FEATURE

How have the past 5 years of research changed clinical practice in paediatric nephrology?

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Arch Dis Child 2007;**92**:357–361. doi: 10.1136/adc.2005.086363

Clinical practice in paediatric nephrology is continuously evolving to mirror the research output of the 21st century. The management of antenatally diagnosed renal anomalies, urinary tract infections, nephrotic syndrome and hypertension is becoming more evidence based. Obesity and related hypertension is being targeted at primary and secondary care. The evolving field of molecular and cytogenetics is discovering genes that are facilitating clinicians and families with prenatal diagnoses and understanding of disease processes. The progression of chronic kidney disease in childhood to end-stage renal failure (ESRF) can be delayed using medical treatment to reduce proteinuria and treat hypertension. Pre-emptive living-related renal transplantation has become the treatment of choice for children with ESRF, thereby reducing the morbidity and mortality associated with peritoneal and haemodialysis. Although peritoneal dialysis, which is performed in the patient's home, is the preferred modality for children for whom there is no living or deceased donor for transplantation, home nocturnal haemodialysis is becoming a feasible option. Imaging modalities with the use of magnetic resonance and computerised tomography are continuously improving. As mortality for renal and vasculitic diseases improves, the gauntlet is now thrown down to reduce morbidity with secondary prevention of longer-term complications such as atherosclerosis and hyperlipidaemia. Clinical and drug trials in the fields of hypertension, nephrotic syndrome, systemic lupus erythematosus, vasculitis and transplantation are producing more effective treatments, thereby reducing the morbidity resulting from the disease processes and the side effects of drugs.

past 5 years has been extensive in the field of paediatric nephrology, with an increased incidence of systematic reviews and meta-analyses challenging current beliefs, and genetic testing making rapid diagnosis for patients, families and clinicians involved, which sometimes influences clinical decision making with respect to therapeutic interventions. In this article, I will highlight only some of the more relevant articles in the published literature that have affected clinical practice of the general paediatric and paediatric nephrology communities.

ANTENATAL HYDRONEPHROSIS

There has been a change in view over the past 5 years to reduce the investigation of children who were previously labelled as having renal tract abnormalities, particularly with reference to antenatally detected hydronephrosis and urinary tract infections (UTI).

Antenatal hydronephrosis is defined as dilatation of the renal pelvis and/or calyces and is the most frequently detected antenatal abnormality with an incidence of 0.5–5%, although most of the affected fetuses have no associated renal abnormality and the screening programme induces parental anxiety. Gestational age and degree of dilatation are the most important aspects to consider. The clinical problem is to know what postnatal investigations are necessary when there is antenatal diagnosis of hydronephrosis, so that structural abnormalities (such as posterior urethral valves or pelvi-ureteric or vesico-ureteric junction obstruction) are diagnosed. Many authors view that it is important to diagnose vesico-ureteric (VUR) reflux, although moderate antenatal renal pelvic dilatation (5–15 mm), which suggests vesico-ureteric reflux, is not known to predict renal scarring.¹

A recent meta-analysis of 25 articles (25% of which were published within the past 5 years) showed improvement in 98% of patients, with grades 1–2 hydronephrosis (Society of Fetal Urology grades 1–2 correspond to anterior posterior pelvic diameter <12 mm) strongly suggesting that a mild degree of pelviectasis is a relatively benign self-limiting condition with resolution or improvement across all studies. However, severe degrees of hydronephrosis (Society of Fetal Urology grades 3–4 with anterior posterior pelvic

Clinical research influences our clinical practice as paediatricians. Although the practicalities of embarking on research are becoming more bureaucratic, the foundation of the Medicines for Children Research Network with local infrastructure will continue to increase the number of randomised controlled trials in paediatric practice, thereby guiding therapeutic regimens. Therefore, those clinical questions will be answered (to the high standards attained by our paediatric oncological colleagues) and clinical practice will become more evidence based, instead of the continued extrapolation of data produced from research in adult patients. Research in the

