Nephrol Dial Transplant (2016) 31: 609–619
doi: 10.1093/ndt/gfv105
Advance Access publication 28 April 2015

Considerable variations in growth hormone policy and prescription in paediatric end-stage renal disease across European countries—a report from the ESPN/ERA-EDTA registry

M. van Huis[1], M. Bonthuis[2], E. Sahpazova[3], F. Mencarelli[4], B. Spasojević[5], G. Reusz[6], A. Caldas-Afonso[7], A. Bjerre[8], S. Baiko[9], K. Vondrak[10], E.A. Molchanova[11], G. Kolvek[12], N. Zaikova[13], M. Böhm[14], G. Ariceta[15], K.J. Jager[2], F. Schaefer[16], K.J. van Stralen[2] and J.W. Groothoff[1]

[1]Department of Pediatric Nephrology, Emma Children's Hospital, Academic Medical Center, Amsterdam, The Netherlands, [2]ESPN/ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, Amsterdam, The Netherlands, [3]University Pediatric Clinic, Skopje, FYROM, [4]Nephrology and Dialysis Unit, Department of Pediatrics, Azienda Ospedaliero Universitaria Sant'Orsola-Malpighi, Bologna, Italy, [5]Department of Nephrology, University Children's hospital, Belgrade, Serbia, [6]Semmelweis University Budapest, Budapest, Hungary, [7]Serviçio de Pediatria, Hospital de S. João, Porto, Portugal, [8]Department of Pediatrics, Oslo University Hospital, Rikshospitalet, Norway, [9]2nd Children's Hospital, Minsk, Belarus, [10]University Hospital Prague-Motol, Prague, Czech Republic, [11]Department of Kidney Transplantation, Russian Children's Clinical Hospital, Moscow, Russia, [12]Paediatric Department, Faculty of Medicine, Safarik University, Kosice, Slovakia, [13]Research Institute for Mother and Child Health Care, Chisinau, Moldova, [14]Department of Pediatric Nephrology, University Children's Hospital, Vienna, Austria, [15]Servicio de Nefrología Pediátrica y Hemodiálisis, Hospital Universitario Materno-Infantil Vall D'Hebron, Barcelona, Spain and [16]Department of Paediatric Nephrology, University of Heidelberg, Center for Pediatrics and Adolescent Medicine, Heidelberg, Germany

Correspondence and offprint requests to: Karlijn J. van Stralen, E-mail: k.j.vanstralen@amc.uva.nl

Downloaded from https://academic.oup.com/ndt/article-abstract/31/4/609/2459969 by guest on 13 December 2018

ORIGINAL ARTICLE

ABSTRACT

Background. Growth retardation in paediatric end-stage renal disease (ESRD) has a serious impact on adult life. It is potentially treatable with recombinant growth hormone (rGH). In this study, we aimed to quantify the variation in rGH policies and actual provided care in these patients across Europe.

Methods. Renal registry representatives of 38 European countries received a structured questionnaire on rGH policy. Cross-sectional data on height and actual use of rGH on children with ESRD aged <18 years were retrieved from the ESPN/ERA-EDTA Registry.

Results. In 21 (75%) of 28 responding countries, rGH is reimbursed for children with ESRD. The specific conditions for reimbursement (minimum age, maximum age and chronic kidney disease stage) vary considerably. Mean height standard deviation scores (SDS) at renal replacement therapy (RRT) [95% confidence interval (CI)] were significantly higher in countries where rGH was reimbursed −1.80 (−2.06; −1.53) compared with countries in which it was not reimbursed [−2.34 (−2.49;−2.18), $P < 0.001$]. Comparison of the mean height SDS at onset of RRT and final height SDS yielded similar results. Among the 13 countries for which both data on actual rGH use between 2007 and 2011 and data from the questionnaire were available, 30.1% of dialysis and 42.3% of transplanted patients had a short stature, while only 24.1 and 7.6% of those short children used rGH, respectively.

Conclusion. Reimbursement of rGH associates with a less compromised final stature of ESRD children. In many countries with full rGH reimbursement, the actual rGH prescription in growth-retarded ESRD children is low and obviously more determined by the doctor's and patients' attitude towards rGH therapy than by financial hurdles.

Keywords: disparities, Europe, growth, growth hormone, policies

INTRODUCTION

Recent data have shown that currently 43% of patients with childhood onset end-stage renal disease (ESRD) do not achieve an adult height within the normal range [1]. At the same time, short stature affects health outcomes, health-related quality of life and psychosocial development which adds to the psychosocial burden of ESRD itself [2–6]. Longitudinal growth may

© The Author 2015. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved.

therefore be considered as a marker of quality of paediatric renal care.

Treatment of growth failure in paediatric ESRD consists of correcting any nutritional, water and salt deficiencies as well as metabolic abnormalities. In case of persistent growth failure, recombinant growth hormone (rGH) might be indicated [7]. Although rGH use is found to be safe and efficacious in children with ESRD [8–12], its use has been reported as limited [13].

Although some national guidelines are available, general European guidelines on rGH use in paediatric ESRD are lacking and, therefore, the care provided to growth-retarded children could differ between countries. Previous studies have highlighted the variation in management of children with ESRD between European countries [14–16]. As the use of rGH is expensive, reimbursement and subsequently the possibility to prescribe rGH to every patient may vary per country. These factors may lead to different policies and actual provided care per country, which could possibly explain the variation in the extent of growth retardation among the European countries [17]. Furthermore, because of the lack of international guidelines, variation might occur in the chronic kidney disease (CKD) stage in which rGH therapy is initiated—only at the time of dialysis or already in CKD stage 2–4—in the age range in which rGH is being provided, as well as in the measures used to identify growth retardation, for example short stature or a decline in growth velocity.

In this study, we aimed to describe the variation in growth hormone policies in paediatric nephrology patients across European countries and relate these policies to outcomes, including height at start of renal replacement therapy (RRT), height during childhood RRT and final height by using data from the ESPN/ERA-EDTA registry.

MATERIALS AND METHODS

Data sources

We developed a structured questionnaire on growth hormone policies in European paediatric renal care. To ensure content validity, we used input from four paediatric nephrologists from different countries. An overview of all questions in the questionnaire is shown in Appendix 1.

The questionnaire was sent to the paediatric renal registry representatives in 38 countries in the European region.

Cross-sectional data on height of children on RRT were retrieved from the ESPN/ERA-EDTA Registry. Within this registry, demographic data on all European children starting RRT are collected annually. Moreover, a variable set of data on anthropometric, clinical and medication-related parameters are collected [18]. For this study, height data collected from 2007 onwards were used.

Definition of variables

Standard deviation scores (SDS) for height were calculated according to recent national growth charts whenever available or according to the recently developed Northern and Southern European growth charts [17]. SDS was defined as the following: (individual patient height—mean height for age- and sex-related healthy peers)/SD of height for age- and sex-related healthy peers.

