HHS Public Access

Author manuscript

Pediatr Nephrol. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Pediatr Nephrol. 2015 May ; 30(5): 829–837. doi:10.1007/s00467-014-3008-z.

Healthcare burden of venous thromboembolism in childhood chronic renal diseases

Bryce A. Kerlin[1,2], **William E. Smoyer**[1,2], **James Tsai**[3], and **Sheree L. Boulet**[4]

[1]Dept. of Pediatrics, The Ohio State University College of Medicine

[2]Center for Clinical & Translational Research, The Research Institute at Nationwide Children's

[3]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention

[4]National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention

Abstract

Background—Chronic renal diseases (CRD) are associated with ~5% of pediatric venous thromboembolism (VTE) cases, but the epidemiology of VTE in CRD is ill-defined.

Methods—Children (<18 years) with CRD were identified from MarketScan®. VTE diagnosis during 6 months after the first CRD diagnosis was ascertained. Demographics, healthcare utilization, mortality and co-morbid conditions were assessed.

Results—22,877 children with predefined CRD ICD-9-CM codes were identified between April 1, 2003 and June 30, 2012, 0.55% of these children had VTE. In-hospital mortality was more likely in children with VTE compared to those without VTE (11.9% vs. 0.9%; p<0.0001). Healthcare utilization was also significantly higher with VTE (p<0.0001 for: number of inpatient admissions, length of stay, outpatient visits and pharmaceutical claims), and total mean healthcare expenditures for the 6 month follow-up period were 13 times greater in the VTE group ($338,338 (±$544,045) vs. $25,171 (±$90,792); p<0.0001). In a multivariate model infection, hemodialysis and trauma/surgery significantly increased the likelihood of VTE.

Conclusions—VTE is rare in children with CRD, but is associated with higher mortality and healthcare utilization when present. Among children with CRD, the likelihood of VTE was increased among those with co-morbid, non-renal chronic conditions.

Keywords

Thrombosis; Embolism; Chronic Kidney Disease; Vascular Disease; Infection; Surgery; Hemodialysis

Corresponding Author: Bryce A. Kerlin, 700 Children's Dr.; W325 Columbus, OH 43205-2696, USA Telephone: 614.355.2731 Facsimile: 614.722.3330 Bryce.Kerlin@NationwideChildrens.org.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflict of interest disclosure The authors have no actual or potential conflict of interest. Specifically they have no financial, personal, or other relationships with other people or organizations that could inappropriately influence this work.

Introduction

Venous thromboembolism (VTE), which encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE), is an increasingly important cause of morbidity and mortality in children with chronic health conditions [1]. Approximately 5% of all childhood inpatient VTE episodes are associated with co-morbid chronic renal diseases (CRD) [1-4]. Furthermore, in comparison to other chronic conditions of childhood, CRD is associated with the highest rate of hospital-associated VTE in children [5]. VTE occurs in approximately 3% of children with nephrotic syndrome [6, 7], whereas the prevalence in other types of CRD has not been well-established. The rate of graft failure due to thrombosis of vascular anastomoses following renal transplantation is approximately 3% [8-10]. The estimated thrombus-free survival of arteriovenous fistulae (AVF) for long-term hemodialysis is 74% at 1-2 years [11, 12]. However, the distribution and determinants of VTE (including non-graft, non-AVF VTE) have not been established for children with CRD.

Pediatric VTE is associated with a 2-6 fold increased mortality risk, a 5-10% prevalence of post-thrombotic syndrome (disabling venous insufficiency), and about 10% of VTE patients develop recurrent VTE [13]. Better understanding the epidemiology and risk factors for this potentially devastating complication is a necessary step toward VTE prevention and improved treatment. In this study, we sought to define the prevalence of VTE in a large cohort of children with CRD, estimate the healthcare burden imposed by VTE, and evaluate associated risk factors for VTE.

Methods

Data source

The data for this study were obtained from the 2003-2012 Truven Health Analytics MarketScan® Commercial Databases [14]. These databases include de-identified insurance claims from employees and dependents covered by large self-insured employers and regional health plans. In addition to diagnostic codes, actual payments on all billed services, including prescription drug, outpatient and inpatient care claims are captured, allowing for a true cost analysis rather than estimates from provider charges. Additionally, the databases assign each enrollee a unique identification number, eliminating duplication from the analyses (providing that they did not switch between participating insurance companies during the study period). In 2012, the database included information on approximately 53 million enrollees and their dependents from over 150 contributing employers and 25 contributing health plans.

