamento depende da concentração da proteína cistatina C na amostra; a concentração analítica da amostra pode ser determinada por comparação com diluições de um padrão de concentração conhecida. Para o ensaio laboratorial, todos os passos foram executados automaticamente pelo aparelho (Sistema BN), que inclui um *software*.

As amostras de soro foram diluídas a 1:100 com diluente N; esse reagente N é composto por uma suspensão de partículas de poliestireno carregadas com aproximadamente 0,03g/L de anticorpo de coelho anticistatina C humana.

O controle de qualidade é dado pelos controles do material do calibrador, cuja fonte é um purificado de cistatina C humana (*control cystatin c*). A curva de calibração fornece intervalos de medidas de 0,23-7,25mg/dL. A variação intraensaio é de 2,3 a 4,1%; a variação interensaio de 2,6 a 3,3%; o valor de referência é de 0,50 a 0,96 mg/dL.

3.8.6 Dosagem de Uréia Plasmática

A ureia foi dosada em amostra de soro pelo método cinético, que utiliza o sistema enzimático urease/glutamato desidrogenase (GLDH).

A ureia contida na amostra é hidrolisada em amônia e CO2 na presença da enzima urease. A amônia formada reage com alfacetoglutarato e NADH (dinucleotide adenina de nicotinamide), na presença de GLDH, gerando NAD, L-glutamato e água. A diminuição na absorbância devido ao consumo de NADH é medida cineticamente.

Nós convertemos o resultado de ureia em mmol/L para o resultado de BUN em mg/dL, dividindo-a por 0,357.

3.9 Análise Estatística

A análise estatística foi executada com o *Software* livre *R* versão 13.0. Os dados foram previamente avaliados quanto à sua distribuição, tendo sido aplicado o teste de normalidade de Kolmogorov-Smirnov. O teste Mann-Whitney foi utilizado para comparação entre medidas, quando apropriado.

As medidas de depuração foram normatizadas para 1,73m² de superfície corpórea. Para cálculos da superfície corporal foi utilizada a equação de DuBois: SC (m²)= (0,007184)*(Altura ^{0,725})*(Peso^{0,425}), com peso em kg e altura em cm.

3.9.1 *Bland-Altman* para medidas repetidas com modelo misto

O desempenho de seis fórmulas foi comparado com o clearance de inulina. Para análise dos dados, foram utilizadas a razão média entre a TFG estimada e a TFG real com representação gráfica de *Bland-Altman*[23,40].

A análise estatística de *Bland-Altman* foi utilizada para avaliar o grau de concordância entre a depuração de inulina e as fórmulas de estimação. A razão média das diferenças representa uma estimativa de erro ou *bias,* uma diferença sistemática entre os métodos de depuração da inulina e das fórmulas; o desvio padrão dessas razões mede as flutuações ao redor da média. Noventa e nove por cento dessas diferenças estarão entre dois limites definidos como limites de

concordância: o limite inferior, dado pela média das diferenças subtraída de 1.96xdp; e o limite superior, dado pela média das diferenças somado a 1.96xdp. Para medir o grau de concordância, foram considerados o erro (*bias)* e os limites de concordância. A TFG estimada (TFGe) e a TFG medida (TFGm) foram comparadas entre e intra indivíduos.

A terminologia de medidas repetidas é usada para nomear medidas dispostas na mesma variável ou na mesma unidade experimental, em mais de uma ocasião.Os modelos mistos proporcionam a modelagem intraindivíduo, muitas vezes em dados agrupados. As observações no mesmo indivíduo não podem ser consideradas não correlacionadas e os modelos mistos constituem uma ferramenta conveniente para adequar essa análise intraindivíduo. Diversos planejamentos com medidas repetidas são corriqueiros, sejam longitudinais, transversais e Split plot (parcelas subdivididas). Nós optamos pelo tipo transversal, já que a análise longitudinal não foi possível, pela pouca variância durante o tempo.

As medidas repetidas foram mensuradas através de agrupamentos de pacientes e ajustadas por modelo linear de efeito misto[41]. Foram estimados os limites de 95% de intervalo de confiança para razão das médias associando a variância entre e intrassujeito[24]. Foi utilizado o seguinte modelo:

$$lme(\log.difference \sim 1, random = \sim 1 \mid \text{patient})$$

Onde: log**.**difference = log (valor de TFGe) – log (valor de TFGm). Como o resultado em diferenças de Logaritmo Taxa não é fácil de interpretar, foi utilizada a operação inversa (anti-log = log (TFGe) / log (TFGm)). Desta forma, para tornar a apresentação de dados mais clara, os mesmos são apresentados diretamente em razão TFGe / TFGm. A razão para cada par de medidas ***(j)*** no indivíduo (***i*)** foi modelada como segue:

$$R_{ij} = \beta + I_i + E_{ij}$$

Sendo R_{ij} a razão entre a fórmula e a inulina, **β** a razão média entre essas medidas, ***I*** a interação entre indivíduos e E_{ij} os efeitos randômicos intraindivíduo para cada razão entre a fórmula e a inulina. Foram estimados os limites de concordância, somando as variâncias intra e interindivíduos, e calculando o desvio padrão da razão média, como o modelo:

$$\lim ag = \beta \pm 1.96 * SD$$

A razão média foi utilizada para corrigir a variância de *bias*, visto que a diferença média entre TFGe e TFGm no mesmo sujeito não eram constantes. Houve um aumento na variabilidade com aumento dos valores de inulina. A razão representada entre o *bias* das fórmulas e a inulina quando o valor é 1, demonstra ausência de *bias* entre as médias da população.

3.9.2 Coeficiente de correlação de concordância (CCC)

O coeficiente de correlação de concordância (CCC), descrito por Lin, é uma medida de ajuste na correlação de Pearson[25]. Essa análise avalia o quanto a correlação entre as medidas de TFG afastam-se da linha de 45^0, refletindo a acurácia (Cb) e a precisão (ρ). A primeira analisa o quanto a reta de regressão se desvia da linha de concordância perfeita (valor= 0 - 1). A precisão descreve o quanto as observações se distanciam da reta de regressão.

Foi utilizada apenas a primeira medida da TFG para cada paciente. O grau de concordância entre a inulina e as equações respeitou o pressuposto matemático do quadrado das diferenças:

$$E\left[(formula\_value - iGFR\_value)^2\right] = (\mu_1 - \mu_2)^2 + \left(\sigma_1^2 + \sigma_2^2 - 2\sigma_{12}\right)$$

$$= (\mu_1 - \mu_2)^2 + (\sigma_1 - \sigma_2)^2 + 2(1-\rho)\sigma_1\sigma_2),$$

onde ρ é o coeficiente de Pearson. Se em cada par, fórmula e inulina tivessem perfeita concordância, o valor esperado de E seria zero. Uma transformação é realizada para que os valores de CCC estejam escalonados de -1 a 1.

Para comparar os CCCs entre as fórmulas, o intervalo de confiança de 95% das diferenças foi estimado pelo método de *bootstrap* usando o CCC macro descrito por Crawford et al[25].

3.9.3 Acurácia

Segundo recomendações do NFK-KDOQI[1-2], verificamos transversalmente a medida da **acurácia**, definida como a descrição do percentual de medidas de TFG

estimado que estivessem dentro de 10 e 30% das medidas de TFG por Inulina (valor verdadeiro).

3.10.4 Curvas de Características de Operação do Receptor (Curvas ROC-Receiver Operating Characteristic).

Utilizamos a área sobre a curva ROC (AUC) para determinar a habilidade da TFGe em discriminar pacientes com ou sem insuficiência renal crônica (definida por TFGm < 60 ml/min/ per 1.73 m^2).

Para calcular o AUC é necessário calcular a o diagnóstico de IRC estimado pelo padrão ouro que é a inulina. O AUC sobre os pontos de grade é calculado de acordo com:

$$: \frac{\sum_{m=1}^{M}\left[(P_m - P_c)-(O_m - O_c)\right]}{\left[\sum_{m=1}^{M}(P_m - P_c)^2 \sum_{m=1}^{M}(O_m - O_c)^2\right]^{\frac{1}{2}}}$$

Na equação acima, Pc representa o valor médio da variável no ponto m obtido pelo modelo e Oc o valor médio observado (inulina) da variável no ponto m. Caso as anomalias simuladas e observadas sejam ambas positivas ou negativas, o numerador na equação acima será positivo. Já quando as anomalias são opostas em sinal, o numerador contribuirá negativamente. Dessa forma, quanto mais positivo (negativo) for o valor de AUC, maior será a semelhança entre as anomalias simuladas e observadas. O valor de AUC sempre estará entre –1 e 1.

O método de Delong Clarke-Pearson comparou AUCs[43]. O valor de $p<0.05$ foi considerado como estatisticamente significativo. Para análise foi utilizado programa R para Windows versão 2.13.

3.10 Aspectos Éticos

O estudo encontra-se dentro das normas e diretrizes regulamentadoras de pesquisas envolvendo seres humanos, conforme a Resolução nº 196/96, do Conselho Nacional de Saúde.

Considera-se que toda pesquisa com seres humanos envolve risco, podendo causar dano eventual imediato ou tardio, comprometendo o indivíduo ou a coletividade. Não obstante, os riscos potenciais do presente estudo são admissíveis, pois o estudo oferece elevada possibilidade de gerar conhecimento para entender, prevenir ou aliviar um problema que afeta o bem-estar dos sujeitos da pesquisa e de outros indivíduos.

O projeto foi aprovado pelos Comitês de Ética das instituições participantes do estudo (anexos).

4 RESULTADOS - PUBLICAÇÕES

4.1 PRIMEIRO ARTIGO. Publicado em junho de 2012 no *Journal of the American Society of Nephrology Jun;23(6):989-96.*

CLINICAL RESEARCH www.jasn.org

GFR Estimation in Adolescents and Young Adults

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ABSTRACT

The performance of creatinine-based equations to obtain the estimated GFR in adolescents and young adults is poorly understood. We assessed creatinine-based GFR estimating equations in a cross-section of 751 adolescents and young adults (1054 measurements), using inulin clearance (measured GFR [mGFR]) as the reference method. We evaluated the following: Cockcroft-Gault, four-variable Modified Diet in Renal Disease, and the Chronic Kidney Disease Epidemiology Collaboration equations for adult participants, as well as the Schwartz 2009 and Schwartz-Lyon equations for pediatric age groups. Participants ranged in age from 10 to 26 years (mean 16.8 years); we divided the population into four groups according to age (10–12 years, 13–17 years, 18–21 years, and 21–25 years). Evaluation of the agreement between these formulas and mGFR (*e.g.*, correlation, Bland–Altman plots, bias, and accuracy) showed that there was a good correlation between mGFR and both pediatric formulas in all age groups, whereas the adult formulas substantially overestimated mGFR. In conclusion, we recommend the use of pediatric equations to estimate GFR from childhood to early adulthood.

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GFR is the most widely used index of renal function; therefore, accurate estimation of GFR is often needed in both clinical practice and research. Reference methods to determine GFR require an exogenous marker, such as inulin, ^{51}Cr-EDTA, iohexol, or iothalamate, and cannot be used in daily practice because of its complexity and costs.[1] Plasma creatinine (PCr) is the most commonly used biochemical marker of renal function. However, several factors other than GFR can affect PCr, including its generation from muscle metabolism, tubular secretion, and the creatinine assay method. In addition, PCr is insensitive for detection of mild to moderate reductions of GFR.[2] Therefore, clinical guidelines on CKD management recommend the use of GFR estimating equations as an alternative noninvasive method to estimate GFR.[3] Several formulas have been developed for daily clinical practice. Among them, the Cockcroft-Gault (CG) formula and the Modification of Diet in Renal Disease (MDRD) simplified formula are the most frequently used in adults.[4,5] More recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed to reduce bias compared with the MDRD equation, especially among patients with an estimated GFR (eGFR) >60 ml/min per 1.73 m^2.[6] The original Schwartz formula developed in children in 1976 has been recently adapted to current methods of PCr assay and its use is now recommended to estimate GFR in

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children.[7,8] Another locally adapted Schwartz formula to our creatinine assay method has very good agreement with standardized creatinine measurement.[9,10] However, all of these adult or pediatric equations have been determined for a specific population and their external validity in adolescents and young adults is limited. Therefore, this study was conducted to assess the performance of the most commonly used creatinine-based formulas in adults and children in a large cross-sectional cohort of adolescents and young adults with a broad spectrum of GFRs.

RESULTS

We analyzed data from 1054 inulin clearance measurements in 751 patients. Demographic and clinical characteristics of patients at the time of GFR assessment—including age, height, body weight, body mass index, and body surface area—are presented in Table 1. Our results showed that 11% of patients had weight or height under the third percentile. Diagnoses included glomerular disease (20%), tubulointerstitial disease (26%), kidney transplant recipients (19%), and others (35%). The number of blacks was insufficient to analyze the race component in either series. The median PCr and measured GFR (mGFR) for all participants were 67.6 μmol/L (range, 54.4–91.1) and 91.0 ml/min per 1.73 m^2 (range, 66.0–109.7), respectively. According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) classification, 51%, 30%, 17%, and 2% of patients had stage 1, 2, 3, or 4–5 CKD, respectively.

Evaluation of Performance of PCr-Based Formulas to Estimate GFR

In the Whole Population

Mean eGFR as well as mean ratios (eGFR/mGFR), accuracies (10% and 30%), and univariate correlation coefficients between mGFR and eGFR obtained with the PCr-based formulas in the whole cohort are summarized in Table 2. Figures 1 and 2 correspond to the different correlation and Bland–Altman plots obtained in the whole population for adult and pediatric formulas, respectively. The adult formulas (*i.e.*, CG, MDRD, and CKD-EPI) substantially overestimated mGFR in the whole population, with mean ratios of 1.42±0.35, 1.41±0.47, and 1.38±0.36 ml/min per 1.73 m^2, respectively. That is, the adult formulas overestimated mGFR by 42%, 41%, and 38%, respectively. At the same time, the mean ratios for the pediatric formulas (*i.e.*, 2009 Schwartz and Schwartz-Lyon) were 1.00±0.22 and 0.95±0.20 ml/min per 1.73 m^2, respectively. The Schwartz 2009 has no over- or underestimation of mGFR, and Schwartz-Lyon underestimated the mGFR by 5%. The correlation between eGFR and mGFR according to the Bland–Altman plot of all formulas highlighted a strong overestimation of GFR by the CG, MDRD, and CKD-EPI formulas, with marked scattering of values (Figure 1) compared with the pediatric formulas (Figure 2). Accuracies (10% and 30%) were much lower with adult formulas than with pediatric formulas (Table 2).

According to Age

Mean eGFR as well as mean ratios, accuracies (10% and 30%), and univariate correlation coefficients between mGFR and eGFR obtained with the PCr-based formulas according to each age

Table 1. Description of the whole population and characteristics of each age group

Characteristic	All	Group 1 (10–12 yr)	Group 2 (13–17 yr)	Group 3 (18–21 yr)	Group 4 (22–25 yr)
n	1054	225	322	262	245
Male	54	58	57	50	52
mGFR (ml/min per 1.73 m^2)	91.0 (66.0–109.7)	95.0 (73.9–113.0)	87.0 (66.5–108.7)	94.0 (69.0–112.0)	84.0 (62.0–105.0)
Age (yr)	17.0 (13.0–21.0)	11.0 (10.0–12.1)	15.0 (14.2–16.1)	20.0 (19.1–20.3)	23.1 (22.3–24.0)
Weight (kg)	52.0 (41.0–61.3)	34 (28.2–39.5)	51.0 (43.1–59.1)	56.0 (49.0–65.0)	60.0 (52.0–70.1)
Weight percentile		30.8 (8.8–64.2)	37.2 (9.2–67.6)		
Height (cm)	151.4 (149.7–170)	140.7 (134.0–147.0)	160.0 (152.0–166.5)	166.0 (159.0–174.0)	169.0 (161.0–175.0)
Height percentile		28.1 (8.7–67.7)	34.5 (5.6–63.7)		
BSA (m^2)	1.5 (1.3–1.7)	1.1 (1.0–1.2)	1.5 (1.3–1.6)	1.6 (1.4–1.7)	1.7 (1.5–1.8)
BMI (kg/m^2)	19.7 (17.4–21.9)	16.7 (15.3–18.8)	19.5 (17.5–21.8)	20.6 (18.6–22.4)	21.1 (19.3–23.6)
PCr (μmol/L)	67.6 (54.4–91.1)	51.6 (44.1–61.0)	66.7 (54.4–84.2)	73.7 (61–95.8)	83.6 (64.8–106.1)
KDOQI classification					
1	541 (51)	134 (60)	149 (46)	144 (55)	114 (46)
2	312 (30)	59 (26)	109 (34)	71 (27)	73 (30)
3	178(17)	29 (13)	57 (18)	42 (16)	50 (20)
4–5	23 (2)	3 (1)	7 (2)	5 (2)	8 (4)
Diagnosis					
glomerulopathies	217 (20)	35 (15)	71 (22)	58 (22)	53 (22)
tubulointerstitial disease	260 (25)	53 (24)	57 (18)	71 (27)	79 (32)
kidney transplant recipients	227 (21)	35 (15)	81 (25)	48 (18)	63 (26)
others	350 (34)	102 (46)	113 (35)	85 (33)	50 (20)

Values are median (IQR) or *n* (%) unless otherwise specified. BSA, body surface area; BMI, body mass index.

Table 2. Mean bias and accuracies according to age groups and equations

Group	CG	MDRD	CKD-EPI	Schwartz 2009	Schwartz-Lyon
All measurements (*n*=1054)					
mGFR=88.7±30.8					
eGFR	123.0±45.3	122.9±56.6	116.7±34.0	85.8±27.7	81.8±27.7
correlation coefficient (*r*)	0.83	0.76	0.80	0.85	0.86
mean ratio (eGFR/mGFR)	1.42±0.35	1.41±0.47	1.38±0.36	1.00±0.22	0.95±0.20
95% limits of agreement	0.73, 2.10	0.48, 2.32	0.69, 2.06	0.55, 1.45	0.55, 1.34
10% accuracy	15	22	18	38[b]	36[b]
30% accuracy	41	50	49	86[b]	87[b]
Group 1 (10–12 yr) (*n*=225)					
mGFR=93.4±29.3					
eGFR	150.9±45.2	179.3±59.0	144.6±25.6	98.6±25.6	88.7±25.0
correlation coefficient (*r*)	0.87	0.84	0.84	0.88	0.89
mean ratio (eGFR/mGFR)	1.65±0.32	1.95±0.42	1.65±0.39	1.10±0.21	0.98±0.18
95% limits of agreement	1.02, 2.28	1.13, 2.77	0.89, 2.41	0.69, 1.51	0.63, 1.33
10% accuracy	1	1	3	47[a]	48[a]
30% accuracy	10	4	17	86	92[b]
Group 2 (13–17 yr) (*n*=322)					
mGFR=87.3±32.5					
eGFR	127.1±45.4	125.3±50.9	119.9±32.5	87.2±28.3	85.7±29.7
correlation coefficient (*r*)	0.88	0.86	0.85	0.89	0.89
mean ratio (eGFR/mGFR)	1.50±0.33	1.46±0.37	1.44±0.32	1.04±0.21	1.01±0.20
95% limits of agreement	0.85, 2.15	0.74, 2.18	0.81, 2.07	0.63, 1.45	0.62, 1.40
10% accuracy	6	14	10	41[a]	37[a]
30% accuracy	31	41	38	88	90
Group 3 (18–21 yr) (*n*=262)					
mGFR=90.4±30.1					
eGFR	113.2±39.3	102.9±40.1	106.9±30.5	82.0±26.4	79.4±27.3
correlation coefficient (*r*)	0.85	0.85	0.86	0.86	0.85
mean ratio (eGFR/mGFR)	1.28±0.29	1.16±0.30	1.23±0.27	0.94±0.22	0.90±0.41
95% limits of agreement	0.71, 1.85	0.57, 1.75	0.96, 1.56	0.51, 1.37	0.49, 1.31
10% accuracy	25	36	27	32	28
30% accuracy	59	75	69	84[a]	83[a]
Group 4 (22–25 yr) (*n*=245)					
mGFR=84.1±30.3					
eGFR	102.5±35.5	89.3±31.8	97.3±28.4	76.0±25.7	73.0±25.2
correlation coefficient (*r*)	0.85	0.85	0.86	0.86	0.85
mean ratio (eGFR/mGFR)	1.27±0.31	1.10±0.27	1.21±0.28	0.94±0.21	0.90±0.23
95% limits of agreement	0.66, 1.87	0.57, 1.63	0.66, 1.76	0.53, 1.35	0.45, 1.35
10% accuracy	29	36	33	33	31
30% accuracy	64	78	72	85	82

mGFR and eGFR are measured in milliliters per minute per 1.73 m^2.
[a]$P<0.05$ between pediatric formulas and other equations, favoring pediatric equations, but without significant difference between Schwartz 2009 and Schwartz-Lyon.
[b]$P<0.05$ between pediatric formulas and other equations, favoring Schwartz-Lyon. All results are expressed as mean ± SD.

group are summarized in Table 2. Mean ratios were significantly higher with adult formulas than with pediatric formulas even for patients aged >17 years. The Schwartz 2009 and Schwartz-Lyon formulas had superior accuracy (10% and 30%) in all populations and in each age group. The performance of adult formulas was comparable with those of pediatric formulas only for patients aged >21 years.

According to KDOQI Classification Subgroups

Results for mean eGFR, mean ratio, and accuracies (10% and 30%) are presented in Table 3 with respective SDs. Pediatric formulas (*i.e.*, Schwartz 2009 and Schwartz-Lyon) performed better than adult formulas in the whole normal GFR population with mean eGFR/mGFR ratios of 0.92±0.16 and 0.89±0.16 ml/min per 1.73 m^2, respectively. This superiority was found at any stage of CKD. The accuracies (10% and 30%) were similar for pediatric formulas when mGFRs were >30 ml/min per 1.73 m^2, but were poor when mGFR was below this value.