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Accepted 31 October 2006

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; CRF, chronic renal failure; ESRF, end-stage renal failure; PKD, polycystic kidney disease; RRT, renal replacement therapy; SLE, systemic lupus erythematosus; UTI, urinary tract infections; VUR, vesico-ureteric reflux

diameter >12 mm) were more variable across studies requiring further investigation, substantiating the conclusion that the outcomes for more severe degrees of hydronephrosis are largely uncertain. However, before defining management protocols, we still need a large controlled trial with a thorough examination of all possible end points to conclusively determine the outcome of patients with more severe pelviectasis and to determine the most appropriate means of reporting these outcomes.² These findings were echoed in another recent meta-analysis which also found that there is a considerable risk of postnatal pathology with moderate and severe antenatal hydronephrosis, indicating that comprehensive postnatal diagnostic management should be performed.³

URINARY TRACT INFECTIONS

The diagnosis, management and investigation of UTI are hotly debated topics. After the consultation of the draft guideline, the National Institute for Health and Clinical Excellence will publish the clinical guideline in March 2007 on the investigation and long-term management of children up to 8 years with UTI (current information can be obtained from <http://www.nice.org.uk/page.aspx?o=guidelines.inprogress.urinarytract>), which should unify protocols in paediatric units throughout the UK.

Although all paediatricians know how and when to diagnose UTI, the practicalities of collecting urine samples can be complicated. Furthermore, the myth surrounding the investigation of children with UTI and resultant parenchymal damage in detecting or excluding VUR no longer exists. Even so, a randomised controlled trial of prophylactic antibiotics after acute pyelonephritis showed that mild and moderate VUR does not increase the incidence of UTI, pyelonephritis or renal scarring.⁴ A Cochrane review with meta-analyses of randomised controlled trials highlighted the uncertainty of whether the identification and treatment of children with VUR conferred clinically important benefit. Assuming a UTI rate of 20% for children with VUR taking antibiotics for 5 years, nine reimplantations would be required to prevent one febrile UTI, with no reduction in the number of children developing any UTI or renal damage.^{5, 6}

The main clinical objective is to prevent the long-term complications of developing hypertension, deterioration in renal function and/or pregnancy complications. However, epidemiological studies from Sweden have shown a reduction in chronic renal failure (CRF) secondary to pyelonephritis with VUR from 5% to 0%,^{7, 8} which may be due to differences in terminology. However, childhood UTI is common, the occurrence of CRF is rare and the likelihood of acute pyelonephritis causing renal damage progressing to CRF is also rare. The only large population-based epidemiological study was from an original cohort of 1221 children with UTI.⁹ There was a low risk of hypertension 16–26 years after the first UTI in children with no blood pressure difference and only 9% (5 of 53 children) with scarred kidneys and 6% (3 of 47 children) without renal scarring became hypertensive. The median glomerular filtration rate two decades after the first recognised UTI in childhood was normal in both those with and without scarring.¹⁰ The view that a renal ultrasound performed at the time of acute illness in childhood UTI is of limited value¹¹ is not easily extrapolated to the UK population. This is because third-trimester antenatal ultrasounds, which can exclude significant renal pathology, are not current routine obstetric practice in many centres.

NEPHROTIC SYNDROME

The risk–benefit ratio of intervention in paediatric nephrology is exemplified by the initial presentation of childhood nephrotic syndrome, which should be treated more aggressively to

minimise relapses, although longer-term corticosteroid treatment is associated with side effects. A meta-analysis by the Cochrane Database of 19 randomised controlled trials has shown that children in their first episode of steroid-sensitive nephrotic syndrome should be treated for at least 3 months, with an increase in benefit being shown for up to 7 months of treatment.¹² However, a UK double-blind placebo-controlled trial, which has been endorsed by the British Association of Paediatric Nephrology, will answer this question comparing standard prednisolone treatment (60 mg/m²/day for 4 weeks and then 40 mg/m² on alternate days) with a prolonged course (60 mg/m²/day for 4 weeks followed by tapering alternate-day treatment over a total of 12 weeks). Information on this trial and how to recruit patients can be found on the Clinical Trials website at <http://www.clinicaltrials.gov> and searching under the trial identifier of NCT 00308321.