Study population

Subjects with CRD identified for inclusion in this study were 0-17 years of age at the time of their first CRD diagnostic code and also had available health plan enrollment information and outpatient pharmaceutical claims data. CRD was defined using ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) codes for 1) congenital anomalies of urinary system, 2) nephrotic syndrome, 3) chronic glomerulonephritis, and 4) chronic kidney disease (Table 1), as previously described [15,

16]. All inpatient codes were considered valid; outpatient diagnostic codes without a corresponding inpatient diagnosis were only included if there were ≥2 of the above codes recorded at least 30 days apart. To allow for 6 months of follow-up data (see *VTE subjects*), subjects were ascertained through June 30, 2012. Subjects were excluded if they had not been continuously enrolled for at least 6 months prior to CRD diagnosis (except for infants) or if they were not continuously enrolled for at least 6 months after CRD diagnosis (unless an in-hospital death was reported). Subjects were classified as dialysis patients if dialysis was coded at least twice, regardless of their inpatient or outpatient status, using the presence of either ICD-9-CM codes (Table 1) or CPT (Current Procedural Terminology) codes 4052F, 4053F, 4054F, 90935, 90937, 90940, or 99512. Renal transplantation patients were determined by the presence of at least 1 inpatient or outpatient code (ICD-9-CM codes (Table 1) or CPT codes 50360, 50365, 90967, 90968, and 90969).

VTE subjects

The VTE status of subjects who qualified for this study was subsequently determined by the presence of an ICD-9-CM code for VTE concurrently with their first CRD diagnosis or in the subsequent 6 month follow-up period. Six months of follow-up was chosen due to the known epidemiology that the majority of nephrotic syndrome-, AVF-, and transplant anastomosis-related VTE occur within this time frame [8, 11, 12, 16]. Previously described ICD-9-CM diagnosis codes for VTE were utilized (Table 1) [1, 17-19]. Thrombectomy procedure codes were also included (ICD-9-CM codes (Table 1) and CPT codes: 34401, 34421, 34451, 34471, 34490, 37187, 37188, 33910, 33915, and 33916), as previously described [1]. All inpatient VTE codes were considered valid; outpatient diagnostic codes without a corresponding inpatient diagnosis were considered valid if there was evidence of a filled anticoagulant prescription within 90 days following the VTE diagnosis, as previously described [18].

Co-morbid conditions

Co-morbid chronic conditions were categorized as previously described by Feudtner *et al* and subsequently applied to the study of pediatric VTE [1, 15, 20]. This categorization includes codes for neuromuscular, cardiovascular, respiratory, gastrointestinal, hematology and immunodeficiency, metabolic, genetic and malignant chronic conditions, in addition to those in the renal category. Thus, non-renal complex chronic conditions (nrCCC) were ascertained using the Feudtner *et al* ICD-9-CM classification system for 3 months prior to CRD diagnosis through 6 months post-diagnosis (regardless of when VTE may have been diagnosed during the time-frame). All inpatient nrCCC were considered valid; outpatient diagnostic codes without a corresponding inpatient code were considered valid if there were ≥2 nrCCC codes reported >30 days apart and within the 9 month reporting period. To allow for the 3 month pre-diagnosis co-morbidity window, subject ascertainment commenced on April 1, 2003.

Acute co-morbid conditions were categorized into trauma, surgery and infection groups, which are the major, identifiable acute conditions associated with pediatric VTE [1]. Subjects were classified as positive for any acute condition if it was coded in the 3 months prior to their VTE diagnosis or in the 3 months prior to CRD diagnosis for subjects without

a VTE diagnosis. Additional three-month periods of potential exposure to acute conditions post-CRD diagnosis for the non-VTE group were considered in a sensitivity analysis. Trauma was defined using previously published American College of Surgeons National Trauma Data Bank criteria (Table 1) [1, 21]. Surgery was identified using diagnosis-related group codes, as previously described [18]. Infections were recognized using ICD-9-CM codes grouped into clinical classification categories defined by the Medical Expenditure Panel Survey (MEPS), HC-120: Appendix 3, Clinical Classification Code to ICD-9-CM Code Crosswalk, available from the US Department of Health & Human Services Agency for Healthcare Research and Quality [22], with minor modifications (see Table 1). Additionally, because they are less specific, all ICD-9-CM "V" codes were eliminated from these clinical classification categories.

Statistics

Two-tailed chi-square and Student's t-tests were used to compare the distribution of demographic and clinical characteristics of children afflicted with CRD with and without VTE. Mean and median estimates of health service use and expenditures were calculated for inpatient admissions, outpatient visits and pharmaceutical claims. Claims for outpatient visits were aggregated by date of service. Because the use and cost data were right skewed, the Wilcoxon rank sum test was used to compare distributions for children according to VTE status. An alpha of ≤0.05 was used to determine statistical significance.

Logistic regression models were used to calculate unadjusted and adjusted odds ratios and 95% confidence intervals for the association between demographic and clinical characteristics and VTE among children with chronic renal disease. The variables included in the initial multivariable models were age at first renal diagnosis (continuous), nrCCC, trauma/surgery, infection, hemodialysis and evidence of renal transplantation (trauma and surgery were combined into a single variable to allow the model to fit with adequate power). Significant interactions were noted between nrCCC and hemodialysis and nrCCC and renal transplantation; thus, the final models were stratified by nrCCC.