DISCUSSION

The accurate and repeated estimation of GFR is a major concern in patients, especially during the transition period

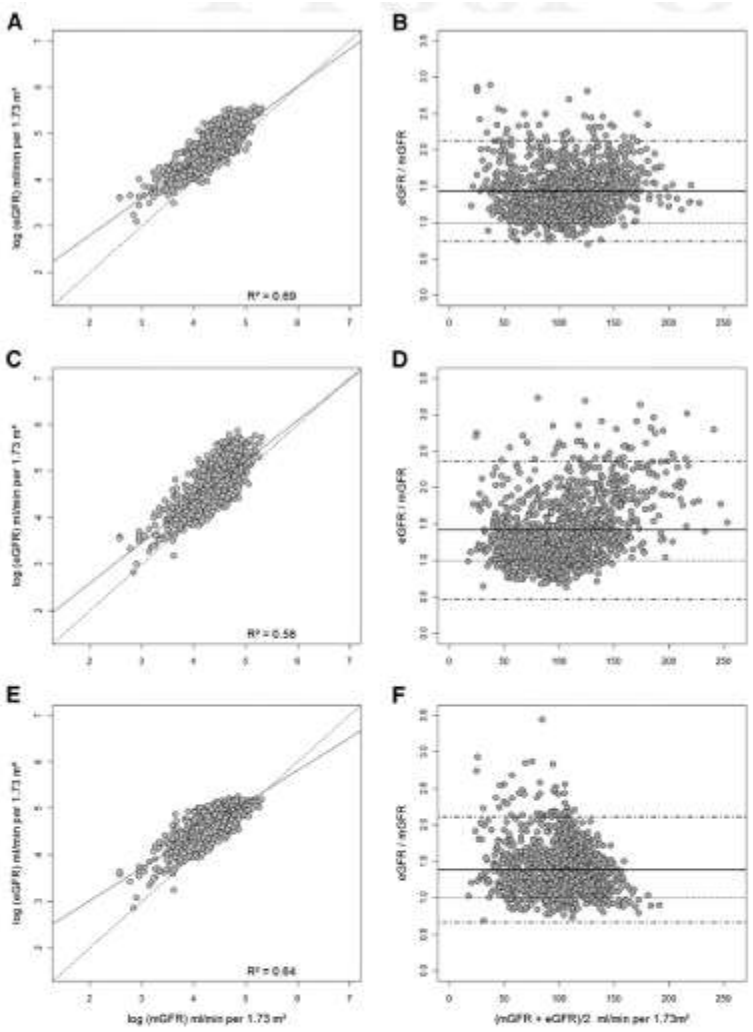

Figure 1. Comparison between different adult-based formulas (eGFR) and inulin clearance (mGFR). The left column shows Univariate relationship plots of the (A) CG, (C) MDRD, and (E) CKD-EPI formulas, using logarithmic transformation. The right column shows Bland–Altman plots of the (B) CG, (D) MDRD, and (F) CKD-EPI formulas, using ratios of eGFR/mGFR against (eGFR + mGFR)/2.

from childhood to adulthood in which rapid growth and changes of body composition occur. Reference methods for assessing GFR are difficult to perform and estimations of GFR by PCr-based formulas are widely used in clinical practice. However, if the performance of the equations to estimate GFR has been largely studied in children and in adults,[11] it has been very rarely evaluated in adolescents and young adults. In this study, we compared five GFR estimating equations (CG, MDRD, CKD-EPI, Schwartz 2009, and Schwartz-Lyon) with measurements of inulin clearance in a large cross-sectional adolescent and young adult population.

The main findings of this study are as follows: (*1*) the demonstration of the validity of the 2009 published "new bedside Schwartz" formula in a population of adolescents and young adults with different characteristics than the original one, mainly in terms of GFR and age; (*2*) the validation of the "locally adapted" Schwartz formula in this population; and (*3*) the demonstration that adult formulas should not be used in adolescents.

The Schwartz 2009 formula is very close to our locally adapted formula, but it does not take age into account, especially in adolescent boys. Indeed, Schwartz *et al.* developed this formula in a cohort of 349 North American children with mild to severe CKD (median GFR 41 ml/min per 1.73 m^2) and notable growth retardation. In contrast, the Schwartz-Lyon formula has been developed in the same way than the original Schwartz formula, that is with different coefficients according to age and sex (k=33 for females and males aged <13 years and k=37 for males aged ≥13 years) and has been validated in a pediatric population of 252 patients aged 10.7±4.0 years (range, 4.4–19.9) with mild or any renal insufficiency (mean mGFR 101±32 ml/min per 1.73 m^2) and no significant growth retardation.[10] The results of our study demonstrated that the 2009 Schwartz and Schwartz-Lyon are bedside formulas that had superior accuracies (10% and 30%) than the adult formulas in the whole population and in each age group. In addition, they are simpler to use and they can therefore be reliable in an extended population from about 5 to 25 years, which allow an easy follow-up of renal function. Comparison of the two pediatric formulas showed that in the whole population and for patients aged ≥13 years, they have a similar performance to estimate GFR with comparable concordance (mean ratio), correlation coefficients, and accuracies. However, in children the performance was slightly improved ($P<0.05$) (Table 2), likely due to the specific k coefficient used in these subgroups of patients.

Despite the good performance of the pediatric formulae, an underestimation of GFR of about 10% is observed in patients with normal renal function (GFR ≥90). These results are in accordance with those of Fadrowski *et al.*, which suggested that the bedside Schwartz 2009 formulae may underestimate renal function in normal patients with 8.9% of normal adolescents having an eGFR <75 ml/min per 1.73m^2.[12]

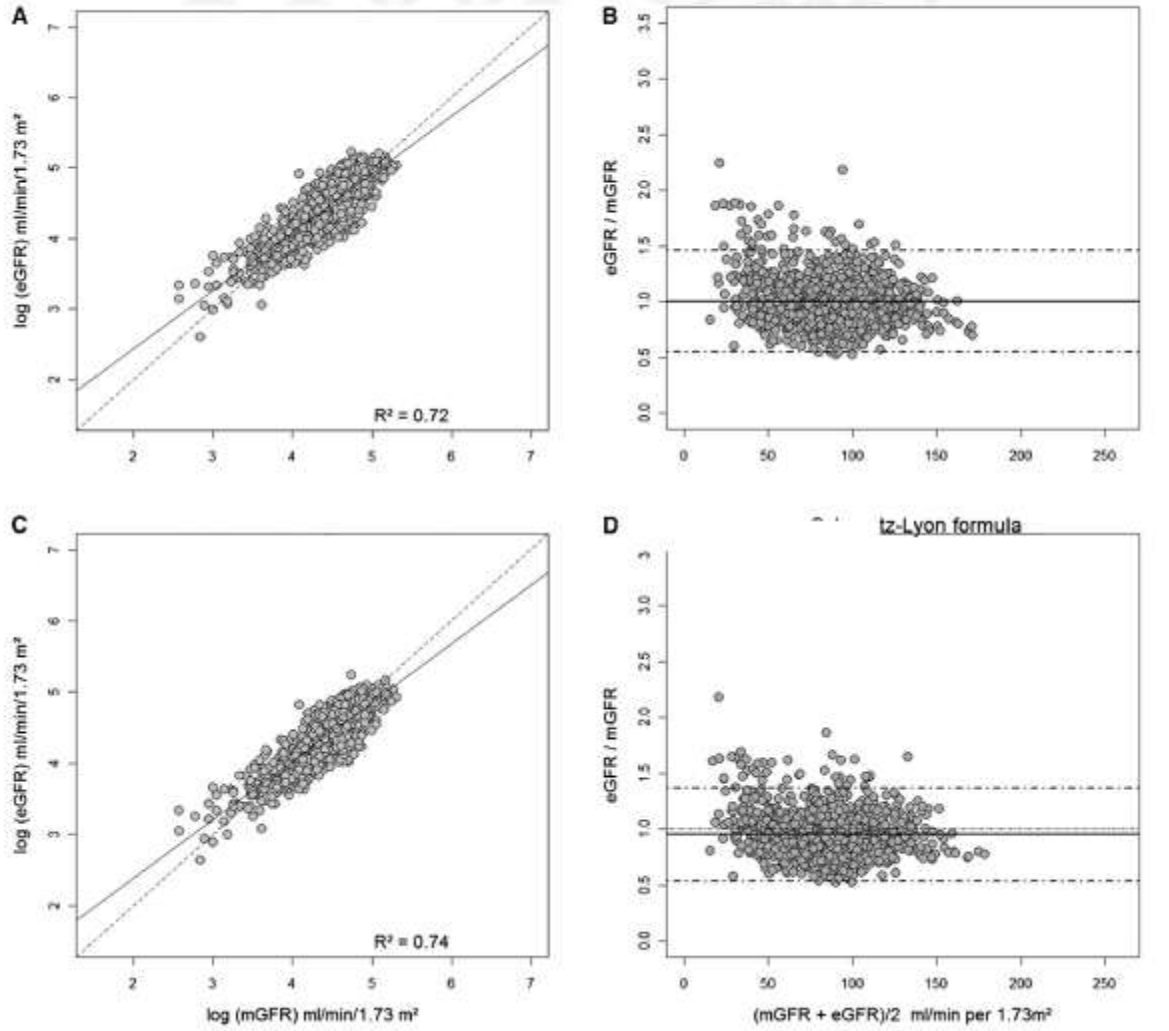

Figure 2. Comparison between pediatric-based formulas (eGFR) and inulin clearance (mGFR). The left column shows univariate relationship plots of the (A) Schwartz 2009 and (C) Schwartz-Lyon formulas, using logarithmic transformation. The right column shows Bland–Altman plots of the (B) Schwartz 2009 and (D) Schwartz-Lyon formulas, using ratios of eGFR/mGFR against (eGFR + mGFR)/2.

Chavers *et al.* found comparable results with the Chronic Kidney Disease in Children formula, which includes PCr, cystatin C, and BUN.[13]

The three most used creatinine-based formulas in adults (CG, MDRD, CKD-EPI) considerably overestimate the true GFR in the whole population, probably due to anthropometry. The overestimation of GFR by adult formulas was reduced after 18 years of age but was still present in patients aged between 22 and 26 years, whereas children's formulas tended to underestimate GFR of about 10%. In fact, the adult creatinine–based formulas were developed in middle-aged or aged populations of patients with various pathologic conditions and were not designed to study renal function in young adults or adolescents. The CG formula was developed in 1976 by using the mean 24-hour urine creatinine excretion from two urine collections obtained in 249 adult men aged from 18 to 92 years. The use of the CG equation for children and adolescents is controversial.[11,14] The MDRD study prediction equation was developed in 1628 patients (males and females) with a mean age of 50.6 ±12 years and a mean GFR of 39.8±21.2 ml/min per 1.73 m^2 and included age, sex, and race to account for average differences in muscle mass in subgroups.[15] The MDRD formula was re-expressed in 2005 using PCr standardized to reference methods.[5] MDRD equation performance to estimate GFR in adults with moderate to severe CKD is now accepted worldwide,[3] but is grossly inaccurate in children and not validated under 18 years of

Table 3. Mean bias and accuracies according to KDOQI classification and equations

KDOQI Classification	CG	MDRD	CKD-EPI	Schwartz 2009	Schwartz-Lyon
Stage 1: GFR ≥90 (*n*=541)					
mGFR=113.4±18.1					
eGFR	150.5±37.0	152.1±53.9	136.0±21.0	103.4±20.4	99.6±21.0
mean ratio (eGFR/mGFR)	1.33±0.29	1.35±0.45	1.22±0.21	0.92±0.16	0.89±0.16
10% accuracy	19	25	26	41[a]	35[a]
30% accuracy	51	55	66	91[a]	90[a]
Stage 2: 60< GFR ≥90 (*n*=312)					
mGFR=75.2±8.4					
eGFR	110.5±28.8	110.2±38.9	113.2±26.4	78.4±17.8	74.0±17.2
mean ratio (eGFR/mGFR)	1.47±0.35	1.46±0.48	1.50±0.33	1.04±0.21	0.98±0.20
10% accuracy	12	19	10	39[a]	37[a]
30% accuracy	34	47	32	84[a]	86[a]
Stage 3: 30< GFR ≥60 (*n*=178)					
mGFR=46.6±8.4					
eGFR	71.5±19.0	67.4±24.1	73.7±23.6	51.9±13.3	48.0±11.5
mean ratio (eGFR/mGFR)	1.55±0.35	1.45±0.46	1.60±0.46	1.12±0.25	1.05±0.21
10% accuracy	7	20	8	32[b]	36[b]
30% accuracy	29	41	30	80[b]	87[b]
Stages 4–5: GFR <30 (*n*=23)					
mGFR=22.2±4.7					
eGFR	44.4±12.3	37.7±12.1	40.8±13.5	32.5±9.0	29.9±8.1
mean ratio (eGFR/mGFR)	2.03±0.49	1.7±0.51	1.80±0.54	1.48±0.36	1.36±0.32
10% accuracy	0	4	4	9	22
30% accuracy	4	30	22	39	43

mGFR and eGFR are measured in milliliters per minute per 1.73 m^2.
[a]$P<0.05$ between pediatric formulas and other equations, favoring pediatric formulas, but without significant difference between Schwartz 2009 and Schwartz-Lyon.
[b]$P<0.05$ between pediatric formulas and other equations, favoring Schwartz-Lyon. All results are expressed in mean ± SD. CKD stages 4–5 were combined due to the small number of patients.

age.[11,14,16] More recently, the CKD-EPI equation has been developed using data from 26 studies (12,150 patients with a mean age of 47–50 years and a mean GFR of 67 ±40 ml/min per 1.73 m^2).[6] However, the number of adolescents and young adults is limited in these studies and equations has not been adapted to this specific population. In the adult formulas, the term age forms a central component in order to integrate that muscle mass decreases with time resulting in higher eGFR in younger participants. However, the opposite is true for children, whose muscle mass increases with age and is, in fact, more closely correlated with height than age. Therefore, it is logical that adult creatinine-based equations (*i.e.*, CG, simplified MDRD, and CKD-EPI) overestimate GFR in adolescent and young adults. Several studies reported that the CG or MDRD equation tends to underestimate GFR when renal insufficiency is light or moderate (*i.e.*, GFR >60 ml/min per 1.73 m^2),[17] and the CKD-EPI equation was proposed to increase the precision of eGFR, especially when GFR is in the higher range.[6] The overestimation due to the inadequate role of age in adult formulas is likely much more important than the expected underestimation of GFR due to the higher GFR of our population compared with those of the training data sets of the MDRD and CKD-EPI. This is confirmed by the progressive decrease of the overestimation of GFR from group 1 to group 4 (Table 2). In conclusion, adult creatinine-based equations (*i.e.*, CG, simplified MDRD, and CKD-EPI) are not reliable in adolescents and young adults and should not be use to estimate GFR in clinical practice. We recommend the use of pediatric GFR prediction equations, especially the Schwartz 2009, to estimate and to follow GFR from childhood to early adulthood.

CONCISE METHODS

Patients

We compared eGFR using various formulas based on PCr with the results of mGFR, *i.e.*, inulin clearance in a retrospective cross-sectional cohort of 751 patients (1054 measurements) which included all of the patients aged 10–25.9 years referred to our center between July 2003 and July 2010 to perform inulin clearance for suspected or established renal dysfunction. An appropriate informed consent was obtained from all patients and/or their families. Height, weight, and age were recorded and for patients aged <18 years, and height and body weight percentiles were expressed in medians and IQRs, according to the Centers for Disease Control and Prevention body weight and height for age and sex growth charts.[18] Growth retardation was defined by a height and/or body weight below the third percentile. The whole population was divided into four groups according to age: 10–12 years, 13–17 years, 18–21 years, and 22–25 years. The groups were then further divided by renal function according to the KDOQI classification as follows: stage 1 (mGFR ≥90), stage 2 (60≤ mGFR <90), stage 3 (30≤ mGFR <60), and stage 4–5 (mGFR <30). Stage 4–5 CKD data were combined due to the small number of patients.

PCr Measurements

PCr was obtained from a kinetic colorimetric compensated Jaffe technique (Roche Modular, Meylan, France) for which the imprecision of the assay method was checked (intra-assay coefficient was 0.7%; interassay coefficients were 4.0% at low concentration PCr (45–60 μmol/L) and 1.5% at high concentration PCr (580 μmol/L), respectively). All PCr measurements were performed with the same method over the entire study period. The results for PCr were standardized by linear regression adjustment of the concentrations obtained by the compensated Jaffé assay and the concentrations obtained by liquid chromatography-mass spectrometry (LCMS). Briefly, the LCMS apparatus was calibrated with three European standards (BCR; Bureau community Reference 573, 574 and 575) and two American standards (Standard Reference Material) in which creatinine concentrations ranged from 66.5 to 404 μmol/L. The parameters for the linear regression line were obtained for 54 patients with serum creatinine values ranging from 41 to 220 μmol/L; 94.2% (993) of our PCr values were within this range. Calibration equation was as follows: standardized serum creatinine = 0.9395 × (Jaffé compensated serum creatinine in μmol/L) + 4.6964. The intercept (4.6964; 95% CI, −2.4619 to 11.8656) and slope (0.9395; 95% CI, 0.8719–1.0072) were not significantly different from 0 and 1, respectively. The coefficient of correlation (r) was 0.97. Mean difference between LCMS and compensated Jaffé was 1.24±10.05 μmol/L. Stability of the PCr assays was assessed during the study. Blinded Pro-BioQal controls were tested every 5 weeks and a nationwide-blinded control was tested each year.[19]

GFR Measurement

The GFR was measured by the renal clearance of inulin method (polyfructosan, Inutest; Fresenius Kagi, Graz, Austria). A standard technique was used by a trained staff with a continuous infusion after a priming dose of 30 mg/kg polyfructosan. Water diuresis was induced by oral administration of 5 ml/kg of water followed by 3 ml/kg every 30 minutes combined with an intravenous infusion of 0.9% sodium chloride. This enabled the patients to spontaneously empty their bladder every 30 minutes; patients needing intermittent urethral catheterization were excluded from this study. Three to four urine samples were collected and a blood sample was drawn mid-way through each collection period. The clearance values, calculated by the standard UV/P formula, were obtained from the mean values of the three to four clearance periods. Measurements of plasma and urine polyfructosan were performed using the same enzymatic method[20] for which we previously checked the imprecision of the assay method (within-run precision values in plasma and urine of 0.3% and 0.7%, respectively; between-run precision values were 3.5%, 1.6%, and 2.4% at mean polyfructosan values of 117, 198, and 285 mg/L, respectively).[18] The results were expressed to 1.73 m^2, according to the Dubois formula: body surface area = $height^{0.725} \times weight^{0.425} \times 0.007184$.[21]

GFR Estimation

GFR was estimated using five formulas: CG,[4] simplified MDRD,[5] CKD-EPI,[6] 2009 Schwartz (bedside),[7] and Schwartz-Lyon.[10] The eGFR was normalized by body surface area and expressed in milliliters per minute per 1.73 m^2. Standardized creatinine values were used for the calculations of simplified MDRD, CKD-EPI, and 2009 Schwartz formulas. The equations used to determine eGFR are presented in Table 4.

Statistical Analyses

Statistical analyses were performed in the entire population and in each group separately. Performance of each eGFR equation was assessed in terms of mean ratio (eGFR/mGFR), the Pearson correlation coefficient (r), and accuracy (proportion of eGFR results within 10% and 30% of mGFR).[3] The mean ratio was used in order to correct the variance of bias that was not constant.[22] The eGFR mean ratios were compared each other using the paired t test. The accuracies of the eGFR equations were compared using McNemar's test. We used the Kolomogorov–Smirnov and Kruskal–Wallis tests to evaluate the normalization of quantitative data. Bland–Altman plots illustrated the agreement between eGFR calculated by different formulas and the reference mGFR. A value of $P<0.05$ was considered to indicate statistical significance. These calculations were performed with IBM SPSS software (version 17.0 for Windows).

Table 4. Equations used to determine eGFR

Name	Formula
CG adjusted to BSA[4]	eGFR = (1.73/BSA) × [(140 − age) × weight]/72 × (PCr × 0.0113) × 0.85 if female
MDRD[5]	eGFR = 175 × (PCr × 0.0113)$^{-1.154}$ × (age)$^{-0.203}$ ×0.742 if female ×1.212 if black
CKD-EPI[6]	k1 × [(PCr/88.5)/k2)]^{k3} × 0.993^{age} with k1 = 141 or 144 for white male and female, respectively K1 = 163 or 166 for black male and female, respectively k2 = 0.7 or 0.9 for female and male, respectively k3 = −0.411 or −1.209, for male with PCr ≤80 and PCr >80 μmol/L, respectively K3 = −0.329 or −1.209, for female with PCr ≤62 and PCr >62 μmol/L, respectively
Schwartz 2009[7]	eGFR = K × height/PCr K = 36.5
Schwartz-Lyon[10]	eGFR = K × height/PCr K = 37 if males aged >13 yr K = 33 if others

eGFR is measured in milliliters per minute per 1.73 m^2. PCr is expressed in micromoles per liter; height in centimeters, weight in kilograms, and age in years. BSA, body surface area.

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DISCLOSURES

None.

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4.2 SEGUNDO ARTIGO. Publicado em outubro de 2012 na *Transplantation-Proceedings Oct;44(8):2357-9.*

Comparison of Cystatin C– and Creatinine-Based Glomerular Filtration Rate Formulas With Inulin Clearance in Pediatric Renal Transplantation

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ABSTRACT

Background. It has been suggested that plasma cystatin C (Cyst-C) concentrations provide better indicators of changes in glomerular filtration rate (GFR) than plasma creatinine concentration (PCr).

Methods. We compared the performance of five equations—2009 Schwartz, Local Schwartz, Larsson, Le Bricon, and Schwartz Combined—in 60 renal transplant children by calculating the mean bias, Pearson correlation coefficient (R) and determination (R^2), 10% (P10) and 30% (P30) accuracies, and Bland-Altman plots. GFR was measured by inulin clearance.

Results. For the whole population, R^2 was slightly lower for formulas based on Cyst-C or PCr, but the mean bias was lower, and P10 and P30 were greater, than using combined Schwartz equation. However, the mean estimated GFR by Schwartz 2009, Local Schwartz, and Schwartz combined equations was not statistically different from the mean inulin clearance measurement.

Conclusions. In our pediatric transplant population, the combined Schwartz formula exhibited better performance to estimate GFR than formulae based on Cyst-C or combined PCr.

Glomerular filtration rate (GFR) is the most important parameter for functional assessment in the renal transplant population.[1–5] Although inulin clearance is regarded to be the gold standard to measure GFR, its use is limited in clinical practice.[6] Unlike plasma creatinine (PCr), cystatin C (Cyst-C) has been described to meet many of the characteristics of an ideal GFR marker: It is endogenously produced at a constant rate, freely filtered, neither reabsorbed nor secreted in the renal tubule, and is at least as accurate as the commonly used PCr.[1–8] The present study was designed to test the hypothesis that plasma Cyst-C correlated more closely with GFR than PCr among an unselected consecutive cohort of pediatric renal transplant recipients who underwent GFR determinations using the gold-standard inulin method.

PATIENTS AND METHODS

Study Population

This cross-sectional study of 60 pediatric transplant recipients was approved by the Institutional Research Ethics Board.