The long-term outcome of childhood-onset steroid-sensitive nephrotic syndrome is good, with normal growth and renal function and an overall low morbidity from common adulthood relapses.¹³ Although the optimal treatment for steroid-resistant nephrotic syndrome is still unknown,¹⁴ paediatric nephrology practice is changing with recent genetic data. Children with steroid-resistant nephrotic syndrome who are homozygous or compound heterozygous for NPHS2 (podocin) mutations do not respond to standard steroid treatment of nephrotic syndrome and have a reduced risk for recurrence of nephrotic syndrome (with focal segmental glomerulosclerosis) after renal transplantation.¹⁵ Podocin mutational analysis is now available through the UK Genetic Testing Network for all children with nephrotic syndrome that is resistant to treatment with steroids, presents in the first 3 months of life or has a histological picture of focal segmental glomerulosclerosis on renal biopsy.

Children with nephrotic syndrome have easily recognised hyperlipidaemia, and lowering cholesterol levels during childhood may reduce the risk for atherosclerotic changes and thus benefit certain patients with nephrotic syndrome. Although an extensive amount of data is available in adult nephrotic syndrome, which shows its efficacy in reducing lipid levels and mortality, there is still a lack of evidence in the paediatric literature. However, children unable to obtain nephrotic syndrome remission and remaining nephrotic may benefit from a reduction of their lipid levels, although there are only small uncontrolled studies showing short-term safety and efficacy of these agents in children. In adults with nephrotic syndrome treated with hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), their total plasma cholesterol is reduced by 22–39%, low-density lipoprotein cholesterol by 27–47% and total plasma triglycerides by 13–38%.^{16, 17} Their safety and efficacy over years and extrapolation to other renal conditions (including CRF, ESRF, hypertension, vasculitis and systemic lupus erythematosus (SLE)) are required with intervention studies (such as the current ongoing trial called Atherosclerosis Prevention in Pediatric Lupus Erythematosus, which is a multicentre, randomised controlled trial testing the efficacy of statins in preventing premature atherosclerosis in children and adolescents with SLE).¹⁸

RENAL GENETICS

The most common cause of ESRF is renal dysplasia, which accounts for 23% of the current UK paediatric population requiring dialysis or transplantation. We now screen increasing numbers of families for known genetic mutations, which can also assist in prenatal genetic diagnosis.¹⁹ Branchio-oto-renal syndrome, caused by mutations in the *EYA1* gene, is an autosomal dominant disorder characterised by the association of branchial cysts or fistulae, external ear malformation and/or

preauricular pits, hearing loss and renal anomalies, including renal dysplasia and agenesis. The renal-coloboma syndrome caused by *PAX-2* mutations is a rare autosomal dominant syndrome that involves optic nerve colobomas and renal anomalies.²⁰

The link between renal cysts and the development of diabetes mellitus has been proved with the identification of hepatocyte nuclear factor-1 β mutations, which have also been implicated in other cystic diseases such as glomerulocystic kidney disease.^{21–22} *OFD1* is the gene responsible for the oral-facial-digital syndrome type 1, another cause of inherited cystic renal disease.²³

Ciliary defects can lead to a broader set of developmental and adult phenotypes, with mutations in ciliary proteins now associated with Bardet–Biedl syndrome,²⁴ Alstrom syndrome, Meckel–Gruber syndrome and nephronophthisis. Juvenile nephronophthisis is the most frequent genetic cause for ESRF in the first two decades of life, with an imprecise clinical and radiological diagnosis. This recessive cystic kidney disease can now be detected by genetic mutational analysis (including *NPHP1*, 2, 3 and 4 genes).²⁵

Polycystic kidney disease (PKD) may only account for 3% of paediatric patients with ESRF in the UK,¹⁹ as most children requiring RRT are affected with autosomal recessive PKD. PKD is the primary renal disease of 9% of all adults requiring RRT, as the requirement for RRT in autosomal dominant PKD is usually in adulthood. The genes and their protein products involved in cystic diseases of kidney disorders have been identified, which provide key insights into the cellular processes that underlie cyst development and mediate disease progression, such as the proteins implicated in pathogenesis localised to the cilia/centrosome complex.²⁶ Unravelling the spatial and functional relationship between these cystoproteins and the cilia/centrosome complex will undoubtedly provide a better understanding of the pathogenesis of cystic diseases. As our understanding of renal genetics in collaboration with renal development^{27–28} continues to improve, we will potentially be able to offer windows for therapeutic intervention in the next decade.²⁹

Genetic advances have also been made in the context of renal tubular disorders, including Bartter syndrome,³⁰ Gitelman's syndromes,³¹ Dent's disease³² and renal tubular acidosis.³³

PROGNOSIS AND PROGRESSION OF RENAL DISEASE

Systematic reviews have provided new information on the prognosis for certain diseases such as Henoch–Schönlein purpura and multicystic kidney diseases, which has allowed us to change patient follow-up and be more reassuring to patients.

