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Chronic Kidney Disease in Children: Recent Update

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Abstract: The incidence of end stage of renal disease (ESRD) in US children age 0-19 years is 12.9 per million/year (2012). The economic and social burden of diagnosing, treating and preventing chronic kidney disease (CKD) in children and adults remains substantial. Advances in identifying factors that predict development of CKD and its progression, as well as advances in the management of co-morbid conditions including anemia, cardiovascular disease, growth, mineral and bone disorder, and neurocognitive function are discussed. Despite recent reports from retrospective registry data analysis and multi-center prospective studies which have significantly advanced our knowledge of CKD, and despite advances in the understanding of the pathogenesis, diagnosis and treatment of CKD much work remains to be done to improve the long term outcome of this disease.

1. INTRODUCTION

The economic and societal burden of diagnosing, treating and preventing chronic kidney disease (CKD) in children and adults remains substantial. In the US, the incidence of end stage renal disease (ESRD) in children age 0-19 years was 12.9 per million/year in 2012 compared to 352.6 per million/year in all age groups [1]. Efforts are ongoing to improve early diagnosis, intervention and long term outcome. Recent reports from retrospective registry data analysis and multi-center prospective studies significantly advanced as per our knowledge. In this report we will review recent data from North American Pediatric Renal Trials and Cooperative Studies (NAPRTCS), Kidney Disease Outcomes Quality Initiative (KDOQI), Kidney Disease Improving Global Outcomes (KDIGO), Chronic Kidney Disease in Children (CKID) studies, International Society for Peritoneal Dialysis (ISPD), as well as salient individual studies.

2. SOURCES OF BEST CLINICAL PRACTICE GUIDELINES AND STUDIES

2.1. KDOQI (Kidney Disease Outcomes Quality Initiative)

In 2003, National Kidney Foundation proposed the new definition and staging for CKD in children [2]. Patient with CKD defines as functional or structural damage of the kidney or decrease in glomerular filtration rate (GFR) to less than 60 ml/min/1.73m^2 for more than 3 months. Damage to the kidney can be manifested by abnormalities in blood, urine, imaging test or pathology on the kidney biopsy. Staging of CKD is classified by GFR as shown in Table **1**.

Table 1.   K/DOQI classification of the stages of chronic kidney disease.

Stage	GFR (ml/min/1.73m^2)
1	≥90
2	60-89
3	30-59
4	15-29
5	<15

2.2. KDIGO (Kidney Disease - Improving Global Outcomes)

In 2013, KDIGO published new definition and classification of CKD. CKD is defined as presence of abnormalities of kidney structure or function for more than 3 months. Abnormalities consist of either of albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, or history of kidney transplantation [3]. The KDIGO classification of the stages of chronic kidney disease is shown in Table **2**.

2.3. North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS)

NAPRTCS was initiated in 1987 aimed to collect retrospective data from pediatric renal transplant and dialysis patients. It has expanded to include pediatric CKD patients since 1992. Recent data from NAPRTCS about anemia and growth in pediatric CKD patients will be discussed [4-6].

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Table 2.   KDIGO classification of the stages of chronic kidney disease.

Stage	GFR (ml/min/1.73m^2)	Terms
1	≥90	Normal or high
2	60-89	Mildly decreased
3a	45-59	Mildly to moderately decreased
3b	30-44	Moderately to severed decreased
4	15-29	Severely decreased
5	<15	Kidney failure

2.4. Chronic Kidney Disease in Children Study (CKiD Study)

CKiD study is a prospective observational multi-center study. It was initiated in 2005 by Warady *et al.* [7] The study has enrolled more than 500 pediatric CKD patients aged 1-16 years old who had eGFR between 30-90 ml/min/1.73m^2. Recent data from this cohort has been published and will be discussed later.

2.5. International Society for Peritoneal Dialysis (ISPD)

ISPD is an International society aimed to advance knowledge of peritoneal dialysis and to promote advancement of such knowledge through scientific meetings and publications. In 2012, ISPD developed practice guideline for the management of peritonitis in pediatric patients with peritoneal dialysis [8].