Laboratory Assessment

GFR was measured (mGFR) by plasma clearance of inulin (polyfructosan infusion; Inutest; Fresenius Kagi, Austria). PCr was obtained with a kinetic colorimetric compensated Jaffe technique (Roche Modular, Meylan, France) and Cyst-C with a nephelometric technique (BN2, Behring, France). The following equations were used to determine estimated GFR (eGFR):

- PCr based 2009 Schwartz = $36.5 \times$ [height (cm)/PCr]; Local Schwartz = eGFR = $k \times$ [height (cm)/PCr]; ($k = 37$ in boys >13 years old; $k = 33$ in other children).
- Cyst-C based: Le Bricon = $[(78) \times (1/\text{Cyst-C})] + 4$; Larsson = $77.239 \times \text{Cyst-C}^{-1.2623\ 28}$
- Cyst-C and PCr associated: Schwartz Combined = $39.1 \times [\text{height/PCr}]^{0.516} \times [1.8/\text{Cyst-C}]^{0.294} \times [30/\text{BUN}]^{0.169} \times (1.099$ if male) $\times$ [height/1.4]

Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics software 17.0 for Windows. To assess the performance of formulas, we calculated the Pearson product-moment correlation coefficient

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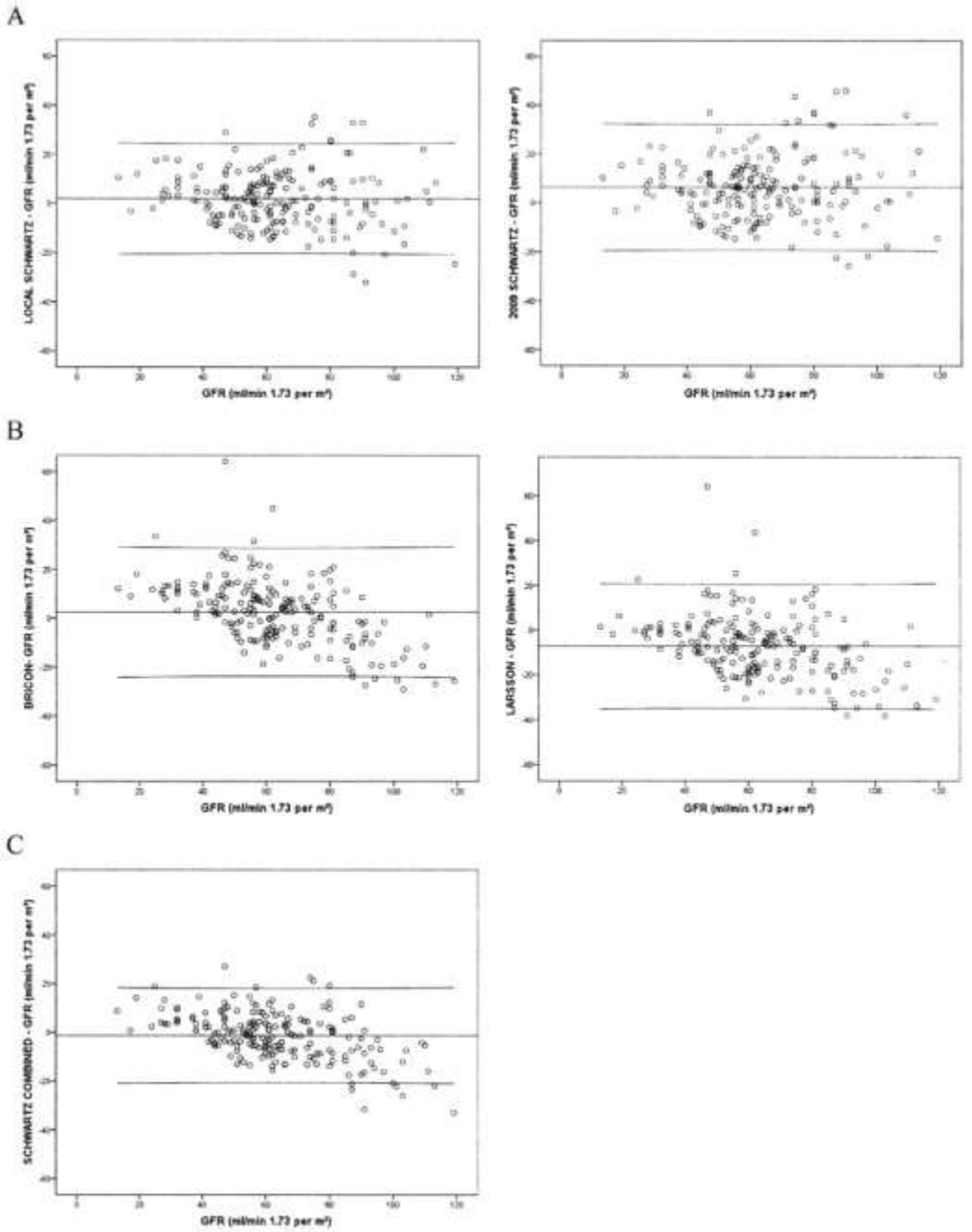

Fig 1. Bland-Altman graphs, showing the agreement between GFR measured by inulin clearance and GFR estimated by formulas based on creatinine **(A)**, Cystatin-C **(B)**, and combined **(C)**. The solid lines show the mean values and the dotted lines show the ranges of 95% of the values.

(R), the coefficient of determination (R^2), the mean bias (eGFR − mGFR), and 10% and 30% accuracies.

RESULTS

The 60 patients including 30 boys had a mean age of 13.5 ± 3.8 years. For the whole population, the mean GFR was 63 ± 20 mL/min/1.73 m^2 based on 196 measurements. The correlation between mGFR and eGFR was significant for the 5 formulas with R^2 values of 0.72, 0.72, 0.58, 0.56, and 0.75 for 2009 Schwartz, Local Schwartz, Le Bricon, Larsson, and Schwartz Combined, respectively. The mean absolute bias was 6.5 ± 1.3, 2.1 ± 12, 2.5 ± 13, −7.5 ± 14, and −1.2 ± 10 mL/min/1.73 m^2. Figure 1 shows the agreement for each formula according to the Bland-Altman method. P10 and P30 were 34% and 82% for 2009 Schwartz, 38.5% and 89.5% for Local Schwartz, 37% and 83% for Le Bricon, 36% and 92% for Larsson, and 47.5% and 98% for Schwartz Combined. However, the equations of 2009 Schwartz, Local Schwartz, and Schwartz Combined showed no significant difference of either the mGFR or eGFR (P = .7).

DISCUSSION

GFR assessments in renal transplant patients are useful for early recognition of rejection or of renal toxicity due to calcineurin inhibitors.[1,3,9] An ideal GFR marker should provide accurate and sensitive results to detect mild renal dysfunction, it should also show low variability over time when compared with the gold-standard inulin method.[2,6,8] When compared with PCr in pediatric and adult renal transplant recipients Cyst-C has been reported to produce conflicting results with changes in GFR.[3,4,7,8] This lack of a uniform superiority of Cyst-C over PCr can be attributed to several factors related to the measurement methods for Cyst-C or PCr, differences in the techniques which was reference for GFR, as well as various studied populations.[2,6,8] The present study, performed exclusively in pediatric renal transplant recipients, showed equations with PCr or combined with Cyst-C to correlate more closely with inulin GFR than those with isolated Cyst-C, a small but significant difference.

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BRIEF REPORT

Early renal abnormalities in children with postnatally diagnosed autosomal dominant polycystic kidney disease

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Abstract
Background Autosomal dominant polycystic kidney disease (ADPKD) in children is often regarded as a benign condition. However, previous studies pointed out renal-related anomalies which may benefit from early appropriate treatments. This study was conducted to evaluate the prevalence and severity of early renal dysfunction in ADPKD children.
Methods An extensive renal evaluation was performed in 52 consecutive ADPKD patients diagnosed either from prenatal screening or post-natal ultrasound (US) examination (54 % males, mean age 10±4 years [1–17]).
Results Three patients had both systolic (SBP) and diastolic (DBP) blood pressure above the 95th percentile, one patient had a "high normal" DBP, and one child was treated with an angiotensin-converting enzyme inhibitor (ACEI). The mean± SD glomerular filtration rate (GFR ml/min per 1.73 m^2, inulin clearance) was 115±26 [47–168] but six children (12 %) had a GFR<90 and 11 (21 %) experienced hyperfiltration (GFR> 135). Microalbuminuria (2<Ualb/Ucr≤20mg/mmol) was found in 25 patients and five had macroalbuminuria (>20 mg/mmol).
Conclusions Early renal manifestations are frequent in ADPKD children, including hypertension in 6 %, albuminuria in 58 %, and decreased GFR in 12 %. In conclusion, renal function in children with ADPKD should be regularly assessed in order to manage early renal dysfunction and even consider further therapeutic intervention.

Keywords Autosomal dominant polycystic kidney disease · Children · Renal function · Glomerular filtration rate · Arterial hypertension · Microalbuminuria

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent inherited renal disease. Despite the usual onset of end-stage kidney disease during adulthood, presymptomatic screening for ADPKD in children is now considered as necessary in order to initiate an appropriate follow-up to delay or prevent long-term consequences, including renal failure and cardiac complications [1]. Early

renal manifestations of ADPKD have been reported in children but their frequency and severity remains debated, especially concerning prevalence of renal function impairment. In this study, we focused on reviewing the phenotypic characteristics (i.e., modifiable risk factors), such as arterial blood pressure, albuminuria, and renal function, neglecting both ultrasound (US) and genetic testing data, which were not available and/or reliable for all children.

Methods

The 52 consecutive ADPKD patients (28 males, 1–17 years) seen at the Pediatric Nephrology ambulatory (Lyon, France) between December 1989 and May 2011 were referred for renal evaluation and their data were collected. Among them, 19 patients were assessed at least two times with a mean delay between the first and the last follow-up of 5.0± 2.1 years [2–5]. The diagnosis of ADPKD was made by prenatal screening or by post-natal US examination [1]. ADPKD was confirmed before examination by US demonstrating bilateral cysts in the setting of a family history of ADPKD or multiple cysts clinically consistent with a new diagnosis of ADPKD.

However, children were mostly referred with an ultrasound-based report performed in various centers and the exact kidney size and/or numbers and size of renal cysts were not known.

Height, body weight, age, and blood pressure were recorded. Percentiles for systolic (SBP) and diastolic (DBP) blood pressure were determined according to age, height, and gender [6, 7]. Blood pressure (BP) measurements were recorded by an oscillometric device regularly calibrated against an auscultatory method. The mean value of three consecutive readings in resting state was then compared with BP standards based on gender, age, and height. Hypertension was defined as systolic and/or diastolic BP greater than or equal to the 95th percentile for age, sex, and height on at least three different occasions. High-normal blood pressure (HNBP) was defined as a DBP and/or SBP between the 90th and the 95th percentile [7].

Blood samples were collected from each patient for plasma creatinine (Pcr) and fresh second-morning urine samples were collected for albuminuria (Ualb) (nephelometry, BM2; Behring Siemens, Paris, France). Albuminuria was expressed as urine albumin to urine creatinine ratio (Ualb/Ucr) and patients were divided into two groups according to Ualb/Ucr: (i) Group 1 (G1): normal (≤ 2.0 mg/mmol) and (ii) Group 2 (G2): increased Ualb/Ucr (>2.0 mg/mmol) [8]. True glomerular filtration rate was measured by the standard method of urinary clearance of inulin (iGFR) (Inutest®, Fresenius Kabi, Graz, Austria) based on a priming dose followed by a continuous intravenous infusion of inulin with 3–4 timed urine collections. Estimated glomerular filtration rate (eGFR) was calculated from Pcr according to the Schwartz formula [9]. Pcr was obtained from a kinetic colorimetric compensated Jaffe technique (Roche Modular, Meylan, France; compensation according to manufacturer's recommendations) for which we checked for good agreement with an enzymatic Roche method ($y=1.019\times+1.556$, $R^2=0.997$).

Statistical analysis

Descriptive analysis was done using mean ± SD for continuous variables. Student's parametric unpaired *t* test and analysis of variance (ANOVA) were used for comparison between the groups, and paired Student's *t* test was used for comparison of repeated measurements. Qualitative variables were compared using the Chi-square test. A p value of <0.05 was considered statistically significant. Analyses were performed with SPSS software version 15.0 (SPSS, Inc., Chicago, IL).

Results

Whole population at presentation

The main clinical and biological characteristics of the patients are given in Table 1. None presented growth retardation or low body mass index. Three patients had both SBP and DBP above the 95th percentile, one patient had HNBP, and one child was already being treated with an angiotensin-converting enzyme inhibitor (ACEI) for previously established hypertension. The mean iGFR was in the normal range but six (12 %) children had an iGFR<90 ml/min per 1.73 m^2 (1<60) and 11 (21 %) showed hyperfiltration (GFR>135). Mean eGFR was significantly decreased compared to iGFR ($p<0.05$) with a mean difference eGFR-iGFR of –6.2±22.2 ml/min per 1.73 m^2 (–53.1-+54.1). However, it is noteworthy that eGFR underestimated iGFR in 33 patients with a mean eGFR-iGFR of –19.4±13.2 [–53 to –0.08] leading to the misclassification of a more severe chronic kidney disease (CKD) stage for 9/52 patients. Thirty patients (58 %) had elevated albuminuria.

Evolution of renal function

In 19 patients, two assessments of renal function were performed with a mean time interval of 5.0±2.1 [2–9] years. Mean SBP and DBP percentiles tended to decrease (61.0± 21.3 vs. 52.7±28.2 ($p=0.16$) and 62.6±4.7 vs. 48.6±26.9, $p=0.01$, respectively), probably due to a better BP control in hypertensive children. An ACEI treatment was given prior

Table 1 The main clinical and biological characteristics of the whole population and of each Ualb/Ucr groups (G1: Ualb/Ucr≤ 2 mg/mmol and G2: Ualb/Ucr>2 mg/mmol)

Clinical features	All (n=52)	G1 (n=22)	G2 (n=30)
Male gender	28	16	12*
Age (years)	10.1±4.2 [1–17]	9.0±4.1 [1–17]	10.9±4.1 [3–17]
Weight (kg)	36.9±15.6 [11–66]	32.5±14.1 [11–57]	40.1±16.0 [14–66]
Height (cm)	141.4±25.9 [83–182]	134.5±25.7 [83–169]	146.4±25.2 [94–182]
SBP percentiles (mmHg)	52.6±27.9 [1–100]	56.4±21.6 [13–98]	49.8±31.7 [1–100]
> 95th	3	1	2
Between 90th and 95th	0	0	0
DBP percentiles (mmHg)	53.4±28.6 [5–100]	55.9±21.6 [9–87]	51.5±33.1 [5–100]
> 95th	3	0	3
Between 90th and 95th	1	0	1
Plasma creatinine (μmol/l)	51.0±18.3 [29–137]	45.3±8.9 [30–63]	53.2±19.9 [29–137]
Ualb/Ucr (mg/mmol)	11.3±22.2 [0.5–128]	1.4±0.1 [0.5–2]	17.5±26.7 [2.1–128]**
≤ 2	22	22	0
2–20	25	0	25
>20	5	0	5
iGFR (ml/min per 1.73 m^2)	114.6±25.5 [47–168]	123.5±23.4 [80–168]	108.0±25.4 [47–168]*
iGFR>135	11	8	3
90 ≤ iGFR<135	35	13	22
iGFR<90	6	1	5
eGFR (ml/min per 1.73 m^2)	108.3±28.3 [37–166]	112.3±31.1 [66–166]	105.4±26.3 [37–146]
eGFR>135	10	6	4
90 ≤ eGFR<135	30	10	20
eGFR<90	12	6	6

*p<0.05, **p<0.001

to the second renal assessment to three other children and the percentage of patients with an abnormal Ualb/Ucr decreased from 58 to 42 %). In the meantime, iGFR did not change between the two measurements (114.8±28.8 vs. 114.5±19.5) and no patient changed CKD stage.

Renal function according to Ualb/Ucr

For further analyses, ADPKD patients were divided into two groups according to Ualb/Ucr. The characteristics of the subjects in the two groups were similar with regards to age, body weight, and body surface area, but G1 included a greater percentage of boys than G2 (73 vs. 40 %, p< 0.05) (Table 1). The frequency of hypertension or HNBP was not increased in albuminuric children. The mean iGFR was significantly decreased in the albuminuric group of patients and the percentage of patients with renal impairment was greater in G2 (16.6 vs. 4.5 %). Hyperfiltration was significantly more frequent in G1 (36.4 vs. 10 %).

Discussion

ADPKD is not only an adult-onset disease, but may have early renal manifestations during childhood (hypertension, albuminuria, CKD) affording maximal anticipatory care and future opportunity to benefit from new therapies [1–5].

Compared to adults, few studies have been conducted in children and the prevalence and severity of renal manifestations remains debated, especially concerning renal function insufficiency. In this study of 52 consecutive ADPKD patients referred to our unit and aged 10±4 years old, we focused on reviewing ADPKD-associated morbidity. The main findings of this study are (1) the confirmation that early clinically relevant renal manifestations of ADKPD (hypertension, albuminuria, or renal insufficiency) are frequent in children (40/52 patients have at least one abnormality); (2) the demonstration of the lack of reliability of the current Schwartz formula to properly assess GFR and classify ADPKD-children in CKD stages; (3) the confirmation that albuminuria can be considered as an early severity marker of the disease during childhood; (4) the demonstration that hyperfiltration may be present early in the disease.

Renal function

Twenty-one percent of the children experienced hyperfiltration, mainly in the group of patients with normal albuminuria. These results are consistent with findings from previous studies in pediatric ADPKD of about the same

age where the authors concluded that there was no correlation between renal structural abnormalities and GFR [4]. Helal et al. found that hyperfiltration and increased renal volumes may be early markers for a more severe form of ADPKD in children [10]. In addition, Meijer et al., regarding young adult patients, found that hyperfiltration is present before the occurrence of microalbuminuria [11]. Increased levels of vasopressin have been demonstrated in ADPKD and its potential role in ADPKD progression has been suggested. Indeed, vasopressin V2 receptor activation reduces sodium concentration at the macula densa, inhibits tubuloglomerular feedback, stimulates renin release, and could result in glomerular hyperfiltration, proteinuria, and renal damage in APKD patients [12, 13].

The incidence of CKD among ADPKD children is probably biased due to discrepancy between GFR measurement methods. Renal function was regarded as normal when GFR was estimated from the former Schwartz formula (which usually overestimates GFR in CKD) [2, 5] whereas Mekahli et al. [6] found 39 % of patients with a CKD stage≥2 with a locally adapted Schwartz formula (k=33). In the present study, 11.5 % of patients have an iGFR<90 ml/min per 1.73 m^2. This discrepancy may be explained by the underestimation of GFR with the current Schwartz formula (k=36.5), which is adapted to our Per measurement method and which is very close to that used by Mekahli et al. [6]. In our study, the use of the current Schwartz formula would lead to an overestimation in the rate of CKD (23 vs. 11.5 %).

Blood pressure

Office measurements of BP in the entire cohort showed SBP and DBP above the 95th percentile in 6 % of patients. These results are consistent with previous studies [2, 6], which identified 9 to 43 % of hypertensive patients depending of the characteristics of the population and the method of BP measurement.

Albuminuria

The rate of pathological albuminuria in our patients at first presentation was higher (58 %) compared to previous studies (from 5 to 36 %) [3, 4, 6], which may be related to the various reference ranges (2 mg/mmol in our study). However, pathological albuminuria is associated with a decreased iGFR, with an increased rate of CKD, and a decreased number of patients with hyperfiltration. The occurrence of hyperfiltration mainly in the group without albuminuria may indicate that this process occurs early in the disease even before the onset of microalbuminuria. We did not find any differences in BP in relation to albuminuria. These results confirm that microalbuminuria can appear early in the course of ADPKD and may be a marker of the disease severity as previously suggested by Sharp et al. [3], but does not seem to be the first, and underlines the importance of a search for other markers of disease severity.

Finally, the 5-year follow-up of 19 children showed no progression of CKD course as reported by Fick et al. [14], but did show an increased rate of albuminuria. These data are consistent with previous conclusions [6, 15] about the necessity of a close follow-up of these patients to slow down the natural evolution of the disease, and early adequate renal investigation in the scope of intervention clinical trials.

In conclusion, this study confirms the high incidence of ADPKD-linked renal manifestations (77 % with at least one symptom: hypertension, high-normal blood pressure, elevated albuminuria or abnormal GFR) in this population. The rate of CKD during childhood can be estimated at 12 % when a reference method of GFR measurement is performed. Progression of renal insufficiency seems to be slow during childhood, and early evaluation of disease severity could be a major task to initiate an appropriate clinical/biological follow-up. To better initially assess the severity of the disease, we recommend measurement of renal function with a reference method.

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Which GFR estimating equations can be reliably used in children with standardized creatinine and cystatine C measurements?

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Summary

The limitations of estimates of glomerular filtration rate (GFR) based only on plasma creatinine measurements have spurred an interest in more sensitive markers of GFR. Cystatin C, a low-molecular-weight glycoprotein freely filtered through the glomerular basement membrane and with minimal non-renal elimination, may be such a marker. The diagnostic accuracy of cystatin C estimated GFR (eGFR) by various cystatin C. equations have varied in different studies. We hypothesized that the age range and GFR of enrolled patients affects the diagnostic accuracy of a cystatin C and creatinine equations. We analyzed 259 consecutively enrolled children and adolescents at a single French center in a prospective and cross-sectional study. Cystatin C was analyzed with nephelometry and IDMS-traceable plasma creatinine to eGFR was estimated by the equations validated in children. GFR was measured by inulin. GFR was estimated using the plasma creatinine–based the *2009 Schwartz bedside* and a *Schwartz Lyon* equations, and 4 cystatin C-derived equations (2 simples cystatin, *Filler* and *Bricon*, and 2 combined with creatinine, CKiD and *Zappitelli*). In children, *Schwartz Lyon* had low median ratio bias and high accuracy such that 93% of estimates were within 30% of measured GFR. In adolescents, the median mean ratio bias of 2 equations, *Schwartz Lyon and CKiD,* was low and accuracy was high such that 90–93%. In the GFR categories <60 and <90 ml/min per 1.73 m^2, the Receiver-operating characteristics (ROC) to children and adolescents wasn't between haven't significantly different between CKiD, *Filler*, *2009 Schwartz bedside* and *Schwartz Lyon.* These results were an improvement compared to the other equation based cystatin C and 2009 Schwartz bedside, both of which had high median bias and reduced accuracy. The diagnostic accuracy of various equations varies with GFR and range age. In addition, we found no evidence that serum cystatin C–based estimates of renal function are superior to serum creatinine-based estimates.

INTRODUCTION

Assessment of glomerular filtration rate (GFR) is an important tool for monitoring renal function. GFR has to be determined by measuring the clearance of an exogenous marker totally and exclusively eliminated by glomerular filtration, such

as inulin[4, 26-27]. However, in clinical practice, determination of the GFR by inulin is quite cumbersome[27-29].

Therefore, plasma creatinine (PCr) and creatinine clearance are widely used as non-invasive methods for the assessment of GFR, although several drawbacks have been identified[1, 4, 27, 29]. The monitoring of GFR based on equations of creatinine may have a bias compared with the current gold standard[4]. PCr production is proportional to muscle mass and varies considerably intra- and inter-individually[1, 26]. PCr is freely filtered by the glomerulus, not reabsorbed by the proximal tubules and is secreted in small amounts. PCr is also not sensitive for detecting small decreases in GFR because of the non-linear relationship between its plasma concentration and GFR. PCr values have to be adjusted for body height and body composition to reflect renal function in paediatric patients accurately[1, 4, 20, 26-29].

Unlike PCr, cystatin C (Cys-C) is produced at a constant rate by all nucleated body cells. Cys-C is a non-glycosylated basic protein (13.36 kDa) and can be found in a variety of biologic fluids[6]. Cys-C serum concentration is not influenced by gender, inflammation, or lean tissue mass and is regarded to be mainly determined by GFR. Cys-C has been described as meeting many of the characteristics of an ideal GFR marker (e.g., endogenously produced at a constant rate, freely filtered in the glomerulus, neither reabsorbed nor secreted in the renal tubule, not extrarenally eliminated) and has been reported to be at least as accurate as the commonly used serum creatinine to detect impaired renal function in various patient groups, including renal transplant patients and children[1, 6-9, 11-13, 16, 18-19, 28, 30-32].

Several prediction equations have been derived from both paediatric and adult patients to estimate GFR from the serum Cys-C concentration[8, 12-13, 20-21]. Until recently, however, studies that have evaluated Cys-C have used the serum concentration rather than an estimate of GFR based on the measured concentration[20, 22, 33-40].

Accordingly, the objective of this study was to compare GFR level with equations that include Cys-C, PCr, or both levels adjusted for staging of chronic kidney disease (CKD) at in a cohort of children and adolescents.The equations were compared with inulin GFR reference measurement.