Results

Demographics

Utilizing the MarketScan® commercial databases for 2003-2012, 22,877 unique qualifying CRD subjects aged 0-17 years were identified between April 1, 2003 and June 30, 2012 (Table 2). A qualifying VTE episode was identified in 126 (0.55%) of these subjects. Of those, 112 (88.9%) had a DVT only and 14 (11.1%) had a PE with or without a DVT. The age of subjects with VTE was distributed in a bimodal fashion (χ^2 $p<0.001$) and the mean age of subjects with VTE was significantly greater (6.6±6.9 vs. 4.6±5.7 years; $p=0.002$). In-hospital mortality was considerably more frequent in subjects with VTE (11.9% vs. 0.9%; $p<0.0001$). However, there was no gender specific risk ($p=0.23$). Only 63 (0.32%) of 19,769 children with congenital anomalies had VTE, in contrast to 1.12-1.93% VTE in the other categories, with the highest prevalence in children with nephrotic syndrome (Table 2). Children with VTE were more likely to also have an nrCCC (73.8% vs. 20.2%; $p<0.0001$), recent trauma (13.5% vs. 4.6%; $p<0.0001$), recent surgery (41.3% vs. 9.5%; $p<0.0001$), or

recent infection (34.1% vs. 7.0%; $p<0.0001$) than were those without VTE. Because infectious complications may be treated during a single encounter and thus, would only be coded a single time, we performed a sensitivity analysis to determine whether it would be prudent to require a filled antibiotic prescription to fulfill the criteria for accepting an infection diagnosis. However, accepting a single code vs. also requiring an antibiotic prescription did not significantly alter the relationship (data not shown). Similarly, trauma and surgery would also both be expected to be coded only for a single encounter. However, it would be unusual for them to be coded as a suspected or "rule-out" diagnosis, thus we accepted all of these codes without additional criteria or analysis. A sensitivity analysis examining exposure to these acute conditions (trauma, surgery and infection) during the additional follow-up periods did not materially alter the results (data not shown). Children with CRD who had evidence of end-stage kidney disease were more likely to develop VTE; of those on hemodialysis 6.32% (11 of 174) were affected by VTE (vs. 0.51% of those not on hemodialysis, $p<0.0001$), similarly 2.74% (9 of 329) renal transplant recipients had VTE (vs. 0.52% without a transplant, $p<0.0001$).

Univariate and multivariable relationships

Logistic regression was performed to determine the likelihood of VTE. In this analysis, the presence of co-morbid, nrCCC interacted significantly with the likelihood of VTE. As shown in Table 3 (top section), for children with CRD but no co-morbid nrCCC, age, recent trauma/surgery, recent infection, hemodialysis and renal transplantation were all associated with VTE. Following adjustment, age, recent infection and hemodialysis remained predictive with adjusted ORs of 1.09 (95% CI 1.03-1.15), 3.41 (95% CI 1.33-8.68) and 11.39 (95% CI 3.00-43.21), respectively. In contrast, in the presence of an nrCCC, age, recent trauma/surgery, recent infection and hemodialysis were significantly associated with VTE, but after adjusting for the remaining variables only recent trauma/surgery and recent infection remained predictive of VTE (adjusted ORs of 3.50; 95% CI 2.29-5.36 and 3.32; 95% CI 2.15-5.14, respectively).

Healthcare utilization and expenditures

Four healthcare utilization variables were examined: 1) number of inpatient hospitalizations, 2) cumulative inpatient length of stay, 3) number of outpatient encounters, and 4) number of pharmaceutical claims (Table 4). Both mean and median measures of healthcare utilization were increased dramatically by the development of VTE. Subjects with VTE were admitted to hospital over twice as frequently (mean 2.47 vs. 0.62 admissions; $p<0.0001$) and the length of these inpatient stays were over 10 times longer (mean 62.06 vs. 5.89 days; $p<0.0001$). VTE subjects also attended >2.5 times more clinic visits (mean 30.65 encounters) than did their non-VTE counterparts (mean 11.30 encounters; $p<0.0001$). Similarly, the VTE group filled over 3 times more prescriptions than did the non-VTE group (mean 18.92 vs. 5.82; $p<0.0001$).

The MarketScan® Commercial Databases include data on healthcare claims payments (expenditures). Thus, through this database we are able to analyze actual healthcare expenditures, rather than charges (which may not be reflective of actual costs). For this analysis, no attempt was made to adjust expenditures for inflation. Not surprisingly, VTE

was associated with increased expenditures commensurate with the increased level of utilization. A mean of $307,328 was expended on inpatient care for the VTE cohort, which was over 16 times the amount spent on non-VTE CRD subjects (mean $18,147; $p<0.0001$). Similarly, outpatient expenditures ($27,511 vs. $6,476; $p<0.0001$) were quadrupled and pharmaceutical expenses ($3,499 vs. $548; $p<0.0001$) were 639% higher. This resulted in mean total expenditures that were over 13 times greater for the VTE group ($338,338 vs. $25,171; $p<0.0001$).