3. ADVANCES IN REFINING MARKERS OF CKD

Glomerular filtration rate (GFR) is the best functional marker representing overall renal function. The ideal method for estimation of GFR is inulin clearance [9]. However; measuring inulin clearance requires constant intravenous infusion of inulin and serial urine collection often through bladder catheterization, in young children. Iohexol and Iothalamate are additional markers that have been used to measure GFR. Single intravenous injection of ^{125}I-iothalamate (m-GFR) with repeated blood sampling is used to calculate with plasma disappearance. The CKiD study used iohexol as another marker for GFR. However, these methods are costly and labor intensive. While iothalamte is, Iohexol to date is not FDA approved to measure GFR in the US. Either method is not ideal method for bedside practice. Over the past few years, several formulas were developed to estimate GFR. These formulas were proven to be cohort specific [10]. Practically, the well-known bedside method for GFR estimation is the calculation of the Schwartz's formula as shown below.

eGFR = k x height (cm)/serum creatinine (mg/dl)

The value of k is 0.45 for term infant, 0.55 for children and adolescent girl and 0.7 for adolescent boy [11-13]. These k values were derived from the study using Jaffe chromogen reaction for measurement of serum creatinine (sCr). Recently, serum creatinine assay has been changed to enzymatic method. The new k value also has been re-

adjusted to 0.413 for patient aged 1-16 year regardless of gender as it has been shown in the CKiD study [14]. Nonetheless, serum creatinine is still not the good marker as its production is related to overall muscle mass of the patients [15]. Thus, estimation of GFR using serum creatinine in CKD patients with malnutrition may be overestimated.

Cystatin C is another endogenous substance that has been proposed to correlate well with renal function. It is freely filtered by glomerular filtration and completely re-absorbed and metabolized by proximal tubules [9]. It is produced not only by muscle cells but by all nucleated cells. Schwartz *et al.* has shown that taking serum cystatin C (sCysC) into the creatinine-based equation as shown below improved GFR estimation with 91% of eGFR within ±30% of mGFR [16].

$$eGFR = 39.8 \text{ x } [height(m)/sCr(mg/dl)]^{0.456} \text{ x } [1.8/sCysC(mg/L)]^{0.418}$$

$$\text{x } [30/BUN(mg/dl)]^{0.079} \text{ x } 1.076^{male} \text{ x } [height(m)/1.4]^{0.179}$$

Nonetheless, we have shown that this formula is not very accurate in estimation of GFR in the transplant population [10].

4. ADVANCES IN IDENTIFYING FACTORS THAT PREDICT DEVELOPMENT OF CKD AND ITS PROGRESSION

4.1. Hypertension

Hypertension is one of the modifiable co-morbid variables that should be evaluated and managed properly in children with CKD. An increase in blood pressure (BP) causes increase intra-glomerular pressure and hyper-filtration that leads to progressive deterioration of renal function [17]. The CKiD study has shown that as high as 64% of pediatric CKD patients required anti-hypertensive medications to control their BP [18]. Furthermore, comparing between the patients with uncontrolled BP and controlled BP, uncontrolled group used significantly less renin-angiotensin antagonists than the controlled group. Some pediatric CKD patients may have normal BP in the clinic but they have elevated BP over the period of 24 hours (masked HT). Samuels *et al.* [19] conducted a cross sectional study about ambulatory blood pressure monitoring (ABPM) pattern in children with CKD. Interestingly, among 332 CKD patients, 35% of patients were found to have masked HT diagnosed by ABPM. Moreover, patients who were on ACE-inhibitor also were 89% more likely to have normal ABPM than those who did not. These patients with masked HT were also found to have left ventricular hypertrophy as much as the patients with confirmed HT [20]. Thus, renin-angiotensin antagonist (ACE-I or ARB) should be considered as the first line regimen in pediatric CKD patients with HT. ABPM also should be used for diagnosis and monitoring of HT in pediatric CKD patients.

The optimal target of BP in pediatric CKD patient has also been studied in the randomized control study "Effect of strict BP control and ACE inhibition on progression of CKD in pediatric patients" also known as "ESCAPE trial" [21]. It has shown that intensified BP control showed a substantial benefit on slowing CKD progression in pediatric patients.