Macro-economic indicators were obtained from the WorldBank [19] and expressed as Gross Domestic Product (GDP) per capita. We compared national growth hormone policies with actual use of rGH and with the percentage of children with a short stature defined as height SDS of −2 or below. Within the registry data on rGH use are limited, and no data are available on the duration of rGH treatment. Therefore, to study the effect of actual rGH use, we calculated the percentage of patients with a short stature that used rGH (yes/no) during 5 years of follow-up (2007–12, whenever available). Data on actual rGH use of each specific country was included in the analyses when data on both rGH use and growth parameters was available for at least 50% of the patients. The paediatric renal registry representatives were asked in a qualitative manner to explain any differences between the actual provided care of rGH and the number of eligible patient for rGH.

Statistical analysis

In the ESPN/ERA-EDTA registry, the number of height measurements differed between patients and countries. To correct for the correlation of measurements within the same patient, we used linear mixed models. Only countries for which height data were available for a sufficient number of patients (at least 10 or all patients in case of a particularly small country) were included in the analyses. χ^2 analysis and Kruskal–Wallis one-way analysis of variance were used to compare differences between groups. For Italy and the FYR of Macedonia, only height data on dialysis patients were available from the registry. Therefore, to test the possible confounding effect—of country policy in combination with information only on the (shorter) dialysis patients—we performed a sensitivity analysis excluding these patients from these countries. In order to adjust for differences in economic indicators across countries, we included GDP per capita in our analyses. Values are presented as mean (SE) unless stated otherwise. *P* values of <0.05 were considered statistically significant. All analyses were performed in SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA) and SPSS version 20 (IBM, SPSS Statistics 20, Chicago, IL, USA).

RESULTS

Policies in rGH use

Twenty-eight of 38 (response rate 74%) of the countries completed the questionnaire. The mean height SDS at start of RRT, mean height SDS during RRT and final height SDS by country are presented in Table 1.

In 21 (75%) of 28 countries, rGH was reimbursed for children with CKD, and in 7 there was no reimbursement under any circumstances, except in 2 of these countries which indicated that, in exceptional cases (e.g. in case of strict endocrinological criteria being satisfied), its use was allowed.

Of the 21 countries where rGH was reimbursed, 15 reported to have a national policy on rGH use in CKD. Policies were

Downloaded from https://academic.oup.com/ndt/article-abstract/31/4/609/2459969 by guest on 13 December 2018

Table 1. Mean height SDS at the start of RRT, mean height SDS and mean final height SDS

Country	*N*	Mean height SDS start RRT[a] (SE)	Mean height SDS (SE)	Mean final height SDS (SE)	% Boys	Mean age at start RRT	Mean duration dialysis (years)	Mean duration Tx (years)
Albania	6	−1.41 (0.82)	−1.67 (0.60)		66.7	10.9 (1.8)	0.0 (0)[b]	0.0 (0)[b]
Belarus	65	−2.18 (0.29)	−2.54 (0.20)		56.1	9.7 (0.2)	1.5 (0.8)	0.2 (0.03)
Belgium	134	−2.47 (0.31)	−1.60 (0.16)	−1.48 (0.41)	57.9	7.7 (0.3)	1.4 (0.1)	4.1 (0.3)
Bulgaria	26	−1.18 (0.42)	−1.18 (0.30)		55.6	11.2 (0.6)	0.0 (0)[b]	0.0 (0)[b]
Czech Republic	76	−1.53 (0.33)	−1.66 (0.20)	−1.54 (0.41)	55.6	8.0 (0.5)	0.8 (0.1)	2.3 (0.3)
Estonia	4	−1.99 (0.99)	−2.44 (0.70)		50.0	7.7 (0.6)	1.9 (0.4)	0.5 (0.07)
Finland	165	−1.44 (0.24)	−1.77 (0.16)	−1.70 (0.26)	54.6	3.7 (0.2)	1.1 (0.04)	6.0 (0.2)
Greece	75	−0.18 (0.30)	−2.09 (0.20)	−2.56 (0.50)	58.1	6.1 (0.3)	2.2 (0.3)	1.9 (0.3)
Italy[c]	312	−1.64 (0.21)	−2.16 (0.13)	−2.95 (0.28)	55.0	8.1 (0.1)	1.7 (0.06)	0.3 (0.04)
Lithuania	36	−2.33 (0.82)	−1.50 (0.26)		55.6	10.2 (0.5)	1.8 (0.2)	1.2 (0.2)
FYR of Macedonia	11	−1.87 (0.64)	−1.97 (0.43)		72.7	7.1 (0.4)	3.2 (0.6)	0.01 (0.004)
Montenegro	3	−1.47 (1.14)	−1.38 (0.83)		75.0	3.2 (0.3)	0.3 (0.3)	0.0 (0)[b]
The Netherlands	174	−0.93 (0.16)	−1.54 (0.10)	−1.92 (0.19)	58.6	8.3 (0.2)	1.8 (0.09)	0.4 (0.02)
Norway	80		−1.80 (0.20)	−1.58 (0.33)	61.3	6.5 (0.4)	0.4 (0.04)	4.9 (0.3)
Portugal	141	−1.68 (0.24)	−1.78 (0.16)	−1.90 (0.40)	55.6	7.9 (0.2)	1.9 (0.09)	1.1 (0.07)
Russia	458	−1.84 (0.21)	−2.31 (0.12)		56.3	9.4 (0.1)	1.1 (0.05)	0.8 (0.05)
Serbia	85	−1.63 (0.34)	−1.77 (0.19)	−1.69 (0.32)	57.5	8.1 (0.3)	2.0 (0.1)	2.6 (0.2)
Slovenia	16	−0.85 (0.57)	−1.58 (0.36)		68.8	8.8 (0.6)	1.8 (0.2)	0.5 (0.1)
Slovakia	31	−1.70 (0.39)	−1.78 (0.28)		62.5	10.6 (0.4)	1.1 (0.2)	1.1 (0.2)
Spain	704	−1.35 (0.18)	−1.42 (0.12)	−1.40 (0.21)	61.9	8.9 (0.09)	0.8 (0.02)	3.4 (0.07)
Turkey	275	−1.99 (0.22)	−2.42 (0.14)	−3.00 (0.38)	55.1	8.8 (0.2)	1.5 (0.1)	0.7 (0.08)
United Kingdom	1304	−1.96 (0.17)	−2.00 (0.11)	−1.98 (0.21)	59.5	8.9 (0.07)	1.3 (0.03)	3.1 (0.06)

SDS, Standard Deviation score; SE, standard error.
[a]Renal replacement therapy.
[b]No follow-up.
[c]Only dialysis patients.

based on either international guidelines (50%), national consensus (32%), local consensus among either paediatric nephrologists or paediatric endocrinologists (25%), government policies (11%) or health insurance companies (18%). The minimum age to prescribe rGH varied between 0 and 60 months, whereas the maximum age for prescription ranged from 14 years to no maximum age. Countries were either allowed to prescribe growth hormone in CKD stage 1–4 and when glomerular filtration rate was reduced in transplanted patients or in CKD patients only (not on dialysis or after renal transplantation). One country was allowed to prescribe growth hormone in dialysis patients only. An overview of all reported policies is presented in Appendix 2.