Discussion

This large retrospective administrative data cohort study reveals that VTE is a rare but potentially devastating complication of childhood kidney diseases. VTE complicated 0.55% of childhood CRD cases, but was associated with significantly increased healthcare utilization (2-10 fold), costs (13 fold) and mortality (13 fold). In children with isolated CRD, VTE was most likely in older children, those on hemodialysis, or those with a recent infection. For those children with CRD and a co-morbid nrCCC, recent trauma/surgery and recent infections were independently predictive of VTE. Children with congenital anomalies of the urinary system were least likely to develop VTE (0.32%), those with nephrotic syndrome were more likely to develop VTE (1.93%), and those with end-stage kidney disease (transplant recipients or hemodialysis patients) were most likely to suffer from VTE (2.74% and 6.32%, respectively).

Childhood VTE is predominantly a complication of tertiary care for children with chronic illnesses, infections and/or surgery/trauma [1]. Despite the recent rise in the incidence of this complication [17], childhood VTE remains a rare disease [1, 19]. Thus, the epidemiology of childhood VTE within disease subgroups has not been well defined due to the challenge of obtaining adequate sample sizes. However, the pathophysiology of prothrombotic risk may not be identical among the various subgroups [11]. Therefore, defining subgroup epidemiology is an important step toward preventing this potentially devastating complication. The recent development of large administrative databases provides a means toward ascertainment of adequately sized subgroup samples, but is limited to retrospective designs. Thus, these studies are limited by both selection and information bias. For instance, in this study, selection was limited to subjects with health insurance recorded within the MarketScan® database, which may not be representative of the childhood CRD population in general, especially those covered by Medicaid and Medicare (for those children on chronic dialysis) and those outside of the United States. Furthermore, the study population may have been subject to information bias due to misclassification with regard to CRD and/or VTE diagnosis related to the limited sensitivity and specificity of ICD-9-CM coding, despite our strategies to improve the specificity of these codes using multiple diagnostic identifiers [23, 24]. Obviously, the ability to discern some types of relevant risk factors, such as thrombophilia status (e.g. factor V Leiden, prothrombin gene mutation, etc) and central venous catheter utilization is not possible when analyzing administrative data. Nonetheless, the epidemiologic understanding gleaned from these studies is important to determine adequate sample sizes needed for the proper design of future prospective studies.

Despite these limitations, the prevalence of VTE in children with nephrotic syndrome (1.93%) was similar to that reported in recent studies (1–3.6%) where, likewise to this study, passive monitoring for VTE was utilized [25, 26]. However, as recently reviewed by our group, clinicians should be aware that the prevalence of VTE may be much higher than these estimates when active monitoring (i.e. asymptomatic screening) for VTE is utilized [6, 7]. Moreover, the design employed here, to only detect VTE in the first 6 months after diagnosis is more likely to capture incident VTE than recurrent VTE, and is unlikely to capture incident VTE in children who progress to end-stage kidney disease more than 6 months after their initial diagnosis, thus the true burden of VTE in children with CRD is likely higher than estimated.

Importantly, these data may not be relevant to other forms of renal disease in children. We chose to utilize previously published definitions of chronic diseases of the kidney. It should be noted that these are all conditions which may be considered to have a chronic course. For example, the congenital anomalies category includes children with conditions that have no ready cure. Thus, these data are unlikely to apply to children with acute kidney disease (e.g. acute tubular necrosis, pyelonephritis, etc.). Similarly, the epidemiology of VTE in chronic renal conditions not included in this analysis may differ. Furthermore, an individual patient may progress from one form of CRD to another (e.g. a child with steroid-resistant nephrotic syndrome may have progressive loss of glomerular function and eventually develop chronic kidney disease) which likely explains, at least in part, why we observed some overlap in types of CRD within our population (see Table 2). This study was not adequately powered to assess the effect of this type of progression over time on VTE risk.

In addition to nephrotic syndrome, which was included in this study, other forms of CRD are associated with a known hypercoagulability [27], but may also be associated with a bleeding diathesis, particularly in uremic patients [20, 28]. The latter may be somewhat protective against VTE in this population and explain why CRD is less commonly associated with VTE than other childhood chronic diseases [1]. Furthermore, the bleeding diathesis may complicate anticoagulant therapy for those children who do develop VTE and explain some of the increased utilization and costs associated with VTE care.

VTE in this childhood CRD cohort had a bimodal age distribution, which is consistent with other studies of childhood VTE [3, 6, 17]. Further consistent with previous reports, the VTE cohort was about 2 years older than the non-VTE cohort [1]. In contrast, the number of children with CRD in the database decreased with age (see Table 2), which may be reflective of the high prevalence of congenital anomaly cases in this study (86.4%), which was also the group with the lowest overall prevalence of VTE (0.32%) [29-31]. Recent epidemiologic data demonstrate conflicting data on the prevalence of end-stage kidney disease by age, but imply that older children have the greatest proportion of prevalent disease [29-32]. Thus, VTE is most likely to occur in the older children with CRD, particularly those with end-stage kidney disease, which is consistent with the overall epidemiology of childhood VTE [1].

The likelihood of in-hospital mortality was substantially greater in subjects with VTE. This is also consistent with other childhood VTE studies [1, 2, 17]. Because cause of death is not

captured in the MarketScan® database, similarly to other administrative data analyses, it is not possible to determine whether this correlation represents causality for VTE-related deaths or is simply reflective of VTE being more highly predominant in the most critically ill children. One previous report suggested that only about 23% of VTE-associated deaths are directly attributable to VTE, with the remaining portion being attributable to underlying diseases [2]. Nonetheless, VTE (specifically PE) has recently been reported to significantly impact mortality in adults on dialysis [33]. It is not possible to assess reasons why subjects may have dropped out of this dataset (e.g. death vs. changing health plans). Therefore, we were unable to assess non-hospital mortality in this analysis.

One of the remaining important questions in childhood VTE epidemiology is the impact that superimposed chronic-on-chronic and/or acute-on-chronic illness has on the likelihood of VTE [1]. Thus, in this study, we evaluated the impact of other nrCCC on VTE probability and found a significant interaction. Interestingly, the presence or absence of superimposed chronic-on-chronic (i.e. nrCCC-on-CRD) illness significantly altered the epidemiology of VTE. Infections were independently associated with VTE in children with CRD regardless of nrCCC status. In contrast, hemodialysis was independently associated with VTE only without a co-morbid nrCCC, whereas recent trauma/surgery was independently associated with VTE only in those with an nrCCC. This may indicate that children who have been on hemodialysis are more prone to catheter infection and catheter-associated thrombosis, due to the known interactions between bacterial infection and thrombotic risk [34]. For children with chronic-on-chronic illness, recent trauma/surgery significantly increased the probability of VTE, suggesting that this group is at highest risk during an acute-on-chronic event associated with transient immobilization and an inflammatory stimulus. Importantly, both surgical interventions and infections have known associations with both adult and pediatric VTE [1, 35].

In this study, children with end-stage kidney disease (reflected by use of hemodialysis or renal transplantation) were significantly more likely to suffer from VTE. However, we were not able to reliably assess the use of peritoneal dialysis with currently available coding strategies from this database and were, thus not able to compare hemodialysis vs. peritoneal dialysis risk. It is reasonable to speculate that VTE may be more common with hemodialysis due to the necessity of large-bore venous access devices.

VTE was significantly associated with both healthcare resource utilization and expenditures. Utilization is likely reflective of increased admissions for VTE and anticoagulant management, additional clinic visits for anticoagulant management, and additional prescriptions for anticoagulants. However, it is possible that this is reflective of more intense management for more severe underlying renal pathology, assuming that underlying disease severity drives the likelihood of VTE. The increased expenditures were commensurate with the additional resource utilization. Importantly, the expenditures reported in MarketScan® include the expected copayment and deductible amounts and, thus, represent actual healthcare costs. We did not attempt to adjust these expenditures for inflation. However, inflation would be expected to affect VTE and non-VTE associated expenditures equally. Thus, we are confident that the increased expenditures associated with VTE would remain significantly elevated after inflationary adjustment.

In summary, these results demonstrate that, although rare, VTE in children with CRD carries a significantly increased burden of healthcare utilization, costs and mortality. Furthermore, this study provides important information regarding which children with CRD are at greatest risk for VTE, who might be targeted for non-pharmacologic VTE prevention measures or enrolled in clinical trials of thromboprophylactic therapies [7]. This knowledge may inform the development of targeted VTE prevention strategies in these children as well as helping to estimate sample sizes needed to power future studies of this complication.

Acknowledgements

This project was supported by grants 239409 from The Research Institute at Nationwide Children's and U54DK083912-05S1 from the National Institute of Diabetes and Digestive and Kidney Diseases (both in support of BAK) and Award Number UL1RR025755 from the National Center for Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIDDK, NCRR, or the National Institutes of Health.

References

1. Setty BA, O'Brien SH, Kerlin BA. Pediatric venous thromboembolism in the United States: a tertiary care complication of chronic diseases. Pediatr Blood Cancer. 2012; 59:258–264. [PubMed: 22038730]
2. Andrew M, David M, Adams M, Ali K, Anderson R, Barnard D, Bernstein M, Brisson L, Cairney B, DeSai D. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood. 1994; 83:1251–1257. [PubMed: 8118029]
3. Massicotte MP, Dix D, Monagle P, Adams M, Andrew M. Central venous catheter related thrombosis in children: analysis of the Canadian Registry of Venous Thromboembolic Complications. J Pediatr. 1998; 133:770–776. [PubMed: 9842042]
4. van Ommen CH, Heijboer H, Buller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. J Pediatr. 2001; 139:676–681. [PubMed: 11713446]
5. Takemoto CM, Sohi S, Desai K, Bharaj R, Khanna A, McFarland S, Klaus S, Irshad A, Goldenberg NA, Strouse JJ, Streiff MB. Hospital-associated venous thromboembolism in children: incidence and clinical characteristics. J Pediatr. 2014; 164:332–338. [PubMed: 24332452]
6. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and Pathophysiology of Nephrotic Syndrome-Associated Thromboembolic Disease. Clin J Am Soc Nephrol. 2012; 7:513–520. [PubMed: 22344511]
7. Kerlin BA, Haworth K, Smoyer WE. Venous thromboembolism in pediatric nephrotic syndrome. Pediatr Nephrol. 2014; 29:989–997. [PubMed: 23812352]
8. Singh A, Stablein D, Tejani A. Risk factors for vascular thrombosis in pediatric renal transplantation: a special report of the North American Pediatric Renal Transplant Cooperative Study. Transplantation. 1997; 63:1263–1267. [PubMed: 9158019]
9. Latin American Pediatric Nephrology Association; Latin American Pediatric Renal Transplant Cooperative Study. Latin American Registry of Pediatric Renal Transplantation 2004-2008. Pediatr Transplant. 2010; 14:701–708. [PubMed: 20525000]
10. McDonald RA, Smith JM, Stablein D, Harmon WE. Pretransplant peritoneal dialysis and graft thrombosis following pediatric kidney transplantation: a NAPRTCS report. Pediatr Transplant. 2003; 7:204–208. [PubMed: 12756045]
11. Haricharan RN, Aprahamian CJ, Morgan TL, Harmon CM, Barnhart DC. Intermediate-term patency of upper arm arteriovenous fistulae for hemodialysis access in children. J Pediatr Surg. 2008; 43:147–151. [PubMed: 18206473]
12. Sheth RD, Brandt ML, Brewer ED, Nuchtern JG, Kale AS, Goldstein SL. Permanent hemodialysis vascular access survival in children and adolescents with end-stage renal disease. Kidney Int. 2002; 62:1864–1869. [PubMed: 12371990]

13. Kerlin BA. Current and future management of pediatric venous thromboembolism. Am J Hematol. 2012; 87(Suppl 1):S68–74. [PubMed: 22367975]
14. Hansen LG, Chang S. Health research data for the real world: the Thomson Reuters MarketScan databases. Thomson Reuters. 2011
15. Feudtner C, Hays RM, Haynes G, Geyer JR, Neff JM, Koepsell TD. Deaths attributed to pediatric complex chronic conditions: national trends and implications for supportive care services. Pediatrics. 2001; 107:E99. [PubMed: 11389297]
16. Kerlin BA, Blatt NB, Fuh B, Zhao S, Lehman A, Blanchong C, Mahan JD, Smoyer WE. Epidemiology and risk factors for thromboembolic complications of childhood nephrotic syndrome: a Midwest Pediatric Nephrology Consortium (MWPNC) study. J Pediatr. 2009; 155:105–110. 110, e101. [PubMed: 19394032]
17. Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics. 2009; 124:1001–1008. [PubMed: 19736261]
18. Boulet SL, Amendah D, Grosse SD, Hooper WC. Health care expenditures associated with venous thromboembolism among children. Thromb Res. 2012; 129:583–587. [PubMed: 21872297]
19. Boulet SL, Grosse SD, Thornburg CD, Yusuf H, Tsai J, Hooper WC. Trends in venous thromboembolism-related hospitalizations, 1994-2009. Pediatrics. 2012; 130:e812–820. [PubMed: 22987875]
20. Mannucci PM, Remuzzi G, Pusineri F, Lombardi R, Valsecchi C, Mecca G, Zimmerman TS. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. N Engl J Med. 1983; 308:8–12. [PubMed: 6401193]
21. National Trauma Data Bank (NTDB). American College of Surgeons; 2009. (http://www.facs.org/trauma/ntdb/index.html). [September 2009]
22. Medical Expenditure Panel Survey. HC-120: Appendix 3, Clinical Classification Code to ICD-9-CM Code Crosswalk. Agency for Healthcare Research and Quality; 2012. (http://meps.ahrq.gov/mepsweb/data_stats/download_data/pufs/h120/h120_icd9codes.shtml). [September 2012]
23. White RH, Garcia M, Sadeghi B, Tancredi DJ, Zrelak P, Cuny J, Sama P, Gammon H, Schmaltz S, Romano PS. Evaluation of the predictive value of ICD-9-CM coded administrative data for venous thromboembolism in the United States. Thromb Res. 2010; 126:61–67. [PubMed: 20430419]
24. Branchford BR, Gibson E, Manco-Johnson MJ, Goldenberg NA. Sensitivity of discharge diagnosis ICD-9 codes for pediatric venous thromboembolism is greater than specificity, but still suboptimal for surveillance and clinical research. Thromb Res. 2012; 129:662–663. [PubMed: 22104422]
25. Gipson DS, Messer KL, Tran CL, Herreshoff EG, Samuel JP, Massengill SF, Song P, Selewski DT. Inpatient health care utilization in the United States among children, adolescents, and young adults with nephrotic syndrome. Am J Kidney Dis. 2013; 61:910–917. [PubMed: 23434062]
26. Rheault MN, Wei CC, Hains DS, Wang W, Kerlin BA, Smoyer WE. Increasing frequency of acute kidney injury amongst children hospitalized with nephrotic syndrome. Pediatr Nephrol. 2014; 29:139–147. [PubMed: 24037143]
27. Adams MJ, Irish AB, Watts GF, Oostryck R, Dogra GK. Hypercoagulability in chronic kidney disease is associated with coagulation activation but not endothelial function. Thromb Res. 2008; 123:374–380. [PubMed: 18486198]
28. Mannucci PM. Hemostatic drugs. N Engl J Med. 1998; 339:245–253. [PubMed: 9673304]
29. Soylemezoglu O, Duzova A, Yalcinkaya F, Arinsoy T, Suleymanlar G. Chronic renal disease in children aged 5-18 years: a population-based survey in Turkey, the CREDIT-C study. Nephrol Dial Transplant. 2012; 27(Suppl 3):iii146–151. [PubMed: 23115139]
30. Orr NI, McDonald SP, McTaggart S, Henning P, Craig JC. Frequency, etiology and treatment of childhood end-stage kidney disease in Australia and New Zealand. Pediatr Nephrol. 2009; 24:1719–1726. [PubMed: 19373494]
31. Lewis M, Shaw J, Reid C, Evans J, Webb N, Verrier-Jones K. Demography and management of childhood established renal failure in the UK (chapter 13). Nephrol Dial Transplant. 2007; 22(Suppl 7):vii165–175. [PubMed: 17724044]

32. Nogueira PC, Feltran Lde S, Camargo MF, Leao ER, Benninghoven JR, Goncalves NZ, Pereira LA, Sesso RC. Estimated prevalence of childhood end-stage renal disease in the state of Sao Paulo. Rev Assoc Med Bras. 2011; 57:436–441. [PubMed: 21876928]

33. Ocak G, van Stralen KJ, Rosendaal FR, Verduijn M, Ravani P, Palsson R, Leivestad T, Hoitsma AJ, Ferrer-Alamar M, Finne P, De Meester J, Wanner C, Dekker FW, Jager KJ. Mortality due to pulmonary embolism, myocardial infarction, and stroke among incident dialysis patients. J Thromb Haemost. 2012; 10:2484–2493. [PubMed: 22970891]

34. Engelmann B, Massberg S. Thrombosis as an intravascular effector of innate immunity. Nat Rev Immunol. 2013; 13:34–45. [PubMed: 23222502]

35. Heit JA. The epidemiology of venous thromboembolism in the community: implications for prevention and management. J Thromb Thrombolysis. 2006; 21:23–29. [PubMed: 16475038]

Table 1

Diagnostic Classifications and Specific ICD-9-CM Codes

Diagnostic Classifications	Sub-Classifications	ICD-9-CM Codes
Chronic Renal Diseases	Congenital Anomalies	753.0-753.9
	Nephrotic Syndrome	581.0-581.9, 583.1
	Chronic Glomerulonephritis	582.0-582.9
	Chronic Kidney Disease	585.1-585.9
	Dialysis	39.95, V45.11-V45.12, V56.0, V56.8
	Renal Transplantation	55.6, 55.69, V42.0
Venous Thromboembolism	Cerebral Sinus Thrombosis	325
	Pulmonary Embolism	415.1, 415.11, 415.12, 415.9
	Lower Extremity DVT	451.1x, 451.2, 451.81, 453.4x
	Upper Extremity DVT	451.83, 451.84, 451.89
	Renal Vein Thrombosis	453.3
	Other DVT	451.9, 452, 453.0, 453.2, 453.8, 453.9, 572.1
	Thrombectomy	38.07, 38.09
Non-renal CCC[a]		Renal Codes Omitted
Trauma		800.00-904.9, 925.0-929.9, 940.0-959.9
Infections	Septicemia	MEPS Category 2, 38.12, 771.81, 995.1, 995.92
	Pneumonia	MEPS Category 122, 487.0, 482.42
	Urinary Tract Infections	MEPS Category 159
	Cellulitis	MEPS Category 197, 528.3
	Abdominal Infections	MEPS Category 142 & 148, 567.31
	Skeletal Infections	MEPS Category 201

DVT: Deep Venous Thrombosis

[a]CCC: Complex Chronic Conditions – see methods and reference #15 for details, MEPS: Medical Expenditure Panel Survey – see methods and reference #22 for details.

Table 2

Characteristics of children with CRD (N=22,877) with and without VTE, MarketScan® Commercial Databases 2003-2012

	VTE (n=126)	No VTE (n=22,751)	p-value
	n (%)	n (%)	
Age (Y)			
<1	55 (43.7)	10,486 (46.1)	
1-4	12 (9.5)	3,572 (15.7)	
5-9	9 (7.1)	3,367 (14.8)	<0.001
10-14	21 (16.7)	3,062 (13.5)	
15-17	29 (23.0)	2,264 (10.0)	
Mean Age (SD)	6.6 (6.9)	4.6 (5.7)	0.002
Male Gender	71 (56.3)	14,017 (61.6)	0.23
Type of CRD[a]			
Congenital Anomalies	63 (50.0)	19,706 (86.6)	<0.0001
Nephrotic Syndrome	32 (25.4)	1,623 (7.1)	<0.0001
Chronic Glomerulonephritis	10 (7.9)	883 (3.9)	0.03
Chronic Kidney Disease	55 (43.7)	3,041 (13.4)	<0.0001
In-Hospital Mortality	15 (11.9)	214 (0.9)	<0.0001
Co-Occurring Conditions and Procedures			
Non-renal Complex Chronic Conditions	93 (73.8)	4,595 (20.2)	<0.0001
Recent Trauma	17 (13.5)	1,039 (4.6)	<0.0001
Recent Surgery	52 (41.3)	2,172 (9.5)	<0.0001
Recent Infection	43 (34.1)	1,589 (7.0)	<0.0001
Evidence of End Stage Kidney Disease			
Hemodialysis	11 (8.7)	163 (0.7)	<0.0001
Renal Transplant Recipient	9 (7.1)	320 (1.4)	<0.0001

[a] Some patients met criteria for more than a single category.

Table 3

Logistic regression model for association between demographic and clinical characteristics with VTE among children with CRD (N=22,877), MarketScan® Commercial Databases 2003-2012

	Without non-renal CCC (n=18,189)					
	Crude OR	**95% CI**	***p*-value**	**Adjusted[a] OR**	**95% CI**	***p*-value**
Age	1.11	(1.05-1.17)	0.0001	1.09	(1.03-1.15)	0.005
Recent Trauma/Surgery	2.57	(1.16-5.71)	0.02	1.50	(0.64-3.54)	0.35
Recent Infection	4.16	(1.72-10.10)	0.002	3.41	(1.33-8.68)	0.01
Hemodialysis	35.64	(12.21-104.04)	<0.0001	11.39	(3.00-43.21)	0.0003
Renal transplant	10.22	(3.09-33.79)	0.0001	2.69	(0.61-11.83)	0.19
	With non-renal CCC (*n*=4,688)					
Age	1.03	(1.00-1.07)	0.05	1.03	(1.00-1.06)	0.09
Recent Trauma/Surgery	4.17	(2.76-6.31)	<0.0001	3.50	(2.29-5.36)	<.0001
Recent Infection	3.88	(2.54-5.93)	<0.0001	3.32	(2.15-5.14)	<.0001
Hemodialysis	3.94	(1.78-8.75)	0.0007	1.89	(0.77-4.64)	0.17
Renal transplant	2.13	(0.92-4.96)	0.08	1.67	(0.65-4.27)	0.28

CCC: Complex Chronic Condition

[a] Adjusted for all covariates in this table.

Table 4

Healthcare utilization and expenditures for childhood CRD (N=22,877) with and without VTE, MarketScan® Commercial Databases 2003-2012

	VTE		No VTE		*p*-value[a]
	Mean (SD)	**Median**	**Mean (SD)**	**Median**	
Utilization					
Inpatient Admissions (n)	2.47 (1.75)	2	0.62 (0.95)	0	<0.0001
Length of Stay (Days)	62.06 (72.32)	29	5.89 (21.06)	0	<0.0001
Outpatient Visits (n)	30.65 (25.55)	26	11.30 (12.72)	8	<0.0001
Pharmaceutical Claims (n)	18.92 (17.65)	16	5.82 (8.14)	3	<0.0001
Expenditures (USD)					
Inpatient Admissions	$307,328 (540,769)	$79,027	$18,147 (85,891)	$0	<0.0001
Outpatient Visits	$27,511 (55,731)	$14,675	$6,476 (17,126)	$2,951	<0.0001
Pharmaceutical Claims	$3,499 (7,502)	$702	$548 (2,702)	$49	<0.0001
Total Expenditures	$338,338 (544,045)	$126,708	$25,171 (90,792)	$5,332	<0.0001

[a] Wilcoxon rank sum test