MATERIAL AND METHODS

Study Population

Children cohort of 259 French children who were followed at the Hopital *Mére-enfants* at *Lyon*, aged 1 to 18 years, who underwent renal functional assessments between October 2003 and July 2011 (695 GFR measurements in all with an average of 2 measurements per patient). The baseline population was divided into two age groups: 165 children (<13 years, 318 measurements) and 194 adolescents (13-18 years, 341 measurements). The age limits for adolescents was chosen to allow comparisons with the original Schwartz cohort.

The study was approved by the Research Ethics Board.

Laboratory Assessment

Measure of glomerular filtration rate (mGFR) was measured by the plasma clearance of radiolabel by the clearance of inulin (polyfructosan infusion, Inutest®; Fresenius Kagi, Graz, Austria). A standard technique was used by a trained staff with a continuous infusion after a priming dose of polyfructosan (30 mg/kg). Water diuresis was induced by oral administration of 5 ml/kg of water followed by 3 ml/kg every 30 minutes combined with an intravenous infusion of 0.9% sodium chloride. This enabled the patients to spontaneously empty their bladder every 30 minutes. Three to four urine samples were collected, and a blood sample was drawn mid-way through each collection period.[22]

The clearance values were obtained from the mean values of the three to four 30-minute clearance periods. Patients needing intermittent urethral catheterization were excluded from this study. To obtain valid results in patients with mild urologic abnormalities, polyfructosan was diluted in mannitol 10%, and water diuresis was induced before the arrival of the patients; thus, the increase of urine volume and the secondary decrease of urinary concentration of inulin allows minimization of the errors caused by mild urological problems, by allowing a diminution of sample variability and a facilitation of vesical voiding. In addition, whatever the pathology of the patient, a maximum scatter of 20% between the three or four clearance periods

was accepted to assess the validity of mGFR measurement in each period. Measurements of plasma and urine polyfructosan were performed using an enzymatic method. The results were expressed to 1.73 m2, according to the *Dubois* formula of body surface.

Plasma creatinine (PCr) was obtained from a kinetic colorimetric compensated Jaffe technique (Roche Modular, Meylan, France; compensation according to manufacturer's recommendations) for which the imprecision of the assay method was checked (intra-assay coefficient was 0.7%; inter-assay coefficients were 4.0% at low concentration PCr (45 – 60 µmol/L) and 1.5 % at High concentration PCr (580 µmol/L), respectively. All measurements of PCr were performed with the same method all over the study period. The results for PCr were standardized by linear regression adjustment of the concentrations obtained by the compensated Jaffé assay and the concentrations obtained by liquid chromatography-mass spectrometry (LCMS). Briefly, the LCMS apparatus was calibrated with three European standards (BCR; Bureau community Reference 573, 574 and 575) and two American standards (SRM; Standard Reference Material) which PCr concentrations range from 66.5 to 404 µmol/l. The parameters for the linear regression line were obtained for 54 patients with serum creatinine values ranging from 41 to 220 µmol/L. 94.2% (993) of our plasma creatinine values were within this range. Calibration equation was as follows: standardized serum creatinine = 0.9395 * (Jaffé compensated serum creatinine in µmol/l) + 4.6964. Intercept (4.6964; 95% CI [-2.4619 to 11.8656]) and slope (0.9395; 95% CI [0.8719 to 1.0072]) were not significantly different from zero and 1 respectively. The coefficient of correlation r was 0.97. Mean difference between LCMS and compensated Jaffé was 1.24 ±10.05 µmol/l. Stability of the PCr assays was assessed during the study. Blinded ProBioQal controls were tested every 5 weeks and a nationwide-blinded control was tested each year[37].

Blood Urea Nitrogen (BUN) were analyzed centrally at the CKiD's laboratory at the Hopital Edouard Herriot Lyon on an Advia 2400 (Siemens Diagnostics, Tarrytown, NY). BUN [mmol/L]= 2x urea [mmol/L].

eGFR was estimated with equations that used plasma PCr (*Schwartz* 2009 *(bedside*)[20] and the *Schwartz Lyon[22])*, equations that used Cys-C (*Filler and Bricon*)[8, 12] and combined PCr and Cys-C (CKiD and *Zappitelli*)[20-21, 29] (Tables 1). All the eGFRs were normalized by body surface area and expressed in mL/min per 1.73 m^2.

Plasma cystatin C (Cys-C) from a nephelemetric technique (BN2; Behring, Paris, France). We had previously checked that the Roche compensated method closely agreed with an enzymatic Roche method.

Statistical analysis

The eGFR and the mGFR were compared for individual patients using the following measures:

1) Mean ratio= Mean eGFR / mGFR, to asses bias.

2) Concordance correlation of eGFR with mGFR, to asses agreement

The mean ratio was used in order to correct the variance of bias (mean difference between eGFR and mGRF in the same subject), that was not constant. There was an increase in variability when the magnitude of the Inulin measurement increased. The ratio represents the bias between formula and Inulin clearance; that means, no bias if the mean ratio is equal to 1[23].

The concordance correlation coefficient (CCC) is a measure of agreement that adjusts the Pearson correlation downward if there is a systematic bias between the measures being compared[25].

We performed comparisons in the overall data set and in age subgroups. Also, we used accuracy 10 and 30% according K/DOQI guidelines. Accuracy 10% and 30% are defined as a proportion of mGFR that were within 10 and 30% of the mGFR[27].

Comparing performance of creatinine-based and cystatin C equations

We compared performance of the 5 based formulas with mGFR in our overall data set and in age subgroups. For data analysis, we used mean ratio, CCC, and Bland Altman graph.

In order to compare the CCCs between all formulas, the 95% confidence intervals of the differences were estimated by a bootstrap method using the CCC macro described by Crawford et al.[25]

The repeated measurements were grouped by patient and adjusted by a linear mixed effects model. We estimated the 95% limits of agreement of mean ratio by adding the within-patient and between-patient variances.

We used area under the ROC curves (AUC) to determine the ability of the eGFR to discriminate between patients with and without CKD (defined by an mGFR < 60 ml/min/ per 1.73 m)[41]. The Delong Clarke-Pearson method is used to compare AUCs. A value of $p<0.05$ was considered to indicate statistical significance. These calculations were performed using R for windows version 2.13.

RESULTS

Baseline characteristics of the study population are presented in Table 2. 695 measurements of mGFR and eGFR were available in 259 patients. The median [IQR] age was 11.4 yrs [7.9-13.9], and 61% were male. Most subjects (77%) had mGFR superior 60 ml/min/ per 1.73 m^2. Forty-two percent had tubulointersticial disease. Table 2 shows the median IQR [IQR] derived from the five GFR estimating equations with measured GFR at different time points in the study cohort.

The percentage error of the eGFR by all of the equations with respect to the mGFR is shown in table 3.

Bias, Precision, and Accuracy of Estimated GFR

In the whole population

The performance of the various estimates of GFR is shown in Table 2 and (Figure 1). The mean ratio differences between equations and inulin are statistically significantly different of zero ($p< 0.001$). We then compared the diagnostic performance of the combined based prediction (eGFRCom) equations with that of the simplified PCr prediction (eGFRCr) and Cyst-C-based GFR-estimating equations (eGFRCys). The *Schwartz Lyon* (Intercept, 1.05; 95% CI, 0.70–1.40), 2009 *Schwartz bedside* (Intercept, 1.10; 95% CI, 0.70–1.50), *Filler* (Intercept, 1.13; 95% CI, 0.69–1.60) and *Bricon* (Intercept, 1.05; 95% CI, 0.57–1.52) equations produced a statistically significant overestimation of GFR.

The *Zappitelli* (Intercept, 1.01; 95% CI, 0.62–1.40) and CKiD equations (Intercept, 0.99; 95% CI, 0.64–1.35) had bias ratio near zero without significantly difference between GFR by inulin. However the percentage of values that fell within 10 and 30 accuracy of the true GFR wasn't different of *Schwartz Lyon* (table 1).

According to age

Children

When the same evaluations were performed in the subgroup of age Group 1 (Table 2, children<13 yrs, G1) with the true GFR, the *Filler*, *2009 Schwartz bedside* and *Bricon* overestimated GFR at 15% (Intercept, 1.15; 95% CI, 0.75–1.55), 12% (Intercept, 1.12; 95% CI, 0.72–1.52) and 4% (Intercept, 1.04; 95% CI, 0.51–1.39), respectively. In contrast to CKID (Intercept, 0.99; 95% CI, 0.62–1.35) and *Zappitelli* (Intercept, 0.98; 95% CI, 0.62–1.34) had prediction at underestimated at 1% and 2% equation for G1 without significantly difference by mGFR. Moreover, eGFR/GFR obtained by the *Schwartz Lyon* (Intercept, 1.00; 95% CI, 0.51–1.39) did not differ significantly from those between GFR values predicted by either the CKiD or *Zappitelli.*

Schwartz Lyon had accuracy superior to eGFRCys and *2009 Schwartz bedside*, the proportions of patients with GFR estimates within accuracy 10 and 30 of measured GFR (Table 2) an weren't significantly higher for eGFRCom.

Adolescents

At adolescents group (Table 2, children≥13 yrs, G2), mean ratio eGFR/GFR to CKID and *Schwartz Lyon* underestimated the mGFR at 1% (Intercept, 0.99; 95% CI, 0.54–1.35) and 3% (Intercept, 0.97; 95% CI, 0.54–1.40) respectively, being statistically difference ($p<0.05$) between both. The *Zappitelli, Filler, 2009 Schwartz bedside* and *Bricon* were significantly different by CKiD and *Schwartz Lyon* ($p<0.01$) and overestimated the mGFR by 5% (Intercept, 1.05; 95% CI, 0.64–1.45), 6% (Intercept, 1.06; 95% CI, 0.59–1.60), 9% (Intercept, 1.09; 95% CI, 0.61–1.58) and 11% (Intercept, 1.11; 95% CI, 0.63–1.57) respectively.

CKiD have 54% of eGFR values were within the 10% cut-off of mGFR, and 93% of the eGFR values were within the 30% cut-off of mGFR, with differ significantly from all other equation ($p<0.05$).

According to K/DOQI classification subgroups

To stage of CKD I (mGFR ≥ 90ml/min per 1.73 m²), the results for mean eGFR, mean ratio and accuracies 10 and 30% are presented in Table 4 with respective standard deviations. CKiD formulas and *2009 Schwartz bedside* had a better and significantly performance than other formulas in the whole normal GFR population with a mean eGFR/mGFR ratio of underestimated of 3% (Intercept, 0.97; 95% CI, 0.55−1.38, p<0.001) and overestimated of 3% (Intercept, 1.03; 95% CI, 0.60−1.48, p<0.001), respectively. However, there wasn't any difference to accuracies 10 and 30 between all equations.

At stage II (60 ≤mGFR > 90ml/min per 1.73 m²), the bias of *Schwartz Lyon* (Intercept, 1.00; 95% CI, 0.64–1.35) was similar with *CKID* (Intercept, 0.99; 95% CI, 0.62–1.35) and near zero. Both equations had accuracies 30 similar and statistically superior to other equations (p<0.05), except *Zappitelli*. To accuracies 10, CKiD was the value better than other formulas.

Schwartz Lyon and *Zappitelli* were superior and significantly all the other equations with overestimated of 11% (Intercept, 1.11; 95% CI, 0.64−1.58, 95% CI, 0.66−1.56, p<0.001) to stage III of CKD (30 ≤GFR >60 ml/min per 1.73 m²). The accuracies 10 and 30 weren't superior to CKiD when mGFR were inferior to 30 ml/min per 1.73 m²:

Agreement and Reproducibility between GFR measurement methods

All the population, the concordance correlation coefficients between the measured GFR and the estimation equation GFR are shown in Table 3. Agreement higher methods were for CKID (CCC of 0.89, 95% CI 0.86, 0.91), *Schwartz Lyon* (CCC of 0.88, 95% CI 0.86, 0.90) and *Zappitelli* (CCC of 0.87, 95% CI 0.84, 0.89) without statistically difference between those equation. The *2009 Schwartz bedside* (CCC of 0.85, 95% CI 0.81, 0.89), *Filler* (CCC of 0.80, 95% CI 0.76, 0.84) and *Bricon* (CCC of 0.81, 95% CI 0.76, 0.84) formulas were lower and significantly inferior than CKiD, *Zappitelli* and *Schwartz Lyon*.

Children

The performance analysis was repeated after subdividing patients by age range. In children, concordance was strongest to the equation *Schwartz Lyon* (CCC of 0.88, 95% CI 0.84, 0.90), but without difference to CKiD (CCC of 0.89, 95% CI 0.86, 0.91) The formulas based strictly on Cys-C (CCC of 0.84, 95% CI 0.80, 0.88, CCC of 0.76, 95% CI 0.70, 0.81) or *Zappitelli* (CCC of 0.84, 95% CI 0.79, 0.88) and *2009 Schwartz bedside* (CCC of 0.84, 95% CI 0.81, 0.89) were statistically lower ($p<0.05$).

Adolescents

In adolescent populations, equation performance varies considerably, particularly between the combined and other equations, with significantly better concordance to CKiD (CCC of 0.92, 95% CI 0.89, 0.95) and *Zapittelli* (CCC of 0.90, 95% CI 0.85, 0.93) formula than to other formulas.

Moreover, the equations based at PCr, *2009 Schwartz bedside* (CCC of 0.86, 95% CI 0.84, 0.91) and *Schwartz Lyon* (CCC of 0.88, 95% CI 0.83, 0.92), were superior only with *Bricon* (CCC of 0.85, 95% CI 0.87, 0.90). *Filler* (CCC of 0.87, 95% CI 0.81, 0.88) had similar concordance with PCr equations that group.

Association between eGFR measurement and CKD classification

ROC curves for the eGFR measurements and CKD classification are shown in Figure 4 and their respective AUC values are provided in Table 3. eGFR values were related to 2 range of mGFR (>60 and >90 ml/min per 1.73 m^2).

In the whole population

The AUC was significantly higher with eGFR measurement based at *2009 Schwartz bedside, Schwartz Lyon* and *Filler* (AUC 0.949; CI 0.925, 0.973, $p<0.01$) than *Zappitelli* (AUC 0.920; CI 0.888, 0.951, $p=0.03$) and *Bricon* (AUC 0.902; CI 0.867, 0.937, $p=0.02$) for diagnosis of mild CKD (mGFR <90 ml/min per 1.73 m^2). Almost, CKiD had AUC lower, isn't significant (AUC 0.943; CI 0.917, 0.970, $p=0.4$)

By contrast, only *Bricon* (0.902; 95% CI 0.867–0.937, p<0.01) was lower than the AUC for others eGFR at moderate CKD (mGFR <60 ml ml/min per 1.73 m^2) with all other equations (Table 4, Fig.4).

According to age

To evaluate the diagnostic validity by age range, the ROC analysis was performed. Within G1 (<13 yrs) or G2 (≥13 yrs) haven't significantly different between CKiD, *Filler*, *2009 Schwartz bedside and Schwartz Lyon* (*P*=0.3) to mild and moderate CKD (table 4). However, the AUC for *Bricon* was significantly smaller than those (*P*<0.05) at both range age and level of CKD. Also, *Zappitelli* had AUC statistically inferior to G1 with moderate CKD.

DISCUSSION

This is the first study to examine the consistency of performance of eGFR with repeated measures Cyst-C and PCr compared with inulin in a cohort comprising a pediatric population. We found no substantial evidence that equations based on Cyst-C alone or in combination with PCr provide better GFR estimates than the PCr equations, notably *Schwartz Lyon* with mild and moderate chronic kidney disease in population with age inferior 13 yrs, or with normal renal function.

For the measurement of GFR, the inulin continuous perfusion method is considered to be the gold standard, because inulin meets the ideal requirements for a glomerular tracer, except for a minor extra-renal clearance. In our study suggest that performance to eGFRCom, eGFRPCr and eGFRCys, changed with level CKD and age range to population pediatric[27-29, 42].

We analyzed the diagnostic accuracy of various equations by three methods: first, by the ability of the equations to classify the measured mGFR appropriately, as tested by the AUC, sensitivity, and specificity; by the accuracy of the equations in predicting the measured GFR, as tested by the ratio bias, ratio SD of bias, and eGFR values within 10% and 30% of the respective inulin and by the concordance correlation coefficients between the mGFR and the eGFR.

We compared the diagnostic performance of these prediction equations for the subgroup to age under of 13 yrs with data for all 341 measurements. The equation of CKiD[20], *Zappitelli*[21] and *Schwartz Lyon*[22] estimated GFR near the real valor to that group, no difference between them (p=0.08). In contrast to the eGFRCys and 2009 *Schwartz bedside*[5] that overestimated and were different to anterior (p<0.01). Thus, the results obtained in this study confirmed the Study CKiD formula in a general pediatric cohort, where *Schwartz et al* described an overestimated less than 15% to *Schwartz 2009* compared with iohexol-based GFR[20, 29]. Unlike the *Schwartz 2009*, *Schwartz Lyon* used 2 coefficients for age and gender which would explain this difference between *biases*. *Filler* and *Lepage* suggested that, like the *Schwartz original* and *2009 bedside* prediction equation overestimates GFR and that eGFRCys might be more suitable for children. Although, *Sharma et al*.[38] report that the reciprocal of had a significantly higher concordance with eGFRCys and mGFR, there wasn't clear the superiority evident with eGFRCys or eGFRCom to agreement with inulin in our population under 13 yrs.

To allow for appropriate clinical and research application, we aimed to examine the distribution of GFRs obtained from eGFR estimating equations in a sample of adolescents from our population. Among adolescents, the CKiD obtained estimated GFR near true GFR by inulin and statistically better than all other equations. Exception *Schwartz Lyon*, the other formulas overestimated, in our study, of 5% to 11%, being inferior *Schwartz Lyon equation* ($p<0.05$). The concordance correlation coefficient with measured GFR was higher in the group of adolescents for all assessments, both eGFRCom. The reason for this is not completely clear, but formulas for eGFRCom also perform better like stipulated *Fadrowski et al*[43], the pediatric GFR estimating equations systematically underestimate GFR because they were derived in children with CKD. It underestimated to adolescents is associated account for the relationship between creatinine production and muscle mass by growth and GFR[29, 44]. Our work is unique that studies the different formulas to estimate renal function in adolescents with the reference method to GFR. Alike the CKiD study failed to demonstrate a difference to adolescents, our findings demonstrated benefits to eGFR with equation CKiD that group. This formula yielded 87.7% of estimated GFR within 30% of the iohexol-based GFR (CKiD), and 45.6% within 10% to general population.[29]

The concordance correlation coefficient with measured GFR was higher in the group of adolescents for all assessments, both eGFRCom. The reason for this is not completely clear, but formulas for eGFRCom also perform better. It is well known that eGFR calculated by the modification of diet in renal disease formula underestimates GFR in the normal range by up to 30% but only by 6% in patients with CKD.[11, 27-28]

With lower estimated GFR (eGFR), we looked for evidence of morbidities that are commonly associated with decreased GFR to support a potential diagnosis of CKD[1, 4, 27-28]. Unlike the findings in previous studies, we found that the ROC plot area of PCr equation wasn't worse than that of only Cyst-C or combined PCr to all population. Indeed, the areas for the equations were not significantly different among equations, exception to *Bricon*. These data confronted to the promising results reported in other recent pediatric studies[37-38]. There wasn't an apparent variance in the diagnostic accuracy of eGFR equations in GFR or age categorization and GFR prediction. *Andersen et al*[45] published a review about the Cyst-C and area under the ROC curve. They described in five studies of the remaining, Cyst-C had a significantly higher area under the curve (AUC) than did PCr, in four studies there was no significant

difference. However, no study found creatinine to be significantly better than Cyst-C. According the authors, to make a reliable assessment of a method's ability to discriminate between normal and moderately decreased GFR the ROC analysis should only include data from patients with GFR values no less than 50%. Otherwise, the diagnostic value of the method will be overestimated. Unfortunately, this was not the case in any of the papers aforementioned.

Furthermore, the diagnostic accuracy of the equations estimated by eGFR values within 10% and 30% of the respective inulin varied more expressively in the GFR ranges ≤30 and <60 ml/min per 1.73 m^2. The CKiD equations had a higher accuracy in the all GFR ranger. However, was significantly only to GFR ranges ≤60 and <90 ml/min per 1.73 m^2 to the Schwartz *Lyon* and *Zappitelli.* No equations had greater accuracy in the GFR categories ≥ 90 ml/min per 1.73 m^2. There was an apparent discrepancy in the diagnostic accuracy of eGFR equations in GFR categorization and GFR prediction. For example, the *Bouvet* equation had an excellent AUC and correlation coefficient overall; however, it had a relatively large relative bias and lower predictive accuracy in the low GFR range. It is important to consider that the AUC and sensitivity of an equation depends on the cutoff points selected for GFR categorization and the equation's tendency to underestimate or overestimate the GFR[38, 41, 45].

On the other hand, the accuracy of an equation for GFR prediction varies by the closeness of an eGFR to the measured GFR, regardless of the equation's tendency to underestimate or overestimate the measured GFR[38, 44]. This point was further evident from a higher percentage error of the eGFRCys and *2009 Schwartz bedside* equation at the low GFR. While *Bachetta et al*[22] concluded that the eGFRCys can be used reliably in a general pediatric population, without significant differences between inulin clearance, we found difference important favoring *Schwartz Lyon* and CKiD.

Variation in creatinine assays is a great concern, adding systematic errors to eGFR. IDMS is considered the gold standard for establishing true creatinine concentration[5, 20, 29, 39]. Thus, creatinine values must be traceable to an IDMS reference value for creatinine measurements to be comparable regardless of method or laboratory used. Concerning the PCr equations, the *CKiD, 2009* Schwartz *bedside,* Schwartz *Lyon were* developed for use only with standardized creatinine values and while the *Zappitelli* equation has not. Therefore, the eGFR using the *Zappitelli*

equation with standardized serum creatinine is generally higher and less accurate than with non-standardized creatinine[29]. Following the latest recommendations, serum creatinine was measured by an IDMS traceable Jaffé method in our study.

In addition, the method of Cyst-C measurement in our study, using Siemens Dade-Behring determination, may differ from the Dako kit, which has been reported as perhaps the less precise measurement of Cyst-C available[20, 29, 39, 44]. Almost, the Cyst-C based estimate formula from original CKiD studies used the Dako kit as well; this formula did perform well with our population. *Zappitelli, Filler* and *Bricon* were built using the Siemens Dade-Behring that not explains the inferior performance with CKiD. Several factors may contribute to the insufficient performance of most of the equations based Cyst-C in our study group cannot be applied our population. It has been demonstrated that cystatin C is affected by factors other than GFR[29]. Thus, in patients with chronic kidney disease, cystatin C was 4.3% lower for every 20 years of age and 9.2% lower in women[33]. In addition, diabetes was associated with 8.5% higher levels of cystatin C. Higher BMI, C-reactive protein and leucocytes count, and lower serum albumin were also associated with higher levels of cystatin C[46-47]. However, were not found in our population. Unlike our laboratory, there is no standardization between assays and laboratories for Cyst-C[47]. According to recent studies, a downward shift in calibration for the Siemens Cyst-C method occurred between 2006 and 2010[48]. Therefore, eGFRcys that were derived from results obtained from older lots of reagent and calibrator cannot be used with the current Siemens method. These observations emphasize the need for an international cystatin C reference value and may partly explain the results of our study. For the time being, the lack of standardization is a serious obstacle for routine use of eGFRcys[38-39, 43, 47-48]. If this obstacle could be overcome, eGFR levels based solely on cystatin C (without the need for correction for age, sex or ethnicity) could provide a more accurate way of estimating GFR than creatinine-based formulae, which require information on patient age, sex and ethnicity[48].