Height SDS criteria for prescribing rGH varied between −1.88 and −3 SDS. Two countries only used height SDS as a criterion, whereas 8 countries used either height SDS and/or a stable or decrease in height SDS (stable or decrease of >0.25 SDS in the previous year) and/or growth velocity (>1 SDS decrease in growth velocity) as a criteria and 11 countries specified no height criteria for prescribing rGH.

Differences between policies in relation to height SDS and economic indicators

Policies and outcomes are shown in Table 2. GDP was significantly higher in countries with rGH reimbursement (31.8) when compared with countries without rGH reimbursement (17.0, $P = 0.01$). GDP was positively associated with mean height SDS during RRT ($\beta = 0.013$), height SDS at start of RRT ($\beta = 0.003$) and final height SDS ($\beta = 0.009$). This association was only statistically significant for mean height SDS during RRT ($P < 0.001$).

Mean height SDS (95% CI) was significantly higher in countries where rGH was reimbursed [−1.80 (95% CI −2.06 to −1.53)] compared with countries where rGH was not reimbursed [−2.34 (95% CI: −2.49 to −2.18), $P < 0.001$]. Similar results were obtained when comparing mean height SDS at the start of RRT and final height SDS. There were no height differences between countries that were allowed to prescribe rGH among CKD patients and dialysis only and among CKD, dialysis and Tx patients (Table 2).

Effect of age limitation of rGH prescription. When categorizing the minimum age at start of rGH, mean height SDS was significantly lower in countries who were allowed to prescribe rGH under the age of 12 months (mean height SDS: −1.98) versus those allowed to prescribe from 12–24 months (mean height SDS: −1.93) and from 24 months and older (−1.52 SDS, $P < 0.001$).

When looking at the upper age limits, mean final height SDS was 0.63 SDS lower ($P < 0.001$) in countries who were allowed to prescribe rGH in children over 18 years, when compared with countries who were not allowed to prescribe rGH in children over 18 years of age.

Height criteria. Mean height SDS tended to be lower in countries who were allowed to prescribe rGH based on height SDS alone or based on height SDS and growth velocity when compared with countries who were allowed to prescribe rGH based on either height SDS or a stable/decrease in growth velocity (Table 2).

Downloaded from https://academic.oup.com/ndt/article-abstract/34/4/609/2459969 by guest on 13 December 2018

Table 2. Policies and outcome parameters

	Mean height SDS[a]	Mean height SDS[a] at start of RRT[b]	Mean final height SDS[a]
rGH[c] prescription			
No	−2.34 (−2.49; −2.18)[d]	−2.19 (−2.49; −1.88)[d]	−2.27 (−2.75; −1.78)[d]
CKD[e] and dialysis	−1.82 (−2.33; −1.30)	−1.85 (−2.58; −1.11)	−2.09 (−3.29; −0.90)
CKD[e], dialysis, Tx[f,h]	−1.80 (−2.06; −1.53)	−1.58 (−2.12; −1.05)	−1.77 (−2.33; −1.21)
Minimum age rGH[c] prescription#			
0 < 12 months	−1.98 (−2.08; −1.88)[d]	−1.92 (−2.08; −1.74)[d]	−2.12 (−2.34; −1.91)[d]
12≤ months <24	−1.93 (−2.14; −1.73)[d]	−1.26 (−1.61; −0.91)	−2.14 (−2.67; −1.61)[d]
≥24 months[f]	−1.52 (−1.82; −1.22)	−1.30 (−1.98; −0.61)	−1.49 (−2.07; −0.91)
Maximum age rGH[c] prescription#			
<18 years[f]			−1.39 (−1.93; −0.84)
≥18 years			−2.02 (−2.27; −1.78)[d]
rGH[c] prescription in CKD[e] stages#			
CKD[e] stage IV–V	−1.78 (−2.00; −1.55)	−1.48 (−1.85; −1.10)[d]	−1.68 (−2.06; −1.31)
CKD[e] stage III–V	−1.55 (−1.66; −1.45)[d]	−1.33 (−1.51; −1.14)[d]	−1.50 (−1.74; −1.27)[d]
CKD[e] stage II–V	−2.16 (−2.33; −1.99)[d]	−1.64 (−1.95; −1.34)	−2.95 (−3.38; −2.52)[d]
CKD[e] stage I–V[f]	−1.98 (−2.26; −1.70)	−1.94 (−2.58; −1.29)	−1.95 (−2.50; −1.40)
Height criteria for rGH[c] prescription#			
Height SDS[a]/or growth velocity[f]	−1.79 (−2.08; −1.50)	−1.75 (−2.44; −1.06)	−1.67 (−2.22; −1.11)
Height SDS[a]	−1.88 (−2.15 −1.61)	−0.93 (−1.37; −0.49)[g,d]	−2.34 (−3.07; −1.61)
Height SDS[a] and growth velocity	−1.88 (−2.00; −1.76)	−1.34 (−1.55; −1.13)[d]	−2.10 (−2.36; −1.84)[d]
Minimum duration of growth retardation#			
<12 months[f]	−1.81 (−2.08; −1.54)	−1.67 (−2.32; −1.02)	−1.78 (−2.33; −1.23)
≥12 months	−1.82 (−1.95; −1.68)	−1.41 (−1.66; −1.15)[d]	−1.74 (−2.02; −1.47)

[a]Standard deviation score.
[b]Renal replacement therapy.
[c]Growth hormone.
[d]Significant difference from reference group.
[e]Chronic kidney disease.
[f]Reference group.
[g]Only data of Bulgaria and Greece.
[h]Transplantation.

CKD stage. Countries were allowed to prescribe rGH at different stages of CKD, varying from CKD stage 1–5 to CKD stage 4–5. There were very small differences in mean height SDS at start of RRT by CKD stage, but there was an inverse relationship between CKD stage and height at start of RRT; height SDS was significantly higher in countries who were allowed to prescribe rGH in CKD stage 4–5 (−1.48, 95% CI: −1.85 to −1.10) or stage 3–5 (−1.33, 95% CI: −1.51 to −1.14) when compared with countries where physicians were allowed to prescribe rGH from CKD stage 1 onwards (−1.94, 95% CI: −2.58 to −1.29).

Actual provided care. We were able to retrieve the percentage of rGH use between 2007 and 2011 in 13 of the 28 countries. We calculated the percentage of children who were eligible for rGH use. Overall rGH use between 2007 and 2011 in dialysis and transplantation was 21.7 and 5.5%, respectively, and major country differences were observed (Tables 3 and 4). A total of 45.9% of dialysis and 38.9% of transplant patients had a short stature (height SDS less than −2) and would therefore be eligible for receiving rGH. In all countries, the actual use of rGH was lower than the number of children eligible for rGH: only 26.0% of short dialysis and 8.9% of short transplant patients actually received rGH. When applying country-specific criteria to define short stature, similar figures were observed (Tables 3 and 4).