A systematic review found no risk of long-term renal impairment in children with Henoch–Schönlein purpura with normal or minimal urinary findings without nephritic or nephrotic syndrome or renal failure.³⁴ If urine analysis is normal at presentation, the testing should be continued for 6 months after the last recrudescence of symptoms (such as rash) with no need to follow-up after the first 6 months for those whose urine analysis remains normal. If there is renal disease at presentation, then the risk for progression to ESRF is associated with increasing mean proteinuria levels during follow-up rather than presentation features of decreased renal function, severe proteinuria, hypertension and/or crescentic glomerulonephritis.³⁵

A recent systematic review on multicystic dysplastic kidneys has shown that the risk of developing Wilms's tumour or hypertension is very low; therefore, routine nephrectomy (which is not without its risks) is not warranted.^{36–37}

A systematic review revealed that the use of angiotensin-converting enzyme inhibitors (ACEi) to treat the microalbumi-

nuria of normotensive adults with diabetes mellitus reduced both albuminuria and the rate of decline of glomerular filtration rate.^{38–39} Extrapolation of these data has now shown that the use of ACEi is both safe and effective, with evidence of prevention of progression of CRF in children. The blood pressure lowering and antiproteinuric effects of ACEi are greatest in children with CRF who have the most severe hypertension and proteinuria.⁴⁰ A trial of angiotensin II type 1 receptor blockers and ACEi is justified in selected patients if blood pressure and/or proteinuria cannot adequately be lowered by ACEi or angiotensin II type 1 receptor blockers alone.^{40–41}

HYPERTENSION AND OBESITY-RELATED HYPERTENSION

Considerable advances have been made in the detection, evaluation and management of hypertension as well as in obesity-related hypertension in children and adolescents. Clinically, we have moved from an era of mercury sphygmomanometers to newer devices, although the gold standard in confirming or refuting the diagnosis of hypertension is by undertaking 24-h ambulatory blood pressure monitoring,⁴² and if present, searching for evidence of end-organ damage. Although some evidence exists in the literature that obesity limited to childhood has little effect on adult outcomes, persistent obesity is associated with socioeconomic and psychosocial problems, and there is a global focus on preventing the persistence of obesity from childhood into adulthood.⁴³ Childhood obesity contributes to the development of adult obesity and subsequent cardiovascular disease, with morbid obesity, arterial hypertension, subclinical inflammation and low physical fitness forming a risk profile associated with the risk of early atherosclerosis in these children.⁴⁴ For paediatric nephrologists, this is clinically relevant as children with CRF and ESRF are at an increased risk of developing atherosclerosis, arterial stiffness and vascular calcification independent of hypertension, resulting in increased cardiovascular morbidity and mortality.^{45–47}

The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents updated clinicians on blood pressure in children and provided recommendations for the management of hypertension based on available evidence and consensus expert opinion of the working group when evidence was lacking.⁴⁸ The additional data from the 1999–2000 National Health and Nutrition Examination Survey were added to the childhood blood pressure database, and the blood pressure data were re-examined with revised blood pressure tables including the 50th, 90th, 95th and 99th centiles by sex, age and height centiles. Hypertension in children and adolescents continues to be defined as systolic and/or diastolic blood pressures, that are, on repeated measurement, ≥ 95 th centile. However, a change in clinical management is that blood pressure between the 90th and 95th centiles in childhood had been designated “high normal” to be consistent with the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. This level of blood pressure is now termed “prehypertensive” and is an indication for continued monitoring and lifestyle modifications.⁴⁹ This adds an additional resource requirement for the National Health Service as the implication is that 10% of all children in the UK require blood pressure monitoring, which may occur at primary, secondary or tertiary care services (depending on age of the child, degree of hypertension and local care providers).

The optimal treatment of hypertension is unknown, although there is little debate that ACEi should be used in children with CRF and proteinuria. In the absence of renal dysfunction, proteinuria and renovascular disease, extrapolation from the

adult studies may not be relevant. The Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm is the multicentre randomised controlled trial in adults in which the amlodipine-based regimen prevented more major cardiovascular events and induced less diabetes than the atenolol-based regimen.⁵⁰ However, there is emerging evidence that this applied to the older adults in this study.