Researchers have developed Cyst-C-based GFR-estimating equations, and have compared their performance with original *Schwartz* equation. *Blufpand et al.*[36] demonstrated that Cyst-C-based equations are more accurate in GFR prediction in oncology paediatric, than PCr equations. *Filler et al.*[9, 19] found that Cyst-C-based equations might diagnostic accuracy of various Cyst-C-based or associated PCr equations varies with mGFR at children.

Examination of the estimating formulas a follow-up period, longitudinal direct measurement of GFR to show substantial differences from the rest of the population (data not shown). *Abraham et al*[49] showed that during a 1-year follow-up period, longitudinal direct measurement of GFR can be complemented with consistent estimates of GFR using transition models and biomarker data. The marriage of direct and estimated GFR provides a continuity of GFR data that befits the longitudinal study platform. Additional follow-up time and the availability GFR data hold the promise for realizing the full potential of longitudinal estimating equations.

CONCLUSION

We have demonstrated that the cystatin C-derived formulas for estimating GFR seem less accurate in non selected pediatric patients. The diagnostic accuracy of eGFRCys does not appear to be superior to that of either creatinine measurements in the pediatric population investigated, notably to age inferior 13 yrs. This study, together with the higher costs and larger assay time of Cyst-C compared PCr, lead us to suggest that use of Cyst-C as marker of the GFR is of no advantage in large pediatrics populations. In assessing the utility of a screening test, cost is a significant factor, as well as its diagnostic sensitivity. It has been reported that the cost of the cystatin C assay is 13-fold greater than the assay for serum creatinine (10). Costing was similar in our laboratory.

The international standardization of creatinine assays with the IDMS method will probably improve the accuracy of “universal” creatinine-based formulas[20, 27, 29], but to date, these cystatin C-derived formulas can be used reliably when reference methods for measuring the true GFR are not available or when the local adaptation of Schwartz formula has not been performed

Further studies on larger populations are required to validate this report and to evaluate the potential utility of eGFRCr, notably *Schwartz Lyon* equations, in the progression and monitoring of CKD in children and adolescents.

Table 1. Formulas used for the estimation of glomerular filtration rate

	Formula (ml/min per 1.73 m²)
With plasma creatinine	
Schwartz Lyon	eGFR = *k* × height (cm)//PCr *k*= 35.5 in boys >13 years of age *k*= 32.5 in other children
2009 Schwartz bedside	eGFR = 36.5 × height (cm)/PCr
With serum cystatin C	
Bricon	eGFR = (78/Cys) + 4
Filler	log(eGFR)= 1.962 + [1.123 × log (1/Cys)
Combined formula	
CKID	eGFR = 39.1 × [height (m)/(PCr/88.4)]$^{0.516}$ × [1.8/Cys]$^{0.294}$ × [30/BUN (mg/dl)]$^{0.169}$ × [1.099]^{male} × [height (m)/1.4]$^{0.188}$
Zappitelli	eGFR = [507.76 × e$^{0.003\times height\ (m)}$]/[Cys$^{0.635}$] × [PCr$^{0.547}$] If renal transplant, × 1.165 If spina bifida, × [PCr$^{0.547}$])/40.45

Table 2 – Baseline of the whole population and each age group characteristics.

	All	Group 1 (1-12 years)	Group 2 (13-18 years)
*Patients	259	165	94
Males (%)	51.5	54.5	46
*mGFR(N)	695	341	354
*mGFR (ml/min/1.73 m²; median [IQR])	85.0 [64.0-109.0]	87.0 [66.0-112.0]	80.5 [57.8-105.5]
*Age (yr; median [IQR])	11.4 [7.9-13.9]	9.3 [7.0-10.9]	14.9 [13.8-15.0]
*Follow-up (months; median [IQR])	29 [16-43]	25 [14-37]	32 [19-47]
*Weight (kg; median [IQR])	34.6 [24.1-47.3]	27 [21.2-33.5]	48.8 [42.3-58.5]
*Weight percentile (median [IQR])	30 [9.7-57.1]	34.5 [12.3-60.3]	24.5 [7.5-56.2]
*Height (cm, median [IQR])	141.7 [122.0-154.0]	140.7 [134.0-147.0]	157.7 [150.5-163.8]
*Height percentile (median [IQR])	32 [5.5-54.5]	32.6 [7.5-57.7]	17.4 [3.6-49.8]
*BSA (m², median [IQR])	1.18 [0.9-1.42]	0.99 [0.84-1.18]	1.47 [1.33-1.59]
*BMI (kg/m²; median [IQR])	17.1 [16.2-20.1]	16.1 [15.1-18.4]	19.5 [18.1-22.0]
*BMI percentile (median [IQR])	43.0 [16.2-72.6]	44.6 [23.0-76.4]	39.4 [12.5-69.1]
*PCr (µmol/l ; median [IQR])	54.5 [42.3-70.5]	48.8 [38.5-63.5]	65.3 [52.4-95.6]
*Cyst C(mg/dl; median [IQR])	1.02 [0.84-1.26]	1.00 [0.83-1.15]	1.07 [0.84-1.45]
BUN (mg/dl; median [IQR])	16.2 [11.8-23.2]	16.3 [11.5-22.1]	16.4 [12.4-24.8]
K/DOQI classification n (%)			
*I	102 (39)	81 (49)	34 (36)
II	97 (38)	60 (37)	36 (38)
*III	60 (23)	24 (14)	24 (26)
Diagnosis n (%)			
Glomerulopathies	53 (21)	31 (19)	22 (23)
Tubulointersticial disease	110 (42)	69 (42)	41 (44)
Kidney transplant recipients	60 (23)	38 (23)	22 (23)
*others	36 (14)	27 (16)	9 (10)

IQR= interquartile range, mGFR= measured glomerular filtration rate by inulin clearance, BSA= body surface area, BMI= body mass index, PCr= plasma creatinine, BUN= blood urea nitrogen) *$p < 0.05$

Table 3 – Bias, SD of bias, Lins'concordance and 30% accuracy of the four estimating GFR formulas (compared with measured GFR) for the total population and each subgroups

		Schwartz 2009	*Schwartz Lyon*	*Filler*	*Bricon*	CKID	*Zappitelli*
A. All measurements (N=695) mGFR= 84 ±32.7 (ml/min per 1.73m²)							
eGFR (ml/min/1.73m²)		91.0 ±34.2	83 ±30.7	93 ±30.7	85 ±24.2	86 ±25.5	84 ±31.3
Lin's concordance correlation coefficient, ρ_c (95% CI)		0.86[b] (0.83 - 0.89)	0.88 (0.85 - 0.90)	0.86[b] (0.82 - 0.89)	0.76[a,b] (0.71 - 0.80)	0.88 (0.86 - 0.90)	0.90 (0.89 - 0.91)
Mean ratio (eGFR / mGFR)		1.10 ±0.23	0.99±0.16	1.13 ±0.22	1.06 ±0.14	1.05 ±0.20	1.01±0.20
95% limits of agreement		0.87, 1.34	0.82, 1.15	0.91, 1.35	0.82, 1.30	0.86, 1.25	0.81;1.21
Accuracy (%)	**10%**	40[a,b]	48	39[a,b]	36[a,b]	40	47
	30%	84[a,b]	92	87[a,b]	86[a,b]	93	90
B. Group 1 (<13 years, N=341) mGFR= 89.4 ±31.9 (ml/min per 1.73m²)							
eGFR (ml/min/1.73m²)		96.5 ±30.1	86.0 ±26.4	86.7 ± 28.5	80.1 ±22.3	78.0 ±23.2	89.5 ±28.2
Lin's concordance correlation coefficient, ρ_c (95% CI)		0.85[a,b] (0.81 - 0.89)	0.87 (0.84 - 0.90)	0.79[a,b] (0.73 - 0.84)	0.71[a,b] (0.64 - 0.77)	0.81[a,b] (0.76 - 0.85)	0.87[b] (0.83 - 0.90)
Mean ratio (eGFR / mGFR)		1.12 ±0.26	1.04 ±0.18	1.13 ±0.20	1.00 ±0.25	1.02 ±0.19	0.94 ±0.19
95% limits of agreement		0.86 , 1.38	0.86, 1.23	0.94, 1.33	0.75, 1.25	0.83, 1.21	0.76, 1.11
Accuracy (%)	**10%**	43[a,b]	48	42[a,b]	37[a,b]	40[a]	51
	30%	84[a,b]	93	88[a,b]	86[a,b]	93	92
C. Group 2 (≥13 years, N=354) mGFR= 80.8 ±32.5 (ml/min per 1.73m²)							
eGFR(ml/min/1.73m²)		85.7 ±37.0	76.3 ±32.9	79.3 ±32.3	74.1 ±25.5	73.1 ±27.4	78.5 ±33.2
Lin's concordance correlation coefficient, ρ_c (95% CI)		0.86[a] (0.80 - 0.91)	0.88[a] (0.83 - 0.92)	0.86[a] (0.82- 0.89)	0.81[a;b] (0.74 - 0.87)	0.89 (0.85 - 0.93)	0.90 (0.87 - 0.93)
Mean ratio (eGFR / mGFR)		1.12 ±0.26	1.06 ±0.25	1.14 ±0.24	1.02 ±0.23	1.05 ±0.16	1.01±0.19
95% limits of agreement		0.86, 1.38	0.81, 1.31	0.90, 1.38	0.80, 1.23	0.89, 1.25	0.83, 1.21
Accuracy (%)	**10%**	36[a]	38	37	35[a]	40	43
	30%	84[a]	90	86[a]	86[a]	92	89

[a] $p < 0.05$ for difference between Zappitelli formula and other equations; [b] $p < 0.05$ for difference between creatinine and cystatin equations, favoring *Schwartz Lyon*; All results are expressed in mean ± standard deviation mGFR= Measured glomerular filtration rate by Inulin clearance, eGFR= estimated glomerular filtration rate.

Table 7 – Means ratio bias and accuracies according to K/DOQI classification and equations

	Schwartz 2009	*Schwartz Lyon*	*Filler*	*Bricon*	CKID	*Zappitelli*
I. GFR ≥ 90ml/min/1.73 m² (N=283) mGFR= 116.1 ±22.4 ml/min per 1.73m²						
eGFR (ml/min/1.73m²)	119.1 ± 29.6	112.6 ± 26.7	107.4 ±24.3	96.3 ± 18.5	97.3 ± 19.6	110.3 ±24.4
Mean ratio (eGFR / mGFR)	1.03 ± 0.23	0.98 ± 0.21	1.06 ±0.16	0.93 ± 0.15	0.96 ± 0.15	0.95±0.18
95% limits of agreement	0.81, 1.25	0.76, 1.19	0.86, 1.26	0.78, 1.08	0.81, 1.11	0.77;1.13
Accuracy 10 %	44 [b,c]	46[c]	41[b,c]	27 [b,c]	27 [b,c]	50
(%) 30%	91[c]	93	90[b,c]	87 [b,c]	90 [b,c]	95
II. 60 ≤GFR >90ml/min per 1.73 m² (N=251) mGFR= 75.2 ±8.4 ml/min per 1.73m²						
eGFR (ml/min/1.73m²)	83.5 ± 15.8	79.0 ± 15.0	77.2 ± 18.5	72.7 ± 14.7	70.0 ± 12.7	77.2 ±15.5
Mean ratio (eGFR / mGFR)	1.12 ±0.18	1.00 ±0.19	1.14 ±0.21	1.07 ±0.19	1.06 ±0.15	1.03 ±0.18
95% limits of agreement	0.94 , 1.29	0.89, 1.22	0.95, 1.33	0.89, 1.26	0.91, 1.21	0.85, 1.21
Accuracy 10 %	43[a,b,c]	49	43[a]	48	46 [b,c]	50
(%) 30%	86 [a,b,c]	93[a]	89[b,c]	93[a]	98	92[a]
III. 30 ≤GFR >60 ml/min per 1.73 m² (N=161) mGFR= 44.5 ±10.8 ml/min per 1.73m²						
eGFR(ml/min/1.73m²)	53.3 ± 14.8	50.3 ± 13.7	53.3 ±15.2	54.8 ± 14.1	49.5 ± 12.8	48.5 ± 14.1
Mean ratio (eGFR / mGFR)	1.25 ± 0.27	1.18 ± 0.18	1.25 ±0.25	1.27 ± 0.27	1.21 ± 0.21	1.11 ± 0.23
95% limits of agreement	0.98, 1.52	0.93, 1.44	0.99, 1.50	0.98,1.56	0.97,1.46	0.89,1.34
Accuracy 10 %	25[a,b,c]	33 [a]	31 [a,b,c]	34[b,c]	52	36[a]
(%) 30%	68[a,b,c]	80 [a]	80[c]	76[a,b,c]	90	80 [a]

[a] $p < 0.05$ for difference between CKID formula and other equations, favoring *CKiD*; [b] $p < 0.05$ for difference between creatinine and cystatin equations, favoring *Schwartz Lyon*, [c] $p < 0.05$ for difference between Zappitelli formula and other equations, favoring *Zappitelli*; All results are expressed in mean ± standard deviation mGFR= Measured glomerular filtration rate by Inulin clearance, eGFR= estimated glomerular filtration rate.

Table8. Area under the ROC curves to detect GFR < 90 and 60 ml/min per1.73

	Schwartz 2009	*Schwartz Lyon*	*Filler*	*Bricon*	CKID	*Zappitelli*
GFR < 90 ml/min per 1.73 m²						
All measurements						
AUC	0.879	0.871	0.792	0.744	0.780	0.849
95% CI	0.834, 0.924	0.823, 0.818	0.732, 0.851	0.608, 0.808	0.726, 0.847	0.798, 0.901
Std Error	0.023	0.024	0.030	0.033	0.031	0.026
Group 1 (<13 yrs)						
AUC	0.853	0.855	0.775	0.727	0.777	0.853
95% CI	0.791, 0.915	0.793, 0.918	0.700, 0.849	0.647, 0.807	0.702, 0.852	0.791, 0.916
Std Error	0.032	0.032	0.038	0.041	0.038	0.032
Group 2 (≥13 yrs)						
AUC	0.925	0.898	0.832	0.784	0.813	0.839
95% CI	0.869, 0.981	0.825, 0.970	0.737, 0.928	0.676, 0.892	0.711, 0.915	0.746, 0.931
Std Error	0.028	0.037	0.049	0.055	0.052	0.047
GFR < 75 ml/min per 1.73 m²						
All measurements						
AUC	0.856	0.862	0.840	0.808	0.862	0.869
95% CI	0.791, 0.904	0.809, 0.915	0.768, 0.894	0.753, 0.864	0.815, 0.908	0.818, 0.919
Std Error	0.029	0.027	0.028	0.028	0.024	0.026
Group 1 (<13 yrs)						
AUC	0.814	0.845	0.805	0.795	0.850	0.859
95% CI	0.732, 0.895	0.772, 0.919	0.727, 0.882	0.722, 0.869	0.790, 0.910	0.789, 0.929
Std Error	0.042	0.037	0.039	0.038	0.030	0.036
Group 2 (≥13 yrs)						
AUC	0.887	0.879	0.885	0.818	0.889	0.865
95% CI	0.811, 0.964	0.802, 0.957	0.810, 0.960	0.802, 0.907	0.816, 0.961	0.786, 0.945
Std Error	0.039	0.040	0.038	0.049	0.037	0.041
GFR < 60 ml/min per 1.73 m²						
All measurements						
AUC	0.813	0.853	0.877	0.879	0.905	0,889
95% CI	0.729, 0.896	0.777, 0.929	0.811, 0.942	0.816, 0.942	0.851, 0.958	0.827, 0.951
Std Error	0.043	0.039	0.033	0.032	0.027	0.032
Group 1 (<13 yrs)						
AUC	0.746	0.785	0.859	0.856	0.884	0.855
95% CI	0.620, 0.873	0.664, 0.906	0.761, 0.958	0.757, 0.954	0.799, 0.968	0.751, 0.959
Std Error	0.065	0.062	0.050	0.050	0.043	0.053
Group 2 (≥13 yrs)						
AUC	0.882	0.923	0.888	0.894	0.922	0.908
95% CI	0.782, 0.981	0.837, 1.000	0.800, 0.975	0.815, 0.973	0.858, 0.986	0.840, 0.977
Std Error	0.051	0.041	0.044	0.040	0.033	0.035

AUC= area under ROC curves, 95% CI= 95% Confidence Interval

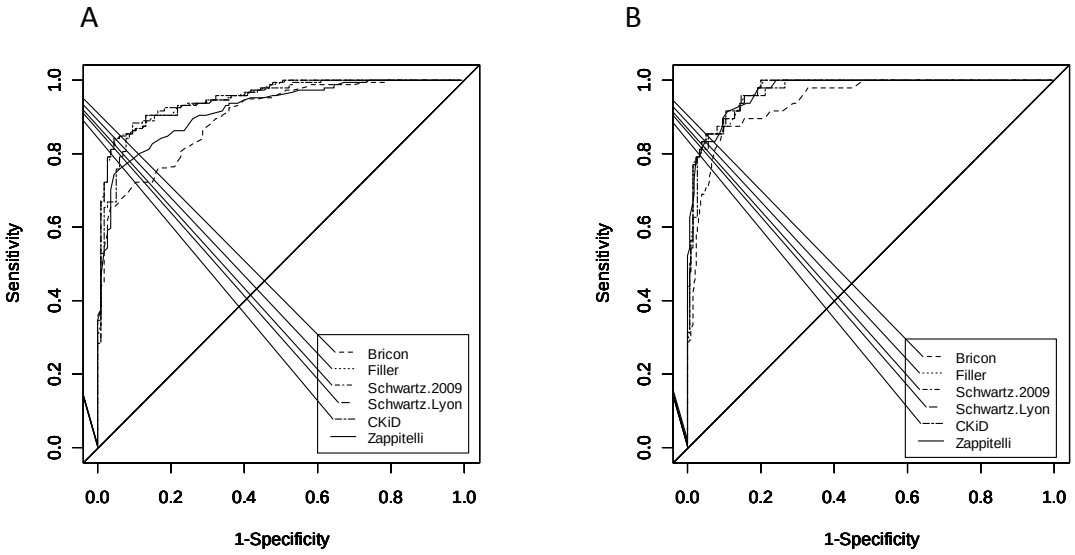

FIG 4 – A. AUC of equations for the diagnosis of moderate chronic kidney disease (GFR <90 ml/min per 1.73m²). **B** AUC of equations for the diagnosis of mild chronic kidney disease (GFR <60 ml/min per 1.73m²)

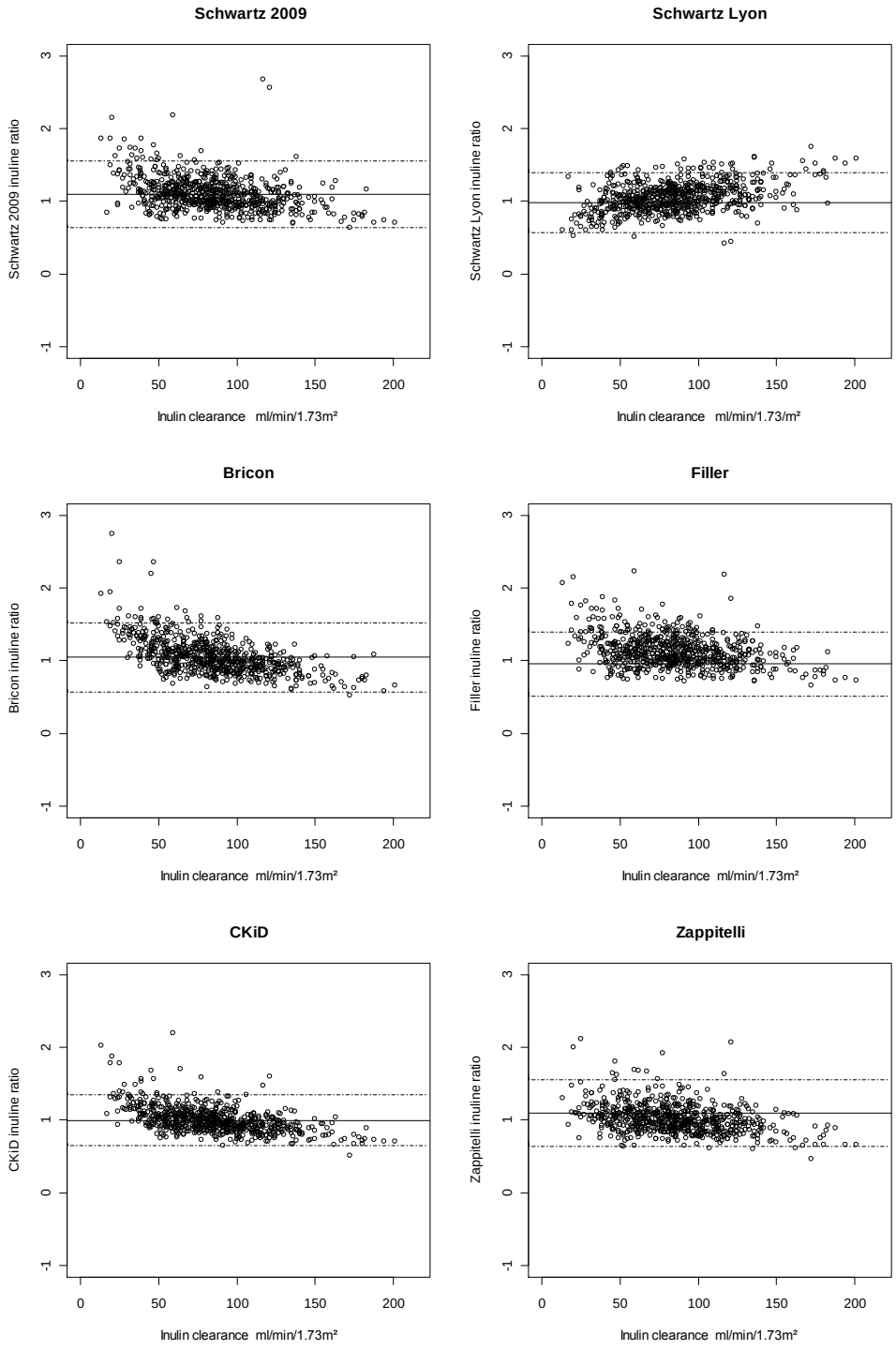

FIG 2 – Estimation equation bias according to level of estimated GFR in ml per min per 1.73m². Bias was calculated by ratio the measured GFR from the estimated GFR and is expressed in ml per min per 1.73m². The mean bias is represented by the solid line and the limits of concordance 95% by the dashed lines.