Physicians stated that the difference between actual rGH use and percentage of children eligible for rGH was due to several factors: patients refused treatment, improving nutritional intake and metabolic bone disease had priority over starting rGH, dialysis adequacy was sub-optimal, and patients were suffering from severe uncontrolled hyperparathyroidism. In addition, physicians stated that delayed prescription could occur when the responsibility for prescribing rGH was under control of the endocrinologist. There was no association between the percentage of rGH use and mean height SDS during RRT (Figure 1A and B) or percentage of rGH use and final height in both dialysis ($\beta = 0.02$, $P = 0.28$; Figure 1C) and transplantation ($\beta = 0.03$, $P = 0.25$; Figure 1D).

DISCUSSION

In this paper, we demonstrated a considerable variation in growth hormone policies across 28 countries in Europe. We found that total absence of reimbursement of rGH indeed was associated with a more compromised final stature of ESRD children. However, specific restrictions to a basic reimbursement policy did not influence final stature or height at RRT. On the other hand, we found that the actual rGH prescription in patients who were eligible for rGH was remarkably low and differed substantially among countries.

Downloaded from https://academic.oup.com/ndt/article-abstract/31/4/609/2459969 by guest on 13 December 2018

Table 3. Actual use of rGH and patients with short stature on dialysis

Country	% of rGH use	Eligibility according to short stature (height SDS less than −2)		Eligibility according to national criteria	
		% of patients eligible for rGH	% of eligible patients receiving rGH	% of patients eligible for rGH	% of eligible patients receiving rGH
Belgium	40.2	33.5	49.7	38.0	39.8
Czech Republic	22.2	42.0	16.7	42.0	16.7
Estonia	50.0	83.3	50.0	83.3	50.0
Greece	18.8	56.3	26.3	56.3	26.3
Italy	20.5	52.8	21.5	15.9	16.5
Lithuania[a]	6.8	40.2	9.1	40.2	9.1
The Netherlands	31.0	26.4	41.9	33.1	33.1
Portugal	22.6	49.7	29.5	33.5	23.2
FYR of Macedonia	33.3	44.4	50.0	15.6	0.0
Serbia	34.9	54.3	42.4	32.7	38.3
Slovenia	43.6	38.1	51.4	44.1	51.4
Spain	24.8	39.2	33.6	47.1	29.1
United Kingdom	11.6	53.8	15.9	47.0	15.5
Overall	21.7	45.9	26.0	30.1	24.1

[a]Although rGH is not reimbursed in Lithuania, a limited number of patients might receive reimbursement from a patient fund and are actually treated with rGH.

Table 4. Actual use of rGH and patients with short stature on transplantation

Country	% of rGH use	Eligibility according to short stature (height SDS less than −2)		Eligibility according to national criteria	
		% of patients eligible for rGH	% of eligible patients receiving rGH	% of patients eligible for rGH	% of eligible patients receiving rGH
Belgium	19.9	51.9	29.3	38.9	22.8
Czech Republic	7.7	30.7	10.0	35.7	8.3
Estonia	0.0	20.0	0.0	38.9	0.0
Greece	6.5	48.4	13.3	48.7	11.1
Lithuania[a]	2.1	57.3	2.8	50.6	8.3
The Netherlands	4.0	25.6	6.0	28.8	10.4
Portugal	0.0	34.3	0.0	26.5	3.8
Serbia	4.6	40.8	9.6	35.4	9.5
Slovenia	0.0	53.6	0.0	46.5	0.0
Spain	8.3	29.4	13.7	39.8	9.2
United Kingdom	3.9	45.4	6.6	47.5	5.3
Overall	5.5	38.9	8.9	42.3	7.6

[a]Although rGH is not reimbursed in Lithuania, a limited number of patients might receive reimbursement from a patient fund and are actually treated with rGH.

Total absence of rGH reimbursement was only apparent in 7 of 28 countries. These were all countries with a relatively low GDP. Two of these countries used the escape of strict endocrinological criteria, which makes prescription in this category of patients virtually impossible. As in CKD, GH levels are usually normal and GH stimulation tests are often positive [10, 20]. Two countries stated not being allowed to prescribe rGH in transplanted children. For one country, this was due to a fear of graft loss in rGH treatment in transplanted children with already a shortage in available donor kidneys. Although older studies indeed suggest rGH treatment in transplanted children to be associated with an increased risk of allograft loss [21, 22], more recent studies did not show an increased risk of allograft loss or adverse events in children treated with rGH after renal transplantation [23–28]. Therefore, the policies in which rGH is not allowed in transplanted children might need to be reconsidered.

We found a large variation in the minimum age for prescribing rGH, which was associated with mean (final) height SDS; mean height SDS was lowest in the countries who were allowed to prescribe rGH before 24 months of age. This is surprising, unless the policy is adapted to the mean (final) height SDS in those countries, where the policy is to treat children at a younger age in order to achieve a better final height. In interpretation of this association, we need to take into account that we performed a cross-sectional study and that it is impossible to determine whether rGH treatment preceded the outcome (final height) or the other way around. Data from Mencarelli *et al.* [29] and a study by Fine *et al.* [9] showed a significant improvement in height SDS in growth-retarded children with chronic kidney failure when treated with rGH at a young age. Nevertheless, other studies [30, 31] hypothesized that growth failure at a young age is mainly a reflection of nutritional influences and could be treated conservatively. The *Kidney Disease Outcomes Quality Initiative (KDOQI)* [7] recommends frequent

Downloaded from https://academic.oup.com/ndt/article-abstract/31/4/609/2459969 by guest on 13 December 2018