This study enrolled 385 children aged 3-18 years of age with eGFR between 15-80 ml/min/1.73m^2. The patients were randomly assigned to intensified blood pressure control (mean 24 hours BP below 50th percentile) or conventional BP control (mean 24 hours BP between 50th-95th percentiles). The intervention for baseline BP medication in both groups was ramipril 6 mg/m^2/day. The other BP medications except renin-angiotensin antagonists were added in order to achieve BP goal in each group. After 5 year follow up, only 29.9% of the patients in the group of intensified blood-pressure control reached the primary end point (progressed to CKD stage 5 or 50% decline in GFR) compared with 41.7% in the group of conventional BP control (hazard ratio, 0.65 with confidence interval, 0.44 to 0.94; P = 0.02). This reno-protective effect of lowering BP is independent of using renin-angiotensin antagonist. These findings have not yet been validated using casual BP readings. This study further suggests that ABPM confers additional benefit to office BP monitoring that could miss silent HT. The effect of other anti-hypertensive medication that targets the renin-angiotensin system such as angiotensin receptor or renin blocker, on progression of CKD awaits further studies.

4.2. Proteinuria

Proteinuria has been shown to be associated with progression of CKD in adult population. In the pediatric population, there was a randomized control trial of low protein diet on the progression of CKD [22]. There was no benefit of low protein diet to slow progression of CKD course. In multivariate analysis, proteinuria was one of the predictor of CKD progression. As in the adult study, pediatric patients who had glomerular cause of CKD were found to have lower proteinuria associated with treatment of renin-angiotensin antagonist [23]. Moreover, CKiD investigators recently found that two-fold higher level of baseline proteinuria was associated with faster rate of GFR decline about 0.3 ml/min per 1.73 m^2 per year (95% CI, 0.4 to 0.1) in non-glomerular origin of CKD [24]. Thus, treatment with renin-angiotensin antagonist would be essential for pediatric CKD patients with the aim to slow declining of GFR.

Interestingly, Omoloja *et al.* [25] recently reported effect of secondhand smoke exposure in the CKiD study. Investigators found that patients who reported secondhand smoke exposure had higher urine protein/creatinine ratio compared to the group without smoke exposure (0.6 *vs* 0.4, p<0.01). Smoke exposure in this study was confirmed by higher urinary cotinine level (metabolite of nicotine) in the group with smoke exposure. The pathogenesis of smoke exposure and deterioration of renal function remains unclear. Jaimes *et al.* [26] discovered that nicotine in the tobacco activates proliferation of mesangial cell and mesangial matrix *via* nicotinic acetylcholine receptors. Nicotine also increases production of reactive oxygen species and also may lead to inflammation of mesangial matrix [26].

4.3. Oxidative Stress

Oxidative stress is an imbalance in the reactive oxygen species (ROS) production/degradation ratio. Under normal conditions, ROS (which include various compounds such as superoxide anions, hydrogen peroxide, and hydroxylradical) can accelerate renal injury progression. Inflammatory markers such as C-reactive protein and cytokines increase with renal function deterioration suggesting that CKD is a low-grade inflammatory process. In fact, inflammation facilitates renal function deterioration. Several factors can be involved in triggering the inflammatory process including oxidative stress. Statin administration is accompanied by risk reduction in all major vascular events in high risk CKD patients. These beneficial effects seem to be a consequence of their hypolipidemic as well as their direct effect [27].

4.4. Low Birth Weight, Prematurity and Risk for Progression of CKD

The metanephros gives rise to definitive kidneys which continue to develop until 36 weeks of gestation. Although glomerulogenesis still occurs in premature infant, many of the glomeruli are abnormal such as cystic dilatation [28]. Another study by Mañalich *et al.* [29] showed that low nephron number was directly correlated with birth weight and inversely correlated with glomerular size. These infants have low nephron number and abnormal glomeruli leading to hyper-filtration of the remaining glomeruli, proteinuria and CKD later in life [30].