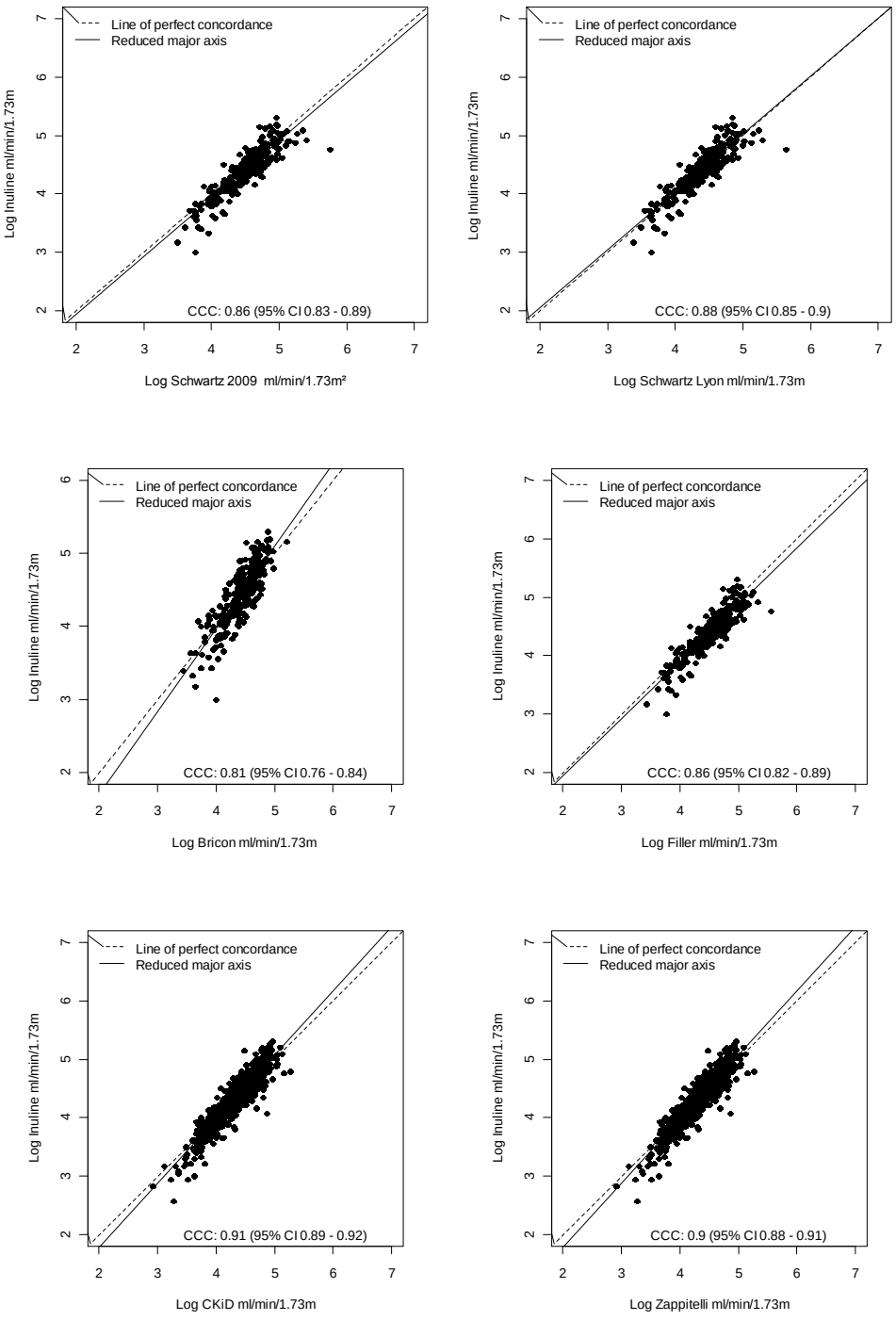

FIG 3 – Concordance Correlation Coefficient (CCC) graphs using logarithmic transformation of mGFR and eGFR. Performance of five formulas in comparison mGFR. From left to right, and from top to bottom: *Schwartz 2009*, *Schwartz Lyon*, *Bricon*, *Filler*, CKiD and *Zappitelli.* Line of perfect concordance: (---), Regression line: (–)

Abbreviations

BMI Body mass index

BSA Body surface area

PCr Plasma creatinine

Cys-C Plasma cystatin C

BUN Blood Urea Nitrogen

mGFR Measure glomerular filtration rate

eGFR Estimated glomerular filtration rate

eGFRCys Cys-C based eGFR equations

eGFRPCr PCr based eGFR equations

eGFRCom Combined PCr and Cys-C based eGFR equations

CKD Chronic kidney disease

CKiD A Prospective Cohort Study of Kidney Disease in Children equation

IQR interquartile range

SD Standard deviation

K/DOQI Kidney Disease Outcomes Quality Initiative

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DISCLOSURES

None

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4.6 CAPÍTULO DE LIVRO *ENTRETIENS DE BICHAT 2011 – Revisão sistemática da técnica de aferição de TFG*

Entretiens
de Bichat
29 sept. 2011
Salle 352A
14 h 30 - 14 h 45

Médecine générale ■

Interprétation d'une clairance Ou comment estimer la fonction rénale en 2011 ?

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Résumé

L'évaluation du débit de filtration glomérulaire (DFG) est une étape indispensable à la prise en charge ou au suivi de tout patient. L'utilisation de formules d'estimation du DFG à partir de la créatininémie (MDRD, Cockcroft, Schwartz) est suffisante dans la majorité des cas. Lorsque la créatininémie n'est pas fiable (dénutrition, pathologie chronique), l'utilisation de formules dérivées de la cystatine C doit être préférée. Enfin, dans des situations particulières (drogues néphrotoxiques, don de rein, morphotypes extrêmes), une mesure précise du DFG par des marqueurs glomérulaires reste nécessaire.

Mots-clés

Débit de filtration glomérulaire, créatininémie, Cystatine C, MDRD, Cockcroft, Schwartz

L'évaluation de la fonction rénale et plus particulièrement du débit de filtration glomérulaire (DFG) est une étape indispensable lors de la prise en charge de tout patient quelle que soit sa pathologie. De nombreux travaux se sont intéressés à ce problème et des recommandations sont maintenant proposées par les autorités de santé, à la fois chez l'adulte et chez l'enfant[1,2].

Rappel : évolution de la filtration glomérulaire au cours de la vie

Le DFG évolue au cours de la vie. Ainsi le DFG du nouveau-né est très faible (≈20 ml/min/1,73m²) et va augmenter rapidement au cours des premiers mois de la vie pour atteindre une valeur comparable à celle de l'adulte (100 – 120 ml/min/1,73 m²) vers l'âge d'un an. Le DFG reste ensuite stable jusqu'à 40 ans puis décroit ensuite de 1 ml/min/an pour conduire à une insuffisance rénale « physiologique » chez le sujet âgé[3].

Mesures du DFG

Le DFG est le principal élément d'appréciation de la fonction rénale. Idéalement, il devrait être déterminé par la mesure de la clairance d'un marqueur glomérulaire. Cependant ces mesures ne sont pas réalisées en routine et sont réservées à des indications spécifiques au sein de services spécialisés. En pratique quotidienne, le praticien doit savoir utiliser d'autres moyens d'évaluation que nous évoquerons successivement.

Mesure de la clairance rénale

Les marqueurs glomérulaires exogènes

La mesure du DFG fait appel au concept de clairance rénale d'un indicateur glomérulaire comme l'inuline. Un tel indicateur a comme propriété d'être filtré librement par le glomérule et de n'être ni réabsorbé ni sécrété par les tubules. Ainsi, la quantité filtrée au niveau du glomérule (produit de la concentration plasmatique par le DFG (P x DFG)) est égale à celle qui est excrétée dans l'urine (concentration urinaire x débit urinaire (U x V). En mesurant la concentration plasmatique de cet indicateur P, sa concentration urinaire U et le débit urinaire V on peut calculer la filtration glomérulaire par la formule suivante DFG = U x V / P. Les principaux indicateurs glomérulaires sont l'inuline ou le polyfructosan (marqueurs de référence), les radio-éléments (51Cr-EDTA, 99Tc-DTPA) et les marqueurs iodés (iohexol, iothalamate). La mesure de la clairance rénale par perfusion continue avec recueil d'urines est généralement réalisée en utilisant l'inuline ou le polyfructosan et reste la méthode de référence. Cependant, cet examen nécessite une perfusion continue et surtout une bonne vidange vésicale, ce qui limite son utilisation et rend cette méthode difficilement réalisable chez le jeune enfant ou lors d'uropathie sévère.

La créatinine

La créatinine est considérée en pratique courante comme un marqueur glomérulaire (librement filtrée), mais un marqueur imparfait puisqu'elle est sécrétée par le tubule et ce d'autant plus que la fonction rénale est altérée. C'est pourquoi la clairance de la créatinine surestime le DFG et cette surestimation est d'autant plus importante que l'insuffisance rénale progresse. Quoi qu'il en soit, la mesure de la clairance de la créatinine sur des urines de 24 heures ou sur 2 à 3 périodes d'une heure reste une alternative simple et utile si la fiabilité du recueil d'urines est vérifiée. Cependant, pour de nombreux auteurs, son intérêt ne persiste

que dans les cas où la créatininémie n'est pas fiable (myopathie, dénutrition, etc.).

Mesure de la clairance plasmatique

Du fait des contraintes et/ou des limites importantes de la mesure du DFG par la technique de perfusion continue avec recueil d'urines, la mesure de la clairance plasmatique est souvent privilégiée. Elle repose sur des techniques de décroissance plasmatique d'un marqueur glomérulaire (généralement le 51Cr-EDTA ou l'iohexol) et permet ainsi la mesure du DFG sans recueil d'urines. Cette technique présente cependant l'inconvénient de nécessiter deux voies d'abord vasculaire, de nécessiter des prélèvements prolongés (minimum 4 heures après l'injection) et de ne pas être utilisable s'il existe un troisième secteur ou si l'insuffisance rénale est avancée (nécessité de prolonger l'examen jusqu'à 24 heures après l'injection).

La mesure du DFG (clairance rénale ou plasmatique) par des indicateurs glomérulaires comme l'inuline, le 51Cr-EDTA ou l'iohexol nécessite un personnel formé et des structures spécialisées et ne peut donc pas se faire en routine. En général, les indications de ces examens sont réservées à certaines situations particulières où une détermination précise de la fonction rénale est nécessaire : situation à risque sur le plan rénal (bilan avant don de rein, maladie de système, chimiothérapie ou traitement néphrotoxique, etc.) ou adaptation de la posologie de certains médicaments à élimination rénale (ex : carboplatine).

Estimations indirectes de la fonction rénale

La concentration plasmatique de substances endogènes dont l'élimination est uniquement rénale est un reflet indirect du DFG (lorsque le DFG diminue, la concentration plasmatique de ces substances augmente). C'est ainsi que la créatinine et la cystatine C plasmatiques sont utilisées en pratique quotidienne pour apprécier la fonction rénale pour des raisons de simplicité.

La créatininémie et les formules d'estimation du DFG à partir de la créatininémie

La créatininémie

La mesure de la créatininémie est de loin la méthode la plus utilisée pour estimer le DFG en pratique quotidienne, mais c'est aussi la méthode la moins sensible. En effet, la créatinine provient du catabolisme de la créatine musculaire et la quantité de créatinine formée quotidiennement (et donc la créatininémie) dépend de la masse et de l'activité musculaire. Son interprétation doit donc tenir compte de l'âge, du sexe, de l'ethnie mais aussi de la pathologie du patient (dénutrition, maladie chronique, etc.).

Malgré l'utilisation ancienne de la créatininémie, son dosage reste difficile. Plusieurs méthodes sont utilisées selon les laboratoires (méthodes colorimétriques dérivées de la réaction de Jaffé, méthodes enzymatiques) et les variations de concentration doivent être appréciées en tenant compte de ce paramètre. Du fait des difficultés d'harmonisation entre laboratoires, des recommandations concernant les techniques de dosage sont proposées[4]. En pratique, la créatininémie doit toujours être interprétée en fonction de l'âge et de la technique de dosage (valeurs de référence du laboratoire pour la technique utilisée) et les dosages itératifs devraient être réalisés par le même laboratoire (excellente reproductibilité).

Les formules d'estimation du DFG à partir de la créatininémie

Pour pallier les difficultés d'interprétation liées aux variations de la masse musculaire, des formules d'estimation du DFG ont été proposées chez l'adulte (Cockcroft, MDRD (*Modification of Diet in Renal Disease study equation*), etc.[3]) et chez l'enfant (Schwartz[5]) permettant ainsi de « pondérer » la créatininémie en fonction des caractéristiques anthropométriques du sujet. À noter que certaines formules (MDRD, Schwartz) ont été réévaluées récemment en fonction des nouvelles techniques de mesure de la créatininémie, dont les valeurs de référence en général plus basses conduisaient à une surestimation du DFG[3,5]. Enfin une nouvelle formule (CKD-EPI), plus complexe et encore en cours d'évaluation, a été proposée dans le but d'améliorer la fiabilité de l'estimation du DFG chez les patients avec une fonction rénale normale ou peu altérée[6]. L'estimation de la fonction rénale par les formules est recommandée par les autorités de santé lors de chaque dosage de créatininémie et doit être systématique du fait de ses avantages : rapidité, absence de recueil urinaire, faible coût et surtout fiabilité qui a été maintenant démontrée dans une large part de la population générale[1]. Bien que la formule de Cockcroft soit largement utilisée, la supériorité du MDRD a été démontrée dans de nombreuses pathologies et son utilisation doit être recommandée pour l'évaluation du DFG en pratique courante. Enfin, les formules « adultes » – MDRD et Cockcroft – ne doivent pas être utilisées chez l'enfant et l'adolescent pour lesquels la formule de Schwartz (k = 36,5) reste la référence. Cependant, les limites de ces formules doivent être connues. Les erreurs les plus importantes sont celles liées à une diminution de la masse musculaire ou à une dénutrition, situations où la baisse de la créatininémie conduit à une surestimation importante du DFG estimé.

Utilisation d'autres marqueurs

Les petites protéines plasmatiques comme la β2microglobuline et la cystatine C sont éliminées par voie rénale exclusive et ont été proposées comme marqueurs de la fonction rénale. La β2microglobuline a été pratiquement abandonnée du fait des variations de sa concentration plasmatique lors d'états inflammatoires. La cystatine C est proposée comme un indicateur de la fonction rénale plus fiable que la créatininémie puisque sa concentration plasmatique n'est influencée ni par l'âge (chez l'enfant de plus de 1 an), ni par la masse musculaire, ni par des pathologies extra-rénales. En revanche, sa concentration serait augmentée par certains facteurs extra-rénaux (traitement par corticoïdes, hyperthyroïdie). Plusieurs formules d'estimation du DFG ont été proposées en utilisant la concentration plasmatique de cystatine C et un bon nombre sont utilisables chez l'enfant[7]. Certaines formules associent la créatininémie, la cystatine C et parfois l'urée, augmentant sensiblement la performance des équations, mais au dépend d'une plus grande complexité du calcul. L'utilisation de la cystatine C n'est pas encore de pratique courante en parti-

culier du fait de son coût (cystatine C: BHN 100 soit 27 euros, créatininémie : B7 soit 1,9 euros), mais elle se développe comme moyen de dépistage de l'insuffisance rénale surtout dans les cas où l'utilisation de la créatininémie n'est pas fiable.

Conclusion

L'estimation de la fonction rénale grâce aux équations (MDRD, Cockcroft, Schwartz) est fiable dans la population générale du fait 1) des progrès des techniques de dosage de la créatininémie 2) des avancées vers une harmonisation des techniques de dosage entre les laboratoires et 3) de l'adaptation des formules aux nouvelles techniques de dosage ; elle doit donc être systématiquement associée à toute mesure de la créatininémie. La cystatine C doit être privilégiée dans les cas où la créatininémie ne peut pas être utilisée pour estimer la fonction rénale. Enfin, la mesure de la fonction rénale par les techniques de référence garde sa place dans les cas où une détermination précise (et parfois itérative) du DFG doit être réalisée.

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ANNEXE - Principales formules d'estimation du DFG à partir de la créatininémie (exprimé en ml/min/1,73 m²)
PCr : créatinine plasmatique (µmol/l), SC : surface corporelle)

Formule de Cockcroft (ou de Cockcroft-Gault, CG)

CG = (1,73/SC (m2)) x [(140-âge (années)) x poids(kg) x k]/PCr

avec k = 1,23 chez l'homme et 1,04 chez la femme

MDRD

MDRD = k x (PCr/88,5)-1.154 x âge (années) -0.203 x 0,742 (chez la femme) x 1,21 (chez les patients de couleur noire)

avec k = 186 pour les méthodes non standardisées et k = 175 pour les méthodes traçables à la méthode et aux matériaux de référence de niveau supérieur.

Formule CKD-EPI

CKD-EPI = k1 x [(PCr/88,5)/k2)]k3 x 0.993 âge avec :

- k1 = 141 ou 144 pour les hommes et femmes d'origine caucasienne et k1 = 163 ou 166 pour les hommes et femmes de couleur noire, respectivement
- k2 = 0,9 ou 0,7 pour les hommes et les femmes, respectivement
- k3 = -0,411 ou -1,209 pour les hommes avec une PCr ≤ 80µmol/l et > 80µmol/l, et k3 = -0,329 ou -1.209 pour les femmes avec PCr ≤ 62µmol/l et > 62µmol/l, respectivement.

Formule de Schwartz

Schwartz = taille (cm) x 36,5 / PCr

4.7 TEMAS LIVRES DE CONGRESSOS

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HOW TO ESTIMATE THE GLOMERULAR FILTRATION RATE IN ADOLESCENTS AND YOUNG ADULTS?

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Abstract

INTRODUCTION AND AIMS: The measure of glomerular filtration rate (GFR) is challenging in adolescents and young adults. The reference methods are difficult to use in daily practice and the estimated GFR by formulas incorporating plasma creatinine (Pcr) are still commonly used. These estimators are widely studied either in children or in adults but rarely in adolescents. We therefore evaluated the performance of six formulas for estimating GFR (GFRe): Cockcroft-Gault (CG), MDRD simplified, CKDEPI, Schwartz 2009, Léger, and locally adapted Schwartz (Local Schwartz, k=33 or 37) in adolescent patients and young adults compared with a reference method: inulin clearance (GFRin).

METHODS: 1,277 measurements of GFRin were performed in 927 patients (54% males) aged between 10 and 25 years (mean±SD: 16.8+4.5 yrs - median 16 yrs. The BMI was of 19.4+4 kg/m2. We studied four groups: 1 (10-13 yrs, n=348, 57% M, GFRin=92+31 ml/min per 1.73 m2, 2 (14-16 yrs, n=288, 51.5% M, GFRin =93+31 ml/min per 1.73 m2, 3 (17-20 yrs, n=334, 54% M, GFRin =94+30 ml/min per 1.73 m2), 4 (21-25 yrs, n=307, 53% M, GFRin=85+30 ml/min per 1.73 m2. Pcr was measured by a colorimetric method (Roche compensated). We checked the correlation with the Roche enzymatic technique (n = 199, y = 1.0 x + 1.6, r2 = 0.997).

RESULTS: The mean (ml/min/1.73m2) estimated GFR by CG, MDRD, CKDEPI, Schwartz 2009, Léger and Local Schwartz were 83+47, 177+92, 124+37, 92+32, 94+32 and 86+29, respectively. The bias for CG, MDRD, CKDEPI, Schwartz 2009, Leger, Local Schwartz were 39±31, 64±67, 34±25, 0,7±19, 3+22 and -5±18, respectively. The precisions 10%, 30% and 50% were 25.5%, 46%, and 23% for CG; 7%, 16%, 19% for MDRD; 14%, 31%, 28% for CKDEPI; 38%, 49%, 12% for Schwartz 2009; 36%, 53%, 11% for Local Schwartz and 34%, 52%, 14% for Léger. The correlation of Spearman was 0.44 for CG, 0.68 for MDRD, 0.68 for CKDEPI, 0.80 for Schwartz 2009, 0.81 for Local Schwartz and 0.76 for Léger.

CONCLUSIONS: The three most conventional formulas widely used in adults (CG, MDRD, CKDEPI) overestimate the GFR in adolescents and young adults. The use of the modified Schwartz formula (2009 or Local) is an accurate and simple estimation of GFR in clinical practice in this population of patients.

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Pharmacovigilance centres, from October 21, 2009 to June 15, 2010 for Pandemrix® (AS03 adjuvanted vaccine, indicated in adults and children over 9 years) and Panenza® (a non-adjuvanted vaccine, mainly administered to children under 9 years old and pregnant women), the two mainly used vaccines in France.
Methods: French Health Authorities heightened awareness to extensive notifications with online health practitioners' reports and patients' reports via the Regional Pharmacovigilance Centre concerned. All reports were reviewed daily, analyzed and input into the French Pharmacovigilance Database. Adverse effects (AEs) were coded according to MedDRA (Medical Dictionary for Regulatory Activities). Particular attention was given to AEs of special interest (AESIs) as defined by European Medicines Agency, mainly demyelinating disorders and Guillain-Barré syndrome (GBS).
Results: During the campaign, 4.1 millions doses of Pandemrix® and 1.6 million doses of Panenza® were administered. Following Pandemrix®, 4183 AEs were reported (including 193 'serious'). Concerning Panenza®, 591 AEs were reported (including 99 'serious'). The most frequently reported 'serious' AEs were neurological for both Pandemrix® (38.9%, mainly isolated ascending paresthesia without any other neurological symptom and complication) and Panenza® (39.9%). Febrile convulsions were the most common neurological AEs with Panenza® in children. All reported deaths (n = 22) described causes other than recent A(H1N1)v vaccination. No causal relationship was established between these AEs and vaccination. Among AEs of 'special' interest, 13 reports of confirmed GBS and 15 reports of demyelinating disorders were notified. No report of narcolepsy was made during the study period.
Conclusion: For both vaccines, neurological AEs (medical recording paresthesia with Pandemrix® and febrile convulsions with Panenza®) were among the most frequently reported serious' AEs. This survey based on spontaneous reporting did not detect any safety signals, at least with an 8-month follow-up.

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Diversion of three benzodiazepines in three areas of South France
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Introduction: Doctor shopping is one of the principal mean of diversion for psychoactive medications. Diversion of psychoactive medications in real life setting can be approached by measuring doctor shopping on prescription databases. We performed an analysis of doctor shopping in three French areas to assess the abuse potential of three benzodiazepines.
Methods: We extracted all medications dispended and reimbursed by the General Health Fund during year 2008 in three French areas, PACA-Corse, Rhône Alpes and Midi Pyrénées (more than 14 million inhabitants), for oral route formulations of three benzodiazepines: zolpidem, flunitrazepam and clonazepam. We used two indicators to evaluate the diversion of each benzodiazepine: doctor shopping quantity (quantity obtained by doctor shopping in Defined Daily Dose (DDD)) and doctor shopping indicator (doctor shopping quantity divided by the total dispensed quantity).
Results: Doctor shopping indicators of flunitrazepam were 27.0% in PACA-Corse, 11.1% in Rhône Alpes and 8.7% in Midi Pyrénées. The total delivered quantity of flunitrazepam is more than 1 million DDD in PACA-Corse, 268 184 DDD in Rhône Alpes and 91 835 DDD in Midi Pyrénées. For clonazepam, doctor shopping indicators were 2.6% in PACA-Corse, 1.0% in Rhône Alpes and 0.8% in Midi Pyrénées. Doctor shopping indicators for zolpidem were 2.5% in PACA Corse, 1.1% in Rhône Alpes and 1.1% in Midi Pyrénées.
Conclusion: For all the benzodiazepines under study, PACA Corse was the area with the highest doctor shopping indicators. Abuse potential of flunitrazepam was largely higher than the two others benzodiazepines in the three areas.