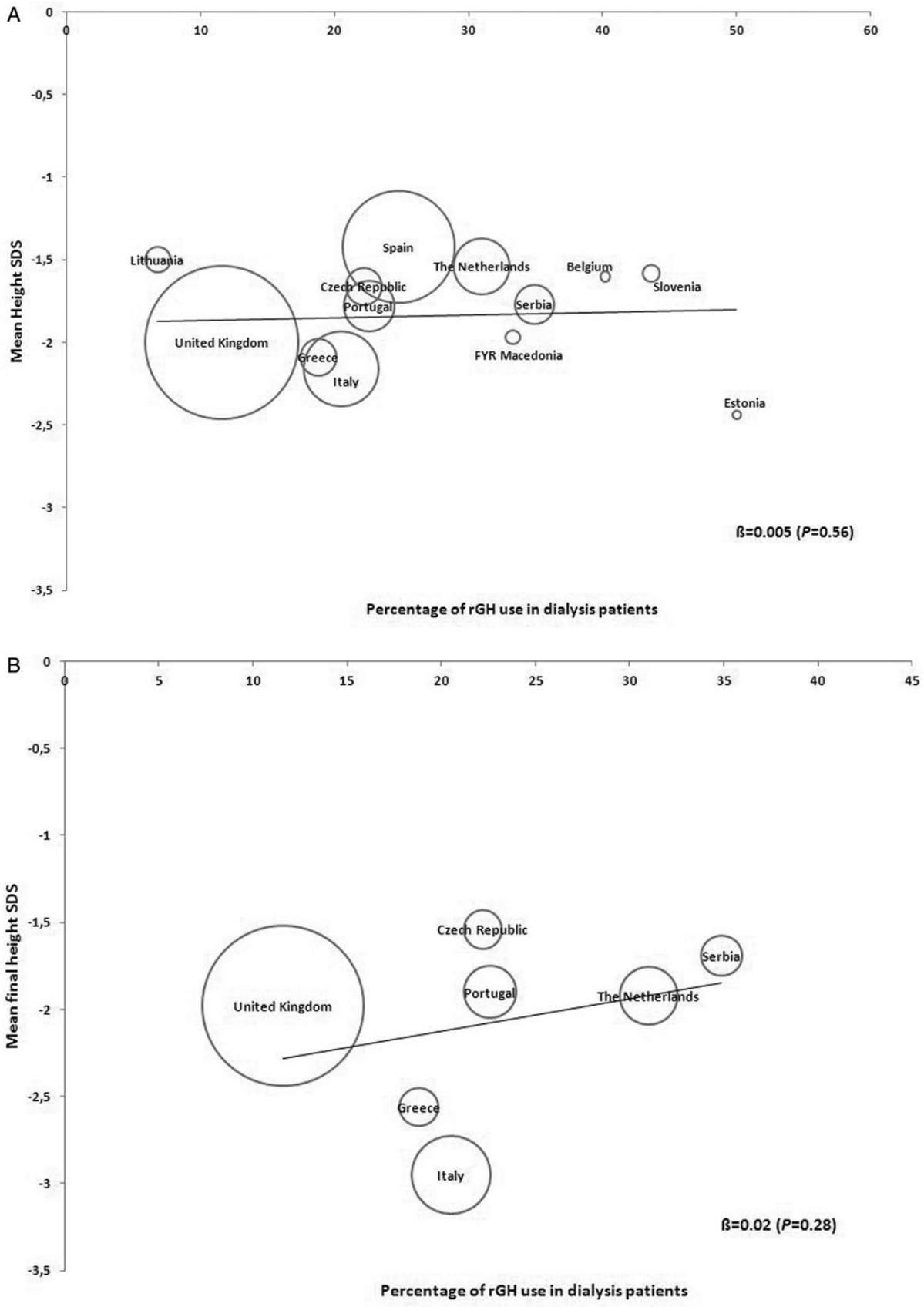

FIGURE 1: (**A**) Percentage of rGH use in dialysis patients and mean height SDS. (**B**) Percentage of rGH use in dialysis patients and mean final height SDS. (**C**) Percentage of rGH use in transplantation patients and mean height SDS (**D**) Percentage of rGH use transplantation patients and mean final height SDS.

Downloaded from https://academic.oup.com/ndt/article-abstract/31/4/609/2459969 by guest on 13 December 2018

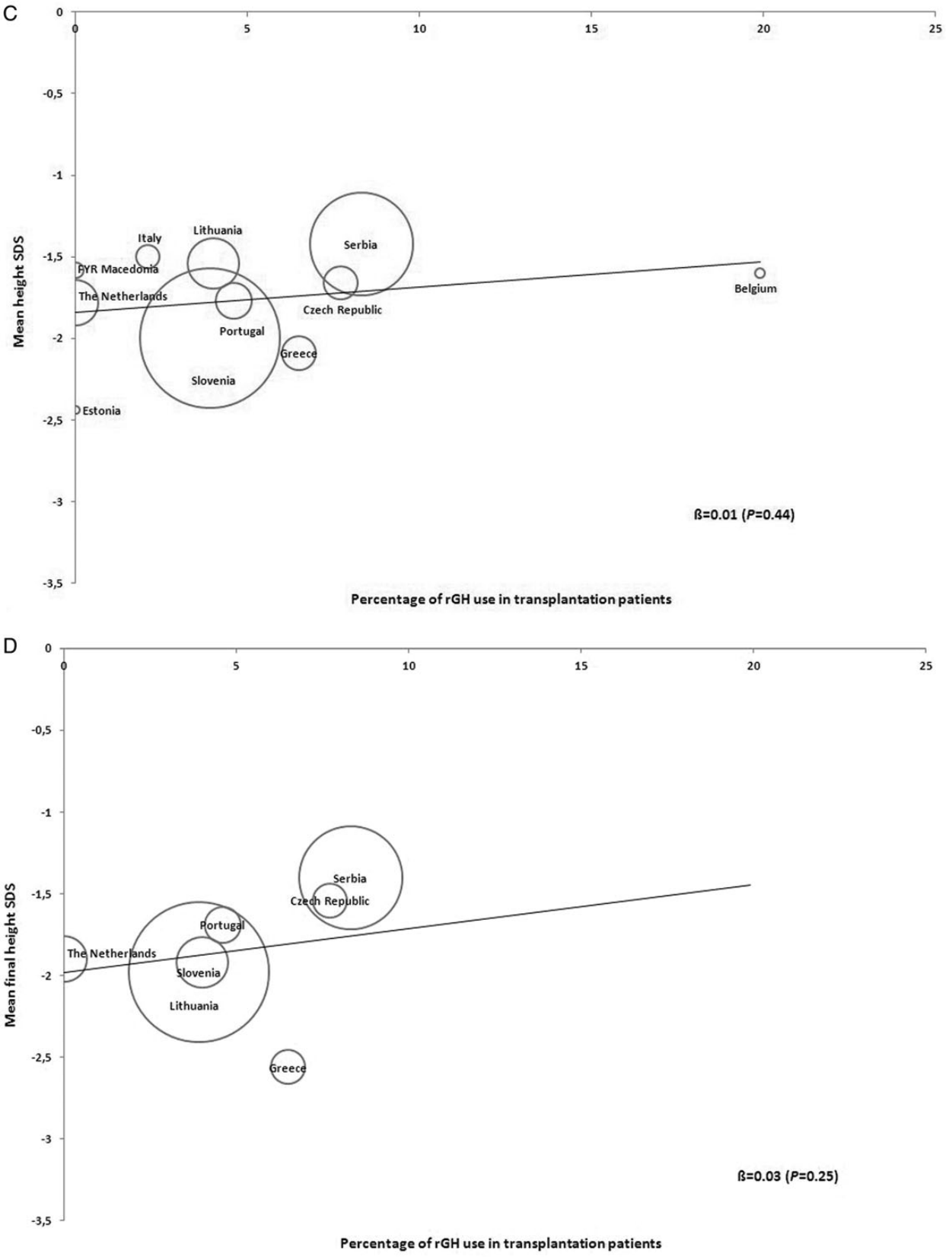

Fig. 1 *Continued*

monitoring of nutritional deficiencies and adequate caloric intake before starting rGH therapy in children aged under 3 years. Although most nephrologists probably follow the KDOQI guidelines on adequate caloric intake, there is still much debate about the definition of 'optimal feeding' and hence on the exact indication for growth hormone therapy. Data on supplemental

Downloaded from https://academic.oup.com/ndt/article-abstract/31/4/609/2459969 by guest on 13 December 2018

feeding are not available from the registry. Therefore, we were not able to investigate this subject.