5. Advances in the Management of Co-morbid Conditions

5.1. Anemia

Anemia is a common co-morbid condition in pediatric CKD. Report from NAPRTCS in 2010 has found that as high as 73% of children with CKD stage 3, 87% of CKD stage 4, and over 93% of CKD stage 5 were anemic. (4) Anemia has been shown to be associated with risk of hospital admission. Staples *et al.* [31] investigated 2,779 pediatric CKD patients from NAPRTCS and found that patients with anemia (hematocrit <33%) were 55% more likely to be hospitalized that non-anemic patients. The causes of anemia in pediatric CKD patients include iron deficiency, blood loss, erythropoietin deficiency and anemia of chronic disease. These factors have varying effects at the particular stage of CKD. Iron deficiency is more prominent cause at the early stage of CKD but erythropoietin deficiency is major cause at the late stage. Baracco *et al.* [32] investigated 50 pediatric CKD patients and found that 25% of patients with stage 2 and 55.5% of patients with CKD stage 3 had iron deficiency defined by low transferrin saturation (<20%) and low serum ferritin for age. Thus, pediatric CKD patients with anemia should be worked up for iron deficiency before starting erythropoietin stimulating agent (ESA).

In 2013, KDIGO published the new recommendation about target hemoglobin in pediatric CKD patients. Anemia is defined as hemoglobin concentration of <11.0 g/dl in children 0.5-5 years, <11.5 g/dl in children 5-12 years, and <12.0 g/dl in children 12-15 years [3]. Generally, pediatric CKD patients require larger starting dose of ESA (200-300 units/kg/week) comparing to adult CKD patients (100-150 units/kg/week) [31]. Over treatment of ESA with higher level of hemoglobin than 13 g/dl is not recommended as it

has been shown to increase cardiovascular events in the adult population. However, no pediatric data has been reported [33]. Patients who require higher dose of ESA should be investigated for blood loss, iron deficiency, secondary hyperparathyroidism, inflammation from original disease etc. Vitamin D deficiency also needs to be in the differential diagnosis as it has been shown that treatment of vitamin D deficiency decreased the dosages of ESA in pediatric CKD patients [34,35].

Hepcidin, an acute phase protein made from liver, has been recently discovered and found to be elevated in pediatric CKD patients. High hepcidin level inhibits iron absorption from the intestine and impairs release from body storage through the inhibition of ferroportin [36]. Meredith *et al.* [37] has reported from CKiD cohort that higher hepcidin level is associated with decreased hemoglobin especially in those with low GFR. Although, serum hepcidin has been found to decrease with hemodialysis or treatment with erythropoietin stimulating agent (ESA), treatment effect of lowering hepcidin on improvement of anemia in pediatric patients has never been reported [38,39]. Nonetheless, hepcidin is currently the prospective target for the treatment of anemia in CKD patients as it has been shown in the animal model that the LDN-193189 (hepcidin lowering agent) lowered hepatic hepcidin mRNA and mobilized iron storage into plasma and increased hemoglobin content of reticulocytes in the adenine-induced CKD rats [40].

Replenishing iron stores to a transferrin saturation of 20-30% is desirable. The objective of iron management is to maintain Hemoglobin in the 11-12 g/dl range. Due to relative Fe malabsorption in CKD, oral iron may not be sufficient to achieve this goal and one may have to resort to parentral iron supplementation. Recently, iron formulations (Ferric Citrate and Sucroferric Oxyhydroxide) with the dual purpose of replenishing iron stores and phosphate binding became available. Original studies showed that ferric citrate is superior in delivering iron but patients could run the risk of increased aluminum absorption and toxicity due to the citrate [41].

5.2. Cardiovascular Disease

Children with CKD are at an increased risk to develop cardiovascular disease [42]. Parekh *et al.* [43] has shown that pediatric patient with CKD who were on dialysis had cardiac death rate as high as 20 per 1,000 patient-year. Increase in sympathetic activity has been associated with increase in cardiovascular risk as shown in the adult patient with CKD [44]. The nature of cardiovascular death in children is different than that in adults. In adults, coronary artery disease and congestive heart failure are the leading causes, while in children, cardiomyopathy and arrhythmia are most prevalent [45]. Recently, the CKiD study found that pediatric CKD patients with HT also had decreased heart rate variability and increased BP variability. Both findings are signs of sympathetic nervous system over-activity [46]. Dyslipidemia is also a known risk factor of cardiovascular disease. Saland *et al.* [47] has shown that 45% of pediatric CKD patients had dyslipidemia. Low GFR, overweight and nephrotic proteinuria were significantly associated with dyslipidemia. Carotid intima-media (cIMT) thickness is another predictor of cardiovascular events. Brady *et al.* [48] has found that

there is greater cIMT in pediatric patients with CKD than with healthy controls. In multivariate analysis, dyslipidemia and HT were significantly associated with greater cIMT [48]. Thus, CKiD investigators recommend screening pediatric patients with CKD for dyslipidemia especially those who have high BMI, lower GFR and nephrotic proteinuria [49].

5.3. Growth

Poor linear growth is a well described and discernable complication of CKD. The etiology of poor growth is multifactorial. Growth hormone-pituitary axis is often maintained. The main issue in later stages of CKD is the low bioavailability of insulin-like growth factor 1 (IGF-1) due to decreased insulin-like growth factor binding protein 3 (IGF-BP3) and increase in other carrier proteins. Other factors contributing to poor growth in children with CKD include protein energy wasting, metabolic acidosis, malnutrition, renal osteodystrophy, and medications such as steroids [49,50]. It should be emphasized that in CKD stage 3 through CKD stage 5, poor linear growth occurs because of growth hormone resistance rather than deficiency. Some proposed mechanisms of growth hormone resistance include reduced density of growth hormone receptors in target organs, impaired growth hormone-activated post-receptor Janus kinase/signal transducer and activator of transcription signaling, and reduced levels of free IGF-1 due to increased inhibitory IGF-binding proteins [50].

In 2006, Seikaly *et al.* [51] evaluated the NAPRTCS enrollment registry data of 5,615 children aged birth to 21 years to correlate factors associated with short stature in children with CKD. They found that older patients (>12 years), those with GFR >50 ml/min/1.73 m^2, black patients and patients with focal segmental glomerulosclerosis were at lower risk of being short at entry. Anemia (hematocrit below 33%) was an independent risk factor for short stature. Acidosis, serum phosphorous, calcium, albumin and PTH at registration were poor predictors of short stature.

Greenbaum *et al.* [52] identified low birth weight (<2,500 grams) and small for gestation age (birth weight <10th percentile for gestational age) as novel risk factors for short stature and lower weight percentiles in children with mild to moderate CKD independent of kidney function from the CKiD cohort. In another study from the CKiD cohort, Rodig *et al.* [53] found that girls with non-glomerular CKD were the shortest and compared to those with a serum bicarbonate (HCO$_3$) level of $\geq$ 22 mEq/L, children with HCO$_3$ of <18 mEq/L had a height standard deviation score (SDS) that was on average 0.67 lower. Only 23% of children with a height SDS of $\leq$ -1.88 were prescribed growth hormone therapy [53]. Pharmacological doses of recombinant human growth hormone (rhGH) can improve linear growth. Children should have hip x-rays and a wrist bone age prior to initiation of therapy. From the NAPRTCS registry, it was shown that long term rhGH therapy enhances height velocity for at least 2.5 years, was well tolerated without an increase in the rate of progression of CKD, and had no effect on BMI [5]. Mahan *et al.* [54] constructed growth curves for assessing a patient's first year of growth response from Genentech's National Cooperative Growth Study and proposed that a height velocity below the mean -1SD was an inadequate response.

KDOQI recommends a dose of rhGH of 0.05 mg/kg/day or 30 IU/m²/week as a subcutaneous injection with close monitoring of calcium, phosphorus, PTH, and alkaline phosphatase. In a recent study by Akchurin *et al.* [55] examining medication adherence and growth; it was found that self-reported non adherence to rhGH was associated with poorer growth velocity in children with CKD.

5.4. CKD - Mineral and Bone Disorder

CKD causes disordered regulation of mineral metabolism with subsequent alterations in skeletal and cardiovascular biology which is now referred to as CKD - mineral and bone disorder (CKD-MBD) [56]. Hyperparathyroidism in advanced CKD is secondary to the deficiency of 1, 25 - dihydroxyvitamin D (1,25 (OH)$_2$D) combined with hyperphosphatemia leading to abnormal bone turnover and mineralization. Fibroblast growth factor 23 (FGF23) is a bone derived circulating hormone that inhibits renal phosphate reabsorption and suppresses the synthesis of 1,25 (OH)$_2$D thereby acting as a phosphaturic hormone. Circulating FGF23 was significantly elevated in patients with CKD and its concentration correlated with renal creatinine clearance [57]. FGF23 normalizes serum phosphate and decreases 1,25 (OH)$_2$D levels in early stage CKD, and suggests a pathological sequence of events for the development of secondary hyperparathyroidism triggered by increased FGF23, followed by a reduction of 1,25 (OH)$_2$D and calcium levels, thereby increasing parathyroid hormone secretion [58]. Portale *et al.* [59] found that serum FGF23 is the earliest detectable abnormality in mineral metabolism, and levels are highest in glomerular diseases. Serum phosphorus levels, adjusted for age, were significantly lower at GFR of 60-69 ml/min per 1.73 m² than higher GFR, but thereafter they became higher in parallel with fibroblast growth factor 23 as GFR declined [59].

Recent studies have shown that induction of vascular calcification begins in early normophosphatemic CKD by the reduction of vascular Klotho and increased FGF23 secretion [60]. Studies of the vasculature in CKD indicate the presence of osteoblastic differentiation in the vessel wall suggesting that uremic serum and high phosphate stimulate osteoblastic differentiation of calcifying vascular cells and vascular smooth muscle cells [61]. Vascular calcifications occurring in the uremic milieu develop primarily in the tunica media contrary to the calcifications of athleroslerotic plaques that develop with age in the vascular intima [62] Data from Faul *et al.* [63] demonstrated that chronically elevated FGF23 levels have a direct effect on the pathogenesis of left ventricular hypertrophy through a Klotho independent mechanism. There is ongoing research whether FGF-23 is a modifiable risk factor that can be translated into an earlier clinical management of disordered mineral metabolism in CKD [64].

5.5. Neurocognitive Aspect

The vulnerability of the central nervous system to atrophy, delayed conduction velocity on electrophysiology studies, and specific cognitive deficits has been identified in CKD patients [65]. A report of baseline neurocognitive function in the CKiD cohort revealed 21% to 40% of participants scored at least one standard deviation below the normative data on measures of intelligence quotient, academic achievement, attention regulation, and executive functioning [66]. Higher iohexol-based GFR predicted a lesser risk for poor performance on measures of executive function [66]. Participants having elevated proteinuria (urine protein/creatinine >2) scored lower on verbal IQ, full-scale IQ, and attention variability than those without elevated proteinuria [66].

Children with CKD perform less well on standardized tests of intelligence and academic achievement than their unaffected siblings [67]. Mendley *et al.* compared test performance across the range of estimated GFR and duration of CKD with relevant covariates including maternal education, household income, IQ, BP, and preterm birth. It was found that in a population with mild-to-moderate CKD, the duration of disease rather than estimated GFR was associated with impaired attention regulation and inhibitory control [68].

With ongoing pharmacological advances, children with CKD are surviving into adulthood. There has been an increase in the development and utilization of pediatric health-related QOL (HRQOL) measures as a tool to evaluate healthcare services and as an effort to improve patient health and well-being [69]. In the first study to assess depression in pediatric CKD patients living in the USA and the largest study to identify the clinical and demographic factors associated with depression in this patient population, Kogon *et al.* [70] found a high proportion of children with CKD are depressed and that those with a diagnosis of kidney disease for >3 years and those with CKD stage 3 may be particularly susceptible.

CONCLUSION

Despite recent advances in the understanding of the pathogenesis of CKD and its management, all these findings and recent advancement remain in working progress as much more needs to be elucidated.

ABBREVIATIONS

ABPM   =   Ambulatory blood pressure monitoring

BP   =   Blood pressure

CKD   =   Chronic kidney disease

CKiD   =   Chronic Kidney Disease in Children

ESA   =   Erythropoietin stimulating agent

ESRD   =   End stage renal disease

GFR   =   Glomerular filtration rate

HT   =   Hypertension

ISPD   =   International Society for Peritoneal Dialysis

KDIGO   =   Kidney Disease Improving Global Outcomes

KDOQI   =   Kidney Disease Outcomes Quality Initiative

NAPRTCS   =   North American Pediatric Renal Trials and Cooperative Studies Kidney

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

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