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Which psychoactive drugs are illegally obtained by internet? About oppidum and opema surveys
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Introduction: Even if it is illegal in France, internet can provide prescription drugs, and more widely any sort of psychoactive drugs. Our main objective is to describe acquisition of psychoactive drugs by patients presenting an abuse or a dependence to psychoactive drugs or following an opioid replacement therapy in France.
Methods: For this study, two of the tools developed by the French CEIP-Addictovigilance network, allowed to assess getting by internet: OPPIDUM is a cross sectional survey led each year in October in specialised addiction care units; and OPEMA, led each November in ambulatory environment thanks to general practitioner's network. In this study, we focused on each psychoactive drugs obtained by internet, between 2007 and 2009 for OPPIDUM and during years 2008 and 2009 for OPEMA.
Results:
OPPIDUM surveys: Between 2007 and 2009, the OPPIDUM surveys have collected data on 31 278 drugs (illicit or prescriptions drugs). Illegal acquisitions have been reported for 15% of these drugs. Internet acquisition represents 0.4% (n = 48) of the different ways of illegal acquisition and concerns 37 patients (among 15 465 included).
Among drugs obtained by internet, 28 illicit psychoactive drugs are notified, like cannabis (n = 12), heroin (n = 6), amphetamine (n = 3) or cocaine (n = 3). Also 12 psychoactive prescriptions drugs and eight other psychoactive substance, have been obtained by internet: methylphenidate (n = 3) and hallucinogen mushrooms (n = 3) are respectively, the most reported substance of these two categories.
Between 2007 and 2009, most of these patients live in couple (78%), in stable housing (86%) and get a professional activity (58%). The average age of the patients is 27.9 ± 6.3 years.
OPEMA surveys: During the 2 years of surveys, two psychoactive drugs (diazepam and amphetamine) among 1792 notified, have been obtained by internet (by two patients among 1046 recorded).
Conclusion: OPPIDUM and OPEMA surveys are able to described different ways of acquisition of psychoactive drugs. Internet is not very reported by this population. However, our results can not be extrapolated to whole French population because our target populations are very specific.

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Perception of avatar and human faces in patients with autism: eye tracking and fMRI study
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Autism is a neurodevelopmental disorder, characterized by abnormal neuropsychological development associated with severe impairment of social interaction and communication, combined with restricted and repetitive behaviors (DSM-IV R, 2000). The impairment of social skills observed in patients with autism may be due to disorders of perception of faces and emotional expressions. They present a lack of interest in faces, and an early impairment in orienting visual attention to human faces could result in difficulties in the development of the face processing expertise which normally develops in unaffected subjects. Moreover, patient with autism show an early preference for inanimate objects compared to social stimuli such as faces. This apparent absence of interest in human biological substrate could explain the present focus on therapy using robots. Based on the hypothesis of a stronger attentional attraction towards robots (hybrid between objects and humans), this study examined physiological (pupil diameter), attentional (visual attention) and neural responses (fMRI) to human facial expressions of emotion and those of virtual faces (avatars), hybrids between human faces and objects, in a healthy population and in adults with autism.
Eight individuals with autism and nine matched control subjects (18–35 years of age) were evaluated using eye-tracking and fMRI investigations. For both studies, color images (avatars, neutral human faces, happy human faces, sad human faces and natural scenes) were presented in random order.
The eye tracking study in healthy subjects revealed a visual preference for human faces when compared to objects but not to avatars. No such visual preference was observed in the autistic group, suggesting that human faces are not more salient than objects or avatars. However, differences in pupil dilatation were observed between groups and stimuli. MRI study in subjects with autism revealed greater activation in the amygdala for avatars than for faces compared to healthy subjects. Eye tracking findings, particularly pupil responses, suggested that the use of avatars influences arousal in subjects with autism, and fMRI study showed that avatars seem to increase attentional arousal by activation of the amygdala. Avatars may thus be of therapeutic value in the rehabilitation of responses to facial emotions, by focusing the interest of subjects with autism.

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Drug induced and/or exacerbated psoriasis
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Introduction: Psoriasis is a common skin disorder. Knowledge of factors may induce, trigger, or exacerbate the disease is of primary importance in clinical practice. Drug intake is a major concern in this respect. We report three cases of drug-induced psoriasis (two cases) or drug exacerbated pre-existing psoriasis (one case) notified in pharmacovigilance centre of Sfax.
Method: An inquiry of pharmacovigilance has been realized according to French imputation method.
Results: Case 1: The responsibility of Atenolol was suspected in induction of psoriasis for 80 years-old man. The score of imputability was C1S2I1B3.
Case 2: The responsibility of α-interferon therapy was strongly suspected in induction of psoriasis for 61 years-old woman with a chronic hepatitis C. The score of imputability was C2 S2 I2 and B3.
Case 3: The responsibility of Carbamazepine in exacerbation of pre-existing psoriasis was strongly suspected for 37 years old man. The score of imputability was C2 S2 I2 and B3.
Discussion: The most common drugs that have induced or exacerbated psoriasis were lithium, beta adrenergic receptor blocking agents, antimalarials and miscellaneous drugs such as α-interferon, β- interferon. The pathogenesis mechanism of drugs influence on the course of psoriasis is unknown. It includes an immunologic mechanism, an impaired lymphocyte transformation, a decrease cAMP in intraepidermal with consequent increase of epidermal cell proliferation and an accumulation of leukotrienes.

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How to estimate the glomerular filtration rate in adolescents and young adults?
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Introduction: The measure of glomerular filtration rate (GFR) is challenging in adolescents and young adults. The reference methods are difficult to use in daily practice and the estimated GFR by formulas incorporating plasma creatinine (Pcr) are still commonly used. These estimators are widely studied either in children or in adults but rarely in adolescents. We therefore evaluated the performance of six

formulas for estimating GFR (GFRe): Cockcroft-Gault (CG), MDRD simplified, CKDEPI, Schwartz 2009, Léger, and locally adapted Schwartz (Local Schwartz, k = 33 or 37) in adolescent patients and young adults compared with a reference method: inulin clearance (GFRin).
Patients and methodes: One thousand two hundred and seventy-seven measurements of GFRin were performed in 927 patients (54% males) aged between 10 and 25 years (mean ± SD: 16.8 ± 4.5 years – median 16 years. The BMI was of 19.4 + 4 kg/m^2. We studied four groups: 1 (10–13 years, n = 348, 57% M, GFRin = 92 + 31 mL/min/1.73 m^2, 2 (14–16 years, n = 288, 51.5% M, GFRin = 93 + 31 mL/min/1.73 m^2, 3 (17–20 years, n = 334, 54% M, GFRin = 94 + 30 mL/min/1.73 m^2), 4 (21–25 years, n = 307, 53% M, GFRin = 85 + 30 mL/min/1.73 m^2). Prr was measured by a colorimetric method (Roche compensated). We checked the correlation with the Roche enzymatic technique (x = 199, y = 1.0 x + 1.6, r^2 = 0.997).
Results: The mean (mL/min/1.73 m^2) estimated GFR by CG, MDRD, CKDEPI, Schwartz 2009, Léger and Local Schwartz were 83 + 47, 177 + 92, 124 + 37, 92 + 32, 94 + 32 and 86 + 29, respectively. The bias for CG, MDRD, CKDEPI, Schwartz 2009, Leger, Local Schwartz were 39 ± 31, 64 ± 67, 34 ± 25, 0.7 ± 19, 3 + 22 and −5 ± 18, respectively. The precisions 10%, 30% and 50% were 25.5%, 46%, and 23% for CG; 7%, 16%, 19% for MDRD; 14%, 31%, 28% for CKDEPI; 38%, 49%, 12% for Schwartz 2009; 36%, 53%, 11% for Local Schwartz and 34%, 52%, 14% for Léger. The correlation of Spearman was 0.44 for CG, 0.68 for MDRD, 0.68 for CKDEPI, 0.80 for Schwartz 2009, 0.81 for Local Schwartz and 0.76 for Léger.
Conclusion: The three most conventional formulas widely used in adults (CG, MDRD, CKDEPI) overestimate the GFR in adolescents and young adults. The use of the modified Schwartz formula (2009 or Local) is an accurate and simple estimation of GFR in clinical practice in this population of patients.

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Autonomic responses to respiratory events through heart rate variability analysis
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Introduction: Autonomous nervous system reacts to apnea and hypopnea events by enhanced parasympathetic activity during respiratory events and sympathetic burst at the end of the event. However, it remains unclear whether such a sympathetic reactivity at the end of respiratory events is modulated by sleep stage, total or partial upper airway occlusion, oxygen desaturation or cortical arousal. Furthermore, the impact of autonomic activity during respiratory events on the occurence of cortical reactivity is not well recognized.
The goal of this study is to assess autonomic reactivity to respiratory events and its modulation by obstructive respiratory events, sleep stages, oxygen desaturation and presence of respiratory related cortical arousal (CA) and the relation between autonomic activity during respiratory events and subsequent CA.
Methods: Fourteen untreated OSAHS patients (48.1 ± 10.9 years; three women, with a mean obstructive apnoea/hypopnea index of 38.3 ± 14.4 events/h) underwent nocturnal polysomnographic recordings (Embla, Remed). RR intervals (RR), spectral analysis of RR using wavelet transform were used to study sympathetic (LFWV and LFWV/HFWV ratio) and parasympathetic (HFWV) activity at the end of each respiratory event and according to total or partial upper airway occlusion (hypopnea vs. apnoea), according to oxygen desaturation, sleep stages and presence of cortical arousals.
Results: At the end of respiratory events, RR decreases ($P < 0.01$) and LFWV ($P < 0.01$) and LFWV/HFWV ratio ($P < 0.01$) increase without any impact of sleep stages, of oxygen desaturation and of type of respiratory events. While the decrease in RR ($P < 0.01$) and the increase in LFWV ($P < 0.01$) and LFWV/HFWV ratio ($P < 0.01$) were observed with and without CA, decrease in RR ($P < 0.01$) and LFWV/HFWV ratio ($P < 0.01$) were significantly higher when respiratory events gave rise to CA. Moreover, high LFWV/HFWV ratio during respiratory events was related to more frequent cortical arousal.
Conclusion: These results suggest that, first, apneas/hypopneas induce a sympathetic cardiac reactivity at the end of respiratory events related to CA rather than to sleep stages, total or partial upper airway occlusion or oxygen desaturation. Reciprocally, sympathetic dominance during respiratory events could facilitated cortical arousal.

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Effects of bortezomib on the central nervous system: risks and potential benefit
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Introduction: The success of bortezomib (Bor) in the treatment of multiple myeloma has encouraged its development in other domains: solid tumors, ischemia-reperfusion and inflammation, occurring peripherally or in the central nervous system (CNS). Neuropathies and dysautonomia are the leading causes of Bor withdrawal, indicating a high Bor toxicity of for peripheral neurons. We thus investigated its counterpart toxicities for the CNS and search for evidence of its potential interest in CNS diseases.
Methods: Evaluation of Bor toxicity for the CNS was based on (i) literature data, (ii) the cases reported at Cochin hospital for 3 years, and (iii) the analysis of the French Pharmacovigilance database up to 2010. Potential benefit of Bor on CNS was evaluated from published experimental and clinical data.
Results: Two cases of leukoencephalopathy were recently published. In vitro, Bor is neurotoxic, particularly on dopaminergic neurons. For 1 year at Cochin hospital, 96 patients received Bor and three had CNS toxicity (3%), including one patient with hypertensive posterior encephalopathy leading to death. A total of 25 cases were retained in the pharmacovigilance database, mainly encephalopathy/leukoencephalopathy, delirium/hallucinations, convulsions, and one case of Parkinson syndrome. Most reactions occurred early, suggesting an individual susceptibility, and five patients had severe renal failure. Experimental benefits after peripheral administration of Bor at 0.2–1 mg/kg in rats or mice, were shown for autoimmune encephalomyelitis, tissue ischemia after arterial occlusion, cerebral hemorrhage, and brain tumors.
Conclusion: Proteasome inhibition can explain neuroprotective and anti-inflammatory properties of Bor via inhibition of NFkB, but also its neurotoxicity via accumulation of ubiquitinylated proteins. Our results suggest that Bor can reach the CNS, at least in some patients. Renal failure may be a risk factor for its central neurotoxicity. In the future, to readily evaluate benefit/risk ratio of such drugs on CNS, their passage through the blood brain-barrier should be evaluated. Few data in rats indicate that concentrations of Bor in the brain are several fold lower than those in blood but similar to those in plasma. Long term effects are unknown.

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The antiepileptic efficacy of stiripentol is not exclusively be depending on the inhibition of the cytochrome P450 2C19
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Stiripentol (STP), an antiepileptic drug, has a conditional Marketing Authorisation, as add-on therapy (with clobazam and valproate) in patients with Dravet syndrome. Two randomized controlled trials (STICLO France and STICLO Italy) compared STP to placebo. After a baseline period of 1 month, placebo or stiripentol (50 mg/kg/day) was added to valproate and clobazam during a double-blind period of 2 months. Overall, 64 patients were included and STP resulted in an odd ratio for responders of 47% (CI: 5.1, 438) in STICLO France and 20 (CI: 1.85, 216) in STICLO Italy. It has been argued that the efficacy of stiripentol, an inhibitor of CYP P450, in particular 3A4 and 2C19, might be explained by an increased concentration of clobazam and its active metabolite norclobazam. However, STP enhances central GABA transmission suggesting that STP has proper antiepileptic properties.
During these clinical studies, already initiated concomitant antiepileptic drug therapy was allowed, such as progabide (PGB) that was found to significantly reduce the phenytoin and phenobarbital clearances. This drug-drug interaction suggested a potential inhibition of the CYP P450 2C19 pathway involved in the metabolism of the both drugs. Likewise, CYP2C19 is a polymorphically expressed enzyme.
Patients and methods: In patients receiving stiripentol (n = 33), norclobazam (NCLB) and clobazam (CLB) plasma concentrations, determined by HPLC-UV assay during the baseline period and after the introduction of STP were analysed. CYP 2C19 genotyping was performed by PCR using TaqMan technology. The changes of the NCLB/CLB ratio were analyzed using a non parametric statistical test.
Results: The data were available in 31 patients receiving STP and the mean CLB, NCLB and the NCLB/CLB ratio concentration was multiplied by 1.5, 5.8 and 4.3 respectively compared to baseline. In eight of 31 patients (26%) no change of the NCLB/CLB ratio was observed. The absence of NCLB and CLB concentration increase when STP was added could be explained by PGB as co-medication (n = 5/8) and the heterozygous CYP2C19 genotype *1/*2 (n = 2/8). Sixty-five percent responders were observed in the subset with a change in the NCLB/CLB ratio and 75% responders in patients with no change in the NCLB/CLB ratio. No significant difference was observed between these two groups in term of response ($P > 0.05$, Fisher test).
Conclusion: The antiepileptic effect of stiripentol cannot exclusively be depending on the inhibition of the CYP P450 2C19 suggesting that STP has a proper antiepileptic effect.

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Changes in the temporal relationship between onsets of alea nasi activity and thoracic inspiratory muscles activity during auditory entrainment of the respiratory rhythm
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Introduction: Temporal relationship between the onsets of the alae nasi activity (AN-onset) and the thoracic inspiratory muscles activity (TH-onset) was studied in six awake subjects when the breath rhythm was driven by an auditory stimulus.
Methods: Both onsets (AN-onset and TH-onset) were determined on surface EMG recordings using an automatic detector algorithm. The relationship between onsets was assessed by the delay between AN and TH onsets, the AN preactivation time (preAN). Tidal volume (V_t) was assessed with inductive plethysmography and normocapnia monitored with nasal PeTCO2 measurements. Control resting breathing was compared to breathing driven by auditory stimulus. Auditory stimulus rate was set in a random order at (i) a frequency matching the control respiratory rhythm, (ii) 25% above and (iii) 25% below the control respiratory rhythm. The subjects were asking to follow the different auditory rhythms and to adjust their V_t in order to maintain normocapnia.
Results: The driving of breathing rhythm by auditory stimulus decreased PreAN time (240 + 110 vs. 160 + 90 ms, $P < 0.05$). The PreAN time did not depend on breathing pattern or entrainment rate but depended on the auditory stimulus occurrence: when auditory stimulus occurred after TH-onset, the PreAN time remained in the control range (about 300 ms). On the opposite, when auditory stimulus occurred before AN-onset, in almost all cycles the PreAN time was about 100 ms. When auditory stimulus occurred between AN-onset and THS-onset, the THS-onset shortly followed the auditory stimulus (about 100 ms) and the PreAN time was determined by the delay between AN-onset and the auditory stimulus leading to values above normal range (>300 ms).

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ABSTRACTS

european society for paediatric nephrology

44th Annual Scientific Meeting of the European Society for Paediatric Nephrology

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ABSTRACTS

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survival in children with ESRD. International efforts should be made to increase access to Tx for children throughout Europe.

OS4-FRI-362

Acute renal failure in children in Norway, 1999–2008

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Objectives and study: Acute renal failure (ARF) is defined as sudden sustained loss of kidney function, with declining GFR. ARF is classified as prerenal, renal or postrenal. Hemolytic-uremic syndrome (HUS) is one of the most common etiologies. Our objective was to estimate yearly and age-specific rate of and distribution of etiologies of ARF, particularly the HUS proportion, in children in Norway (aged 0–16), 1999–2008.

Methods: A retrospective, descriptive study, based on data from patient journals from pediatric departments in Norway. Search criteria were ICD-10 codes N17 (ARF), D59.3 (HUS) and N0/N01/N05 (nephritis - with episodes of elevated serum creatinine >35 (<1 years) or >90 mmol/l (>1 years)). N17 diagnosed cases of birth asphyxia or post-TX etiology were excluded.

Results: We identified 316 cases of ARF. This predicts an overall incidence rate of 3,29 per 100000 children/year. Estimated distribution of cases is 72 (22,8%) prerenal, 239 (75,6%) renal and 5 (1,6%) postrenal, based on probable clinical mechanism. 53 etiologies have been identified. Nephritis, 138 (43,7%) cases, followed by HUS, 49 (15,5%) cases, are the largest categories. Year of highest occurrence is 2006 (51 (16,1%) cases). Remaining nine years has a mean distribution of 29/year. Most frequently affected age group is 0–4 years, with 136 (43,0%) cases. 0- and 1-year-olds have the highest proportions, 57 (18,0%) and 35 (11,1%), respectively.

Conclusions: Total incidence of ARF in Norway is low. Most common cause is nephritis, followed by HUS. There is a wide spread of etiologies related to ARF. Children aged 0–4 years have the largest proportion of cases. 0-year-olds constitute nearly half the total number of cases. Results are probably underestimates due to the study design.

OS4-FRI-521

Can we accurately use the "new" Schwartz-formula to estimate glomerular filtration rate in pediatric renal transplant recipients?

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Objectives and study: Reference methods to measure GFR are difficult to perform in clinical practice and the creatinine-based Schwartz formula is commonly used. However, little is known about its validity in renal transplant patients. We aimed at evaluating the revised 2009-Schwartz formula and the locally adapted Schwartz formula in kidney transplant patients.

Methods: Inulin clearance (iGFR, ml/min per 1.73 m²) was measured in 254 paediatric renal transplant recipients (male=136, mean age=12.6± 3.48 [1–18] years) between 2003 and 2010. Two formulas were applied: Schwartz 2009 (K=36.5) and local-Schwartz (Schwartz formula with our laboratory-specific optimized value of k: 37 in boys >13 yrs and 33 in others). The agreement between formulas and iGFR was assessed by Bland Altman method and Lin concordance correlation coefficient. The difference between formulas and iGFR was expressed as a percentage (relative bias) in two levels: ±10% and ±30%.

Results: The mean±SD iGFR was 65±20. For Schwartz 2009 and local-Schwartz the Bland Altman mean difference was 6.32(±13.40) and 1.36 (±12.42), and the Lin coefficient(IC 95%) was 0.79(0.74–0.83) and 0.82 (0.78–0.86), respectively. Percentages of patients (%) who had relative bias below 10% were 33.9 for Schwartz 2009 and 41.7 for local-Schwartz and below 30% were 82.4 for Schwartz 2009 and 89.8 for local-Schwartz.

Conclusions: This study demonstrated the good performance of Schwartz formula (2009 and local Schwartz) in the pediatric renal transplant recipients, with results similar to the pediatric general population. However, they display considerable limits of agreement and they cannot replace a reference method when a valid measurement is needed. Finally, the determination by each laboratory of its own k coefficient can increase the performance of the prediction equation.

OS5-SAI-120

Causes of death and predictors of survival in pediatric PD: insights from the International Pediatric PD Network (IPPN) registry

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Objective: We sought to describe patient survival and assess risk factors for death in a global pediatric peritoneal dialysis (PD) population.

Methods: We assessed patient survival in a prospective registry study of 1,373 pediatric PD patients from 70 centers, treated in 27 countries between 2007 and 2011. Median age at dialysis initiation was 3.6 years (iqr 0.95–5.4).

Results: 45 children died during the observation period; the average death rate was 1 per 31.3 patient years. Causes of death included congestive heart failure in 15 cases, infections related to PD in 7 and unrelated to PD in 10 cases, non-infectious dialysis complications in 4, cerebral complications in 4, malignancy in 2 and portal hypertension in 1 case. In 2 patients, therapy was electively discontinued due to severe co-morbidities.

Among the 936 patients followed from PD initiation, actuarial survival rate was 98, 95 and 92% at 12, 24 and 36 months on treatment, respectively. Independent risk factors for death were patient age <6 years (Cox hazard ratio (HR) 4.4, p<0.0005), the presence of a defined syndrome (HR 2.96, p<0.01), severe metabolic acidosis (HR 4.5 for serum bicarbonate <20 mM, p<0.001), hyperparathyroidism >800 pg/ml (HR 2.4, p<0.05), hypoalbuminemia <25 g/L (HR 7.5, p<0.0001), and body weight exceeding estimated dry weight by more than 4% on average (HR 3.1, p<0.01). The region or country of residence was not predictive of death on dialysis.

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female ratio was 5:1. The initial dose was 0.5 mg/kg and it ranged from 0.5 mg/kg to 3 mg/kg during the course of the treatment. There was a 42 % reduction in PTH levels noted. The calcium phosphate product was unchanged. Duration of treatment ranged from 3 – 27 months. In 2 patients the treatment was stopped, 1 after 18 months due to improvement in PTH levels and the 2nd underwent a renal transplant; in others the treatment is still ongoing. There were no side effects noted

Conclusions: Calcimimetic agents are useful in reducing PTH levels in CKD patients with or without dialysis. We did not see any side effects of cinacalcet although the long term effect on growth is yet to be determined.

P297 - Which equation to estimate Glomerular Filtration Rate in renal hyperfiltrating children?

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Introduction: Monitoring renal function is crucial in pediatric patients with glomerular hyperfiltration: the use of plasma creatinine (PCr) to estimate glomerular filtration rate (GFR, mL/min per 1.73 m²) is hampered by its lack of reliability and data on the performance of cystatin C (CystC) are sparse. The aim of this study was to evaluate the performance of CysC-based, PCr-based, and combined (CysC+PCr) equations in hyperfiltrating children.

Material and methods: We assessed the perfomance of 6 GFR estimating equations eGFR) in hyperfiltrating patients: i) CysC-based equations: Filler, le Bricon, ii) PCr-based equations: bedside Schwartz, Schwartz-Lyon, iii) combined equations: CKiD and Zapitelli; using inulin clearance (mGFR) as the reference method. The agreement between eGFR and mGFR was assessed using bias (eGFR-mGFR) and 30 % accuracy.

Results: 37 patients (52 measurements) aged 2–18 years (11.3±4.2) with various systemic disease (liver transplantation (9), glomerulonephritis (8), uropathy (5) glycogen-storage diseases (4), others (11)) and a GFR ≥135 were studied. Mean GFR was 152.7±16.8 [135–201]). The bias (ml/min per 1.73 m2 [IC 95 %]) were of −7 (−1,-14), -28 (−21,-35), -10 (−2,-18), -18 (−10,-26), -27 (−21,-32), -23 (−15,-30), for the Filler, Bricon, bedside Schwartz, Schwartz-Lyon, CKiD, and Zappitelli equations, respectively. The ability to classify hyperfiltration patients by areas under the ROC curves was better for Filler, bedside Schwartz and Schwartz-Lyon (0.81, 0.75 and 0.70) than for the others (0.63, 0.64, and 0.65 for Bricon, CKiD, and Zappitelli respectively). The 30 % accuracies were 96 %, 77 %, 96 %, 86 %, 88 %, and 83 % for the Filler, Bricon, bedside Schwartz, Schwartz-Lyon, CKiD, and Zappitelli equations, respectively. The performance of Filler equation was significantly better for all the studied parameters.

Conclusions: The Cyst C based Filler equation which is 1) simple to use and 2) a reliable equation in hyperfiltrating children should be used when hyperfiltration is suspected.

P298 - Schwartz formula: is one K coefficient enough for all children?

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Introduction: The equations used to estimate glomerular filtration rate (GFR, mL/min per 1.73 m²) based on plasma creatinine (PCr) have been recommended by guidelines. In 2009, Schwartz et al. updated the traditional Schwartz equation to IDMS-standardized creatinine assay, but they cannot demonstrate K coefficient variation with puberty as previously proposed. We aimed 1) to determine the usefulness of using different coefficients according to age and gender for the bedside Schwartz formula (Schwartz-Lyon formula) and 2) to validate them in an external population, and 3) to compare the performance of these 2 revisited Schwartz formulae.
Material and methods: A linear mixed effects model was used to determine coefficients according to age and sex in a French cohort of 360 children and adolescents aged 1–18 yrs (190 males, 965 measurements, GFR=86.0±34). We model the inulin clearance (mGFR) according to the ratio of height over PCr. These coefficients were validated in a Swedish cohort of 109 children and adolescents (55 males, GFR=66.0± 37), aged 4–17.9 years.
Results: We found two coefficients (k=36.5 for boys> 13 years of age and 32.5 for others) for the Schwartz-Lyon formula. In the Swedish cohort, the performance of Schwartz-Lyon assessed by the mean ratio eGFR/mGFR (expressed in mL/min per 1.73 m²±SD) for all patients, children, and adolescents was 0.96 ±0.19, 1.04 ±0.22, 0.92 ±0.16 respectively. These results are significantly better than those of the 2009-Schwartz formula (p=0.018) in children, but comparable for adolescents.
Conclusions: The good performance of the bedside Schwartz and the Schwarz-Lyon formulas and their simplicity to use in clinical practice are strong arguments to recommend these formulas in routine in children and adolescents. The best performance of Schwartz-Lyon less than 13 years of age was probably linked to the specific lower k coefficient used in that population.

P299 - RISK FACTORS FOR DEVELOPMENT OF CHRONIC KIDNEY DISEASE IN CHILDREN WITH NEUROGENIC BLADDER

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Introduction: Children with neurogenic bladder due to myelomeningocele are at increased risk for chronic kidney disease (CKD). Nephroprotective measures with clean intermittent catheterization (CIC) and anticholinergic drugs are standard treatment used to decrease the incidence of CKD. The aim of the study was to assess the risk factors for kidney damage in this group of patients.
Material and methods: 115 patients with MMC were included. The stage of CKD was classified according to estimated GFR (Shwartz formula), presence of albuminuria and results of imaging tests. Logistic regression analysis was used to select the risk factors, including: duration of CIC and anticholinergic therapy, presence of urinary tract infections (UTI, vesicoureteral reflux (VUR) in 1st year of life, history of recurrent UTIs, urodynamic results in 1st year of life and presence of paraplegia.
Results: CKD was diagnosed in 43,5 % children. The majority presented with CKD stage I (80 %). Children who did not develop CKD were without paraplegia (p=0,009), had a negative history of UTI (p=0,003) and no VUR in 1st year of life (p=0,0039). Neither duration of CIC (p=0,431), anticholinergic therapy (p=0,258) nor urodynamic findings (LPP> 40 cm) in first year of life (p=0,194) significantly influenced the development of kidney damage. The presence of UTI in first of life (OR=3,2), recurrent UTIs (OR=3,53), paraplegia (OR=2,66) and the presence of VUR in first year of life (OR= 2,99) were the risk factors for CKD.
Conclusions: 1. Children with neurogenic bladder due to MMC are still at increased risk for kidney damage, despite early introduction of nephroprotective therapy with CIC and anticholinergic drugs. 2. Paraplegia, the presence of UTI and VUR in the 1st year of life and recurrent UTIs are risk factors for CKD in MMC patients.

P300 - HELICOBACTER PYLORI SEROPOSITIVITY IN CHILDREN WITH CHRONIC RENAL FAILURE

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5 PONDERAÇÕES FINAIS

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A pesquisa científica pode ser caracterizada como atividade intelectual intencional que visa responder às necessidades humanas, percebidas no indivíduo como sensação permanente de insatisfação. Pesquisar é o exercício intencional da pura atividade intelectual, visando melhorar as condições práticas de existência. Para que a pesquisa científica aconteça, é necessário estar imbuído do espírito científico.

Dessa forma, presumimos na hipótese de que a CrP não seja adequada para medir TFG na pediatria. Para essa proposição, optamos em utilizar inulina como padrão para aferição da TFG.

Devido à inexistência de inulina para investigação no Brasil em crianças, referenciamos a amostra ao serviço de nefrologia pediátrica de Lyon (França) que rotineiramente utiliza inulina em avaliação de crianças portadoras de doenças renais.

No projeto, estudamos o uso de inulina na aferição da TFG na faixa etária entre 10 e 25 anos. Concomitantemente, comparamos o comportamento das fórmulas pediátricas baseadas na CrP para estimação da TFG. Concluímos que essas equações possuem uma melhor relação com o padrão-ouro (inulina) do que as aplicadas de uso rotineiro no adulto (CKD-EPI, MDRD e Crockfot-Gault). Verificamos que essas fórmulas de adultos, quando aplicadas em crianças e adolescentes, superestimam muito a TFG, enquanto as pediátricas, mesmo se aplicadas numa população de jovens adultos (18 a 25 anos), subestimam a TFG em 10%. Em função destes achados e da simplicidade da fórmula de Schwartz 2009 simplificada, recomendamos seu uso na estimação da TFG de crianças, adolescentes e adultos jovens. São circunstâncias consideradas inéditas na literatura até a publicação da nossa pesquisa no JASN.

Concomitantemente a essa publicação, organizamos um artigo de revisão da aferição da TFG para a *Revista da Sociedade Médica Francesa*, com a orientação da professora Laurence Dubourg. Também foi apresentada, em conclave nacional, a experiência do grupo de Lyon na investigação da função renal em vários aspectos.

Então, confinamos o pressuposto que a Cyst C poderia substituir a CrP na estimativa da TFG na população pediátrica. Para tanto, averiguamos o estudo transversal da coorte de Lyon. Idealizamos o estudo com modelagem estatística utilizando o programa R. Para tanto, foi realizado estágio de 4 meses no serviço de bioestatística e epidemiologia de Lyon.

Nesse trabalho, propomos uma nova maneira na busca pela eficiente análise da reprodutibilidade. Grande parte dos estudos práticos nos diversos campos da ciência envolve o uso de algum tipo de modelo de regressão, com o objetivo de descrever comportamentos, identificar fatores que afetam e/ou explicam certos fenômenos, entre outros objetivos relacionados.

Os resultados aqui obtidos sugeriram uma nova maneira de verificação da reprodutibilidade, não baseada exclusivamente em médias, mas na correspondência entre as medidas obtidas nos dois momentos distintos e na distribuição dos valores para a diferença entre as medidas em tempos diferentes.

O coeficiente de correlação de Pearson mede a correlação entre as duas séries de medidas, mas não o quanto as medidas desviam da reta a 45º, portanto, era impossível detectar a acurácia entre as duas séries de medidas feitas. Como complemento ao teste de Pearson, realizamos o coeficiente de correlação de concordância proposto por Lin que possibilitou, pela primeira vez em estudos de TFG, identificar a acurácia em medidas repetidas.

Outro fato original da nossa pesquisa, foi a aplicação da inulina como padrão-ouro para TFG, a Cyst C e CrP IDMS como modelo de referência laboratorial. Podemos criticar algumas deficiências, como a ausência de marcador de puberdade e o delineamento da coorte que não foi estruturada prospectivamente para o tipo de análise realizada.

O nosso estudo é o primeiro a examinar a consistência no desempenho na eGFR com Cyst C associada ou não à CrP usando o clearance de inulina como padrão ouro na pediatria. Não encontramos nenhuma evidência substancial de que a Cyst C isolada ou em combinação com CrP forneceestimativa superior do que o uso isolado da CrP, em pacientes com função renal normal ou com perda moderada na TFG.

Outrossim, quando investigamos os indivíduos transplantados renais, encontramos uma associação estreita entre o padrão-ouro e as fórmulas conjugadas de CrP com Cys C para a TFG. Possivelmente, essa associação poderia ser uma

compensação balanceada entre a baixa produção de CrP pela massa muscular e o uso de corticoides que elevariam os níveis de Cys C nos transplantados.

Em outro momento, no subgrupo das crianças portadoras de doença renal policística autossômica dominante, corroborando várias publicações anteriores, nós demonstramos alteração na função renal, seja associada à microalbuminúria seja à redução da TFG, em fases precoces do diagnóstico. Salientamos, nessa publicação, que somente a aferição de CrP como índice de estimação da TFG acarretaria uma diferença em até 12%, quando comparada ao uso de inulina. Concluímos que haveria necessidade de acompanhamento precoce desses pacientes e, se possível, que se fizesse o uso de algum método de referência para aferir a TFG.

Não podemos nos delegar de comentar sobre os benefícios e importância da internacionalização. O programa internacional trouxe-nos o aprimoramento nas habilidades cognitivas, no pensamento crítico, na busca de informação, na resolução de problemas, na tomada de decisão e na capacidade de lidar com mudanças.

Vimos que o estabelecimento de parcerias estratégicas para ampliação do horizonte acadêmico e fortalecimento e promoção da imagem institucional são essenciais para melhora da qualidade da produção do conhecimento acadêmico. Infelizmente, num primeiro momento, ficamos constrangidos por notar que nosso estado não era conhecido fora do eixo Rio-São Paulo. Mas, paulatinamente, começamos a mostrar nossa região, com inserções culturais e científicas.

Dessa forma, ficou evidenciada a importância estratégica da internacionalização para a comunidade acadêmica, condição básica para o êxito das nossas iniciativas. O processo de internacionalização exige o comprometimento da alta administração, professores, funcionários e estudantes, atuando como força integradora e com resultados imediatos sobre as atividades de ensino, pesquisa e extensão.

6 CONCLUSÕES

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Os resultados da presente tese permitem que se estabeleçam as seguintes proposições:

1. Verificamos a aplicabilidade das fórmulas pediátricas para a população adulta jovem até os 25 anos;
2. Demonstramos que o uso de um padrão de referência para TFG é fundamental para detectar alterações em pacientes pediátricos portadores de Doença Renal Policística Autossômica Dominante;
3. Estatisticamente, na população de transplantados renais, a associação da cistatina C isolada não aparenta superioridade com a creatinina plasmática;
4. A cistatina C isolada em crianças menores de 13 anos não se demonstrou superior à creatinina plasmática para estimar a TFG;
5. Em pacientes com estágio I de doença renal crônica, a cistatina C associada à creatinina plasmática demonstrou grau de superioridade para estimação da TFG.
6. Apesar do surgimento de novos índices, verificamos que a creatinina plasmática permanece como um marcador de eleição para a função renal. Entretanto, salienta-se que adequação na técnica laboratorial e estandardização internacional (IDMS) na medida da creatinina são fundamentais para a decisão clínica.

7 REFERÊNCIAS BIBLIOGRÁFICAS – PROJETO

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ANEXOS

ANEXO 1

APROVAÇÃO DO COMISSÃO CIENTÍFICA E PARECER DO COMITÊ DE ÉTICA

Pontifícia Universidade Católica do Rio Grande do Sul
FACULDADE DE MEDICINA
PÓS-GRADUAÇÃO EM MEDICINA E CIÊNCIAS DA SAÚDE

Of. 239/10-PG

Porto Alegre, 21 de julho de 2010.

Ao Pós-Graduando
Luciano da Silva Selistre
N/Faculdade

Prezado Pós-Graduando:

Comunicamos que a proposta de tese intitulada **"Avaliação da depuração de cistatina C para detecção precoce de alterações na função do enxerto após o transplante renal em pacientes pediátricos"** foi aprovada pela Comissão Coordenadora do Programa de Pós-Graduação em Medicina e Ciências da Saúde.

A mesma deverá ser encaminhada ao Comitê de Ética em Pesquisa, através do setor de **Pesquisas e Estágios**, 2º andar do Hospital São Lucas/PUCRS. Após aprovação do CEP entregar cópia na secretaria do Programa. Em anexo, cópia da avaliação.

Atenciosamente,

Prof. Dr. Carlos Eduardo Poli de Figueiredo
Coordenador em Exercício do Programa de
Pós-Graduação em Medicina e Ciências da Saúde

C/c: Prof. Dr. Ivan Carlos Ferreira Antonello

PUCRS
Campus Central
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Pontifícia Universidade Católica do Rio Grande do Sul
FACULDADE DE MEDICINA
PÓS-GRADUAÇÃO EM MEDICINA E CIÊNCIAS DA SAÚDE

PARECER DO PROFESSOR AVALIADOR

1. Título: adequado, claro, conciso?

Sim

2. Introdução: fundamentação, justificativa e relevância adequadas e pertinentes? Hipótese é apresentada?

Fundamentação, justificativa e relevância, adequadas. Hipótese não apresentada

3. Objetivos: claros e adequados?

Sim

4. Métodos

a) Delineamento:
b) Pacientes ou material:
c) Aferição das variáveis:
d) Estatística:

Sim

5. Referências bibliográficas:

Sim

6. Avaliação final

a. (X) Aprovado
b. ( ) Retornar com modificações para avaliação
c. ( ) Reprovado

Questões específicas (em caso de retorno com modificações):

Vejo problemas para a realização da Fase 2, que o investigador deve antecipar: o **n** de sua amostra e o tempo de acompanhamento da coorte.

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Pontifícia Universidade Católica do Rio Grande do Sul
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
COMITÊ DE ÉTICA EM PESQUISA

OF. CEP- 763/12

Porto Alegre, 06 de agosto de 2012.

Prezado Pesquisador,

O Comitê de Ética em Pesquisa da PUCRS em resposta à carta encaminhada em 12 de julho de 2012, referente ao Estudo "**Avaliação da depuração de Cistatina C para detecção precoce de alterações na função do enxerto em transplantados renais pediátricos**", informa que por este estudo já ter acontecido, o CEP tomou ciência quanto à sua execução, bem como em relação à produção científica decorrente do mesmo.

Atenciosamente,

Prof. Dr. Rodolfo Herberto Schneider
Coordenador do CEP-PUCRS

Ilmo. Sr.
Dr. David Saltovitch
HSL
Nesta Universidade

c/c
Ilmo. Sr.
Dr. Ivan Carlos Antonello
FAMED
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ANEXO 2

APROVAÇÕES DO SERVIÇO FRANCÊS

GROUPEMENT HOSPITALIER EST
Hôpital Femme Mère Enfant
59 boulevard Pinel
69677 Bron cedex - France

Hôpitaux de Lyon

Université Claude Bernard Lyon 1

SERVICE DE PÉDIATRIE
Chef de Service : Pr Pierre Cochat
Télécopie 04 27 85 67 68

NÉPHROLOGIE
CENTRE DE REFERENCE DES MALADIES RENALES RARES NEPHROGONES

Pr Pierre Cochat
Professeur des Universités
Praticien Hospitalier
Secrétariat – Fabienne Cazet
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Dr Bruno Ranchin
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Dr Aurélia Liutkus
Praticien Hospitalier
Secrétariat – Florence Garcia
04 27 85 61 28

Dr Odile Basmaison
Praticien Hospitalier
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Dr Guillaume Mestrallet
Assistant Chef de Clinique
Secrétariat – Annick Berthet
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Dr Valérie Pichault
Assistant Chef de Clinique
Secrétariat – Florence Garcia
04 27 85 61 28

Dr Christian Grand
Praticien Attaché
Secrétariat – Martine Bochard
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EXPLORATION FONCTIONNELLE
Dr Laurence Dubourg
Maître de Conférence - Praticien Hospitalier
Rendez-vous 04 27 85 61 34

RHUMATOLOGIE
CENTRE DE COMPETENCE DES MALADIES AUTO-INFLAMMATOIRES ET AMYLOSES HEREDITAIRES

Dr Agnès Duquesne
Praticien Attaché

Dr Marine Fouillet-Desjonquères
Praticien Hospitalier
Secrétariat Christine Thevenet
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HOPITAL DE JOUR
Rendez-vous 04 27 85 61 34
Secrétariat 04 27 85 61 26

HOSPITALISATION
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Cadre – Annick Bourdin
04 27 85 60 42
Cadre adjointe – Christine Andres
04 27 85 59 80

SERVICE SOCIAL
Isabelle Turaud 04 72 12 94 25

e-mail
prenom.nom@chu-lyon.fr

Dear Madam, Dear Sir,

It will be my pleasure to accept Dr Luciano Da Silva Selistre as a research fellow in our department.

We have been in charge of renal transplantation in children for more than twenty years and we have the opportunilly to collaborate with the physiology department from the very beginning.

It will be a unique opportunity to start with a prospective investigation of kidney transplant children using cystatin C measurement for early detection of abnormal GFR in transplant patients.

Doctor Luciano Da Silva Selistre will be in charge of designing the project, collecting patients and renal investigations, analyzing data and publishing the results in order to validate this biochemical parameter compared to inuline clearance which is currently the gold standard method.

Of course, I fully support the application of Dr Luciano Da Silva Selistre.

Sincerely,

Pierre Cochat

Direction Générale
Direction des Affaires Médicales

Hôpitaux de Lyon

dossier suivi par : B.CAZELLES

Lyon, le 20 OCT. 2010

Monsieur le Professeur G. BAVEREL
Exploration fonctionnelle rénale et métabolique
Pavillon P
Groupement Hospitalier Edouard Herriot

Objet : stage de Monsieur Luciano DA SILVA SELISTRE

Monsieur le Professeur,

J'ai été informé par courriel du 18 octobre dernier de la venue dans votre service de Monsieur L. DA SILVA SELISTRE, pour un stage de médecin observateur non rémunéré, à compter du 1er octobre.

J'ai l'honneur de vous donner mon accord concernant le séjour de ce médecin en qualité d'observateur. Ce statut n'autorise pas son titulaire à exercer des activités à visée diagnostique ou thérapeutique au sein du service qui l'accueille, y compris par délégation. Durant son stage, je vous précise que Monsieur L. DA SILVA SELISTRE est placé sous votre responsabilité et couvert par l'assurance des Hospices Civils de Lyon.

Il lui est toutefois conseillé de souscrire une assurance de responsabilité individuelle et professionnelle à titre personnel pour les dommages dont il pourrait être victime.

Je vous prie d'agréer, Monsieur le Professeur, l'assurance de ma considération distinguée.

Le Directeur Adjoint des Affaires Médicales,

B.CAZELLES

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Université Claude Bernard Lyon 1

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04 27 85 61 30

EXPLORATION FONCTIONNELLE
Dr Laurence Dubourg
Maître de Conférence - Praticien Hospitalier
Rendez-vous 04 27 85 61 34

RHUMATOLOGIE
CENTRE DE COMPETENCE DES MALADIES AUTO-INFLAMMATOIRES ET ARTHRITES JUVENILES IDIOPATHIQUES

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04 27 85 61 26

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Dr Marine Fouillet-Desjonquères
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Dr Alexandre Belot
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Bron, le 7 juin 2012

ATTESTATION D'AUTORISATION D'UTILISATION DE DONNEES

Je soussigné Pierre Cochat, chef du service de Néphrologie Rhumatologie Dermatologie Pédiatriques de l'Hôpital Femme Mère Enfant du CHU de Lyon, France, autorise le Professeur Luciano SELISTRE qui a travaillé dans le service d'Aôut 2010 à octobre 2011, à utiliser, à des fins de recherche et de publication, les données cliniques et biologiques des patients suivis dans le service. Ces données ont été soumises au consentement éclairé des patients ou de leur représentants légaux.

Les données recueillies par le Professeur Luciano SELISTRE sont uniquement rétrospectives et ne nécessitent pas, en France, de demande d'autorisation spécifique auprès du comité d'éthique. Cependant, ce travail a été réalisé selon les recommandations éthiques données par les autorités françaises pour l'utilisation des données de patients.

Fait à Bron le 7 juin 2012

Pr Pierre Cochat, MD, PhD

ANEXO 3

ATA DE DEFESA DE TESE

Pontifícia Universidade Católica do Rio Grande do Sul
FACULDADE DE MEDICINA
PÓS-GRADUAÇÃO EM MEDICINA E CIÊNCIAS DA SAÚDE

ATA DE DEFESA DE TESE Nº 146

Aos dezoito dias do mês de dezembro do ano de dois mil e doze, no Curso de Doutorado em Medicina e Ciências da Saúde, área de concentração em Nefrologia da Pontifícia Universidade Católica do Rio Grande do Sul, o pós-graduando **Luciano da Silva Selistre** defendeu a tese intitulada **"Avaliação da estimativa do ritmo de filtração glomerular com cistatina C em pacientes pediátricos"** sob as orientações dos Professores **Dr. David Saitovitch** e **Dr. Ivan Carlos F. Antonello** e sob a Co-orientações dos professores **Dra. Laurence Dubourg** e **Dr. Joseph Pierre Cochat**, em sessão pública, sala 317 da Pós-Graduação no Prédio 60, 3º andar do Hospital São Lucas da PUCRS. A sessão foi aberta pelo Professor Orientador que saudou os presentes e passou a presidir os trabalhos da comissão examinadora constituída pelos professores: Dra. Clotilde Druck Garcia (UFCSPA), Dr. Paulo Cesar Kock Nogueira (UNIFESP), Dr. Mário Bernardes Wagner (PUCRS) e Dr. Carlos Eduardo Poli de Figueiredo (PUCRS). O presidente da comissão examinadora informou o doutorando às orientações sobre o processo de defesa de tese concedendo-lhe cinqüenta minutos para expor o trabalho. Após a exposição, o doutorando foi arguido pelos componentes da comissão examinadora, respondendo a cada examinador. Encerrada a argüição os examinadores consideraram o candidato **APROVADO COM LOUVOR**. O presidente da comissão examinadora comunicou a aprovação do doutorando encerrando a sessão pública de defesa. Para constar, lavrou-se esta ata que deverá ser anexada à documentação exigida para posterior expedição do diploma. A presente será assinada pelos integrantes da comissão examinadora, pelo professor orientador, pelo pós-graduando e por mim, Alexandra Brum Correa, secretária que a redigi. Porto Alegre, aos dezoito dias do mês de dezembro do ano de dois mil e doze.

Dr. Clotilde Druck Garcia

Dr. Carlos Eduardo Poli de Figueiredo

Dr. Paulo Cesar Kock Nogueira

Dr. David Saitovitch

Dr. Mário Bernardes Wagner

Luciano da Silva Selistre

Alexandra Brum Correa