Height criteria for initiating rGH therapy also vary between different guidelines. The KDOQI guidelines [7] recommend considering rGH in children with a height SDS less than −1.88 or height for age <3rd percentile and a growth velocity-for-age SDS less than −1.88 or growth velocity-for-age <3rd percentile. The CARI guidelines [32] recommend offering rGH therapy to all children with a height <25th percentile and a growth velocity <25th percentile. Within our study, height criteria for prescribing rGH varied considerably across countries. We found more liberal policies based on either decreased height SDS or growth velocity were associated with a higher mean final height than the more restricted policies.

Children with a functioning graft have a more favourable outcome when compared with children who are on dialysis for a longer time period. Since Italy provided only data of children on dialysis, the same analyses were performed excluding the data from Italy. This sensitivity analyses showed no significant differences in the results. Therefore, we think that the results of this study are not distorted to a large extent by data of children on dialysis.

Whether the differences in outcome are merely the effect of differences in policies remains unclear, since we had limited data on actual rGH use. In keeping with previous studies, we did show that the majority of children with a short stature did not use growth hormone in the preceding period. In the UK, it has been estimated that although 29% of the children on a renal transplant with impaired renal function and 41% of the children on dialysis suffered from growth retardation, <5% of the children receive rGH treatment. Also, the NAPRTCS study found that rGH is used in only a minority (33 and 3% of children on dialysis and on a renal transplant, respectively) [33]. Recently, the Chronic Kidney Disease in Children (CKiD) study group showed that only 23% of children with severe growth retardation (height SDS < −1.88) receive growth hormone therapy [34]. These findings correspond with the results of our study.

There were differences between policies and actual provided care, possibly explained by both doctor- and patient-related factors, such as patients refusing rGH therapy. Improving nutritional intake and treatment of metabolic bone disease sometimes were prioritized over starting rGH. Although improving nutritional intake has proven to be beneficial for linear growth, dietary intervention is most successful in infancy [35, 36]. Therefore, in older children, rGH therapy might be preferred over improving nutritional intake.

Also, non-adherence might be an obstacle in prescribing rGH, as demonstrated in an earlier study by the CKiD group where self-reported non-adherence to rGH, defined by missing at least one dose within 7 days, was 25% [34]. Another study by Greenbaum *et al.* [37] explored the obstacles to prescribing rGH in children with CKD. They found several reasons why children did not receive growth hormone, such as psychosocial reasons (family refusal, non-adherence and 'overwhelmed' family) in 30% of the cases whereas, in 25% of cases, no reason could be identified. Possibly, the fact that many children eligible for rGH are awaiting kidney transplantation might contribute to the extremely low use of rGH in our population. After transplantation, a good catch-up growth is expected in case of good renal function [38]. In anticipation of such a situation, physicians might have decided not to start rGH treatment. The extremely low use of rGH after renal transplantation might be caused by the fear of triggering rejection episodes. Studies in transplant recipients did, however, not show an association between the use of rGH and rejection episodes [24–26, 28, 39]. Finally, under-reporting of rGH use in the registry might at least partly explain the difference between rGH use and percentage of children on rGH.

The reimbursement of rGH affected height outcome, whereas differences between policies in those countries in which rGH was reimbursed did not seem to lead to a difference in height outcome parameters. Therefore, we cannot give any recommendations on what policies seem to work best. Furthermore, the actual care provided by the doctors and their attitudes towards growth hormone therapy also affects height outcome, although data on growth hormone use are limited and no data are available on the duration of rGH treatment. We found that, in a few countries, outdated growth charts are applied, possibly leading to an underestimation of the growth retardation of individual children. Nevertheless, when using the outdated growth charts, still a minority of children eligible for receiving rGH, actually are receiving rGH.

The percentage of children receiving rGH in dialysis and transplantation showed a weak positive association with mean final height SDS, although this did not reach statistical significance. However, this might also be due to the cross-sectional nature of our study, limiting to draw conclusions on cause–effect relationships [40].

Nevertheless, it is clinically relevant, as there is abundant data that rGH improves height. Furthermore, it suggests that, when rGH is not prescribed when actually indicated, other interventions to achieve an adult height within the normal range, such as optimal caloric intake, seem to fail.

CONCLUSION

In this study, we aimed to quantify the variation in growth hormone policies in paediatric ESRD across European countries and their effect on height. We found considerable variation in policies regarding growth hormone between 28 European countries. Furthermore, rGH was significantly less often prescribed than would be expected, suggesting that outcome is not only affected by growth hormone policy, but also by other factors. Both doctors- and patient-related obstacles to prescribe rGH are amenable for interventions in order to improve the use of rGH in children with ESRD and offer those children a chance to achieve more beneficial health outcomes.

ACKNOWLEDGEMENTS

We thank the patients, their parents and the staff of all the dialysis and transplant units who have contributed data via their national registries and contact persons. We also thank

Downloaded from https://academic.oup.com/ndt/article-abstract/31/4/609/2459969 by guest on 13 December 2018

R. Coppo, D. Haffner, J. Harambat and C. Stefanidis for being members of the ESPN/ERA-EDTA Registry Committee, D. Shtiza, R. Kramar, R. Oberbauer, A. Sukalo, K. van Hoeck, F. Collart, J.M. des Grottes, D. Pokrajac, D. Roussinov, D. Batinić, M. Lemac, J. Slavicek, T. Seeman, J.G. Heaf, U. Toots, P. Finne, C. Grönhagen-Riska, C. Couchoud, M. Lasalle, N. Abazi, N. Ristoka Bojkovska, G. von Gersdorff, C. Scholz, B. Tönshoff, K. Krupka, B. Höcker, L. Pape, N. Afentakis, A. Kapogiannis, N. Printza, C.s. Berecki, A. Szabó, T. Szabó, Z.s. Györke, E. Kis, R. Palsson, V. Edvardsson, B. Gianoglio, S. Maringhini, C. Pecoraro, S. Picca, S. Testa, E. Vidal, E. Verrina, A. Jankauskiene, B. Pundziene, V. Said-Conti, S. Gatcan, O. Berbeca, S. Pavićević, T. Leivestad, S. Gatcan, O. Berbeca, S. Pavićević, T. Leivestad, A. Zurowska, I. Zagozdzon, C. Mota, M. Almeida, G. Mircescu, L. Garneata, N.A. Tomilina, B.T. Bikbov, M. Kostic, A. Peco-Antic, G. Milosevski-Lomic, D. Paripovic, S. Puric, D. Kruscic, L. Podracka, J. Buturovic-Ponikvar, G. Novljan, N. Battelino, A. Alonso Melgar and the Spanish Pediatric Registry, S. Schön, K.G. Prütz, L. Backmän, M. Stendahl, M. Evans, B. Rippe, C.E. Kuenhi, E. Maurer, G.F. Laube, S. Tschumi, P. Parvex, A. Hoitsma, A. Hemke, and all centres participating in the RichQ study, R. Topaloglu, A. Duzova, D. Ivanov, R. Pruthi, F. Braddon, S. Mannings, A. Cassula, M.D. Sinha for contributing data to the ESPN/ERA-EDTA Registry.