RENAL REPLACEMENT THERAPY

The optimal management for RRT is renal transplantation, with half the cardiovascular mortality compared with children and young adults undergoing dialysis;⁵¹ the gold standard treatment is for pre-emptive live-related renal transplantation, which has excellent outcomes.^{52–53} Renal transplantation became the accepted treatment for ESRF in children in the 1970s and the outcome of paediatric renal transplantation continues to improve, although adolescent recipients have a poorer prognosis, probably partly due to lack of adherence with immunosuppressive regimens.⁵⁴ Some forms of living donation (such as paired donation, altruistic, non-directed donation and blood group incompatible donor–recipient pairs) may become routine practice in the UK after consideration by the Human Tissue Authority, because of the Human Tissue Act (2004) coming into effect on 1 September 2006.

The immunosuppression used in renal transplantation has evolved over the past two decades. Many paediatric patients in the UK have been entered in a series of randomised controlled trials in renal transplantation, which have led to changes in practice. The data from these trials have been used to provide evidence-based guidelines on immunosuppressive treatment for renal transplantation in children and adolescents, published by the National Institute for Health and Clinical Excellence in March 2006 (the document is available free at <http://www.nice.org.uk/download.aspx?o=295739>).

Ciclosporin, a calcineurin inhibitor, was introduced in most clinical immunosuppressive protocols in the 1980s. However, another calcineurin inhibitor, tacrolimus, is superior to ciclosporin in improving graft survival (by 2%) and preventing acute rejection (by 12%) after kidney transplantation. The cosmetic side-effect profile is better, but it increases neurological and gastrointestinal side effects and also post-transplant insulin-dependent diabetes mellitus (by 5%).^{55–58}

To improve outcomes in renal transplantation, monoclonal antibodies (such as basiliximab and daclizumab) have been increasingly used, especially to avoid the side effects of corticosteroids by adopting steroid-free or early steroid-withdrawal protocols.^{59–60} The balance in paediatric renal transplantation is between that of rejection (from under-immunosuppression) to infection (from over-immunosuppression), with the risk of developing Epstein–Barr virus driven post-transplant lymphoproliferative disorder.⁶¹ In adults and children, B cell depletion with rituximab, a chimeric monoclonal IgG1- κ antibody, has been effective in post-transplant lymphoproliferative disorder,⁶² and its role has been extended to include autoimmune diseases from haemolytic anaemia to SLE in adults and children.^{63–64}

When transplantation is not feasible (as in the case of new presentation of ESRF or no identified living or deceased renal transplantation donor), peritoneal dialysis is usually the favoured modality of RRT for ESRF in paediatric nephrology practice in the UK as haemodialysis usually requires 4-h thrice-weekly in-hospital treatment sessions. However, home nocturnal haemodialysis is being performed in the UK in adult patients. Although this is not yet available for children, it is feasible in selected paediatric patients in North America, allowing free dietary and fluid intake, and reduced drugs with improved patient well-being.^{65–66} However, the burden on the

family is substantial, and nocturnal haemodialysis requires the support of a dedicated multidisciplinary team.

IMAGING IN PAEDIATRIC NEPHROLOGY

Magnetic resonance urography may replace conventional urological investigations, especially in children with urinary tract dilatation.^{67–68} Although conventional (intra-arterial digital subtraction) angiography is the gold standard for native and transplant renovascular disease, non-invasive techniques such as magnetic resonance angiography, computed tomographic angiography and colour-aided duplex ultrasonography are promising alternatives that also allow functional characterisation of renal artery stenosis,^{69–70} with therapeutic success in renovascular hypertension using the interventional radiological technique of percutaneous transluminal angioplasty.⁷¹ However, intra-renal disease (which may be a secondary phenomenon) can only be reliably detected on conventional digital subtraction angiography.

CONCLUSIONS

Basic science and clinical research in the field of paediatric nephrology is continuing to expand dramatically, with an increased understanding of renal development and the aetio-pathogenesis of disease in the context of molecular and cytogenetics. However, the challenges for the next 5 years are to increase evidence-based practice with an increase in collaboration throughout the world with multicentre randomised controlled intervention trials.

Competing interests: None declared.

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