APPENDIX 1

Table A1. Questionnaire

1. Which country are you representing?
2. Is it allowed to prescribe recombinant human growth hormone (rGH) in your country?
3. Is there a national policy on rGH prescription?
4. Is there a written policy on rGH?
5. Upon which of the following is your policy based? (multiple answers possible)
6. How is your (national) policy regarding the reimbursement of rGH?
7. At what minimum age (in months) are you allowed to start rGH?
8. At what maximum age (in years) do you have to stop rGH?
9. When do you have to stop rGH? (multiple answers possible)
10. Are you allowed to prescribe rGH among non-dialysis patients?
11. Are the criteria for rGH prescription different for dialysis, CKD and transplantation (Tx) patients?
12. At what CKD stage, is it allowed to start rGH?
13. At what time (in months) after Tx, are you allowed to (re)start rGH?
14. In some countries, multiple criteria exist for prescribing rGH for example: height SDS less than −2 OR height SDS less than −1.88 and stable or decrease in height SDS over the previous year). Which criteria need to be met in your country, in order to permit prescribing of rGH? (please specify all possible criteria)
15. How long should the growth retardation at least be present before starting rGH?
16. At what time (in months) after Tx, are you allowed to (re)start rGH?
17. You have completed the questionnaire. We highly appreciate any additional comments or questions:

APPENDIX 2

Table B1. Overview policies

	Albania	Belarus	Belgium	Bulgaria	Croatia	Czech Republic	Denmark	Estonia	Finland	France	FYR of Macedonia	Germany	Greece	Italy	Lithuania	Moldova	Montenegro	the Netherlands	Norway	Portugal	Russia	Serbia	Slovakia	Slovenia	Spain	Sweden	Turkey	United Kingdom	Total
rGH allowed																													
Yes	I	I	+	+	+	+	+	+	+	+	+	+	+	+	I	I	+	+	+	+	I	I	+	+	+	+	I	+	21
No		+	I	I	I	I	I	I	I	I	I	I	I	I	+	+	I	I	I	I	+	+	I	I	I	I	+	I	7
National policy		I	+	+	+	I	I	+	+	+	I	+	+	+	I	I	I	I	I	+	I	I	I	+	+	I	I	+	15
Written policy		I	+	+	+	I	I	+	+	+	I	I	+	+	I	I	I	I	I	+	I	I	I	+	+	I	I	I	14
Patients in whom rGH is allowed																I													
Dialysis only	I		I	I	+	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	1
CKD and dialysis	I		I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	+	I	I	I	I	I	1
CKD, dialysis, Tx[a]						+		+	+	+	+	+	+	+		I	+	+	+	+			I	+	+	+	I	+	19
Minimum allowed age																I													
<12 months	I		+	+	I	I	+	+	+	I	I	+	I	+	I	I	I	I	I	I	I	I	I	I	I	I	I	I	7
>12 months	I		I	I	+	+	I	I	+	+	+	I	+	I	I	I	+	+	+	+	I	I	+	+	+	+	I	I	14
Maximum allowed age																I													
<18 years	I	I	I	+	+	I	I	I	I	+	I	I	+	I	I	I	+	I	I	+	I	I	I	+	+	I	I	I	8

Continued

Downloaded from https://academic.oup.com/ndt/article-abstract/31/4/609/2459969 by guest on 13 December 2018

Table B1. Continued

	Albania	Belarus	Belgium	Bulgaria	Croatia	Czech Republic	Denmark	Estonia	Finland	France	FYR of Macedonia	Germany	Greece	Italy	Lithuania	Moldova	Montenegro	the Netherlands	Norway	Portugal	Russia	Serbia	Slovakia	Slovenia	Spain	Sweden	Turkey	United Kingdom	Total
>18 years	–	–	+	–	–	+	+	+	+	–	+	+	–	+	–	–	–	+	+	–	–	–	+	–	–	+	–	–	13
CKD stage allowed																–													
I–V	–	–	–	–	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	3
II–V	–	–	–	–	–	–	–	–	–	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2
III–V	–	–	+	+	–	–	–	–	–	–	–	+	+	–	–	–	–	+	+	+	–	–	+	–	+	–	–	–	9
IV–V	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	3
V without dialysis	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1

GH, growth hormone; CKD, chronic kidney disease.
[a]Transplantation.

REFERENCES

1. Harambat J, Bonthuis M, van Stralen KJ *et al.* Adult height in patients with advanced CKD requiring renal replacement therapy during childhood. Clin J Am Soc Nephrol 2014; 9: 92–99
2. Al-Uzri A, Matheson M, Gipson DS *et al.* The impact of short stature on health-related quality of life in children with chronic kidney disease. J Pediatr 2013; 163: 736–741
3. Furth SL, Stablein D, Fine RN *et al.* Adverse clinical outcomes associated with short stature at dialysis initiation: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatrics 2002; 109: 909–913
4. Geisler A, Lass N, Reinsch N *et al.* Quality of life in children and adolescents with growth hormone deficiency: association with growth hormone treatment. Horm Res Paediatr 2012; 78: 94–99
5. Hartung EA, Furth SL. Growth in children on renal replacement therapy: a shrinking problem? Pediatr Nephrol 2013; 28: 1905–1908
6. Lem AJ, Jobse I, van der Kaay DC *et al.* Health-related quality of life in short children born small for gestational age: effects of growth hormone treatment and postponement of puberty. Horm Res Paediatr 2012; 77: 170–179
7. National Kidney Foundation. KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. Am J Kidney Dis 2009; 53: S1–S124
8. Benfield MR, Kohaut EC. Growth hormone is safe in children after renal transplantation. J Pediatr 1997; 131: S28–S31
9. Fine RN. Growth hormone and the kidney: the use of recombinant human growth hormone (rhGH) in growth-retarded children with chronic renal insufficiency. J Am Soc Nephrol 1991; 1: 1136–1145
10. Gupta V, Lee M. Growth hormone in chronic renal disease. Indian J Endocrinol Metab 2012; 16: 195–203
11. Mehls O, Tonshoff B, Haffner D *et al.* The use of recombinant human growth hormone in short children with chronic renal failure. J Pediatr Endocrinol 1994; 7: 107–113
12. Wuhl E, Schaefer F. Effects of growth hormone in patients with chronic renal failure: experience in children and adults. Horm Res 2002; 58 (Suppl 3): 35–38
13. Lewis M, Shaw J, Reid C *et al.* Growth in children with established renal failure—a Registry analysis (chapter 14). Nephrol Dial Transplant 2007; 22 (Suppl 7): vii176–vii180
14. Harambat J, van Stralen KJ, Schaefer F *et al.* Disparities in policies, practices and rates of pediatric kidney transplantation in Europe. Am J Transplant 2013; 13: 2066–2074
15. Tromp WF, Schoenmaker NJ, van der Lee JH *et al.* Important differences in management policies for children with end-stage renal disease in the Netherlands and Belgium—report from the RICH-Q study. Nephrol Dial Transplant 2012; 27: 1984–1992
16. van Huis M, Schoenmaker NJ, Groothoff JW *et al.* Policy variation in donor and recipient status in 11 pediatric renal transplantation centers. Pediatr Nephrol 2013; 28: 951–957
17. Bonthuis M, van Stralen KJ, Verrina E *et al.* Use of national and international growth charts for studying height in European children: development of up-to-date European height-for-age charts. PLoS One 2012; 7: e42506
18. Tizard EJ, Verrina E, van Stralen KJ *et al.* Progress with the European Society for Paediatric Nephrology (ESPN)/ERA-EDTA Registry for children with established renal failure (ERF). Nephrol Dial Transplant 2009; 24: 2615–2617
19. Worldbank. http://data.worldbank.org/. 2014
20. Mahesh S, Kaskel F. Growth hormone axis in chronic kidney disease. Pediatr Nephrol 2008; 23: 41–48
21. Friedman AL. Growth hormone is not safe for children with renal transplants. J Pediatr 1997; 131: S25–S27
22. Janssen F, van Damme-Lombaerts R, van Dyck M *et al.* Impact of growth hormone treatment on a Belgian population of short children with renal allografts. Pediatr Transplant 1997; 1: 190–196
23. Dharnidharka VR, Talley LI, Martz KL *et al.* Recombinant growth hormone use pretransplant and risk for post-transplant lymphoproliferative disease—a report of the NAPRTCS. Pediatr Transplant 2008; 12: 689–695
24. Fine RN, Sullivan EK, Kuntze J *et al.* The impact of recombinant human growth hormone treatment during chronic renal insufficiency on renal transplant recipients. J Pediatr 2000; 136: 376–382

Downloaded from https://academic.oup.com/ndt/article-abstract/31/4/609/2459969 by guest on 13 December 2018

25. Fine RN, Stablein D, Cohen AH *et al*. Recombinant human growth hormone post-renal transplantation in children: a randomized controlled study of the NAPRTCS. Kidney Int 2002; 62: 688–696
26. Fine RN, Stablein D. Long-term use of recombinant human growth hormone in pediatric allograft recipients: a report of the NAPRTCS Transplant Registry. Pediatr Nephrol 2005; 20: 404–408
27. Longmore DK, Conwell LS, Burke JR *et al*. Post-transplant lymphoproliferative disorder: no relationship to recombinant human growth hormone use in Australian and New Zealand pediatric kidney transplant recipients. Pediatr Transplant 2013; 17: 731–736
28. Maxwell H, Rees L. Randomised controlled trial of recombinant human growth hormone in prepubertal and pubertal renal transplant recipients. British Association for Pediatric Nephrology. Arch Dis Child 1998; 79: 481–487
29. Mencarelli F, Kiepe D, Leozappa G *et al*. Growth hormone treatment started in the first year of life in infants with chronic renal failure. Pediatr Nephrol 2009; 24: 1039–1046
30. Karlberg J, Schaefer F, Hennicke M *et al*. Early age-dependent growth impairment in chronic renal failure. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. Pediatr Nephrol 1996; 10: 283–287
31. van Dyck M, Sidler S, Proesmans W. Chronic renal failure in infants: effect of strict conservative treatment on growth. Eur J Pediatr 1998; 157: 759–762
32. CARI. CARI. 2013
33. Seikaly MG, Salhab N, Warady BA *et al*. Use of rhGH in children with chronic kidney disease: lessons from NAPRTCS. Pediatr Nephrol 2007; 22: 1195–1204
34. Rodig NM, McDermott KC, Schneider MF *et al*. Growth in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children Study. Pediatr Nephrol 2014; 29: 1987–1995
35. Mehls O, Blum WF, Schaefer F *et al*. Growth failure in renal disease. Baillieres Clin Endocrinol Metab 1992; 6: 665–685
36. Rees L, Mak RH. Nutrition and growth in children with chronic kidney disease. Nat Rev Nephrol 2011; 7: 615–623
37. Greenbaum LA, Hidalgo G, Chand D *et al*. Obstacles to the prescribing of growth hormone in children with chronic kidney disease. Pediatr Nephrol 2008; 23: 1531–1535
38. Maxwell H, Haffner D, Rees L. Catch-up growth occurs after renal transplantation in children of pubertal age. J Pediatr 1998; 133: 435–440
39. Mehls O, Fine RN. Growth hormone treatment after renal transplantation: a promising but underused chance to improve growth. Pediatr Nephrol 2013; 28: 1–4
40. Noordzij M, Dekker FW, Zoccali C *et al*. Study designs in clinical research. Nephron Clin Pract 2009; 113: c218–c221

Received for publication: 17.12.2014; Accepted in revised form: 21.3.2015

Nephrol Dial Transplant (2016) 31: 619–627
doi: 10.1093/ndt/gfv115
Advance Access publication 22 April 2015

Downloaded from https://academic.oup.com/ndt/article-abstract/31/4/609/2459969 by guest on 13 December 2018

ORIGINAL ARTICLE

Assessment of current practice and barriers to antimicrobial prophylaxis in peritoneal dialysis patients

Denise J. Campbell[1,2], Fiona G. Brown[3], Jonathan C. Craig[1,2], Martin P. Gallagher[4], David W. Johnson[5], Geoffrey S. Kirkland[6], Subramanian K. Kumar[7], Wai H. Lim[8], Dwarakanathan Ranganathan[9], Walaa Saweirs[10,11], Kamal Sud[12,13], Nigel D. Toussaint[14,15], Rowan G. Walker[15,16], Lesley A. Williams[9], Maha Yehia[17] and David W. Mudge[5]

[1]Centre for Kidney Research, Sydney Children's Hospital Network (Westmead), Westmead, NSW, Australia, [2]School of Public Health, University of Sydney, Sydney, NSW, Australia, [3]Monash University, Clayton, VIC, Australia, [4]University of Sydney and George Institute for Global Health, Sydney, NSW, Australia, [5]University of Queensland at Princess Alexandra Hospital, Brisbane, QLD, Australia, [6]Royal Hobart Hospital, Hobart, TAS, Australia, [7]Gosford Hospital, Gosford, NSW, Australia, [8]Sir Charles Gairdner Hospital, Perth, WA, Australia, [9]Royal Brisbane and Women's Hospital, Herston, QLD, Australia, [10]Whangarei Hospital, Northland District Health Board, Whangarei, New Zealand, [11]University of Auckland, Auckland, New Zealand, [12]Nepean Clinical School, University of Sydney, Sydney, NSW, Australia, [13]Westmead and Nepean Hospitals, NSW, Australia, [14]Western Health, Footscray, VIC, Australia, [15]The Royal Melbourne Hospital, Parkville, VIC, Australia, [16]The Alfred Hospital, Prahran, VIC, Australia and [17]Auckland City Hospital, Auckland, New Zealand

Correspondence and offprint requests to: Denise Campbell; Email: denise.campbell@health.nsw.gov.au

ABSTRACT

Background. Existing Australasian and international guidelines outline antibiotic and antifungal measures to prevent the development of treatment-related infection in peritoneal dialysis (PD) patients. Practice patterns and rates of PD-related infection vary widely across renal units in Australia and New Zealand and are known to vary significantly from guideline

© The Author 2015. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved.