S01.1

NOCTURNAL ENURESIS: Epidemiology

Wendy F Bower

The prevalence of nocturnal enuresis at age 7 years is frequently reported to be 7-10%, however this figure will rank children who wet once per month on par with those who have nightly episodes. The natural history of nocturnal enuresis suggests that primary symptoms remit with age into early adolescence. An annual cure rate of 14% per year has long been accepted, however this is misleading in that it does not describe the severity of the problem in children with persisting enuresis. Investigation of nocturnal enuresis in adulthood has revealed that from the age of 16 onward, prevalence remains constant at around 2.3%, and the majority of sufferers wet more than 3 nights per week. Thus from adolescence onward the severity of the problem is more debilitating than in childhood, and there is a poor expectation of spontaneous cure. Recent findings indicate that underlying urinary tract pathology (OAB, functional bladder outlet obstruction, congenital obstructive lesions) is associated with up to 93% of cases of enuresis in adulthood.
Children with nocturnal enuresis can be classified into one of three groups, allowing each child a treatment approach that targets their underlying pathology. Polyuria will be proven when there is a monosymptomatic presentation, normal FVC parameters, no bladder wall changes and normal bladder storage and emptying. These children are best managed with synthetic anti-diuretic hormone, the assumption being that they have deranged circadian rhythm of ADH, require supranormal levels or have low endogenous secretion.
Underlying bladder dysfunction will be suggested by a small functional bladder capacity revealed on ultrasound, and confirmed functionally by the FVC. The bladder will empty appropriately and with a normal flow, however will commonly display hypertrophy. Specific urodynamic findings in this group may include moderate or severe overactive bladder, sphincter and pelvic floor dis-coordination during voiding and a small cystometric capacity. There is generally no evidence of polyuria. Children with these findings benefit from a combination approach of anti-muscarinics, the bedwetting alarm and urotherapy.
The third diagnostic group accounts for around 35% of sufferers, with children showing nocturnal onset of covert detrusor instability and associated reduction in nocturnal bladder capacity. Optimal management of this group involves a night dose of anti-muscarinics in conjunction with anti-diuretic therapy. Predictive factors for treatment efficacy relate directly to a clear determination of associated and underlying symptoms. Children with altered circadian rhythm of ADH secretion and essentially normal nocturnal bladder capacity will respond well to anti-diuretic medication. A small bladder capacity is generally a poor prognostic sign for anti-diuretic therapy alone. Instead such children do well with a combined approach aimed at increasing nocturnal bladder capacity. It should be noted that successful use of a bedwetting alarm coincides with a significant increase in night bladder capacity. To this end adjunctive anticholinergic medication is often helpful as it reduces the detrusor pressure rises during filling, allowing greater accommodation of urine.
In summary, the bladder, brain and kidneys are equally important in the epidemiology and evaluation of nocturnal enuresis and the clinician needs to clearly identify where the major dysfunction lies for each child and to treat specific pathology.

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S01.2

CLASSIFICATION AND TREATMENT OF ENURESIS BASED ON SLEEP STUDIES

Hiroki Watanabe, M.D.

A classification system of enuresis was proposed based on the overnight simultaneous electroencephalographic (EEG) and cystometric (CM) monitoring. The classification types proposed were as follows:
[Type I] (approximately 60 % of the total): CM is flat after falling asleep. When the bladder becomes full during Stage 4 sleep, an evidence of arousals appears in EEG (transition to Stage 1 or 2 sleep pattern) but enuresis occurs without complete waking.
[Type â…¡a] (approximately 10%): CM is flat. Even the bladder becomes full, no response is observed in EEG and enuresis occurs in deep sleep.
[Type â…¡b] (approximately 30%): An uninhibited contraction of the bladder is observed on CM only after falling asleep (not on awakening). No change in EEG is found and enuresis occurs.
The pathogenesis of Enuresis Type I and Type â…¡a was a disturbance of awakening, while that of Type â…¡b was a disturbance of bladder function not shown in the daytime but only at night. An original systematic therapeutic plan was established with the development of an original therapeutic machine primarily for Enuresis Type I.
The physiological background of Enuresis Type I was investigated in two studies, one in rats and one in children with Type I enuresis. The results of these investigations suggest that in this type of enuresis, the fundamental arousal function following bladder distension, due to an arousal center like the locus coeruleus and its network, is normal. In contrast, the process of multplying the transient connection from light sleep to complete awakening, which probably relies upon functions of the thalamus and the further upper centers, was thought to be abnormal.

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S01.3

Evidence based management of Nocturnal Enuresis

Jonathan HC Evans

Background
In a labile condition with a high spontaneous resolution rate, therapeutic efficacy can only be established in randomised controlled trials (RCT's).
Methods
Data was summarised from a series of recent Cochrane systematic reviews, using evidence only from RCTs.
Results
Placebo: Compared to baseline, placebo reduced wetting by about 1 night/wk (WMD 0.81, 95% CI 0.61 to 1.01).
Simple behavioural interventions: Limited evidence from single small trials suggested that "starcharts" lead to fewer wet nights and lower failure rates during and after treatment but overall success rates were low and drop out rates high.
Enuresis alarms: About 1/3 of children failed to become dry using an alarm in 13 trials (98/304, 32% versus 239/248, 96% in controls, RR 0.36, 95% CI 0.31 to 0.43). About 1/2 were wet at follow-up (RR 0.56 (0.46 to 0.68). There was weak evidence that overlearning or dry bed training improved the success rate. Limited evidence suggested that alarms were more effective than drug treatment: Although desmopressin had a more immediate effect, alarms were more effective after treatment stopped (RR of failure 0.27, 95% CI 0.11 to 0.69). Alarms were better than tricyclics both during and after treatment.
Drugs: Desmopressin, in a variety of doses, reduced bedwetting by 1-2 nights/wk week during treatment compared with placebo (e.g. 20µg: 1.52 fewer wet nights per week, 95% CI 1.8 to 1.23). They were twice as likely to achieve 14 consecutive dry nights (e.g. 77/230, 33% on 40µg) compared with placebo (33/233, 14%), but there was no difference after treatment was finished. There was insufficient data to compare oral and nasal administration.
Tricyclics reduced wetting by about one night/wk during treatment (e.g. imipramine compared with placebo, -1.19, 95% CI -1.56 to -0.82). About 1/5 of the children became dry on treatment (e.g. relative risk (RR) for failure with imipramine 0.77, 95% CI 0.72 to 0.83), but almost all the children relapsed after treatment stopped.
Evidence comparing desmopressin with tricyclics was unreliable or conflicting in two small trials. Adverse events were, subjectively more serious and were objectively more frequently reported with tricyclics (in 25/31 trials) than in those receiving desmopressin (in 13/28 trials).
Conclusions
Alarms are effective during treatment and lead to persisting benefit in half of children but many others drop out from treatment. Both Desmopressin and Tricyclics improve wetting by a similar amount during treatment but there is no evidence of persisting benefit when treatment stops. Frequent & serious adverse effects limit the usefulness of Tricyclics.
The quality of studies was generally poor and few studies compared effective interventions. Only a minority of studies differentiated between children with bladder dysfunction, polyuria or monosymptomatic enuresis, factors that may alter the effectiveness of different therapies. More research is therefore needed in these subgroups.

S01.4

Secondary Nocturnal Enuresis

Lane Robson

About 25% of children who present with bedwetting experience the onset after a minimum of six consecutive months of dryness and are considered to have secondary nocturnal enuresis (SNE). The epidemiological aspects, pathogenesis, treatment, and prognosis of SNE will be reviewed.
The most common cause of SNE is that associated with Urge Syndrome and Dysfunctional Voiding, and presents in the pre-school years, often after a relatively short period of nighttime continence. The bedwetting in children who experience only one to five months of consistent nighttime dryness before the onset of enuresis is currently classified as Primary Nocturnal Enuresis (PNE). Most of these children are not distinguishable from those who present after the arbitrary six months of continence suggested by the International Children's Continence Society (ICCS) definition. Many children with PNE have subtle daytime voiding symptoms compatible with Urge Syndrome. PNE in these children and in those with SNE due to the Urge Syndrome might share a common pathogenesis. Urinary tract infection (UTI) and constipation are frequent co-morbid problems associated with Urge Syndrome, and are also recognized as unique causes of SNE in the absence of pre-existing Urge Syndrome. Psychological problems can trigger SNE. The longer the duration of dryness before the onset of the bedwetting, the more likely a psychological problem is the cause of the SNE. Sexual abuse is a possible cause of SNE. Children might purposely wet the bed to make the setting less attractive to a sexual predator. Obstructive Sleep Apnoea is a possible cause of SNE and usually presents coincidental with maximal adenoidal hypertrophy in the pre-school child or in obese children. Acquired urethral obstruction, neurogenic bladder, and diabetes insipidus are rare causes of SNE.
The underlying cause should be treated. The treatment for children with Urge Syndrome and Dysfunctional Voiding includes urotherapy (bladder physiotherapy), prevention or treatment of UTI and constipation, limiting fluid and solute intake in the evening hours before bed, optimizing the duration and quality of sleep, a visualization exercise, and instructing the parents to take their child to the bathroom before they turn in for the evening. Urotherapy recommendations include voiding according to a schedule and often enough such that urgency is ameliorated, and optimal posture and techniques to insure relaxation of the pelvic floor musculature during voiding. Prevention and treatment of UTI includes optimizing bladder emptying, meticulous attention to genital hygiene, and antibiotic therapy. Prevention and treatment of constipation includes loosening the bowel movements with dietary intervention and stool softeners, encouraging a first morning bowel movement before the child goes to school, and encouraging thorough emptying with optimal posture and other techniques. When treatment of the underlying cause does not improve the SNE, treatment with a medication or a moisture alarm should be considered. The prognosis for almost all children with SNE is excellent.

S01.5

DESMOPRESSIN IN PRIMARY NOCTURNAL ENURESIS

Dominik Müller[1] and Paul Eggert[2]

Desmopressin, is a synthetic analogue of the endogenous pituitary hormone arginine-vasopressin (AVP, Vasopressin). Both bind to at least three different receptors, present in kidney, thrombocytes and the central nervous system. The rationale underlying the use of desmopressin for the treatment of primary nocturnal enuresis (PNE) is based (1) on its renal antidiuretic effect and (2) on the hypothesis of an inadequate AVP secretion at night in enuretic children. However, other symptoms of PNE children like the remarkably deep sleep can not be explained with a low AVP and have led to studies showing that the central nervous system is to a great extent involved in PNE; by demonstrating an altered response of the arousal system in enuretic children. Likewise, studies investigated weather the undisputable therapeutic benefit of desmopressin in PNE might also be attributed to a central nervous action. In a recent study, two families were identified in which nephrogenic diabetes insipidus and PNE were coexisting. Surprisingly, the administration of desmopressin resolved nocturnal enuresis, leaving the nephrogenic diabetes insipidus unaffected. This finding pointed at the fact that desmopressin in PNE might indeed exert its action on extra renal targets. A prospective, randomized, placebo controlled cross over study, demonstrated a stimulating effect of desmopressin on short term memory of children with PNE. Since short term memory is considered to be a function of an individual's alertness, this finding supports the hypothesis of a central nervous effect, more precisely an effect on the arousal system. Ongoing research using cerebral gene expression profiling in desmopressin treated rats revealed a subset of differentially regulated genes when desmopressin treated animals were compared to controls. Besides several ion and water transporting systems, including AQP-4, also GABA-associated proteins were consistently differentially regulated, implicating an important role of the GABA-metabolism in the central action of desmopressin. This finding might also explain the observation that nocturnal enuresis is a common side effect of valproate, an anti convulsive drug that interferes with the GABA pathway. Together, there is increasing evidence of a central nervous effect of desmopressin in the treatment of PNE. In that way, all treatments for PNE with proven effect (1) behavioural therapy (bell pad), (2) tricyclic antidepressants and (3) desmopressin aim at the same target organ, the central nervous system. Future studies are needed to specify the molecular mechanism of their action, which might help to unravel the nature of PNE itself.

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S02.1

MINIMALLY INVASIVE OPTIONS FOR THE MANAGEMENT OF URETERO-PELVIC JUNCTION OBSTRUCTION IN CHILDREN

Hock L Tan

Aim:
Uretero-Pelvic Junction obstruction (UPJO) is the commonest obstructive uropathy in childhood. Conventional open pyeloplasty is the gold standard for the management of UPJO, but it requires a large incision and results in significant physical and permanent cosmetic deformity.

Since 1983, several minimally invasive surgical options including endopyelotomy, radial balloon dilatation and laparoscopic pyeloplasty have evolved in an attempt to reduce the surgical morbidity associated with open pyeloplasty. This presentation examines the current status of these options for managing UPJO and reviews the results and suitability of these techniques in children.

Methods:
The author's own experience and data is presented with the results of a search of all English publication using the key words Endoscopic Pyeloplasty, Radial Balloon Dilatation, Laparoscopic Dismembered Pyeloplasty and Uretero-Pyelostomy. The results of these procedures are compared with published results for open pyeloplasty.

Results:
The success of endopyelotomy (pyelolysis), accucise retrograde endopyelotomy and radial balloon dilatation is inferior to dismembered pyeloplasty, which remains the gold standard. However, the success of laparoscopic pyeloplasty is now approaching that of open surgery and with refinement in surgical techniques, laparoscopic pyeloplasty should now be considered as an acceptable surgical alternative, even in young infants.

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S02.2

LAPAROSCOPIC DONOR NEPHRECTOMY

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There has been renewed interest in live donor kidney transplants as a result of severe shortage of cadaver organs and increasing waiting times. Some motivated donors are hesitant to donate, because of the postoperative pain, hospital stay and recovery time with possible loss of income. Two major technical advances have come to the rescue. They are - replacement of conventional angiogram, an interventional procedure with Spiral CT or MR angiogram and more importantly the introduction of laparoscopic donor nephrectomy. We have been using laparoscopic method since June 1997 and it has replaced open nephrectomy in our unit. In spite of the early scepticism it is now well accepted and many live donors prefer this method.
We have done 135 donor nephrectomies and had to convert to open on 3 occasions (2.2%) to maintain the safety. The major benefits to the donor are reduced postoperative pain, early resumption of diet, shorter hospital stay (usually 48 hours), early return to normal activity and the potential to return to work. Some donors appreciate the cosmetic result as well. There was no mortality or major complication.
Incidence of delayed graft function and graft survival rates are comparable to the open nephrectomy group.

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S02.3

MINIMALLY INVASIVE NEPHRECTOMY AND PARTIAL NEPHRECTOMY

Craig A. Peters, M.D., FACS, FAAP

Minimally invasive nephrectomy and partial nephrectomy are steadily evolving to become the standard of care in pediatric surgical practice. These techniques offer safe and effective ablative surgery of various renal pathologies in a wide variety of patients. Retroperitoneal access has been shown to be as efficient and safe as transperitoneal methods. The development and experience gained with these techniques has provided the basis for more complex reconstructive laparoscopic renal surgery.
The standard laparoscopic nephrectomy is performed retroperitoneally, using either a lateral or posterior prone approach with development of the working space using balloon or direct vision dissection. The renal hilum is first identified and the vessels are controlled individually using surgical clips. The remainder of the dissection is performed and the kidney is removed through one of the incisions. Larger kidneys require morcellation for removal, but many are small after decompression. High risk patients may undergo the procedures with safety, including those with end-stage renal failure and prior renal surgery. Peritoneal dialysis may be resumed within the first post-operative day.
Partial nephrectomy is usually performed retroperitoneally as well, and requires precise separation of the upper and lower moieties with independent vascular control. The affected ureter is usually dissected first, which permits more efficient control of the vessels to the affected segment. Once these are controlled, the border between the affected and the healthy parenchyma is divided. This may be performed using various energy sources such as the harmonic scalpel. Any violation of the healthy collecting system must be repaired. Several series have shown a low, but real incidence of post-operative urinoma, perhaps due to residual renal tissue from the affected pole, but these have not produced clinical problems and are likely to resorb.
The experience with laparoscopic renal surgery in children will continue to expand steadily and should permit application to a wide variety of patients and situations. The relative reduction in morbidity is difficult to document in children, particularly infants, but the subjective reduction in post-operative morbidity is readily apparent to parents and physicians. With equivalent operative times in experienced hands, shorter hospital stays and equal safety, it seems that laparoscopic renal surgery is the intuitively better choice for children.

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S02.4

Edourology and ESWL Management of Urinary Calculi

David Winkle

The management of calculi in the urinary tract in children (and adults) has changed dramatically over the last twenty years. Endoscopic stone management and the non-invasive ESWL have minimised treatment related morbidity and maximised nephron preservation especially in those patients with recurrent calculi secondary to metabolic or anatomic abnormalities. ESWL is the treatment of choice for the majority of renal calculi with stone clearance rates of up to 90%. Advances in miniaturisation of telescopes and camera technology have meant percutaneous nephrolithotomy and ureteroscopic stone management are now standard and safe treatments for those calculi not treatable by ESWL. This paper reviews the safety, efficacy and versatility of current stone management techniques with reference to experience over the last 10 years at the Mater Children's Hospital, Brisbane. Eighty-six children aged 6 months to 16 years have undergone one hundred and twenty-three procedures to treat urinary tract calculi. Management was determined by stone composition, stone size and associated structural abnormalities. Some stones occurred in anatomically abnormal kidneys and required surgical reconstruction but the majority of stones were able to be cleared without open surgical intervention.

Technological advances in the management of urinary tract calculi have been successfully adapted to treat children providing safe and effective management options for children with urinary stone disease.

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S03.1

PROTEINURIA: EFFECTS ON - AND EFFECTS OF -PROXIMAL TUBULAR PROTEIN REABSORPTION

Erik Ilsø Christensen

The endocytic receptors megalin and cubilin are highly expressed and colocalized in the early parts of the endocytic apparatus of the renal proximal tubule consisting of coated pits and vesicles, endosomes and dense recycling apical tubules and colocalize also in several other tissues including the yolk sac and small intestine. The two receptors appear to be responsible for the tubular clearance of most proteins filtered in the glomeruli and thereby also very central for the reabsorption of lipid, vitamins and other trace elements in the renal proximal tubule. Megalin is a 600 kDa transmembrane protein belonging to the LDL-receptor family. The cytoplasmic tail contains two NPXY motifs mediating clustering in coated pits. These and other cytoplasmic motifs may be involved in signalling. Cubilin, also known as the intestinal intrinsic factor cobalamin receptor, is a 460 kDa receptor with no transmembrane domain and no known signal for endocytosis. The variety of filtered ligands identified for megalin include the vitamin binding proteins transcobalamin-vitamin B12, vitamin D binding protein-25-(OH) vitamin D_3 and retinol binding protein-vitamin A, hormones, enzymes, apolipoprotein H, albumin, hemoglobin, myoglobin and $_2$- and $_1$-microglobulin. Among the proteins normally filtered in the glomeruli cubilin has been shown to bind albumin, transferrin, vitamin D binding protein-25-(OH) vitamin D_3, immunoglobulin light chains, hemoglobin, myoglobin and apolipoprotein A-I. Since cubilin is a peripheral membrane protein it has no endocytosis signaling sequence. Cubilin binds to megalin and it appears that megalin is responsible for internalization of cubilin and its ligands in addition to internalizing its own ligands. The importance of the receptors is underscored by the proteinuria observed in megalin deficient mice, in dogs lacking functional cubilin and in patients with distinct mutations of the cubilin gene.
The role of megalin and cubilin mediated endocytosis in renal pathophysiology is illustrated by the association between disorders characterized by tubular proteinuria such as megaloblastic anemia type-1, Dent´s disease, cystinosis and Fabry´s disease and the dysfunction of proximal tubular endocytosis. Furthermore, there appears to be a correlation between the high capacity of endocytosis in the proximal tubule and progressive renal disease in overload proteinurias such as myoglobinuria and hemoglobinuria.

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S03.3

MECHANISMS OF RENAL K TRANSPORT: LESSONS FROM ONTOGENY AND DISEASE

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Somatic growth during childhood is associated with a predictable increase in total body K content, regulated in large part by urinary K excretion. Within the fully differentiated kidney and specifically the cortical collecting duct (CCD), K secretion is accomplished by the passive diffusion of cell K into the urine down a favorable electrochemical gradient through K selective channels. Electrophysiological analyses have identified two apical K channels in the mammalian CCD. The prevalence of the secretory K (SK) channel and its high open probability at the resting membrane potential in the adult has led to the notion that this channel, encoded by ROMK, mediates K secretion under baseline conditions. We have recently proposed that the maxi-K channel, rarely open at the physiologic resting membrane potential but activated by membrane stretch, depolarization, and/or an increase in cell Ca^{2+} concentration ($[Ca^{2+}]_i$), mediates K secretion under conditions of high urinary flow rate (which is associated with increases in net Na absorption and $[Ca^{2+}]_i$) and/or when ROMK is absent (e.g., Bartter syndrome).
In contrast to the high rates of K secretion observed in CCDs isolated from adult rabbits and microperfused *in vitro*, neonatal segments show no significant net baseline K transport until after the 3rd wk of postnatal life. Nor can K secretion be stimulated by high tubular fluid flow rates until after the first month of life. SK channel activity increases progressively after the first wk of life in parallel with increases in abundance of ROMK mRNA and expression of apical immunodetectable ROMK protein in the CCD, and precedes the postnatal appearance of net K secretion. The limitation in flow-stimulated K secretion early in life is not due to an inability of the CCD to respond to an increase in flow with augmented Na absorption or a rise in $[Ca^{2+}]_i$, but appears to be due to a paucity of maxi-K channels; CCD maxi-K channel □-subunit (encoded by *slo*) message and protein are first detectable at ~5 wks of postnatal life.
The temporal delay between postnatal expression of SK channels (baseline K secretion) and maxi-K channels (flow-stimulated K secretion) in the maturing CCD appears to reflect unique developmental programs regulating the transcription and/or translation of ROMK and *slo*. We speculate that the lack of K secretory channels in the neonatal kidney allows for the maturing animal to retain K, as is necessary for growth. The signals directing the developmental regulation of channel expression are as yet unknown.

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S03.4

DENT'S DISEASE

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Dent's disease is an X-linked renal tubular disorder characterized by low molecular weight (LMW) proteinuria, hypercalciuria, nephrocalcinosis / nephrolithiasis and progressive renal failure. Rickets or osteomalacia is complicated in some patients.
Almost all of the Japanese patients with idiopathic LMW proteinuria are school children. They are identified by a national urinalysis screening program every year. Japanese ILMWP has clinical features as follows; 1) positive protein in the early morning urine in the patients, 2) almost all the patients are male, 3) markedly elevated urine beta 2-microglobulin in the patients, 4) slightly elevated urine beta 2-microglobulin in the mothers, and 5) over 60% of the proteins are LMW proteins with MW less than 45,000 daltons.
Dent's disease is due to the mutations in CLCN5. CLCN5 encodes ClC-5 protein, which is a member of ClC family of voltage gated chloride channels. ClC-5 conducts outwardly rectifying chloride currents that are activated by strong depolarizing voltages. ClC-5 is a 746 amino acid channel, which has about 12 transmembrane domains. We identified CLCN5 mutations in 48 families with the disease. The mutations are composed of missense, nonsense, frameshift, splice site mutations, and gene deletion. Each patient fundamentally has his own mutation site. However, three nonsense mutations (codons 279, 648, and 704) were identical between British and Japanese families suggesting that these sites may be mutational "hot spots" in CLCN5. Three missense mutations (S270R, L278F and R280P) were identified at the putative loop between domains 5 and 6. This implies that this putative loop may have a regulatory role in ClC-5 function.
ClC-5 protein is expressed in the proximal tubule, thick ascending limb of Henle, and the intercalated cells of the collecting duct. ClC-5 protein is localized intracellularly to the subapical endosomes with H^+-ATPase in the proximal tubule. This suggests that ClC-5 may function as an electrical shunt for electrogenic hydrogen transport, and that an acidic endosomal pH appears to be necessary for normal endosomal function, including endocytosis, trafficking, and recycling to the surface.
Patients with Dent's disease often manifest hypercalciuria. The precise mechanism of hypercalciuria is not known. Patients with Dent's disease manifest renal calculi and nephrocalcinosis when they are over 20 years old. Crystals in the lumen may be cleared by collecting duct cells to prevent luminal calculi formation. Crystals adherent on apical cell surfaces may be internalized and dissolved within endosome in the collecting duct cells. However, endosomal defect due to ClC-5 dysfunction can disturb this process and will form calcium stone or intracellular Ca deposition in Dent's disease.
Knock-out mouse models identified that megalin's expression was reduced. This may directly explain defective binding of protein with megalin in the luminal membrane of the proximal tubule. This will result in the LMW proteinuria in Dent's disease. We identified decreased urine excretion of megalin in patients with Dent's disease suggesting the decreased expression of megalin in the proximal tubules in the patients.

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S04.1

ALTERATIONS OF THE GROWTH PLATE IN CHRONIC RENAL FAILURE

Fernando Santos

The growth plate of long bones has been extensively studied in the uremic rat model in an attempt to gain some understanding on the mechanism of growth retardation in chronic renal failure (CRF). The tibial growth cartilage of uremic rats often exhibit marked morphological changes characterized by increased height of the columns of chondrocytes resulting from an expansion of the hypertrophic strata. Elongation of the growth cartilage is not always observed and, to a large extent, depends on the severity and duration of the uremia. In association with this finding, the most distal chondrocytes, that is those adjacent to the metaphyseal bone, are of reduced size and the cartilage – metaphyseal bone interphase of uremic rat growth plate is remarkably irregular and disorganized. Although the reasons to explain these abnormalities are not clear, CRF likely causes a disorder of chondrocyte maturation with disequilibrium between the physiologically coupled processes of cartilage production and cartilage resorption. It is of note that the morphological changes caused by CRF in the growth plate seem to be rather characteristic of uremia itself as they are not observed in normal renal function rats with malnutrition or metabolic acidosis, disorders frequently present in CRF. By using in situ hybridization and/or immunohistochemistry analysis of growth plate, some studies have reported decreased expression of several genes such as insulin-like growth factor I, growth hormone (GH) receptor, collagen II, collagen X, parathyroid hormone – parathyroid hormone related peptide receptor, and matrix metalloproteinase 9 in uremia. These alterations in gene expression are not consistently found and its meaning in the pathogenesis of growth retardation of CRF is far from clear. Administration of GH results in acceleration of growth velocity in individuals with CRF. The treatment with GH does not reduce the height of growth cartilage in uremic rats but exerts a marked beneficial effect on the architecture of growth plate as shown by more organized arrangement of the chondrocyte columns, normalization of the size of terminal chondrocytes and regular cartilage – metaphyseal bone junction. Preliminary experiments of our group investigating differential gene expression by DNA microarray analysis indicate that GH therapy significantly modifies expression of a number of genes in the growth plate of uremic rats. Again, the significance of this finding to explain the growth promoting effect of GH treatment in CRF requires further investigations.

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S04.2

RECOMBINANT HUMAN IGF-1: POTENTIAL AS A THERAPEUTIC FOR CRI

Ross Clark

In children with chronic renal insufficiency (CRI) changes in the hormones of the GH/IGF-1 axis can result in growth retardation and the need for hormone treatment, currently with recombinant human GH (rhGH). However, there is evidence that the short stature caused by CRI is a state of GH resistance, rather than of GH deficiency, because GH is present in normal concentrations in blood. The reduced effectiveness of GH is likely due in part to a disordered IGF-1 system with the level of free, bioactive IGF-1 being reduced by increased levels of circulating inhibitory IGF binding proteins (IGFBPs). In addition, less IGF-1 is present in its storage form in blood (i.e. IGF-1 in complex with IGFBP-3 and the acid labile subunit) due to an increased proteolysis of IGFBP-3, and increased levels of the inhibitory IGFBPs, IGFBP-1 and -2. These changes likely result in a low level of free IGF-1, a state of relative IGF-1 deficiency, a decrease in IGF-1 receptor activation, short stature, and because of the effect of IGF-1 on the kidney, possibly a further reduction in renal function. The local effects of GH on bone that are mediated by IGF-1 are likely also blunted in CRI. Long-term replacement therapy with rhIGF-1 is effective at improving height in children with severe IGF-1 deficiency due to GH receptor mutations. In animal models of CRI there are synergistic effects of rhGH and rhIGF-1 on body growth, and beneficial anabolic effects of the combination have been shown in catabolic humans. It is possible that rhIGF-1 alone, or rhGH plus rhIGF-1 as a growth-promoting hormone cocktail, will prove to be the optimal therapy for the treatment of growth disorders characterized by IGF-1 deficiency, including CRI.

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S04.3

LONG-TERM GROWTH HORMONE TREATMENT IN CHILDREN WITH CHRONIC RENAL FAILURE

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Introduction: For many years children with growth retardation due to chronic renal failure are being treated with growth hormone (GH). However, data on adult height after GH treatment are still limited.
Methods: GH treatment was started in 220 Dutch children (142 males, 78 girls) with growth retardation due to chronic renal failure. Data were registered in the Dutch National Registry of Growth Hormone Treatment in Children. Statistical analyses were performed on data of patients who had been treated with GH for at least one year.
Results: Mean (SD) age at the start of GH treatment was 7.8 (2.5) years. Mean (SD) height at start was -3.0 (1.2) standard deviation scores (SDS). Hundred twenty four patients reached their adult height. Forty-six of them were treated with GH for more than 4 years. Prepubertal children with chronic renal failure who were treated with long-term GH reached a mean (SD) adult height SDS of –1.2 (1.0) and a target height adjusted height SDS of –0.4 (1.0). GH therapy had no adverse effect on glomerular filtration rate, bone maturation, serum parathyroid hormone levels and did not induce renal osteodystrophy. GH treatment was not associated with a shortened duration of the pubertal growth spurt. The gain in height SDS was positively associated with the initial target height deficit. Adult height was positively associated with the height SDS at start of GH therapy and negatively with the age at start and the proportion of time on dialysis during GH therapy.
Conclusion: Long-term growth hormone treatment with a dose of 1.3 mg/m2 body surface/day of children with chronic renal failure results in a normalization of height in accordance with their target height SDS, without evidence of deleterious effects on renal function or bone maturation.

S04.4

RHGH POST-TRANSPLANT IN CHILDREN – LONG-TERM (FIVE YEAR) NAPRTCS DATA

Richard N. Fine, M.D.

Four controlled studies utilizing rhGH in growth retarded renal allograft recipients have demonstrated a short-term (six months – 1 year) significant increase in height velocity in the rhGH treated group compared to the control group.
There was no increased incidence of acute rejection episodes (ARE) or graft dysfunction (decline in GFR) in the rhGH treated and the incidence of adverse events (AE) was comparable in the rhGH and control groups. However, these reports included a limited number of recipients treated with rhGH and the follow-up period was not prolonged.
This report includes data on 512 recipients in the NAPRTCS registry who received rhGH at one or more semiannual visits and who were followed for five years. The number of patients receiving rhGH for 1, 2, 3, 4, and 5 years were 251, 167, 54, 42, and 16 respectively. The median time post-transplant at initiation of rhGH was 3.5 years and the age at initiation was <10 years old in 21% and >15 years old in 25%. The median z score at initiation was – 2.7 in both groups.
A control group of 2200 recipients who had survived at least 24 months post-transplant had standardized heights <-1.5 and did not receive post-transplant rhGH were utilized to compare the incidence of ARE, graft failure rate, causes of graft failure, calculate glomerular filtration rate (cGFR), growth, final adult height and AE.
rhGH was discontinued over the five-year period with only 25% still receiving rhGH at 5 years; however, those recipients continuing rhGH had improved growth compared to those that discontinued rhGH. The recipients <10 years old at initiation of rhGH had improved growth compared to older recipients at initiation. The number of ARE both prior to and subsequent to entry in the study in both the rhGH and control group were similar. Graft failure following study entry was 19.5% and 20.5% in the rhGH and control group respectively. Chronic rejection accounted for 63% of graft failures in the rhGH group and 54% of the controls.
Median graft function (cGFR) was 68.6, 65.8, 63.5 and 58.9 at baseline, 1, 3, and 5 years following entry in the control group and 58.6, 59.4, 56.5 and 48.1 at the same-time intervals in the rhGH treated group. Reports of intracranial hypertension were received from 0 growth hormone and 6 control subjects (3 initial, 3 recurring) versus 1 growth hormone recipient (1 initial) reported avascular necrosis/slipped capital epiphyses.
Final adult height in 70 patients >19 years old (mean 20.4 years) was – 1.82 $\pm$1.22 in the rhGH treated group but was –2.6 in a similar subset of control cohort patients. . This large patient database of renal allograft recipients treated with rhGH for up to five years post-transplant compared to an untreated control population indicated that rhGH treatment of recipients is associated with increased height without any increase in AE. This study substantiates the previous findings with more limited follow-up data.

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S05.2

URGE SYNDROME – LONG TERM OUTCOME

Lane Robson

The International Children's Continence Society (ICCS) separates voiding dysfunction into two broad categories. Urge Syndrome is a defined as a filling phase abnormality and Dysfunctional Voiding as an emptying phase abnormality. There is considerable overlap between the two groups. Urge Syndrome is much more common and presents with urgency and daytime incontinence. Modest pelvic floor muscle over-activity is common in Urge Syndrome and can be associated with emptying difficulties. Dysfunctional Voiding is less common; also usually presents with urgency and daytime incontinence, but the emptying difficulties are more severe and presumed due to failure of the pelvic floor muscles, the external sphincter, or both muscle groups to relax. Only the long-term outcome of Urge Syndrome will be reviewed during the presentation.
The few reported studies on the epidemiology and natural history of treated or untreated patients with voiding dysfunction will be reviewed. The available longitudinal studies provide some insight into the long-term outcome of the symptoms of voiding dysfunction, but due to the differences in the diagnostic criteria employed by various clinicians, most of the reports do not allow assessment of the outcome specifically for children with Urge Syndrome.
Modern treatment for Urge Syndrome includes urotherapy, (bladder physiotherapy), and prevention or treatment of urinary tract infection and constipation which are especially common associated problems. The principles of urotherapy include voiding according to a schedule and often enough such that urgency is ameliorated, and optimal posture and techniques to insure relaxation of the pelvic floor musculature during voiding. Consistency is important and requires recruitment of all caregivers including schoolteachers and extended family members to help encourage and reinforce good voiding habits. Bedwetting associated with Urge Syndrome requires further specific treatment.
The prognosis for children with Urge Syndrome is very good with or without treatment. However, early treatment is important since resolution will avoid the embarrassment and self-image problems that might develop consequent to daytime wetting in social situations and will protect the bladder from evolution to more severely expressed bladder problems such as those classified under the category of Dysfunctional Voiding.
With compliance with modern treatment Urge Syndrome will resolve in the majority of affected children within three months of starting therapy, and significant improvement is often noted within several weeks. Pharmacological intervention is usually not necessary. Diagnostic imaging studies should be reserved for those who do not respond to conventional therapy.

S05.4

DYSFUNCTIONAL VOIDING: ASSESSMENT, TREATMENT AND OUTCOME OF TREATMENT

Dr Raes ANN

Although non-neuropathic bladder sphincter dysfunction in children is frequently encountered, there is no consensus on the assessment and the treatment of children presenting this problem.
In the nineties different treatment modalities were propagated by different centres, resulting in comparable results. Some people concluded that not the treatment modality but just the fact of giving attention and treatment was at the origin of the results.
As no prospective randomised controlled studies are available, there is no evidence on the power of the different treatment modalities. Furthermore the natural history of the disease is unclear until today so comparing treatment outcome with natural history is impossible.
An example will be given on how these children can be assessed. After a non invasive screening consisting of history, voiding diary, clinical examination, urinalysis, ultrasound and uroflowmetry, those children that will benefit from further videourodynamic studies are selected. Videourodynamics help to describe accurately the filling phase dysfunction and the voiding phase dysfunction, which helps to line out therapy. By using the described methods we are able to select those patients who will benefit from pharmacotherapy and those who will benefit from urotherapy.
Treatment modalities known as urotherapy, range from explaining the disease to patient and parents, voiding and drinking charts, pharmacotherapy (anticholinergics and alpha blockers), neuromodulation, biofeedback therapy, pelvic floor therapy, voiding camps and voiding schools.
In our experience the results increase with the increase of the intensity of the treatment. Despite the different treatment tools available for treating the condition, some children will be untreatable. The outcome for this patients as adults is unclear until today and can only be speculated.

Ghent University Hospital, Belgium

S06.1

RISK FACTORS AND MANAGEMENT OF URINARY TRACT INFECTION

Masahiro Hiraoka, M.D.

Risk factors for development of urinary tract infection in children may be classified into physiological and organic factors. Physiological factors include phimosis in boys, immaturity in voiding function during infancy, voiding dysfunction and constipation during childhood. Recently, many findings have stressed the importance of physiological factors in the development of urinary infection, and in the development and persistence of high-grade VUR in children. The incidence of urinary infection is very high during early infancy, and almost all children with urinary infection have physiological risk factors, while only a portion of the children have organic abnormalities in urinary tract.
The physiological factors usually resolve or improve as the children grow. Phimosis almost always clears or becomes mild, and voiding function matures in a few years after birth. The second episode of urinary infection almost always develop within six months after the initial one, and rarely develops after this period, suggesting spontaneous resolution of physiological risk factors during this interval and not justifying routine aggressive treatments for phimosis and voiding dysfunction.
Organic factors involve VUR, urinary tract obstruction and neurogenic bladder. Most of VUR is classified into grade I or II. The low-grade VUR in infancy is not found contributory to recurrence of urinary infection. High-grade VUR (grade III or more) is found in approximately one of six to eight children with first urinary infection. Approximately two-thirds of the infants with the high-grade VUR have a second episode of urinary infection, which almost always develop within six months after the initial one. Our investigation in children with high-grade VUR almost confirmed these findings. VUR alone in the absence of upper urinary tract infection does not cause renal damage. Even after the upper urinary tract infection occurred, renal damage would not develop if the infection is diagnosed and treated early enough. These observations justify medical management of VUR, even of high grades.
Medical managements of children with risk factors include instruction on frequent voiding and daily bowel movement and periodic follow-ups. All children with first urinary infection and their parents should be informed on recurrence of urinary infection and possible renal damage, and advised to receive urinalysis, periodically during six months after the previous urinary infection and immediately once the symptoms suggesting urinary infection develop. Children with recurrent urinary infection may be given prophylactic antibiotics to be free from the recurrence for six months.

S06.2

MINIMAL INVESTIGATIONS FOR A FIRST URINARY TRACT INFECTION (UTI)

A. Bensman

The first investigations have to be clinical. They include physical examination of the back and assessment of the spine for deformities, the genitales and the abdomen for signs of constipation. A history including bladder and bowel habits is also important : It has to look for dysfunctional voiding syndromes.
The imaging investigations are discussed in case of pyelonephritis. In most cases the recommendations are not to investigate children with clinical acute cystitis.
Renal ultrasonography and voiding cystourethrography (VCU) are recommended by the American Academy of Pediatrics as standard diagnostic tests for young children with upper urinary tract infection. The rationale of this recommendation is that obstruction, lithiasis and/or vesicoureteral reflux (VUR) in combination with upper UTI can be dangerous for the kidney. The detection of these conditions may avoid recurrences and probable long-term renal damage.
However very few studies provide evidence of the impact of routine imaging on the development of renal scars and clinical outcomes in children with their first UTI.
In a prospective trial involving 309 children Hoberman and al (N. Engl. J. Med. (2003) 348 : 195-202) concluded that renal ultrasonography at the time of acute illness was of limited value because it does not provide information that modifies management. The same conclusions were drawn by U. Alon (Clin. Pediatr, Phila,1999, 38 : 21-25) reviewing the medical records of 124 patients. This seems to be due to the recent widespread use of maternal foetal ultrasonography which already detects a significant number of children with congenital obstructive uropathy prenatally.
The rationale for recommending VCU is to identify children with VUR. In this case prophylactic antimicrobial therapy or surgery is recommended. However the assumption that continuous prophylactic antimicrobial therapy is effective in reducing the incidence of reinfection and renal scarring is based on old data and it is not proven by recent works. A recent preliminary study (Pediatr. Nephrol, 2002, 17 : 506-510) concluded that children who do not have voiding dysfunction or VUR of grade 3 or higher severity do not have an increased risk of UTI recurrence if managed without prophylactic antibiotics after an initial course of suppressive antibiotics.
This report and recent analysis of the literature make it possible to perform a clinical trial evaluating the benefits of continuous prophylactic antimicrobial therapy in children with VUR. This study conducted by C Guyot has already begun in France.
The results of such trials may change the recommendations of VCU in the future.
For the American Academy of Pediatrics, renal cortical scintigraphy (with 99 mTc-DMSA or 99 mTc-glucoheptonate), enhanced computed tomography (but also Magnetic Resonance Imaging) are very sensitive means of identifying acute changes from pyelonephritis or renal scarring, but their role in the clinical management is unclear. For other groups ; in children of 2 years of age and older a normal DMSA scintigraphy excludes reflux of clinical significance and may therefore make a VCU unnecessary.
In conclusion : new concepts are on the way and deserve prospective clinical trials.

- incorporation of antenatal ultrasonography as a branch point in decision analysis
- the benefits of continuous prophylactic antimicrobial therapy in children with vesicoureteral reflux.
- The interest of DMSA instead of VCU.

However important caution is warranted and the classical pediatric guidelines should not be changed until clinical firm demonstrations are achieved.

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S06.3

RECENT STUDIES ON THE MANAGEMENT OF VESICOURETERIC REFLUX

Sverker Hansson

There is a strong correlation between vesicoureteric reflux (VUR) and renal damage. How much of this damage is acquired after birth is not known. Studies on the pathogenesis of renal damage have revealed that a significant number of children, mainly boys, have a congenital abnormality with hypoplastic or dysplastic kidneys associated with VUR of high degree. There is a high correlation between renal damage and the intensity of the first known urinary tract infection (UTI) as well as with the number of pyelonephritic reinfections. Girls may be particularly prone to development and progression of renal damage, probably because of a higher tendency to new febrile infections.
In a recently published study from Sweden the treatment policy for children with dilating VUR (grades III-V) varied considerably within the country. The rate of spontaneous resolution or downgrading of dilating VUR was also found to be high except in young girls with VUR grade IV-V.
The results of reimplantation are excellent with 99% cure, but there is no evidence for any beneficial effect on the long-term renal outcome. The results of subureteric injection are less successful in terms of eliminating VUR although the procedure is easy enough to allow further treatment trials.
Another important question concerns the role of bladder dysfunction. We know that the spontaneous resolution of VUR is high but that in children with bladder dysfunction it is significantly delayed. Studies to evaluate the effect of treatment of bladder dysfunction on the rate of VUR resolution are required. It is also important to investigate if and how VUR itself contributes to the development of bladder dysfunction.
There is a need of prospective studies to show if treatment of VUR is superior to prophylactic regimens or to just observation without prophylaxis, treating each episode of UTI as it occurs. The Swedish Reflux Study is a prospective and randomised study comparing three treatment alternatives: subureteric injection, prophylaxis and observation. In another ongoing study the most severe grade of VUR (grade V) is treated with subureteric injection during the infant period to study the effects on bladder function.

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S07.2

CHALLENGES IN TRANSPLANTATION IN DEVELOPING COUNTRIES

S.A.H.Rizvi

Transplantation is the ultimate therapy for end stage organ failure. ESOF has an estimated prevalence of 100 pmp in the developed and developing countries. However the transplant rates differ being 40-50 pmp in the developed vs 0-10 in the developing countries. This is due to cultural norms, differences in economics' and social attitudes towards organ donation and transplantation. Although the developing world is inhabited by 80% of the world population, it possesses 25% of the world's wealth. Health expenditure is between 0.8 % to 4% of the GNP as compared to 15 to 30 % in the developed world. Economics are not the only drawback. Wealthy countries of the Middle East suffer from lack of education and societal motivation. Infrastructure to support transplantation is absent in many of these countries. In contrast, South Asian countries which have the necessary technical expertise and infrastructure, but suffer from poor economics, cultural and societal apathy towards organ transplantation. In developing countries cadaver donor rates are low and living donors provide 85 to 100% of the organs as compared to 1 to 25% in the developed world. Although brain death cases are similar in the two regions of about 200 pmp annually. Shortage of organ and rampant poverty has lead to commerce in many developing countries. In Pakistan more than 40% of renal transplants are from paid donors and commerce continues in some countries even after the implementation of cadaver law and donation. Although living related donors provide majority of the organs however medical and social problems impinge on donation rates. In our own experience, initially on an average there are 6 donors per recipient but the final number is 1.6 donor per recipient. The hall mark of transplantation is optimal immunosuppression. Developing countries are confronted with two problems, firstly non availability of drugs and secondly high prices.
Living donors have set the trend of renal transplantation in developing countries. However due to organ shortage our salvation lies in cadaver donors. In addition we need to alleviate poverty, improve education and increase transplantation in the public sector, where commerce is less likely to play a major role. The center should have a motivated team of committed workers, providing the best possible care. In the developing world there are two options "pay or die". We at SIUT have tried to create a third option, we do not let any one die because they can not afford to live.

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S07.3

INCLUSION OF CHILDREN IN CLINICAL TRIALS

Patrina Caldwell

Clinical trials have resulted in significant improvements in healthcare, and the inclusion of children is crucial. Unfortunately, trials involving children are not many and are restricted to certain childhood diseases, heavily clustering around cancer. Although a well-designed randomised controlled trial (RCT) offers a patient the optimum treatment approach, the negative public perception of trials has meant that it is often more acceptable to use untested medications on children rather than to enrol them in a trial where the intervention effects can be monitored and analysed.
Government, industry, funding agencies, and clinicians are responsible for research priorities being adult-focused. There is, however, increasing recognition of the importance of including children in trials, and the US now requires evidence from RCTs before approving new therapies for children. The NIH has a policy on the inclusion of children in all clinical trials unless there are scientific and ethical reasons not to include them. Because of the smaller burden of disease, there is less financial incentive for pharmaceutical companies to undertake drug development in children. The FDA attempted to address this by offering additional six-month market exclusivity for products that have been trialled in children. The European Union Health Council has also called on the European Commission to develop similar incentives.
Trials involving children are challenging to conduct. The reasons are multi-factorial, and relate to doctor, parent, child and trial factors. Because of doctors' and parents' attitudes to trial participation, the threshold for gaining consent is often higher. The ethics of paediatric trial participation is complex and complicated by consent being by proxy by the child's parents or guardians. Many paediatric trials are small and inadequately powered to detect small or moderate treatment effects. Multi-centred trials address the problem of power but has added complexities of IRB requirements for each institution and collaboration between multiple centres. Trial methodology such as strategies for recruiting participants, trial type and trial design are also important. How can we address some of these issues? What are the advantages and disadvantages of multicentred paediatric trials compared with inclusion of children in predominantly adult trials? How can we address parents and doctors' concerns? What are some effective methodologies that can be incorporated into paediatric trials? What can we learn from our paediatric oncology colleagues who have succeeded in conducting international multicentre RCTs with astonishing improvements in outcomes? The future of paediatric trials particularly in the context nephrology will be discussed.

S07.4

ETHICS, VALUES AND GOVERNANCE: WHAT BENEFIT TO YOU?

Kate Costello

Shakespeare wrote about governance and the Greeks and the Romans practised it. The term, or rather the concept, is not new it just seems to be. Open any newspaper, annual report or organisational publication and you'll see it mentioned: "good" or "bad" governance contributing to the success or failure of organisations, respectively.
In broad terms governance can be defined as the relationship between an organisation's capital and management, mediated by the board.
In the public sector, "good governance arrangements are essential for an organisation to be able to demonstrate to stakeholders that it can be trusted to do what it is set up to do … efficiently, effectively and ethically".[1]
In the private sector, "the board's key role is to ensure that corporate management is continuously and effectively striving for above-average performance, taking account of risk. This is not to deny the board's additional role with respect to shareholder protection".[2]
Governance requires the most senior decision-making group (usually "the board") in any organisation to set a strategic direction, endorse policies within which management must operate, monitor and supervise performance, mitigate risk and discharge accountabilities to the law, the "owners" and increasingly the community.
Why is this relevant to you? Because the private and public sectors are merging: the private sector, concerned about corporate reputation, now ignores corporate social responsibility at its peril while the public sector is having to account for its use of public funds with greater efficiency and measurable outputs and outcomes; public sector structures are mimicking the private sector; and private and public sector services are co-locating. In addition, public sector organisations are increasingly required to meet funding requirements by attracting funds from the private sector and intellectual property developed in the public sector is being commercialised in private sector structures. Can you benefit from these trends? Yes.

1. Understanding the private sector's concern with community expectations, social responsibility and corporate reputation enables public sector organisations to attract "social capital" funding. The repercussions of the lack of ethics displayed by a pharmaceutical joint venture in its treatment of the moral rights of the Bushman of the Kalahari is one example of the trend to social responsibility as is an Australian financial institution's co-branded credit card with an Australian children's hospital which has seen over AUD 1M flow to capital works at the hospital.
2. If the public sector is to "sleep with the enemy!" it needs to understand commercial practices so as not to be taken advantage of. Various public institutions have failed to truly benefit from the commercialisation of their intellectual property because private sector funders have superior and sophisticated commercial savvy.
3. The recent spate of corporate collapses worldwide has resulted from a cavalier attitude to corporate culture and values. The adage "the fish rots from the head", recognises the board's role in assuming responsibility for organisational values and behaviour. Canadian research[3] has demonstrated that the competence and behaviour of board members is an integral factor in organisational performance. So, as the medical profession is electing or appointing directors to boards in the public or private sector it should seek directors who fall into the 5 optimal director behavioural groups and avoid the 5 dysfunctional behavioural groups. Effective directors lead to an effective board which, in turn, leads to effective organisational performance. Ethics, values and behaviour do count.

[1] Pat Barratt, Australian Auditor-General
[2] Hilmer, F (1992): Strictly Boardroom
[3] Richard LeBlanc

S08.1

ENDOSCOPIC TREATMENT OF VESICOURETERAL REFLUX: CURRENT STATUS

Professor Prem Puri

Primary vesicoureteral reflux (VUR) is the most common urological anomaly in children and has been reported in 30 % to 50% of those who present with urinary tract infection (UTI). The association of VUR, UTI and renal parenchymal damage is well known. Reflux nephropathy is the case of end stage renal failure in 3% to 25% of children and 10% to 15% of adults. There has been no consensus regarding when medical or surgical therapy should be utilised. A number of prospective studies showed low probability of spontaneous resolution of the high grade of reflux during longterm follow-up with low dose antibiotic prophylaxis. Furthermore, all of these studies showed that observation therapy does carry an ongoing risk of renal scarring. Open surgery was the standard for the treatment of high grade reflux. Although ureteral reimplantation is effective, this operation is not free of complications.
Endoscopic correction of vesicoureteral reflux has become an established alternative to long-term antibiotic prophylaxis and surgical intervention in the treatment of vesicoureteral reflux. The majority of the studies reporting longterm effectiveness of the endoscopic approach used polytetrafluoroethylene as a tissue-augmenting substance which has been used in the clinical medicine for nearly 40 years with minimal morbidity. We used this tissue augmenting substance for more than 18 years with no morbidity. However, some have been concerned with the use of polytetrafluoroethylene as implant material because of distant particle migration after periurethral, periureteral and intravenous injection was reported in animal studies. We agree that the possibility of polytetrafluoroethylene particle migration cannot be ignored. For these reasons new injectable substance alternatives to polytetrafluoroethylene paste have been sought and a number of other tissue-augmenting substances have become available for endoscopic treatment of VUR. Presently Dextranomer/hyaluronic acid copolymer (Deflux) appears to be the most promising alternative to Teflon in the treatment of VUR.

S08.2

The Role of Interventional Radiology in the management of Paediatric Urological Disease

Dr. R P Davies

Close co-operation and communication between radiologist, surgeon, anaesthetic team and members of the interventional radiology team are vital ingredients in the treatment of paediatric urological disease by interventional techniques.

While literature reports are (relatively) sparse, a diverse range of interventional radiology treatments has been reported since the late 1970's. The number of radiologists practising in this area remains limited. However, the following description indicates the extent to which an enthusiastic and competent radiologist can assist the paediatric urologist and expand treatment options.

In the neonate and infant, management of acute renal failure can be assisted by nephrostomy for temporary relief of hydronephrosis, or medium term stenting of the ureters, by a cross over left to right ureteric stent.

In older children, the full range of percutaneous nephrolithotomy options can be offered, using combined ultrasound and fluoroscopic guidance and 'down-sized' devices to access and treat renal tract stones. Retrieval of a proximally migrated pediatric double-J ureteral stent is occasionally requested by the referring urologist. Mangement of re-stenosis following PUJ surgery is of value in selected cases. Temporary external drainage prior to formal PUJ surgery may demonstrate significantly greater than expected renal reserve and prompt renal salvage rather than excision.

Hypertensive disease due to renal arterial stenosis can be significantly improved by angioplasty techniques. Assessment by selective renal vein renin assay is recommended as a part of the work-up protocol, as bilateral disease and branch stenosis is more common in the paediatric population as a cause of de-stabilisation of the renin-angiotensin system. This may respond to angioplasty, local ablation by ethanol or branch vessel occlusion as a kidney preserving strategy.

Other vascular interventional techniques applicable in children include management of renal vascular trauma, placement of temporary hemodialysis devices, treatment of angiomyolipomas, percutaneous therapy of paediatric varicocele, treatment of priapism due to arterial fistula, and treatment of traumatic A-V fistula following biopsy and other surgical complications of the transplant kidney.

Conclusion: With good communication and co-operation, an experienced paediatric interventional radiologist can augment the scope and quality of a paediatric urological service.

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S08.3

LAPAROSCOPY AND INTERSEX

Chris Kimber

Laparoscopy is a simple technique used to clarify the phenotype of children with intersex anomalies. Simple endoscopy is easily performed in the neonatal period. The particular situations where it aids diagnosis includes

1) XX males
2) Mixed gonadal dysgenesis
3) Testosterone biosynthetic defects.

At laparoscopy Mullerian structures can be assessed and photographed. Gonadal biopsy may be required. Occasionally this operation decides sex of rearing. Gonadectomy is rarely required at this time. Once the diagnosis is established and sex of rearing determined, laparoscopy plays an important role in genital reconstruction. We employ this technique for

1) resection of utriculus and Mullerian remnants including hysterectomy
2) strip biopsy +/- gonadectomy for mixed gonads.

Several gonads have long term malignancy risks and late gonadectomy is common. In addition the streak gonads of Turner's syndrome are easily removed.
Laparoscopy can also be used to assess and provide definite treatment for the impalable gonad. The length of the testicular vessels are ascertained and a laparoscopic orchidopexy as a one or two (Fowler –Stevens technique) stage procedure is performed.. Several boys with intersex anomalies develop recurrent epididymo-orchitis and laparoscopic division of the vas is required.
Laparoscopy has a widespread role is intersex disorders. It allows tissue diagnosis and biopsy with minimal trauma. Accurate patient assessment is facilitated by this technique.

S09.1

CHRONIC ALLOGRAFT NEPHROPATHY; PATHOLOGICAL FEATURES

Brian Nankivell

Chronic allograft nephropathy is the major cause of kidney transplant failure despite improvements in immunosuppression., and is characterized by progressive renal dysfunction accompanied by chronic interstitial fibrosis, tubular atrophy, vascular occlusive changes and glomerulosclerosis, Its pathophysiology remains poorly understood. Longitudinal histological analysis suggests that chronic allograft nephropathy consists of two distinctive phases of injury occurring at different times after transplantation within different compartments within the kidney. Early tubulointerstitial damage correlated with immunological factors, such as severe acute rejection and the onset of persistent subclinical rejection. Damage from ischemia-reperfusion injury and the quality of the donor would also reduce functioning nephrons after transplantation. Acute cellular rejection causes minimal direct damage if detected and treated promptly, unless it is severe ("steroid resistant") or leads to subclinical rejection. Subclinical rejection may is common early after transplantation and when present may be followed by chronic interstitial fibrosis, tubular atrophy and nephron loss, contributors to chronic allograft nephropathy. Powerful immunosuppression can reduce the risk of this and the onset of true chronic rejection, defined by sequential histology and implying continuous immunological injury, but must be tempered by the risks of viral infections, including CMV, EBV and BK nephropathy within the graft. Later damage occurring months to years after transplantation is histologically characterized by progressive arteriolar hyalinosis, ischemic glomerulosclerosis and further interstitial fibrosis. This appears primarily associated with the histological pattern of calcineurin inhibitor nephrotoxicity, characterized by increasing arteriolar hyalinosis causing small vessel narrowing and progressive ischemic glomerulosclerosis and striped fibrosis. Thus, a kidney transplant initially protected from immunological injury by calcineurin inhibitors may be subsequently damaged and lost to chronic nephrotoxicity caused by these same agents. Immunological factors cause most tubulointerstitial injury early after transplantation, but may recur as a problem if immunosuppression is reduced to subtherapeutic levels or late rejection occurs, often associated with treatment non-compliance. Other late processes that contribute to further damage include incomplete resolution of non-specific tubulointerstitial inflammation, loss of architectural structure of a functioning nephron with the formation of atubular glomeruli, failed remodelling after inflammatory injury and finally recurrent glomerulonephritis. Immunosuppressive treatment should be optimised according to the individual risks within each post-transplant period. Powerful therapy incorporating a calcineurin inhibitor can minimize early immunological injury, but non-nephrotoxic, long-term immunosuppression may be preferable if CAN and/or calcineurin inhibitor nephrotoxicity occurs late after transplantation. Chronic allograft nephropathy represents the histological sequelae of a series of pathological insults that result in incremental and cumulative damage to nephrons within the transplanted kidney from immunological and non-immunological causes. Nephron damage once established, is usually irreversible, resulting in decline in renal function and graft failure. Prevention of damage is key to preserving renal allografts.

S09.2

CHRONIC ALLOGRAFT NEPHROPATHY – THE VIEW OF THE CELL BIOLOGIST

Anette Melk, MD, PhD

Chronic allograft dysfunction is the major cause of late allograft failure in kidney transplantation. Late graft loss can be caused by drug toxicity, de novo and recurrent kidney disease, rejection and allograft nephropathy (AN). AN is defined as reduced renal function without features of other specific entities. AN accounts for about 40% of graft losses after more than 5 years post-transplantation and is the most common cause for ESRD during the later post-transplantation period. There are several risk factors for the development of AN: besides rejection as an immunological cause, most factors are non-immunological such as donor age, acute brain death, harvesting injury, ischemic time, acute rejection, and recipient stresses (hypertension, lipid disorders, possibly infectious agents). The observation that kidney transplants with AN show some features that are similar to the biology of renal aging (loss of function, atrophy, interstitial fibrosis, and fibrous intimal thickening of small arteries) and that these features appear more rapidly in previously aged kidneys, led us to propose that AN could reflect an accelerated aging process. We showed that human renal aging is accompanied by the appearance of cell senescence markers such as telomere shortening and the expression of $p16^{INK4a}$. In a mouse transplant model, we found that acute rejection in kidneys from old donors not only induced $p16^{INK4a}$ but also led to the rapid development of tubular atrophy and loss of tubular cells, despite similar host immune response and donor immunogenicity when compared to young donors. In a study examining whether transplanted kidneys with AN showed excess expression of $p16^{INK4a}$, we found that kidneys at the time of implantation manifested relatively little fibrosis and atrophy and low levels of $p16^{INK4a}$ staining. However, when biopsied for abnormal function, many kidneys showed fibrosis and atrophy and high levels of $p16^{INK4a}$ staining. We found similar changes in native kidneys with chronic renal failure suggesting that $p16^{INK4a}$ is associated with deterioration of renal function. The results indicate that irreversible cell cycle arrest, as manifested by $p16^{INK4a}$, accompanies and may mediate the loss of parenchyma in transplant kidneys and native kidneys with deteriorating function. The observation that cells with the biological features of senescent cells in culture are present in the kidney and may be involved in organ pathology is important. It provides an explanation for the lack of regeneration and the ongoing cell deterioration in renal diseases displaying atrophy and fibrosis. Since $p16^{INK4a}$ is not just a marker for age but also for transplant stress, these results have important implications also for pediatric transplants.

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S09.3

THE VIEW OF THE CLINICIAN

Stephen Alexander

CAN is now redefined to cover the range of chronic renal damage that leads to loss of function in an allograft.
Clinically we now realise that there are patient, donor and treatment issues, all of which can contribute to the longterm development of CAN. How is this important? In paediatrics the survival of kidneys now is better than that of any other age group.
In adults CAN is the major cause of long term graft loss and has also shown the least change over the last 20 years. For paediatrics this is the major problem facing these children in terms of their long-term outlook. A child transplanted at 10 can expect 15-20 years from a LRD kidney. Thus a child can expect to have multiple transplants over their life including periods back on dialysis waiting for an organ. CAN is largely going to be the determining factor.
Donor factors are important. Older donors or those with pre-existing disease are more likely to develop CAN. The state of the donor kidney, including it's size, ischemic time and other surgical factors. In the future it may be possible to define other donor factors predisposing to CAN including cytokine expression and sensitivity to medication. HLA matching has been central to graft outcomes and in CAN may play a role in indirect sensitisation as opposed to direct sensitisation seen in acute graft rejection. Patient factors include the initial cause of graft loss. Hypertension and other factors known to cause progression of renal failure. Urological abnormalities predisposing to recurrent infections may lead to inflammation and chronic damage. Behaviour in particular compliance may have a role in CAN. More biological features may relate to patient polymorphisms involved in inflammation and cell recruitment.
Treatment particularly the use of calcineurin inhibitors play a role in long term kidney damage. Again differences in metabolism of immunosuppressives may be important.
How does the clinician influence the outcome of CAN: A: Choice of donor. B: Features of the patient that are amenable to change. C: Choice of immunosuppression. D: Early monitoring E: Treatment of other contributing factors. F: Participation in trials of newer less nephrotoxic agents.

S10.1

EVOLVING NUTRITIONAL SUPPORT FOR PEDIATRIC ACUTE RENAL FAILURE

Norma Maxvold

Nutritional support for the infant or child with acute renal failure requires a thoughtful review of the development/age of the child and the basal energy and protein needs therein. Rapid growth and development in the first few months of life require higher energy and protein intake/kg/day to meet these needs. As growth slows, likewise there is gradual decrease of the energy/protein/kg needs as the predominant expenditure becomes that of maintenance requirements for cellular and organ function (Heinig MJ, et al Am J Clin Nutr 1993;58:152-161. Widdowson EM. Nutrition. *In* Davis JA, Dobbing J (eds). Scientific Foundations of Pediatrics. Philadelphia:WB Saunders, 1974,p47).
Current recommendations by the Food and Nutrition Board, National Research Counsel, National Academy of Sciences, for Recommended Dietary Allowances reflect these energy/protein needs per developmental stage, starting at ~110kcal/kg/day energy and 2.2g/kg/day for the first 6 months, then gradual decline toward 40kcal/kg/day and ~ 1g/kg/day of protein in late adolescence(Food and Nutrition Board, Commission on Life Sciences, National Research Council, National Academy of Sciences. Recommended Dietary Allowances. 10th ed. Washington, DC:National Academy Press, 1989,p24-38, 52-77.)
The above pediatric nutritional needs coupled with the rapidly progressing knowledge of the neuroendocrine axis during critical illness (Eur J Endocrinol 2000;143: 1-13) and substrate utilization during acute stress (JPEN 1998;22:212-216&Crit Care Med 1998; 26: 860-867), mixed with hypermetabolism caused by the acute illness sets a stage for potential malnutrition during an acute critical illness (Crit Care Med 1981; 9(8): 580-583, Crit Care Med 1991; 19 (12): 1503-1509. & Nutrition 2001; 17(7-8):548-557). Enter now acute renal failure with the heightening of catabolism which further amplifies nitrogen efflux, making a nitrogen balance difficult to obtain (Miner Electrolyte Metab 1998;24:47-54, JPEN 2002; 26:77-92 &. Nutrition 2003;19:733-740). Herein lies the pediatric acute renal failure patient, a potential nutritional catastrophe, not only is energy requirements difficult to predict and support but the aforementioned protein to energy ratios are clearly not applicable.
Additional aspects of uremia likewise affect the nutritional balance, as does the form and prescription of renal replacement therapy (Kidney Int 1985; 28:490-497 & AM J Clin Nutr 1992; 55:468-472 & Kidney Int 2000; 58(6):2564-2570& Kidney Int 1999;56(Suppl 72):S56). The role of leptin in renal failure as well as the altered amino acids spectrum and clearance and what role glutamine may play as a pivotal amino acid in nitrogen balance and protein synthesis, is yet to be defined in acute renal failure (J Am Diet Assoc. 2002; 102(8):1119-1125, Am J Clin Nutr 1994; 60:418-423 ,Nutrition 1996; 12:S68-70& JPEN 1999;23:S45-48). The desire to support the nutritional needs yet not overfeed during critical illness has led to studies of substrate utilization and nitrogen balance (Am J Clin Nutr 2001;74:664-669, JPEN 1996;20:56). Further research, including collaborative, multicentered studies, is necessary to optimize not only nutritional therapies but timing of such therapies.
Much has been learned from our adult colleagues in the timing of interventions during acute illness to obtain restoration of balance/homeostasis during nutritional support. Early exogenous insulin therapy appears to have improved outcomes in critically ill patients, whereas use of growth hormone produced a negative effect on outcome in prolonged critical illness (N Engl J Med 2001;345:1359-1367 & N Engl J Med 1999;341(11):785-792).
A nutritional approach to the pediatric acute renal failure patient is outlined in this presentation with references to the combined accumulative knowledge that is available today.

S10.2

NUTRITION IN CHRONIC KIDNEY DISEASE: THE ROLE OF DIET AND INFLAMMATION

Robert H. Mak, Wilson Cheung, Roger Cone and Daniel Marks

Malnutrition is defined as abnormalities caused by an inadequate diet but is often used inappropriately to describe the syndrome of loss of body weight with muscle mass being replaced by fatty tissue and declining serum proteins present in patients with chronic kidney disease(CKD). This syndrome is more accurately described as cachexia. Malnutrition is rare when a properly monitored diet is prescribed for patients with CKD. Rather, diet intolerance is common in CKD. Foods rich in protein lead to metabolic acidosis and accumulation of uremic toxins. An excess of salt will aggravate hypertension and phosphate rich foods will accelerate secondary hyperparathyroidism. Whilst the initial conclusion of the Modification of Diet in Renal Disease(MDRD) study was that low protein diets did not slow the loss of renal function, it was subsequently found that patients who were successful in lowering their dietary protein by 0.2 g/kg had a reduced loss of renal function and an increase in time to dialysis or death. Successful dietary protein restriction also leads to significant improvements in acidosis, uremia (BUN) and hyperphosphatemia as well as a reduction in proteinuria. Dietary protein restriction did not affect the progression in renal failure in children with CKD. Proteinuria and blood pressure control explain a large part of the variability of large-scale clinical trials and may be causally related to the decline in renal function. There is evidence that children with CKD have suboptimal caloric intakes. Caloric intake correlated with height velocity in children with CKD and animal studies suggested that the energy cost of growth is increased in renal failure. Caloric supplementation improved height velocity in children on dialysis. However when energy intake exceeded 75% RDA, further growth improvement did not occur. Despite the general use of supplemental feedings in children with CKD, it is till not known whether these supplements consistently improve height or weight gain. Most recently, it has been shown that dietary restriction of phosphorus with the aim of preventing secondary hyperparathyroidism leads to catch-up growth in children with mild to moderate CKD.
Cachexia is common and is an important risk factor for poor quality of life and increased morbidity and mortality in both adults and children with CKD. Poor dietary intake, inflammation and acidosis are important causes but the underlying mechanism is poorly understood. Resting metabolic rate is also increased in CKD. Circulating concentrations of cytokines, such as leptin, tumor necrosis factor and interleukins 1 and 6, are increased in patients with CKD and correlate with the degree of cachexia in these individuals. Cytokines signal through the melanocortin receptors(MCR) and neuropeptides such as agouti-related peptide(AGRP) in the hypothalamus. The hypothalamic melanocortin system is important in the regulation of nutrition by modulating appetite and metabolic rate. There is experimental evidence of perturbations of the melanocortin system in renal failure. MC4-R knockout mice and AGRP-treated wild type mice resist the cachetic effects of renal failure on total body weight gain, body composition (lean body mass and fat mass) and metabolic rate. Thus, the melanocortin system may have an important role in the pathogenesis of cachexia in CKD. Understanding the molecular mechanism of cachexia in CKD may lead to novel therapeutic strategies.

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S10.3

NUTRITION OF INFANTS WITH RENAL DISEASE

Tulassay, Tivadar

Newborns and infants with renal disease are a special population in which several aspects of nutrition, differing from those in older patients, should be taken into account.
The nutrition of small infants with chronic renal failure (CRF) affects the patients' growth and condition in several important ways. First, the infant's normal rate of growth and physical development depend on the adequate intake of calories, protein, and micronutrients. Failure to meet the patients' requirements of these has a long-term impact on childhood development. Second, nutrition may induce metabolic and biochemical changes in sick infants with CRF (protein, lipid, and glucose metabolism), influencing the progression of renal disease and associated complications. Nutritional interventions have widely been used in older patients with pre-terminal renal failure to minimize the progression of CRF.
The technical difficulties associated with feeding infants and young children with CRF or end-stage renal failure (ESRF) are well known. While these may be dealt with by taking adequate nutritional measures (i.e. tube feeding or IV supplementation), the ideal composition of food which should be given to these patients is still unknown. This is due to the very limited number of infants with CRF and the restricted amount of available therapeutic data.
The ideal food for infants up to 6 months of age is breast milk. The composition of breast milk is optimal to infants' nutrition; however, it does much more than just provides infants with an adequate supply of nutrients to meet the requirements of their growing bodies. A considerable amount of evidence shows that breast milk also provides infants with a resistance to infectious disease. The protection against infection provided by breast milk is partly connected to the modulation of indigenous microflora. Many of the components in breast milk may influence the development of the microbial ecosystems of breastfed infants which are dominated by bifidobacteria. Breastfeeding plays a substantial role in the postnatal development of the immune system by putting this intestinal microbial machinery in place.
These benefits of breast milk are especially important for infants with CRF. Therefore, it would seem reasonable to postulate that the nutritional support of infants with CRF should be based on breast milk. Depending on the needs of the patient, breast milk should be supplemented with adequate formula, if it becomes necessary.

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S10.4

NUTRITIONAL ASPECTS OF CHRONIC PERITONEAL DIALYSIS IN CHILDREN

A. Edefonti, F. Paglialonga, S.Loi, M.Picca and the Italian Registry of Chronic Peritoneal Dialysis

Malnutrition is a major problem in children treated with Chronic Peritoneal Dialysis (CPD) Risk factors include: inadequate nutrient intake, increased protein losses, insufficient metabolic control, long-term dialysis, insufficient dialysis dose delivery.
The use of different nutritional assessments, like dietary intake, serum albumin and bioimpedance analysis, which take into account different aspects of nutritional status, is probably the best way to diagnose malnutrition.

As an alternative, a nutritional score based on anthropometry and BIA, the ABN score, has been recently applied to children on CPD. It is based on nine non-invasive, inexpensive and easy to apply parameters: A1 (height, weight and body mass index) and A2 (MAMC, AMA and AFA) anthropometric parameters, and BIA parameters (reactance, phase angle and distance). All of these indices are expressed as standard deviation scores (SDS) using a 5-point scale. Average scores are established for each of the A1, A2 and BIA parameters, and then summed to obtain the ABN score using a dedicated software programme.
In order to establish the cut-off value between normal nutritional status and malnutrition, the method was applied to 264 healthy children, and distribution percentiles were calculated: the ABN score corresponding to the 3rd percentile (10.33) was considered the limit of normality.
In order to identify the prevalence and causes of malnutrition, the ABN score was applied to children on CPD in a prospective multicenter study of the Italian Registry of CPD.
Thirty two patients, mean age 9.9 ± 4.2 years, have been enrolled so far in the study. Sixty six % had an ABN score > 10.33, 34% had an ABN score <10.33. Only two children were severely malnourished (ABN score <6).

Two parameters significantly correlated with the ABN score: duration of dialysis and total weekly creatinine clearance (TCrCl). Children with a duration of dialysis >24 months months and values of TCrCl <60l/week/1.73sqm were more frequently malnourished than those with a shorter dialysis duration and higher TCrCla duration. Moreover, in patients with a duration of dialysis > two years, the prevalence of malnutrition was high (33%) even with TClCR>60 l/week/1.73sqm, suggesting that other factors could be responsible for malnutrition in long-term PD.
In conclusion, malnutrition is a common problem in children treated with CPD. Using nutritional score systems allows for a more precise assessment of nutritional status and all the factors causing malnutrition.

S11.2

MONOGENIC FORMS OF RENAL DYSPLASIA: IMPLICATIONS FOR MOLECULAR PATHWAYS INVOLVED IN DYSPLASIA

Norman D. Rosenblum MD

Summary
Renal dysplasia, defined as malformation of renal tissue elements during embryogenesis, is a major cause of kidney failure during childhood. Renal dysplasia, with or without associated urinary tract obstruction, exists as an isolated disorder or as a component of many distinct multi-organ syndromes. Identification of single gene mutations in humans with renal dysplasia coupled with advances in murine developmental nephrology is providing novel insights into critical molecular pathways that control formation of the kidney in health and disease.
Formation of the mammalian kidney is initiated by reciprocal inductive interactions between the metanephric blastema and the ureteric bud. These interactions result, in part, in growth and branching of the ureteric bud and formation of collecting ducts, a process termed branching morphogenesis. Similar to other developmental processes, branching morphogenesis is being defined as a morphogenetic pathway in which three-dimensional tubular structures are built by a combination of cellular events (e.g. cell proliferation) that are controlled, in turn, by interacting molecular signaling pathways.
Identification of genes that are mutated in Branchio-Oto-Renal (BOR) Syndrome and Simpson-Golabi-Behmel Syndrome (SGBS), complemented by investigations of these genes in genetic mouse models, is providing insight into molecular signaling pathways that control renal branching morphogenesis. Patients with BOR Syndrome exhibit renal dysplasia and mutations in *EYA1*, a transcription factor. Mutational inactivation of *Eya1* in mice, results in bilateral renal agenesis due to a failure of ureteric bud outgrowth. Studies of *Eya1* in the context of other genes known to control branching morphogenesis has revealed that *Eya1* controls the expression of Glial-Derived Neurotrophic Factor (GDNF), a metanephric blastema-derived secreted growth factor that activates its cognate ureteric bud cell surface receptor, RET, to stimulate ureteric bud growth and branching. Patients with SGBS exhibit renal medullary dysplasia and mutations in Glypican-3 (*GPC3*), a cell-surface heparan sulfate proteoglycan. *Gpc3* null mice exhibit medullary cystic dysplasia, characterized by massive collecting duct cell apoptosis preceded by enhanced branching morphogenesis and ureteric bud cell proliferation. Studies of genetic and molecular interactions in mice demonstrate that GPC3 modulates the activity of bone morphogenetic proteins, secreted growth factors that act via intracellular Smad proteins to inhibit branching morphogenesis via effects on cell proliferation.
Taken together, these discoveries reveal the existence of opposing signaling pathways that control the amount of branching during early kidney morphogenesis, the influence of early branching on the formation of the renal medulla, and the contribution of these mechanisms to the pathogenesis of renal dysplasia.

S11.3

GENETICS AND MOLECULAR PATHOGENESIS OF NEPHRONOPHTHISIS

Corinne Antignac has kindly agreed to present this topic, however was not able to submit an abstract.

S11.4

GENE-BASED TESTING: INDICATIONS, ETHICS AND PITFALLS

Frances Flinter

The steady progress of the Human Genome Mapping Project means that new genes are identified every week, including several for genetic renal diseases. It may takes months or years before a sufficient proportion of mutations is identifiable to justify setting up a mutation testing service, and obtaining funding for a service which may only perform a handful of tests a year is often difficult. Nevertheless, an increasing range of tests is now available, facilitating confirmation of suspected clinical diagnoses, carrier tests, prenatal diagnosis and occasionally preimplantation genetic diagnosis for certain diseases.
Diagnostic testing is rarely controversial, but presymptomatic testing during childhood for adult onset diseases is generally regarded as unwise by many professionals, although it is regularly requested by the parents of children at risk. The availability of prenatal diagnosis (PND), and the gestation up to which a legal abortion can be performed, varies considerably around the world. Individual couples may also be influenced by their own religious and moral beliefs in deciding whether or not to have PND.
The most controversial area is preimplantation genetic diagnosis (PGD) which is available in countries such as Australia, the UK, France and the USA, but illegal in several other countries. In some countries it is strictly regulated (e.g. the UK) but in the USA it is completely unregulated, and PGD tourism is well recognised. Particular difficulties arise if a couple wishes not only to exclude a recurrence of a genetic disorder, but also to 'design' an HLA matched so-called 'saviour sibling' to provide stem cells for a sick older child in the family, or, theoretically at present, a tissue compatible potential kidney donor.
The Four Principles of medical ethics were developed by Tom Beauchamp and James Childress in the US and first published in 1979. The theory is based on four major moral commitments: autonomy, non-maleficence, beneficence and justice. It can be very useful to consider any ethical dilemma under each category. When more than one person is involved, for example in a family where the actions of one may help another, and the decision making is being done by a third member whose welfare is directly influenced by the wellbeing of the other parties, the situation can become very complicated. Examples will be discussed, and the audience invited to express their views.

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S12.1

A PEDIATRIC INTENSIVIST'S VIEW OF ACUTE RENAL DISEASE

Barry Wilkins MD, MA, BChir, MRCP(UK), FRCPCH, FRACP, FJFICM, DCH(Lond)

Most acute renal failure (ARF) in infants and children occurs in the pediatric intensive care unit (PICU). Outside of PICU, ARF has a low mortality, but an appreciable incidence of chronic renal impairment (CRF). ARF in the PICU is generally believed to have a high mortality, though not as high as in adult ICUs, because it is associated with systemic disease, especially systemic inflammatory response syndrome (SIRS) with distributive shock and multiple organ dysfunction (MOD) secondary to trauma, sepsis, burns, hypoxic-ischemic insults and cardiopulmonary bypass (CPB), and prior normal renal function. Nephrotoxic drugs are also implicated, especially in oncology patients. Exact mortality is unknown, but is likely to be related to the underlying disease. Survivors have a lower incidence of CRF than with renal causes of ARF.
A survey of our own PICU suggests that at least 10% of admissions have clinically relevant acute renal impairment. Epidemiology of ARF in PICU is poorly evaluated, with little information on prognostic factors and outcome. This results partly from the lack of an adequate definition. There are over 30 definitions in the literature. It is clear that ARF is a spectrum from normal to total renal shut-down, and not all renal impairment is of clinical significance to the intensivist. The lack of utility of any reference standard for size (e.g. weight, surface area), and of a single upper limit of normal for creatinine, or lower limit of urine flow, in children of different ages compounds this problem. Not all ARF is oliguric or polyuric. Much ARF in PICU is sodium conserving, i.e. has a low fractional sodium excretion (FENa). Many features of ARF are non-specific. For example, most oliguria, hyperkalemia and uremia are not ARF, and there are other common causes in PICU of hyperphosphatemia and metabolic acidosis. Even when hyperkalemia is associated with ARF, it is not caused by potassium retention, but by redistribution between compartments.
We are conducting a one-year prospective epidemiological survey of ARF in PICU, to identify clinical and biochemical markers, causes, risk factors for CRF and death, to describe management and outcome, and to develop an improved measurement threshold for diagnosing clinically significant ARF based on creatinine and oliguria. The utility of Cystatin C, a more recently described marker of glomerular filtration, is also being evaluated.
Modes of renal replacement therapy (RRT) have evolved over the last 20 years. Continuous RRT (CRRT) has replaced intermittent hemodialysis (IHD) on the basis that hemodynamic stability is improved, especially in patients with SIRS, and management of fluid balance is more flexible and tightly controlled.
Hemofiltration has largely superseded peritoneal dialysis (PD), though some PICUs including ours continue to use PD in CPB patients after open heart surgery for congenital cardiac disease, because a peritoneal drain is placed intraoperatively, and the indication for RRT is most often for fluid control in the presence of brief oliguria. Veno-venous hemofiltration has superseded arteriovenous, and new technology allows a high level of control of blood flow, hemofiltrate flow, regional or systemic anticoagulation and monitoring of filter integrity, without compromising the circulation. Bioartificial filters may be not far ahead. As much CRRT is performed in our unit for non-renal problems as for renal failure, such as water overload, electrolyte disturbances and inborn errors of metabolism. For this reason and the need for integration of CRRT into the total patient management strategy has led to CRRT being adopted as an intensivist-led therapy in Australia. Attention to circulating volume, blood pressure and cardiac output is of paramount importance. The future holds the possibility of new agents such as low dose vasopressin, acetylcysteine, dopamine and adenosine receptor agonists, natriuretic peptides, endothelin A receptor antagonists, growth factors, anti-adhesion molecule compounds and free radical scavengers, and stem cell research.
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S12.2

HAEMOFILTRATION – INDICATIONS, PRESCRIPTIONS, NUTRITION AND DRUG CLEARANCE

Ian Baldwin has kindly agreed to present this topic, however was not able to submit an abstract

S12.3

ANTICOAGULATION, SOLUTIONS AND OUTCOMES IN PEDIATRIC HEMOFILTRATION

Timothy Bunchman

In the last decade, advances in hemofiltration have made it equally adaptable for both pediatrics as well as adults. These advances have primarily been made in the way of techniques.
Data by Barenbrock et al (Kid Int 2000, 58:1751-7) have demonstrated a metabolic and hemodynamic advantage in bicarbonate based solutions as compared to lactate based solutions. Advances in North America as well as Europe have demonstrated the ease of availability of bicarbonate based solutions for hemofiltration. These solutions would be either Biaflac (Edwards), Normocarb□ (Dialysis Solutions, Inc., Toronto, Canada), or Prismasate (Gambro). These solutions ca be used for convective or diffusive modalities (Bunchman et al; Peds Neph 2002, 17:150-4; Bunchman et al; AmJKD 2003, 42:1248-52).
The advantages of these industry solutions are that they are physiologic and they improve acid based metabolism more rapidly than lactate based solutions. A recent survey of the PCRRT listserve has demonstrated a very high morbidity and mortality rate with pharmacy made solutions. Therefore, the use of industry sponsored solutions allows prevention and decreased risk of mortality. Anticoagulation for hemofiltration has classically used heparin. Advances in the last ten years have demonstrated the use of citrate anticoagulation. Heparin has been used in hemodialysis as well as hemofiltration for three decades. Heparin is used by binding the coagulation factors prolonging the ability to clot, and the effectiveness can be measured at bedside by either an activated clotting time (ACT) or by a PTT drawn at the lab (Geary et al; Peds Neph 1991, 5:220-4). An ACT is roughly targeted at 1.5 to twice the normal range as well as the PTT is for anticoagulation. The advantage of heparin is its ease of application, its inexpensiveness, as well as a long history of knowing how to utilize this medication. The disadvantage of heparin is the effect upon systemic bleeding as well as its effect upon heparin induced thrombocytopenia.
Recent advances with the use of citrate anticoagulation have really made heparin less common at many institutions. Citrate works by binding calcium within the blood volume. By binding calcium one then removes calcium from the coagulation process, thereby making the patient less coagulable. By giving citrate post patient but into the circuit one can decrease the calcium of circuit, decreasing the risk of clotting of the circuit. However, one needs to give calcium back to the patient in order to avoid citrate intoxication. Citrate is subsequently cleared both by hemofiltration (coefficient of roughly 1: Chadha et al; Peds Neph 2002, 17:819-24) or by hepatic metabolism (Bunchman et al; Peds Neph 2002, 17:150-4). Citrate also can build up in the patient, causing a citrate gap. This is seen clinically when the total calcium is rising with a stable or dropping ionized calcium of the patient. This concept of citrate gap can easily be remedied by backing off the citrate exposure by increasing clearance. Citrate also metabolizes to bicarbonate. Therefore, one risk of citrate anticoagulation is alkalemia. This may be exacerbated by the combined use of bicarbonate based solutions and citrate. This could easily be offset by infusion of normal saline (pH 5.0-5.4) or by adjustment downward of the bicarb bath of the dialysate or replacement fluid.
Data to date has shown that citrate is equally as effective to heparin for circuit prolongation and may have less risk of clotting (Brophy et al; JASN 2003, 14:731A, Abst su-po 891). Outcome of pediatric hemofiltration has changed over the last ten years. Initial data has suggested that outcome in patients on hemofiltration may be related to the underlying renal disease or the use for pressors (Bunchman et al; Peds Neph 2001, 16:1067-71). More recent data has suggested that the amount of fluid accumulation at the time of initiation of CRRT may predict the outcome (Goldstein et al; Pediatrics 2001, 107:1309-12). A multicenter study within the pediatric perspective of CRRT registry has demonstrated in 130 patients that fluid accumulation at the time of CRRT initiation is the number one predictor of mortality. PRISM scores at the time of initiation of CRRT also predicts outcome, yet at the time of admission to the ICU does not predict outcome.
Finally, data by Ronco et al (Lancet 2000, 356:26-30) has suggested that earlier initiation of CRRT may also affect outcome based on the initial urea at the time of initiation.

In summary, advances in solutions have identified bicarbonate to be superior to lactate. Work on citrate anticoagulation has shown a lessened risk of coagulation to the patient compared to heparin. Finally, work by many authors have demonstrated that earlier initiation of CRRT in order to avoid fluid overload as well as a very catabolic patient will improve outcome in patients. Industry has done an outstanding job of improving machinery allowing for CRRT to be initiated in the smallest of infants or the largest of children.

S12.4

ACUTE RENAL REPLACEMENT THERAPY IN DEVELOPING COUNTRIES

MI MCCULLOCH, PJ Sinclair

INTRODUCTION: Acute renal failure remains a major problem in countries where gastroenteritis and sepsis is common. Continuous renal replacement therapy in form of CVVH/D may not be available due to cost constraints. Peritoneal dialysis (PD) offers an alternative option using simple techniques and relatively cheap equipment.

OBJECTIVES OF STUDY:

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S13.1

CMV : THE INDICATIONS FOR POST-TRANSPLANT PROPHYLAXIS AND TREATMENT.

MF Gagnadoux*

CMV is the most prevalent viral infection after renal transplantation, particularly in children, who are at risk of primary infection. The main risk factors in kidney-transplanted children are a CMV-positive donor and the use of anti-T-cell antibodies for induction or rejection. CMV infection may remain asymptomatic (proved by sero-conversion or by CMV detection in blood or tissue) or induce "CMV-disease", either pauci-symptomatic (fever, leucopenia) or "tissue- invasive" (mainly lung, liver, gut). Since the availability of an effective anti-viral drug (ganciclovir) and the development of rapid and sensitive methods of viral detection (quantitative antigenemia or PCR) allowing an early diagnosis, the prognosis of CMV infection in kidney recipients has greatly improved. However, besides the lethal risk of some organs involvement, CMV-disease may be harmful for graft survival since the immunosuppressive therapy must be reduced. Therefore in the last decade the effort has been put into prevention of CMV infection in recipients at risk (donor or recipient CMV+). Since the use of a CMV+ donor cannot be avoided because of organ shortage, two strategies may be considered : either "prophylactic" post-transplantation treatment of all at-risk recipients, or "pre-emptive" treatment of infected patients as soon as virus is detected in leucocytes, before clinical symptoms. Both strategies have been used in transplanted children, with diverse success rates. Several therapies may be used as prophylactic treatment : CMV-hyperimmune immunoglobulins (no more available in many countries), acyclovir (of limited efficacy), oral ganciclovir (of poor bioavailability), and more recently the prodrugs with good oral bioavailability named valacyclovir and valganciclovir; oral valganciclovir seems as efficient as i.v. ganciclovir and may become the drug of choice. The preemptive strategy uses i.v. ganciclovir as soon as virus replication is detected, followed by oral ganciclovir, or probably valganciclovir in the future. If there are several reports on oral ganciclovir pharmacokinetics and efficacy in transplanted children, there are still very few reported experiences concerning the pediatric use of valacyclovir and valganciclovir. In case of CMV-strain resistance to ganciclovir, foscarnet or cidofovir have been occasionally tried in children, but their nephrotoxicity limits their use in renal transplantation.

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S13.2

EBV VIRAL LOAD MONITORING & PREEMPTIVE THERAPY

Michael Green, MD, MPH

The growing success and increasing number of children undergoing solid organ transplantation has focused attention on the importance of Epstein-Barr virus (EBV) associated clinical syndromes, including post-transplant lymphoproliferative disease (PTLD), in this patient population. Current efforts aimed at the prevention of complications secondary to EBV take advantage of the fact that the EBV viral load in the peripheral blood is typically elevated prior to the onset of clinical symptoms secondary to this pathogen. Serial monitoring of the EBV viral load in patients at-risk for EBV/PTLD offers the potential of introducing a preemptive intervention before patients develop these infectious complications. While the use of anti-viral agents has not been shown to impact on the magnitude of the viral load or progression of sub-clinical infection to EBV/PTLD, reduction of immune suppression in response to elevated loads has been shown to prevent these complications in pediatric organ transplant recipients. The efficacy of this approach is thought to reflect the ability of the restored immune system to mount an effective cell mediated immune response to EBV infected and transformed B-cells, the source of PTLD. While the increasingly wide-spread availability of assays to measure the EBV viral load should enable broad implementation of this preventive strategy, efforts are needed to standardize the laboratory assays used for measuring the EBV load to assure accuracy and comparability of assays used at individual centers. Additionally, despite the promise of this pre-emptive strategy, additional data are needed to refine clinical thresholds for initiation of pre-emptive therapy as well as for enhancing the specificity of an elevated viral load for predicting the development of EBV disease.

S13.3

DIAGNOSIS OF BK NEPHROPATHY: PREDISPOSING FACTORS AND DIFFERENTIATION FROM REJECTION

Graeme Russ

It is now well-established that the BK strain of polyomavirus causes nephropathy in kidney transplant recipients. Up to 80% of adults have serological evidence of previous infection with BK. The virus is tropic for epithelial cells of the kidney and the urogenital tract. However disease is seen only in immunocompromised hosts in whom activation of viral latency occurs.

Histologically, the appearances are those of an interstitial nephritis which is similar to acute cellular rejection. The diagnosis however can be made by the appearance of intra-nuclear viral inclusion bodies in epithelial cells with associated focal necrosis. Immunohistochemistry can be performed using antibodies that detect the SV40 large T antigen. Ultrastructural examination of the tissue demonstrates viral particles. The clinical correlate of the histological appearance is graft dysfunction.

Although the diagnosis of BK nephropathy requires graft biopsy, adjunctive tools for diagnosis and monitoring have been reported. Urine cytological examination for decoy cells has been reported to be useful and is inexpensive and widely available. The presence of viral DNA in the plasma correlates strongly with the presence of nephropathy because the virus gains access to the circulation via peri-tubular capillaries. It can therefore be used to monitor response to therapy. However viral DNA in the urine has a low specificity as it is likely to continue after successful clearing of the nephropathy because of the ongoing latency of virus in uroepithelium.

Risk factors include the level of immunosuppression and possibly the type of immunosuppressive agents used. The recent advent of this infection in clinical renal transplantation corresponds to the introduction of more potent immunosuppressive agents such as tacrolimus and mycophenolate mofetil. In addition epithelial cell damage appears to promote viral infection. Therefore situations leading to such damage eg. rejection and acute tubular necrosis predispose to its development.

The treatment of BK nephropathy is a difficult clinical challenge. Reduction of immunosuppression should be done carefully to avoid the development of rejection. Whereas some patients will respond, persistence of BK virus can be seen with eventual graft loss. Cidofovir has been reported to be effective in treatment. This agent is nephrotoxic but can be used in low dose with successful reduction in viral loads.

BK nephropathy is a significant cause of graft failure. Some advocate regular screening by urine cytology or plasma DNA monitoring of patients at risk eg those with a recent rejection or who have received heavy immunosuppression.

S13.4

PNEUMOCYSTIS CARINII PNEUMONIA (PCP) PROPHYLAXIS POST RENAL TRANSPLANTATION

H L Pilmore

Pneumocystis carinii (PC) is an opportunistic pathogen resulting in severe pneumonia in immunosuppressed individuals. PC is widespread in the environment and serological studies suggest that most healthy children have been exposed by age 4. A recent meta-analysis showed that PCP developed in approximately 5% of renal transplant recipients who were not receiving prophylaxis. The vast majority of PCP occurs in the first 3-6 months after transplantation and is rare after more than a year post-transplant. In the transplant population, PC infection results in a fulminating pneumonia with a mortality of 34 – 58%.

Risk factors for PCP include episodes of acute rejection, CMV infection and increased intensity of maintenance immunosuppression. There does however appear to be a protective effect of mycophenolate mofetil possibly due to its ability to inhibit the inosine monophosphate dehydrogenase from Pneumocystis carinii. Conversely, both tacrolimus and sirolimus appear to be associated with an increased risk of PCP.

Prophylaxis of PCP with trimethoprim-sulfamethoxazole (TMP-SMX) is highly efficacious. A review of retrospective studies demonstrated no cases of PCP in 1177 patients treated with prophylaxis using TMP-SMX in comparison with a 2.1% incidence of PCP in patients not receiving prophylaxis. Only low doses of TMP-SMX are required to prevent PCP. Prophylactic TMP-SMX has also been shown to prevent urinary tract infections in renal transplant recipients. Unfortunately intolerance of TMP-SMX does occur and thus alternative agents may be required. The most commonly used alternative prophylactic agent for PCP is aerosolised pentamidine.

The duration of prophylaxis is controversial. The highest risk for PCP occurs in the first six months after transplantation and after treatment for acute rejection. If prophylaxis is used it should be for at least 4 – 6 months post-transplantation and should also be given after treatment for acute rejection.

Diagnosis of PCP is generally made using induced sputum or broncho-alveolar lavage to identify the PC. Because of the high mortality of PCP in the renal transplant population, treatment should be instituted as soon as possible. The drug of choice is TMP-SMX. In patients with severe PCP, corticosteroids have been shown to reduce mortality and should be included in therapy.

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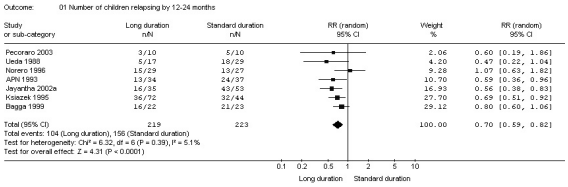
S14.1

EVIDENCE BASED APPROACH TO THE MANAGEMENT OF STEROID SENSITIVE NEPHROTIC SYNDROME (SSNS) IN CHILDREN

EM Hodson

Introduction: Although prednisone and non-steroid agents have been used for over 30 years in children with SSNS, the optimal use of these therapies continues to be debated.

Treatment of first episode of SSNS: The standard regimen of prednisone 60mg/m2/day for 4 weeks followed by 40mg/m2 on alternate days is associated with a high risk for relapse. A meta-analysis of 7 randomised controlled trials (RCT) demonstrated a significant reduction in the risk for relapse at 12-24 months with prednisone therapy for 3 months or more compared with 2 months (Figure). The risk for relapse fell by 11% for each additional month of treatment over 2 months. Assuming a relapse rate of 60% after 2 months' treatment, the relapse rate would fall to 32% with 6 months of therapy. Also the risk for relapse was significantly lower with 6 months of treatment compared with 3 months (2 trials; relative risk [RR] 0.52; 95% confidence intervals [CI] 0.32-0.86). Adverse effects at 1 year were not significantly increased with longer treatment.



Treatment of relapsing SSNS: The risk for subsequent relapse at 2 years is also reduced by prolonged steroid therapy (7 months) compared with daily prednisone till remission followed by alternate day therapy for 4 weeks (1 trial; 64 children; RR 0.60; 95% CI 0.45-0.80). However children with frequently relapsing or steroid dependent SSNS develop steroid toxicity and need alternative treatments. Several small RCTs have shown that cyclophosphamide (2-3mg/kg/d for 8 weeks), chlorambucil (0.2mg/kg/d for 8 weeks), cyclosporin (5mg/kg/d) and levamisole (2.5mg/kg on alternate days) reduce the risk for relapse. Serious adverse effects may be seen with each agent. There was no significant difference in the risk of relapse with azathioprine or mizoribine compared with prednisone or placebo. Mycophenolate appears effective in relapsing SSNS in observational studies but has not been assessed in an RCT.

Conclusions: In children with their first episode of SSNS, data from a systematic review of RCTs indicate that steroid therapy should be administered for up to 6 months. However several trials were of poor methodological quality so treatment benefit could be overestimated. Thus further well-designed RCTs are required to determine the optimal duration of steroid therapy. In children with relapsing nephrotic syndrome, the efficacy of mycophenolate compared with prednisone and with non-steroid agents should be assessed in RCTs. Finally RCTs are required to determine the relative efficacy of non-steroid agents in children with frequently relapsing and steroid dependent SSNS.

S14.2

STEROID RESISTANT NEPHROTIC SYNDROME (SRNS)

Dr.V.K.Sairam

Nephrotic syndrome (NS) is the most common chronic renal disease in children and majority respond to steroids. The hallmark of this disease is characterised by multiple recurrences, which are usually responsive to steroids. A sub-group of children require steroids to be in remission and hence develop dependence (Steroid dependent NS- SDNS). Infrequently less than 10% are resistant to steroid therapy (Steroid resistant NS- SRNS). SRNS group of children are difficult to manage and may show deterioration of renal function, and progress to End stage renal disease (ESRD). The focus of this review will be on steroid resistant nephrotic syndrome.

The initial clinical presentation and laboratory parameters of children with SRNS are similar to the other steroid responsive nephrotics. The clinical course of the disease process however is different as there may be clinical/renal deterioration and no response to steroid treatment. It is required to treat with steroids daily at a dose of 60mg/m2 for four weeks followed by alternate days at a dose of 40 mg/m2 for four weeks and the child who does not show clinical or biochemical response in these eight weeks of treatment qualifies in the group of SRNS.

SRNS group may show renal deterioration and therefore aggressive management is necessary. A renal biopsy is needed in all situations. The suspicion of Focal Segmental glomerulosclerosis (FSGS) is very high and is commonly detected. Other pathological features that are detected are Minimal change disease, IgM nephropathy or diffuse mesangial proliferation. The presence of these pathological findings other than FSGS, in association with steroid resistance makes one think if they belong to the same spectrum of disease as FSGS. This is especially true in several patients, showing lesions consistent with minimal change, mesangial proliferation or IgM deposition on their biopsies, however their clinical behaviour is characterised by steroid resistance and deterioration of renal function and interestingly show the appearance of FSGS only on their subsequent biopsies. Therefore, steroid response is a good predictor of long term prognosis and at times superior.

The child who is steroid resistant after the recommended eight-week course of steroids offers to the Nephrologist very few therapeutic options and is frustrating to manage. Initial treatment with long-term oral steroids and in addition intravenous methyl prednisolone as three-day pulse therapy at a dose of 500mg/m2 body surface area (maximum of 500 mg) twice daily is recommended. The role of extended oral steroid therapy over four months in the treatment of SRNS in the adult populations has been shown to provide better remission rates and is now accepted. There are few reports of success with extended steroid therapy in children as well. The steroid therapy with methyl prednisolone and alkylating agent as described by Mendoza and associates had a remission rate of 66% in the SRNS group. However subsequent studies have not shown similar results. Alternative to steroids are the use of alkylating agents such as cyclophosphamide and chlorambucil and the remission rate is about 20-25% in the SRNS group and the results are variable. In the randomised control study by the International study group of kidney diseases in children it was concluded that cyclophosphamide had no additional benefit to steroid therapy in the treatment of SRNS. There are reports from Gulati and associates with favourable results with the use of intravenous cyclophosphamide for the treatment of steroid resistant focal segmental glomerulosclerosis. This concept of treatment with an alkylating agent has the advantage of lower cost, shorter duration of therapy and longer remission period in the responders. There are also reports of conversion from SRNS to SDNS on receiving treatment with alkylating agent, which is considered beneficial to the child.

Cyclosporin A (CsA) has been used over the last decade in the management of SRNS. The response rate is about 20 to 25%. Children who responded to CsA show a tendency to relapse on tapering or stopping therapy. The relapses are again treated with CsA with response and some develop dependence (CsA dependence). We have reported that a small group of children, who had originally responded to CsA, relapsed when the drug was tapered or discontinued, and then showed diminished or no response to the reinstitution of CsA therapy (Secondary resistance to CsA). The initial steroid response is not a predictor for subsequent development of secondary resistance to CsA, as children with either SDNS or SRNS could develop secondary resistance. The presence of FSGS and complement factors C4 and C1q were found in higher proportion in children with secondary resistance to CsA. How long to treat with CsA? The answer is not clear at this point. Renal biopsy should be considered before tapering or stopping CsA therapy. If there is presence of FSGS or other features such as C4 and C1q immunoreactants, tapering and stopping therapy is associated with the risk of developing secondary resistance to CsA and further deterioration of renal function.

Azathioprine has not been shown to be useful in SRNS. Drugs such as mycophenolate mofetil, tacrolimus are being evaluated for the treatment of SRNS and the results are variable at this point. Plasmapheresis has been attempted and failed in the treatment of SRNS. Other medications that have been used in the treatment of SRNS are vincristine, nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors with none of them showing consistency of favourable results.

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S14.3

MANAGEMENT OF RECURRENT NEPHROTIC SYNDROME (NS) POST TRANSPLANTATION (TX)

Pierre Cochat, Sonia Fargue, Bruno Ranchin

ESRD in patients with NS can occur in those with idiopathic steroid resistant NS, in few patients with an identified form of genetic NS (e.g. nephrin/podocin mutation) and in a limited group of patients with a syndromic form of NS (e.g. Denys-Drash, Frasier, Charcot-Marie-Tooth, Schimke). The risk of post Tx recurrence is limited to patients with idiopathic SRNS who have been shown to produce an abnormal lymphocytic permeability factor whereas those with an inherited podocyte-GBM complex abnormality use to have uneventful post Tx course.
Post Tx recurrent NS has been reported in one third of SRNS children and the risk of graft loss from recurrence after failure of a first graft to recurrence is 40 to 100%. This risk has been approached by using *in vitro* tests such as intragraft gene expression of NF□B and angiotensinogen, and experiments using injection of material into the rat which produce a change in glomerular volume.
Various therapeutic strategies have been proposed as the prognosis of untreated patients is worse than that who are treated. Such a management may be considered at 3 steps of the clinical course. *Pre-treatment*. Bilateral nephrectomy of the native kidneys in patients with residual renal function is recommended to allow an early recognition of post Tx proteinuria. In patients who receive a first graft, pre-treatment using CyA for a week has been proposed if a LRD is available. In those who experienced a first graft loss to recurrence, treatments which have not been tested at the time of the first Tx must be considered including CyA ± plasmapheresis. Indeed any kind of pre-treatment would be hazardous when a cadaver donor is used due to the short time interval to surgery, so that any reasonable pre-treatment is only available with a LRD. *First-line treatment after recurrence*. In patients who were not taking a CyA preventive regime, high dose intravenous CyA should be started at the time of the operation; the potential role of other immunosuppressive drugs has not yet been established. *Second-line treatment after recurrence*. In children who fail to respond to the above treatments, the preferred strategy consists of *ex-vivo* techniques (e.g., plasmapheresis), sometimes in association with cyclophosphamide. Despite controversial results, lasting remissions have been attained by using such a treatment as early as possible.
However, the overall level of evidence for such strategies is low, often based on case reports and expert opinion.

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S14.4

NEPHROTIC SYNDROME IN THE 3RD WORLD – CAUSES, APPROACHES, OUTCOMES, COMPARISONS WITH THE WESTERN PRACTICE

Asiri Abeyagunawardena (Sri Lanka)

Childhood nephrotic syndrome (NS) is a distressing chronic or recurrent renal disorder with potentially life threatening complications. The syndrome can be sub-classified into congenital, primary and secondary forms. The majority of children with primary disease have minimal changes in the glomeruli and 90-95% will respond to corticosteroid therapy. However, the disease is characterised by a relapsing course placing the child at risk of acute complications such as infection, hypovolaemia and thrombosis**.** Frequent relapses result in a significant corticosteroid burden, or the need for cytotoxic immunosupressive therapy, to control the disease. In contrast, steroid resistant (SRNS) and refractory NS have a poorer prognosis with a tendency to progress to end stage renal failure (ESRF). While these latter clinical entities have an unpredictable response to cytotoxic immunosupressive therapy, the favourable long-term renal survival associated with children who enter sustained remission has revived the enthusiasm to treat SRNS with more aggressive immunosuppressive regimens.

The annual incidence of NS is approximately 2-4 per 100,000 in Caucasian children in the United Kingdom while there is racial variation in the susceptibility with a reported incidence of 9-16 per 100,000 British Asian children. Primary NS predominates in the Western hemisphere as well as in the Asian subcontinent. In some African countries however, where hepatitis B and HIV infection is more prevalent**,** secondary forms of NS constitute a significant proportion**.**

In the past 20 years there has been considerable debate regarding the optimisation of the initial corticosteroid protocol. There is a tendency towards treatment with prolonged steroid regimens in the Asian subcontinent compared to the practice in the UK. As a result of the immunosuppression, which is an inherent feature of the disease, immunosuppressive therapy and poor nutrition, infections are a universal concern but more so in the developing world. Relapses are often triggered by viral infections and are probably responsible for the observation of greater proportion of frequently relapsing disease in the Asian subcontinent. Moreover, mortality due to overwhelming infections is not infrequent in the Asian subcontinent while it is a rare occurrence in the western hemisphere.

Children with frequently relapsing, or steroid dependent disease, are the candidates for treatment with cytotoxic or other immunosuppressive drugs. In a cohort of Sri Lankan children compared to a cohort in the UK, cyclophosphamide was used less frequently while levamisole was used in much greater proportion of children. The use of cyclosporine A was limited by financial constraints in the Sri Lankan cohort. A striking difference in the Sri Lankan cohort compared to that in the UK, was the low incidence of SRNS and progression to ESRF in patients with focal and segmental glomerulosclerosis. This probably reflects the relative resistance to use immunosuppressive therapy such as cyclophosphamide in comparison to children in the United Kingdom.

S15.1

BASIC MECHANISMS OF PROGRESSIVE RENAL DISEASE

Allison A. Eddy

Progressive kidney disease is the consequence of a fibrodestructive process. Studies over the past decade have identified key mediators of tubulointertsitial (TI) fibrosis, the primary correlate of renal functional loss. By analogy to a battlefield, the key events in TI fibrosis can be arbitrarily divided into four groups.

(1) The fighters. Macrophages (Mϕ) and myofibroblasts invade the interstitium. Mϕ recruitment involves coordinated efforts between chemokines (eg; MCP-1, chemoattractants (eg; complement) and several leukocyte adhesion molecules. Mϕ release several profibrotic products but may also serve as scavengers to limit the extent of the damage. Myofibroblasts appear to derive from several sources (interstitial fibroblasts, transdifferentiated tubular epilthelium, perivascular cells, circulating precursors) and synthesize the majority of the matrix proteins that accumulate in the interstitium.

(2) Weapons. Mϕ, myofibroblasts and even tubular epithelium synthesize a variety of profibrotic molecules. TGF-β is preeminent but does not act alone. Endoothelin and angiotensin II not only stimulate TGF-β but also have direct fibrosis-promoting effetcs. In addition to promoting matrix protein synthesis, TGF-β may up-regulate the expression of other proteins that have independent fibrogenic effects such as plasminogen activator inhibitor-1 (PAI-1) and connective tissue growth factor.

(3) Kidney defense mechanisms. Within damaged kidneys defense mechanisms may be activated in an attempt to contain the damage. For example, the scavenging activity of Mϕ may be augmented by increased expression of phagocytic receptors (eg; urokinase receptor, angiotensin II type 1 receptor). Production of anti-fibrotic growth factors such as hepatocyte growth factor may be protective.

(4) The battle and destruction. There is no evidence that interstitial deposition of matrix proteins per se is harmful; indeed this is an essential component of successful would healing. Problems ensue when the fibrogenic response destroys the normal kidney cellular architecture. The vulnerable targets are the peritubular capillaries and tubules. Inadequate proliferation and active apoptosis lead to progressive capillary rarefaction, tubular atrophy and ultimately to the formation of atubular glomeruli.

A similar sequence of events typifies the process of progressive glomerulosclerosis although the molecular details of how the resident glomerular cells serve as participants and ultimately as victims is not identical to TI fibrosis. Each of these cellular and molecular participants in the battle of renal fibrosis represents a potential therapeutic target for treatment of human CKD. Furthermore, genetic polymorphic variants may regulate levels of expression and/or activity of some of the fibrogenic proteins leading to speculation that "fibrogenic genotype" may one day prove to be useful as a predictor of CKD risk and to custom design therapy using a pharmacogenomics.

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S15.2

CYTOKINES IN THE PROGRESSION OF GLOMERULONEPHRITIS

A Richard Kitching

Classical immunopathology considers fibrosis and abnormal scarring to be the outcome of persisting inflammation. Progressive injury in glomerulonephritis is characterized by glomerulosclerosis and interstitial fibrosis. Soluble immune messengers (cytokines) potentially contribute to (or protect from) fibrosis at a number of "levels" in progressive glomerulonephritis, including the "direction" of nephritogenic immune responses in secondary lymphoid organs, "activation" (or deactivation) of immune effectors in the kidney, "amplification" of ongoing inflammation and "direct profibrotic effects", independent of effects on inflammation.

As glomerulonephritis is not a single disease, and different forms of glomerulonephritis are driven by different antigenic and non-antigenic stimuli, the participation of different cytokines in this process will vary. Relevant questions include:

1. By acting in professional immune tissues, cytokines direct immune responses in that lead to glomerular inflammation. Which cytokines play key roles in setting up and determining the direction, intensity and chronicity of nephritogenic immune responses?
2. Are there patterns of injury (for example glomerular crescent formation) that are mediated by common cytokines? How do these cytokines play a role in chronic responses?
3. What are the important cytokines at sites of renal inflammation? Do they activate or inactivate effector immune cells or intrinsic glomerular cells?
4. Are the roles of cytokines in chronic inflammation similar to those in acute inflammation?
5. Which cytokines have direct pro- or anti-fibrotic effects in progressive renal injury independent of their effects on nephritogenic immune responses

Potential key cytokines with effects in these areas include T cell directing cytokines (such as IL-12), "proinflammatory" cytokines (such as TNF and IL-1□, "anti-inflammatory" cytokines (such as IL-10) and profibrotic cytokines (such as TGF-□.

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S15.3

EXPERIMENTAL APPROACHES TO MODULATE INTERSTITIAL FIBROSIS

Tim Hewitson

Regardless of etiology, fibrosis represents the final common pathway in progressive renal disease. Its pathogenesis is however complex, involving both molecular and mechanical processes. Various studies have shown that interstitial fibrosis is a fibrocontractive process, resulting from both excess matrix synthesis and contraction of the surrounding matrix to increase its density. Morphometric analysis indicates that at least in some circumstances, these two processes are temporally distinct.

Significance of the interstitial myofibroblast

An increasing body of evidence suggests that recruitment of myofibroblasts is the cellular basis of both these processes. Recognised by their *de novo* expression of □smooth muscle actin, myofibroblasts are derived from a number of cells including resident fibroblasts and tubule epithelial cells. Their local proliferation, matrix synthesis and contraction of surrounding collagen increase the density of extracellular matrix.

Can we alter myofibroblast activity?

Not surprisingly therefore, many investigators have attempted to modulate interstitial fibrosis by inhibiting myofibroblast activity. These strategies have focused on antagonising the cytokines and other agonists produced after injury, inhibiting the intracellular signal transduction pathways that are activated and finally, taking advantage of the naturally occurring inhibitors that moderate fibrogenesis.

In the first instance, direct inhibition of the polypeptide growth factors stimulating myofibroblasts have focused on TGF□1 and PDGF, the best understood fibrogenic factors. Various pharmacological agents, often developed for quite different applications, have been shown *in vitro* to inhibit the signal transduction pathways implicated in fibrogenesis. Amongst others, prenylation and phosphodiesterase inhibitors have direct effects on mesenchymal cells, reducing proliferation, collagen synthesis and lattice contraction. Relaxin, a naturally occurring inhibitor of fibrogenesis, increases collagenase synthesis.

In vivo strategies

The successful identification of *in vitro* moderators has therefore lead to many of these agents being tested in animal models. Specific strategies have shown benefits in targeting vasoactive mediators with endothelin and angiotensin antagonists. Phosphodiesterase inhibitors and HMG-CoA reductase inhibitors, so-called statins, have ameliorated progressive fibrosis in various models, while the polypeptide relaxin has to some extent abrogated progression in experimental interstitial disease.

In conclusion, a better understanding of the molecular and mechanical basis of fibrosis has lead to the identification of therapeutic targets. Validation of these mechanisms *in vitro,* and their evaluation *in vivo* in animal models, has the potential to lead to therapeutic strategies for not only renal disease, but also scarring in general.

S15.4

DELAYING THE PROGRESSION OF RENAL DISEASE: the evidence surrounding clinical approaches, particularly ACE inhibitors and the role of angiotensins.

David Harris

Strategies of proven benefit for slowing disease progression in humans with chronic kidney disease (CKD) include blood pressure control, ACE inhibitors (ACEi), angiotensin receptor blockers (ARB), dietary protein restriction, dietary phosphate restriction (in one trial) and glycaemic control (in early type 1 diabetes). Strategies of possible benefit include lipaemic control, especially with statins, and cessation of smoking. The most convincing and widely accepted evidence exists for ACEi and ARB.

There are a number of large scale, prospective, randomised, controlled "hard endpoint" trials which have established the efficacy of ACEi and ARB. ACEi slow the progression to ESRD or death in patients with type 1 and type 2 diabetes, or with proteinuric (> 3 - 500 mg/d) non-diabetic renal disease (APRI, REIN trials). ARBs slow progression in patients with type 2 diabetes, hypertension and albuminuria (RENAAL, IDNT). The combination of ACEi and ARB has a greater anti-hypertensive, and anti-proteinuric effect than monotherapy, and provides greater protection against progression in non-diabetic proteinuric CKD (CO-OPERATE). In these trials ACEi and ARB reduced risk by 15 to 50%.

ACE and ARB exert protection by modifying systemic and intraglomerular hemodynamics, renal cell proliferation, cytokine production, matrix production and metabolism, and inflammatory cell infiltration and activity. The angiotensin system is complex, with recent description of alternative pathways of angiotensin production, an expanding number of angiotensins and angiotensin receptors, local renin-angiotensin pathways and deleterious effects of aldosterone. ACE and ARB differ in their effects on various angiotensin receptors and angiotensins and other vasoactive hormones, providing a theoretical basis for their additive effects.

ACEi and ARB therapy in CKD is aimed at reducing blood pressure and renal protein trafficking and slowing disease progression, and also reducing cardiovascular risk. The majority of patients with CKD die before requiring dialysis, or while on dialysis, from cardiovascular disease. Thus, the protective effects of ACEi and ARB against cardiac disease (heart failure and post-AMI) are important in CKD.

Unanswered questions regarding the use of ACEi and ARB in patients with CKD include ….

- can CKD progression be halted or even reversed?
- is the apparent additive effect of ACEi and ARB merely due to submaximal monotherapy?
- does the efficacy of ACEi and ARB vary depending on aetiology and stage of disease, and patient age, ethnicity, gender and genotype?
- how should treatment targets vary depending on these disease and patient characteristics?
- how should response to therapy best be monitored?
- is there a role for ACEi and/or ARB in non-diabetic patients with mild proteinuria but normal blood pressure and renal function?
- can novel therapies offer anything more than ACEi and ARB ?

S16.1

WHAT'S NEW IN THE AETIOPATHOGENESIS OF VASCULITIS?

Paul A Brogan BSc(Hon) MBChB(Hon) MRCP MSc PhD

There are a number of exciting insights relating to the aetiopathogenesis of vasculitis

Epidemiology and genetics of vasculitis. Henoch-Schönlein purpura (HSP) and Kawasaki disease (KD) are by far the most common vasculitic syndromes in Europe and North America. Takayasu arteritis is the third commonest paediatric vasculitic syndrome worldwide, with high incidence in Asia and parts of Africa [Current Opinion in Rheumatology 2003; 15: 11-16]. These observations point to underlying genetic influences, which so far have yet to be fully elucidated. Mutations in the mannose-binding lectin gene have recently been described in children with Kawasaki disease and are associated with a higher risk of developing coronary artery lesions [Lancet 2003; 361: 1268-70]. Although there is no clear HLA-association with the ANCA-associated vasculitides (AAV) a number of promising genes involved in the control of chronic inflammation have recently been implicated [Cleveland Clinic Journal of Medicine 2002; 69 Suppl 2: SII61-SII63].

Infections.Infectious agents can cause vascular injury by several mechanisms, including direct invasion of endothelial cells, formation of immune complexes, and production of bacterial superantigens (SAgs) [Cleveland Clinic Journal of Medicine 2002; 69 Suppl 2: SII24-SII26]. As regards this latter mechanism, there is a growing body of evidence that SAgs are involved in the aetiopathogenesis of Kawasaki disease [Cleveland Clinic Journal of Medicine 2002; 69 Suppl 2: SII69-SII78], and indirect evidence that they could be involved in other vasculitides of the young [Clinical and Experimental Immunology 2003; 131: 517-527].

Autoantibodies.Autoantibodies associated with vasculitis include antineutrophil cytoplasmic antibodies (ANCA), anti endothelial cell antibodies (AECA), and anti-annexin V antibodies [Clinical and Experimental Immunology 2003; 134:360-364]. Many other autoantibodies have been described with propensity for vascular injury, but the evidence that ANCA are directly involved in the aetiopathogenesis of vascular injury is the most robust. Whilst much is now known about the downstream events mediating ANCA-associated vascular injury, relatively little is known about the factors which predispose to the loss of immunological tolerance to neutrophil enzymes in the first instance, although exposure to drugs or silica have been implicated [Arthritis Rheum. 2003;48:814-23].

Endothelial injury and repair. An emerging concept is that the endothelium is not only the prime target for many of the pathogenetic mechanisms described above, but is also a protagonist of the inflammatory cascade associated with vasculitis. The vascular response to inflammation results in vascular remodelling and repair-ultimately leading to vessel occlusion and end organ damage. Novel surrogate markers of endothelial injury have recently been described in vasculitis of the young including circulating endothelial microparticles [Arthritis Rheum 2004: In Press], circulating endothelial cells with necrotic phenotype [Clinical and Experimental Immunology 2003; 131: 536-540**,** Lancet 2003; 361: 206-210], and bone marrow-derived endothelial progenitor cells (EPCs). EPCs are believed to be important in the vascular repair process [Science 1997; 275: 964-967 & NEJM 2003; 348: 593-600], and it is anticipated that greater understanding of their biology in health and disease could revolutionise our understanding and current approach to the treatment of vasculitis.

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S16.2

DIAGNOSTIC APPROACHES TO CHILDHOOD VASCULITIDES

Seza Ozen, MD

Childhood vasculitides are associated with some dilemma, starting with how to classify these diseases. The problems related to classification and nomenclature extend to the problems with diagnosis. Consensus is needed even in diagnostic criteria of the most common vasculitides of childhood such as Kawasaki disease and Henoch Schonlein purpura.

Polyarteritis nodosa(PAN) is characterised pathologically by an arteritis with fibrinoid necrosis of small and/or medium-sized arteries. The Chapel Hill nomenclature criteria introduces problems in paediatric PAN patients since there are many overlap cases with no vessel segregation. Furthermore paediatric PAN patients have a different age, gender distribution, as well as some differences in clinical features and outcome when compared to adult patients. The disease may be localised to the skin or it may be a systemic disease with organ involvement. Polyarteritis nodosa may manifest as mid-size arterial involvement where the main clinical feature is organ infarction; this subtype of PAN may also be in the form of an immune complex disease associated with hepatitis B surface antigen as in adults.

A typical microscopic polyarteritis of adults may also be seen in children. This subtype would be associated with a MPO-ANCA. On the other hand similar clinical features with a PR3-ANCA would suggest Wegener's granulomatosis (WG) if the granulomatous lesion is missed. ANCA have been shown to have a pathogenic role in both of these disease processes. In genetically susceptible individuals ANCAs activate PMNs, damage the endothelium, resulting in early lesions. Endothelial cell damage and activation hence produces pro-inflammatory mediators with migration of monocytes and T cells intensifying the damage in the kidney and other target organs.

In the differential diagnosis of these diseases one needs to consider other rare paediatric vasculitides such as Churg Strauss syndrome, and systemic lupus erythematosus as well as other rare diseases. Reaching consensus on classification and diagnostic terms will enable us to initiate studies for the best treatment options and management of these patients.

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S16.3

HENOCH SCHONLEIN PURPURA – RECENT ADVANCES

Arvind Bagga

Henoch Schonlein purpura (HSP), the commonest systemic vasculitis of childhood, is characterized by vascular wall deposits, of predominantly IgA. Small vessel vasculitis in skin, gut and glomeruli presents with purpura, colic, hematuria and arthralgia or arthritis. Renal involvement is the chief determinant of long-term outcome. Nephritis is found in 20-40% cases; in 90% they occur within the first month of onset of HSP. An older age at onset, persistent purpura, severe gastrointestinal symptoms and decreased plasma activity of factor XII are associated with increased risk of renal involvement and severe proteinuria.

While the etiology of HSP is not clear, a number of precipitating factors have been suggested. Increase in serum IgA_1 levels and presence of IgA_1 containing circulating immune complexes, IgA- rheumatoid factor, IgA-ANCA and IgA-AECA are reported. HSP is related to IgA nephropathy. These two diseases can be encountered consecutively in the same patient, have been described in identical twins and bear similar pathological and biological abnormalities. The pathogenesis of HSP is proposed to be secondary to increased production of abnormally glycosylated IgA_1, which is not sufficiently cleared by the liver and leads to the formation of IgA macromolecules that accumulate in the circulation with subsequent deposition in vessel walls and the glomerular mesangium.

Treatment of HSP is controversial, with the use of steroids usually reserved for patients with severe abdominal symptoms. Data from a number of retrospective and uncontrolled studies suggest that treatment with corticosteroids and immunosuppressive agents improves the renal prognosis in patients with HS nephritis. There are anecdotal reports on benefits of therapy following plasma exchange, administration of intravenous immunoglobulin, methylprednisolone with urokinase, oral mycophenolate mofetil, and fish oil. Most children with HSP have no significant sequelae. While less than 2% unselected subjects progress to chronic renal failure and end stage renal disease, the risk is much higher (up to 20%) in subjects with HSP nephritis. Renal involvement in adults is more frequent, tends to persist and is associated with higher risk of chronic renal disease. Patients showing evidence of renal involvement therefore need close and frequent evaluation. Acute nephritis or nephrotic syndrome at presentation, crescentic glomerulonephritis, DD-ACE genotype and abnormally glycosylated IgA_1 are markers of unsatisfactory long-term outcome. Pregnancies may be complicated by recurrence of HSP, proteinuria and hypertension.

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S16.4

NOVEL THERAPEUTIC APPROACHES IN VASCULITIS TREATMENT

Dr David Jayne

While current combination therapy with steroids and cyclophosphamide is secure as first line treatment for systemic vasculitis the potential roles of immunomodulatory strategies and newer immunosuppressives are receiving attention. Standard therapy is a major contributor to morbidity and mortality, infection is the major cause of early death and severe adverse events occur in at least 25% in the first year. The late effects of treatment on malignancy and vascular disease are poorly quantified. Although primary treatment failure is uncommon, relapse occurs in 50% as these toxic drugs are reduced or withdrawn. Recovery of renal function in acute renal vasculitis is unpredictable, and slow remission induction or treatment intolerance are likely to contribute to poor renal outcomes.
Current trials are evaluating the optimal duration of therapy and the role of mycophenolate mofetil in remission maintenance. Leflunomide and deoxyspergualin are being examined for non-renal and refractory disease respectively. The results of recent randomised trials have supported the use of intravenous immunoglobulin in refractory vasculitis and plasma exchange where there is severe renal involvement. The therapeutic mechanisms of these two treatments is not clear and probably multifactorial, although in ANCA associated vasculitis, reduction of the biological effects of ANCA may well be important.
Newer immunomodulatory strategies include blockade of circulating mediators and surface receptors, and lymphocyte depletion and immunoablation. Tumor necrosis factor alpha blockade has improved control of refractory vasculitis and allowed lower steroid dosing in induction therapy. Depletion of circulating T cells with anti-thymocyte globulin or the anti-CD52 monoclonal antibody, CAMPATH-1H, has led to sustained remissions but carries considerable immunosuppressive risk. More recently, B cell depletion with Rituximab has emphasised the role of B cells in supporting T cell autoreactivity and is under evaluation in vasculitis and other severe autoimmune scenarios.
The pathogenesis of vasculitis offers many potential targets for intervention and other approaches in early development include blockade of intra-cellular signalling, p38 MAP kinase inhibition, and blockade of monocyte chemoattractant protein 1, and the adhesion molecules CD11, CD18 and VLA 4. The testing of newer treatments has required an increase in interest from industry and the development of clinical trial networks. The evaluation of disease activity, especially in the kidney, and of therapeutic responses remains a significant area of difficulty.

Michael Dillon will present this abstract by David Jayne

S17.1

CARDIOVASCULAR COMPLICATION IN YOUNG ADULTS WITH CHRONIC KIDNEY DISEASE

Rulan S. Parekh

Cardiac complications of chronic kidney disease (CKD) have assumed increasing importance as cardiac disease now accounts for the majority of deaths in adults with ESRD, and about a quarter of pediatric ESRD deaths. Young adults with chronic kidney disease in childhood are at high risk for cardiovascular morbidity and mortality secondary to sustained exposure of cardiovascular risk factors during CKD and ESRD.
The cardiac abnormalities associated with CKD are diverse. Coronary artery disease is secondary to the clustering of traditional cardiovascular risk factors as well as the presence of a proinflammatory state and endothelial dysfunction. Traditional cardiovascular risk factors such as hypertension, left ventricular hypertrophy, and dyslipidemias occur in over half of the dialysis population. Incidence of atherosclerotic cardiovascular disease is approximately 20% in 3 years in young adults with ESRD. Cardiovascular disease can also be found on non-invasively by echocardiogram, coronary CT, and carotid intimal medial thickness. Preliminary data will also be presented on subclinical evidence of atherosclerosis in young adults by carotid intimal medial thickness and coronary calcification.
As pediatric nephrologists, it is important to understand the long term sequelae of CKD, and practice primary prevention with aggressive management of traditional cardiovascular risk factors.

Division of Nephrology, Departments of Pediatrics and Medicine, Johns Hopkins University

S17.2

ADOLESCENT PSYCHIATRIC ADJUSTMENT

Elena Garralda

The implications of receiving a diagnosis of chronic kidney disease have changed remarkably with advances in physical treatments and led to increased life expectancy. However, successful treatments carry their own burdens. What is the cost in terms of quality of life for the child and family and for the child's psychiatric adjustment?

Adolescence is a transitional stage from childhood dependency to adult autonomy: major physical and psychosocial changes concur and result in a state of enhanced health and social risks behaviours, intensity in social relationships, emotional turmoil and increased risks for psychopathology. Chronic kidney disease adds complexity to the process and affects psychiatric adjustment (ie emotional well-being, social functioning and health risk behaviours being within age appropriate norms, or outside these and associated with undue distress and/or psychosocial/educational impairment). Stage and severity of kidney disease, associated neuro-psychological deficits, pre-existing developmental or psychiatric problems, family function, educational and other environmental supports will influence adolescent psychiatric adjustment. This in turn may be expected to affect adherence to treatment of kidney disease and the young person's physical well being.

The majority of young people with chronic kidney disease and their families are well adjusted. However initial diagnosis of kidney disease in adolescence is likely to lead in a considerable proportion to psychiatric - predominantly emotional - adjustment disorders (ie time-limited symptoms with onset clearly linked to a stressful event). Marked deterioration in the physical condition, hospital admissions for life compromising medical events and major psychosocial stresses may lead to adjustment disorders in chronically affected youngsters. Conversely successful transplantation is linked to improved psychiatric status in children and parents. Early adulthood may be characterised by comparative social immaturity but general stabilisation in psychiatric adjustment. There may however be some reduction in self-esteem and increased risk for depression. Possible interventions in adolescence with the potential to improve adult psychiatric outcome may include the use of psychological techniques to manage adolescent depressive reactions, the promotion of peer interactions and emphasis on educational support and achievement.

S17.3

CANCER RISK AND PREDICTORS OF MALIGNANCY IN PATIENTS WITH END STAGE RENAL DISEASE

Angela Webster

Patients with end stage renal disease (ESRF) are at substantially increased risk for almost all types of cancer. ANZDATA data has been compared to that of the Australian general population, and the sex and age standardised rate ratios (RR) show a risk of non-skin cancer of 1.8 for women and 1.3 for men on dialysis, rising to 3.25 (women) and 2.56 (men) after transplantation. These new data will be presented and the influence of age and gender on these risks discussed, with reference to the world literature and the experience of other registries.
Management of these patients is hindered by the lack of reliable predictive and prognostic information. Understanding the risk factors associated with post-transplant cancers will enable clinicians to target efforts to reduce the impact of malignancy in graft recipients and will inform patient choice. Results of a recent multivariate Cox proportional hazards model using ANZDATA data show that for women, risk of cancer increased by $1/3^{rd}$ for every subsequent decade in age at transplantation (HR 1.38; 1.30-1.47, $p< 0.001$), and primary renal disease (PRD) was not a significant influence. For men, risk of cancer increased by $2/3^{rd}$ for every subsequent decade (HR 1.69; 1.60-1.80, $p< 0.001$) and diabetes appeared protective over other causes of PRD (HR 0.62; 0.39-0.97, $p= 0.04$). The effect of gender diminished as age at transplantation increased. Overall, men and women >55 years at transplantation can expect a >25% risk of ≥1 non-skin cancer after 10 years, whereas women and men aged <35 at transplantation can expect a 7% and 5% risk respectively. The influence of immunosuppressive agents will be explored, further results presented, and world literature summarised.

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S17.4

MAXIMISING COMPLIANCE

Dr Alan R Watson

Non-compliance or non-adherence to treatment is a universal problem but what matters is the degree of non-compliance in each individual and its potential consequences, such as transplant loss. Many studies in a number of chronic illnesses suggest that adolescents and young adults, as a group, have the most challenging compliance issues with rates around 50%. A number of influences are recognised including autonomy, body image and self-esteem issues combined with peer influence and family stresses. The complexity of the treatments and denial of illness may also contribute.

All the members of the multiprofessional team have a role in trying to assess and maximise compliance. Physical, biochemical and drug level parameters act as pointers and detailed accounts of pharmacy records can also be referred to countercheck verbal information. Electronic microprocessors are expensive and still largely confined to research studies. Improving compliance clearly involves trying to improve concordance, ie the clinical team and the individual reaching an understanding and agreement about treatment goals and adapting the regimen to the individual's lifestyle whenever possible. A meta analysis of studies investigating interventions to improve compliance found that behavioural and educational methods are equally effective and are better than methods that primarily focus on the patient's affect. Trying to simplify the dosing regimen - evening doses rather than morning doses. reminder cues and regular discussion about problems with side-effects - are all part of appreciation by clinical staff that the routine can be taxing. Educational techniques including multimedia approaches can also be incorporated. The value of peer support groups and peer counselling should not be underestimated. In our own unit we have employed a youth worker to work directly with the adolescent and young adult group. As well as regular supportive contact peer group contacts are fostered via youth clubs, holidays, weekend residential stays.

To maximise compliance we have to recognise the extent of the non-compliance issue, inform and educate according to the individual's needs and offer more support through the transition period from child to adult. The help of independent advocates within the clinical team, such as youth workers needs to be promoted.

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S18.1

DYSLIPIDAEMIA IN THE METABOLIC SYNDROME: PATHOPHYSIOLOGY AND THERAPY

Professor GF Watts

The metabolic syndrome encapsulates visceral obesity, insulin resistance, diabetes, hypertension and dyslipidaemia. Dyslipidaemia is a consistent abnormality of the metabolic syndrome and manifests in both postabsorptive and postprandial states. It is characterized by high plasma triglycerides, low high-density lipoprotein (HDL)-cholesterol, and high concentrations of apolipoprotein B-containing lipoproteins. The mechanism for dyslipidaemia involves a combination of overproduction of very-low-density lipoprotein (VLDL) apolipoprotein B-100 (apoB), decreased catabolism of apoB-containing particles (including chylomicron remnants), and increased catabolism of HDL apoA-I particles; an expansion in the VLDL-triglyceride pool size together with cholesteryl ester transfer protein (CETP) and hepatic lipase play a critical role in the generation of small dense LDL and accelerating the catabolism of HDL. Lipoprotein transport abnormalities are consequent on a global metabolic effect of insulin resistance, and fundamentally involves impaired insulin signalling in skeletal muscle and liver that increases the availability of lipid substrates. Inflammatory cytokines, particularly high TNF-alpha and IL-6 with low adiponectin levels, may contribute significantly to these abnormalities. Lifestyles modification is the first-line approach for improving dyslipidaemia in the metabolic syndrome. Lifestyle changes can effectively reduce plasma triglycerides and low-density lipoprotein (LDL)-cholesterol, and raise HDL-cholesterol. Kinetic studies show that in visceral obesity weight loss reduces VLDL-apoB secretion and reciprocally upregulates LDL-apoB catabolism, probably owing to reduced visceral fat mass, enhanced insulin sensitivity, increased adiponectin levels and decreased hepatic lipogenesis. Adjunctive pharmacological treatments, such as statins, fibrates, nicotinic acid or fish oils, are often required to further correct the dyslipidaemia, and their use is supported by some clinical trials. Drug treatment improves dyslipidaemia by several mechanisms of action including decreased secretion and increased catabolism of apoB, as well as increased secretion and decreased catabolism of apoA-I. Dual pharmacotherapy may be required, such as statin-fibrate, statin-niacin and statin-fish oils combinations. New therapies, such as cholesterol absorption inhibitors, CETP inhibitors and insulin sensitizers, could also be employed alone or in combination with other agents to optimize treatment. The bases for a multiple approach to correcting dyslipoproteinaemia in the metabolic syndrome relies on understanding the mechanisms of action of the individual therapeutic components. Clinical end-point trials of the effect of existing and new lipid-regulating therapies in subjects with the metabolic syndrome are required. **GFW/March 2004**

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S18.3

TYPE 2 DIABETES IN YOUTH

Dr Jonathan Shaw

The numbers of people with type 2 diabetes has increased dramatically around the world over recent decades As the age of disease onset has fallen, type 2 diabetes has begun to appear in adolescents and even children. In the USA, 8-45% of new cases of diabetes in youth are type 2 diabetes, while in Japanese and Taiwanese youth, type 2 diabetes is now more common than is type 1 diabetes. Comparative studies over time have shown rising rates of type 2 diabetes in youth from the USA, Japan and India, and cases have been reported in many other countries, and virtually every ethnic group. The problem is most serious in ethnic groups with the highest rates of adult onset type 2 diabetes (Indigenous populations in N America, Australia and New Zealand, Pacific Islanders, Hispanics, and South and South-East Asians), but type 2 diabetes has also been reported in white Caucasian British children.

The childhood form of the disease appears to behave very similarly to adult type 2 diabetes. Obesity is almost universal, a family history of both type 2 diabetes and cardiovascular disease is common, and both insulin resistance (sometimes manifest as acanthosis nigricans) and insulin secretory defects are present in most cases. Cardiovascular risk factors are manifest as components of the metabolic syndrome, with evidence of lipid abnormalities and of increases in blood pressure when compared to normal glucose tolerant children. Diabetic complications appear to be at least as common as in type 1 diabetes, with death, dialysis and lower limb amputation reported to occur before the age of 35.

Differentiation from type 1 diabetes can be difficult, with ketoacidosis and ketonuria often being present at diagnosis. Preservation of insulin secretory capacity (as evidenced by insulin C-peptide measurements), and the absence of pancreatic autoantibodies suggest the diagnosis of type 2 diabetes, and despite the presentation with acute metabolic upset, adequate glycaemic control with oral hypoglycaemic agents or lifestyle changes alone often allow the withdrawal of insulin treatment. Differentiation from the autosomal dominant maturity onset diabetes of the young (MODY) can also be difficult, with strong family histories of diabetes occurring in both MODY and type 2 diabetes.

Management can be very challenging with little or no safety or efficacy data available for oral hypoglycaemic agents in children. Lifestyle changes directed at weight loss are crucial, but are only likely to be successful when the family is also involved.

Director of Research, International Diabetes Institute

S18.4

DIABETIC NEPHROPATHY

Mark E Cooper, Merlin C Thomas and Karin A M Jandeleit-Dahm

Over the last 20 years great progress has been made in improving the prognosis of type 1 diabetic patients with renal disease. The major improvements have related to the early diagnosis of this condition by identifying microalbuminuria as part of routine screening for diabetic complications and the early institution of aggressive antihypertensive therapy even in normotensive subjects with microalbuminuria. It has become increasingly evident that blockade of the renin-angiotensin system with ACE inhibitors or AII antagonists confers superior renoprotection than other antihypertensive agents. Nevertheless, despite optimal antihypertensive treatment diabetic nephropathy continues to progress relentlessly, albeit at a slower rate, to end-stage renal failure. Therefore, either alternative or additional strategies are required.

It is evident from both experimental and clinical studies such as the DCCT and the follow-up EDIC study that hyperglycaemia remains a major determinant of progression of diabetic renal disease. A number of glucose induced pathogenic pathways have been identified over the last 20 years with much research continuing particularly in the areas of advanced glycation, activation of intracellular signalling molecules such as protein kinase C and increased expression of certain growth factors. Using a combination of cellular, preclinical and clinical approaches, it is likely that over the next few years not only will new pathways or specific molecules become targets for developing new treatments but the role of exciting compounds that inhibit well documented pathways of renal injury in diabetes will be further defined. Such drugs include PKC beta isoform inhibitors, agents which prevent accumulation of advanced glycated end-products such as the cross-linker, ALT-711 and antagonists of cytokine formation/action such as imatinib. It is anticipated that in the short to medium term combination therapy will be the most suitable approach but hopefully in the longer term identification of critical downstream events in renal injury in diabetes will allow investigators to develop a therapeutic strategy that involves the use of one specific mode of treatment.

Division of Diabetic Complications, Baker Heart Research Institute

S19.1

ENTEROHAEMORRHAGIC *E. COLI*, DIARRHOEA AND THE HAEMOLYTIC URAEMIC SYNDROME IN AUSTRALIA

R Robins-Browne, E Elliott, V Bennett-Wood, J Russell

Objectives. The aims of the study were to: (1) determine the contribution of enterohaemorrhagic *E. coli* (EHEC) to disease, in particular to HUS, in Australia; (2) characterise EHEC isolates obtained from patients in Australia, and (3) evaluate various tests used to detect EHEC in faecal specimens from patients with diarrhoea.
Methods. Samples from patients with diarrhoea presenting to selected hospitals in Melbourne and Sydney were investigated for Shiga toxin producing strains of *E. coli*. Methods used for the detection of bacteria included direct plating, cell culture assay and enzyme immunoassay for Shiga toxin, and PCR for virulence-associated genes of EHEC. Through the APSU we also conducted nationwide surveillance for HUS and examined feacal specimens to determine the microbiological cause. All EHEC isolates were characterised in terms of serotype and carriage of key virulence-associated determinants.
Results. EHEC were identified in the faeces of approximately 1.5% patients with diarrhoea, with similar isolation rates in children and adults. EHEC were found more frequently in samples containing blood than in samples without blood (2.6% versus 0.6%, in one study). Of the diagnostic methods examined, tests based on the detection of EHEC haemolysin and Shiga toxin were the most sensitive and specific. Typing of EHEC isolates revealed considerable serotype diversity in strains obtained from patients with diarrhoea. Serotypes O111:H-; O157:H-; O26:H11 predominated, but serotype O157:H7 was rarely identified. In children with HUS the findings were similar in that EHEC O111:H- was the most frequent serotype in patients with diarrhoea-associated HUS and also caused a major outbreak. During the 7.5-year study of HUS in Australia, the incidence of diarrhoea-associated HUS fell significantly.
Conclusions. EHEC is a relatively infrequent cause of diarrhoea in Australia. Strains that occur here are heterogenous in terms of serotype and carriage of virulence-associated determinants. Because serogroup O157 strains are relatively uncommon in Australia local diagnostic laboratories are advised not to rely on tests designed to detect only this serogroup. Rapid, reliable tests are required for non-O157 serotypes of EHEC.

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The HUS Study Group of the Australian Paediatric Surveillance Unit (APSU)

S19.2

PATHOPHYSIOLOGY OF CHILDHOOD HEMOLYTIC UREMIC SYNDROME: CONTINUING RESULTS FROM A PROSPECTIVE STUDY OF INFECTED CHILDREN IN THE PACIFIC NORTHWEST

Phillip I. Tarr, M.D

Approximately 15% of children infected with *Escherichia coli* O157:H7 develop the hemolytic-uremic syndrome (HUS). Renal failure during HUS is either nonoligoanuric, or oligoanuric. Oligoanuric renal failure obligates dialysis, extends hospitalizations, and is associated with complicated courses and chronic sequelae. Insights into the progression of enteric infection to HUS in humans, and measures to prevent HUS or attenuate its severity, are needed.
In 1997, we established a network in the Pacific Northwest of the United States to identify infected children, characterize the pathophysiology of progression to HUS, and discern risk factors for this complication. As of November 2003, we have studied 230 infected children. Forty-five children had HUS, 28 of whom were enrolled prior to the onset of HUS; 21 of whom were bled within the first four days of illness. Compared to those with uncomplicated courses, infected children who develop HUS have a higher likelihood of receiving antibiotics before HUS developed (OR = 3.5, 95% CI = 1.4 – 8.8, p = 0.0062). Moreover, on or before day 4 of illness, children who subsequently develop HUS have, compared to those with uncomplicated courses:

(1) Higher median prothrombin fragment 1+2 levels (2.5 vs. 1.4 nmol/L, p<0.05).
(2) Higher fibrinopeptide A levels (35±45 vs. 9±13 µg/L, p = 0.15).
(3) Higher concentrations of circulating intact soluble fibrin, and higher fibrin generation rates (33±43 vs. 8±12 pmol/s, p = 0.15).
(4) Accelerated fibrin degradation rates (0.5±0.3 vs. 0.13±0.1 pmol/s)
(5) Higher median tissue-plasminogen activator/plasminogen activator inhibitor-1 complexes (4.5 vs. 2.6 µg/L, p<0.05).
(6) Similar concentrations of free fecal Shiga toxin.

Children with oligoanuric HUS received less intravenous fluid and sodium before HUS developed (1.7 and 2.5-fold differences in medians, P=0.012 and 0.002, respectively); these differences were even greater during the critical first four days of illness (8.5 and 10.4-fold differences in medians; P=0.001 and <0.001, respectively). After adjusting for age, gender, antibiotics, and free water, infused sodium remained protective against developing oligoanuria (P=0.017). Early microbiologic diagnosis appears critical in identifying children at risk, and prompting volume expansion.
Conclusions: (1) Antibiotics should be withheld from possibly or definitely infected children; (2) Profound and dysfunctional fibrinogenesis precede HUS, and are the predominant prothrombotic abnormalities; (3) Circulating inhibitors of fibrinolysis are present, but there is no net impairment in fibrin breakdown; (4) Volume expansion early in illness, especially during the first four days, mitigates the severity of HUS.

Washington University School of Medicine

S19.3

DIARRHOEA-ASSOCIATED HAEMOLYTIC URAEMIC SYNDROME

NEW THERAPIES – TOXIN-BINDING BACTERIA

Adrienne W. Paton, Renato Morona and James C. Paton

Shiga toxigenic *Escherichia coli* (STEC) cause serious gastrointestinal infections in humans, which can lead to potentially fatal systemic complications, such as the haemolytic uraemic syndrome (HUS). The availability of rapid, sensitive methods for diagnosis of STEC infection early in the course of disease has created a window of opportunity for therapeutic intervention. Indeed, during two outbreaks of STEC disease in Adelaide in 1995 and 1998, we diagnosed STEC infection in patients by PCR almost a week before symptoms of HUS became apparent. However, at present, no therapeutic intervention is possible. Neither is there any effective prophylaxis to prevent acquisition of STEC infection by close contacts of confirmed cases. The serious systemic complications of STEC disease, as well as much of the intestinal pathology, are directly attributable to the Shiga toxin (Stx), which is a *sine qua non* of virulence. Thus, *in vivo* binding or neutralization of Stx is a potentially important therapeutic strategy. Substances capable of binding Stx in the gut might also play a role as an adjunct to antibiotic therapy. All Stx types affecting humans recognise the same glycolipid receptor (Gb_3; Galα[1→4]Galβ[1→4]Glc-ceramide). We have developed a novel and powerful Stx-binding probiotic by inserting genes encoding synthesis of Galα[1→4]Galβ[1→4]Glc- into a harmless *E. coli* strain, such that the outer core region of the *E. coli* lipopolysaccharide (LPS) mimics the Stx receptor (1). This was achieved by expressing two *Neisseria* galactosyl transferase genes (*lgtC* and *lgtE*) in an *E. coli* R1 *waaO* mutant (CWG308), which produces a truncated LPS core terminating in Glc. CWG308 expressing *lgtCE* synthesised a modified LPS with a terminal Galα[1→4]Galβ[1→4]Glc- epitope, as judged by reactivity with a monoclonal antibody. The capacity of this recombinant bacterium to bind and neutralize Stx1, Stx2, Stx2c and Stx2d was then examined using lysates of wild-type STEC strains or *E. coli* K-12 carrying cloned *stx* genes as a source of toxin. At a density of 1×10^9 cfu/ml (~2 mg dry wt. cells/ml), the CWG308/*lgtCE* suspension neutralized > 99% of the Stx activity in each of the extracts (measured by Vero cytotoxicity), but CWG308 suspensions had no detectable neutralising activity. Studies using purified toxins indicated that 1 mg dry weight of the recombinant probiotic could bind up to 160 µg of Stx1 or Stx2. Twice-daily oral administration of the recombinant bacterium (8 mg per dose), but not CWG308 alone, completely protected mice from otherwise 100% fatal challenge with either of two highly virulent STEC strains (B2F1 and 97MW1). We have also shown that formalin-killed cells bind and neutralize Stx *in vitro* as efficiently as live cells. Moreover, oral administration of killed receptor mimic fully protected mice from challenge with 97MW1, our most virulent STEC strain. The dose administered was the same as for live cells, but it was necessary to increase the frequency of administration from 2 to 3 times daily. Commencement of therapy could also be delayed for up to 48 hours after challenge without diminishing protection, depending upon the virulence of the challenge strain. These data indicate enormous potential for treatment of humans with proven or suspected STEC infection, as well as for prevention of disease in healthy contacts of such cases. Adjunct therapy with an effective Stx binding agent would also permit the safe use of (currently contraindicated) antimicrobial drugs in cases of STEC disease.

1. Paton, A.W. *et al. Nature Med.* 2000; 6:265-270.
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S19.4

RISK FACTORS ASSOCIATED WITH SHIGA TOXIN-PRODUCING *ESCHERICHIA COLI* INFECTIONS, ARGENTINA

Marta Rivas

Argentina has the highest incidence of hemolytic uremic syndrome (HUS) in the world, 12.2 cases per 100,000 children <5 years old. This rate is 10-fold higher compared with other industrialized countries. HUS is the leading cause of acute renal failure and the second leading cause of chronic renal failure, and is also responsible for 20% of all kidney transplants among children and adolescents. Shiga toxin-producing *Escherichia coli* (STEC) have been shown to be the primary etiologic agent of HUS in Argentina. Prior studies to determine risk factors for STEC infection however have not been done. We conducted a case-control study to identify risk factors of infection for sporadic STEC infections in two cities of Argentina, Buenos Aires and Mendoza. We defined a case as either diarrheal-related HUS or STEC infection in a child <16 years old. Controls were age- and neighborhood-matched. Demographics, course of illness, food and drinks consumed and the activities in the seven days before becoming ill were compared. We enrolled 150 cases and 299 controls. The median age of cases was 1.8 years (range, 4 months to 14 years) and 58% were female. Among the 99 cases with isolated STEC, 61 (59%) were serotype O157:H7 and *stx*2 genes were identified in 93 (90.3%). O145 (12%) and O26 (6%) were the other serotypes most frequently isolated. Adjusted univariate analysis showed that exposures in the 7 days before illness that were significantly associated with STEC infection included beef-related dietary habits, eating at a social gathering, eating any meal at home, drinking from a bottle left at room temperature, exposure to animals or their environment, and behaviors suggesting person-to person spread. On multivariate logistic-regression analysis the variables that remained significant risk factors were eating undercooked beef outside home, (MOR, 17.1; 95% CI, 1.6-187.2), living in or visiting a place with animals (MOR, 4.24; 95% CI, 1.1-16.5), contact with a child < 5 years with diarrhea (MOR, 3.2; 95% CI, 1.0-9.9), and having another household income besides that of parents (MOR, 2.1; 95% CI, 1.2-3.9). Prevention strategies aimed at modifying risk factors may help to reduce the risk of STEC infection and subsequent development of HUS.

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S20.1

BIOCOMPATIBLE PERITONEAL DIALYSIS IN CHILDREN

F.Schaefer

Ultrafiltration loss and peritoneal sclerosis are major causes of technique failure in children on long-term peritoneal dialysis. These changes are related to major alterations of peritoneal morphology, characterized by a progressive loss of the mesothelial cell layer, subintimal fibrosis and neoangiogenesis. A large body of *in vitro* evidence suggests that these degenerative changes are caused by the bioincompatible composition of standard PD fluids, which are acidic, hyperosmolar, contain lactate and glucose in unphysiological doses and are fraught with toxic glucose degradation products (GDPs). GDPs alter the peritoneal growth factor expression profile and promote local and systemic formation of advanced glycation end products (AGE). In addition, local host defense is compromised by acidic pH and high lactate concentrations, potentially facilitating the development of peritonitis.
Recently, PD solutions with neutral-pH, low GDP content and partial or complete replacement of lactate by bicarbonate buffer have become available, which may cause less acute and chronic toxicity to the peritoneum. Indeed, we observed a markedly increased peritoneal outflow of CA125, a marker of mesothelial cell mass, in children on automated PD exposed to a pure bicarbonate PD fluid. In addition, plasma AGE concentrations decreased within few weeks of applying the biocompatible fluid, suggesting a significant contribution of conventional PD solutions to the systemic AGE load. Similar effects were noted in adult patients using lactate or lactate-bicarbonate buffered fluids with low GDP content and neutral or near-neutral pH. Other, less consistent findings associated with the use of biocompatible fluids include a decreased effluent apearance of markers of inflammation (IL-6) and neoangiogenesis (VEGF). Furthermore, recent preliminary evidence suggests a reduced peritonitis incidence with neutral-pH PD fluids.
Notably, our comparative administration of a 34 mM bicarbonate solution resulted in an improved compensation of metabolic acidosis compared to conventional 35 mM lactate fluid in children on APD, with reduced need for oral bicarbonate supplementation. The alkalising effect was most marked in infants, possibly due to an age-related difference in bone carbonate buffer capacity. Finally, we observed subtle differences of peritoneal solute transport properties, compatible with a less marked initial peritoneal vasodilation during exposure to the neutral-pH fluid. The resulting small decreases of creatinine and phosphorus clearance are easily compensated by slightly increasing the dialysis dose.
In summary, there is increasing evidence of superior *in vivo* biocompatibility of low-GDP, neutral-pH dialysis solutions in adults and children on PD. This raises hopes that the use of the novel PD solutions will substantially contribute to an improved long-term preservation of the peritoneal membrane.

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S20.2

THE INTERNATIONAL PEDIATRIC PERITONEAL DIALYSIS REGISTRY: A GLOBAL INTERNET INITIATIVE

Bradley A. Warady, M.D.

Specific recommendations for the management of PD-associated peritonitis in children were published by an international workgroup under the auspices of the International Society of Peritoneal Dialysis (ISPD) in 2000. To access the validity of these clinical practice guidelines, a global consortium of 53 pediatric dialysis centers is collecting peritonitis data to evaluate the impact of treatment in accordance with the guidelines in an internet based registry. Since January 2002, 385 peritonitis episodes have been reported in 288 children.

At the time of diagnosis, 51% of patients were female. An assessment of catheter characteristics revealed the tunnel configuration to be swan neck in 40% of episodes and straight in 52% of episodes. Eighty-six percent of the catheters had two cuffs. Thirteen percent of patients had a prior history of S. aureus nasal carriage and 18% of patients were receiving S. aureus prophylaxis. Upon presentation, 44% of episodes were associated with severe abdominal pain and 43% with no fever. The cause of peritonitis was unknown in 70.5% of episodes and was associated with touch contamination or an exit-site/tunnel infection in 9.4% and 7.9% of cases, respectively. Peritoneal fluid culture results revealed the following distribution: S. aureus 16%, coagulase negative staphylococci 13.8%, streptococci 6.2%, gram negative bacteria 24.6%, fungal 3.3%, and sterile 28.3%. Marked regional variation was observed for the incidence of culture negative, fungal and coagulase negative staphylococcal infections. Disease severity at presentation was mildest in patients with sterile peritonitis and peritonitis secondary to coagulase negative staphylococci. Peritonitis due to Candida, but not any other organisms, occurred more frequently in children with a gastrostomy. Of those patients in whom peritonitis occurred at home, 73% were hospitalized for a mean of 6 (range 4-11) days. The ISPD guidelines recommend stratification of empiric antibiotic therapy (first generation cephalosporin vs. glycopeptide, combined with ceftazidime in all cases) according to risk factors for severe infection (e.g. severe abdominal pain, history of nasal/exit-site colonization with S. aureus, high fever, age <2 years and history of MRSA infection). The impact of this scheme on treatment success awaits the collection and analysis of 500 peritonitis episodes.

The Children's Mercy Hospital, Kansas City, MO USA

S20.3

OPTIMAL HEMODIALYSIS PRESCRIPTION FOR PEDIATRIC PATIENTS

Stuart L. Goldstein, MD

Provision of optimal hemodialysis requires the resources necessary for accurate dialysis dose measurement, nutrition status assessment and malnutrition treatment, ultrafiltration monitoring to decrease intradialytic morbidity and a vascular access management strategy to decrease catheter prevalence and permanent access thrombosis. In the last 5 years, we have investigated methods to address these aspects of hemodialysis provision, including non-invasive means to monitor ultrafiltration and vascular access flow, both of which led to decreased patient morbidity, hospitalization and health care costs. In addition, the predisposing factors for cardiovascular morbidity risk, such as inflammation and malnutrition, recognized as significant for adult patients receiving dialysis also exist in pediatric patients. Recognition and treatment methods will be crucial to improve the cardiovascular status of the pediatric hemodialysis population and allow for healthy transition to young adulthood. The current presentation will focus on the state-of-the-art with respect optimal pediatric hemodialysis provision within the constraints of the current thrice-weekly model. A vision for future study, which will entail multi-center collaboration will be provided

Baylor College of Medicine, Medical Director, Renal Dialysis Unit, Texas Children's Hospital

S20.4

NOCTURNAL HOME HEMODIALYSIS (NHHD) IN CHILDREN

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Slow nocturnal hemodialysis, delivered at home, has been shown in adults to provide superior solute clearance, and improved patient wellbeing, at reduced cost, when compared to conventional thrice weekly in-center hemodialysis. The only report of this dialysis modality in children is limited to 4 children aged 10-19 years, in whom improved growth, bone mineralization, and nutrition were observed. However, few data were provided of the biochemical status of the patients, and no data concerning difficulties or costs of program development.
An NHHD program was established at the Hospital for Sick Children , Toronto, in 2002.
Three teenagers have been maintained on NHHD for periods of 2, 6, and 12 months. Clinical and biochemical indices of wellbeing and delivered dialysis dose have been prospectively collected. Blood access has been through both CVLs (n=3) and fistulae (n=2), blood flows have varied from 100 – 200ml/min and dialysate flows 200 ml/min, and in each case phosphate has been added to the dialysate. Dialysis is supervised by a parent, and provided for 6 – 10 hours nightly x 6-7 nights weekly. Central monitoring of the dialysis procedure is provided via computer or modem.
Though effects on growth and some biochemical data are inconsistent e.g. PTH, lipids, β2 microglobulin, the weekly dialysis dose estimated from Kt/Vurea is consistently > 12. School attendance and performance has improved . The patients have no fluid or dietary restrictions, and each reports improved appetite and general wellbeing.
Parents have reported the performance of NHHD as stressful and having a major impact on their social lives, though they have realized cost savings related to reduced number of clinic visits and reduced absenteeism from work.
Compared to in-centre hemodialysis, NHHD demonstrates overall annualized cost savings of approximately twenty per cent.

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S21.1

STEROID AVOIDANCE (TWO WAYS TO SKIN A KANGAROO)

Minnie Sarwal, MD, MRCP, PhD

Corticosteroids have been invariant transplant immunosuppressives with numerous adverse effects and patient morbidity in adult and pediatric renal transplantation. Hypertension, hyperlipidemia, osteopenia, cataracts and body disfigurement are some of the common steroid-driven toxicities, often resulting in non-compliance and graft loss. Therapies for management of steroid toxicity impose additional cost and care morbidity. Growth retardation occurs in children despite steroid minimization. Alternate-day steroid therapy reduces growth suppression, but regimen compliance may be problematic.
Steroid minimization and complete withdrawal attempts have often led to increased rates of acute rejection, accelerated graft loss and functional decline, although more satisfying results have been described by Jabs et al with alternate day dosing. Newer potent immunosuppressive agents, such as the IL-2 receptor blockers, tacrolimus, mycophenolate mofetil (MMF) and sirolimus, have renewed interest in developing regimens to attempt complete steroid avoidance at any time post-transplantation.
We have employed novel extended Daclizumab induction protocol to avoid steroid usage completely in infant and pediatric renal transplant recipients at a single center. Intended maintenance drugs are tacrolimus and MMF. Endpoint analysis of study patients was compared with 50 historical matched steroid-based children on tacrolimus with 100% 2 year graft survival and without delayed graft function. Study patients have had serial protocol transplant biopsies (n=246) to monitor for sub-clinical acute rejection and tacrolimus toxicity. Interim analysis on 57 enrolled children (14< 5 years of age) with mean follow-up of 2 years, reveals 7 protocol breaks and 98% overall graft and patient survival. At one year post-transplantation, steroid-free recipients showed significant improvements for growth, clinical acute rejection (8% vs 27%, $p<0.05$), graft function and hypertension, without increased infectious complications. Leukopenia, anemia and allograft nephrotoxicity was addressed by solely decreasing MMF and tacrolimus dosing and/or replacing MMF with sirolimus, without increasing acute rejection. Early daclizumab levels of >5 mcg/ml, necessary to inhibit IL2 dependant proliferative responses, were observed for the first time in children of all ages with this Daclizumab protocol.
Pediatric renal transplantation with extended Daclizumab induction, is very effective and safe without steroids and results in unprecedented growth patterns in children. Daclizumab first dose doubling and extended use for 6 months replaces steroids effectively without evidence of over-immunosuppression, and may be the pivotal causative for the reduced acute rejection and improved graft function seen in this trial. This pilot study has provided preliminary data to test this protocol in a prospective, multicenter randomized US study.

Stanford University, USA

S21.1.1

PEDIATRIC RENAL TRANSPLANTATION WITHOUT MAINTENANCE CORTICOSTEROIDS: AIMING FOR SIMPLICITY

Joseph R. Sherbotie, M.D.

Glucocorticoids have been a cornerstone of immunosuppressive therapy and treatment of rejection in solid organ transplantation, but are associated with undesirable side effects. Weaning and stopping steroids to limit side effects has resulted in an increased risk of acute rejection. These rejection episodes are not typically associated with allograft loss. Avoiding the use of maintenance glucocortoids has been successful in several adult series, with consistent lack of steroid related side effects. In a randomized controlled trial in adults, follow up has been reported for up to 9 years; steroid avoidance does not affect allograft survival, and patients initially treated without steroids are not disadvantaged. Beginning in June 2000, our Pediatric Renal Transplantation Program adopted a protocol without maintenance steroids. Initially it included only living donor transplants, but subsequently included all pediatric renal transplants. Immunosuppression consists of three doses of rabbit thymoglobulin, five tapering pulses of methylprednisolone, tacrolimus, MMF, and no maintenance steroid therapy. All patients receive oral ganciclovir or valganciclovir for 3 months, fluconazole and TMP/SMZ for 1 month. Acute rejection rates are between 10-15%, patient survival is 100%, and allograft survival is above 95%. Protocol biopsies were not performed, though 70% of patients underwent at least one biopsy. One third of patients showed calcineurin nephrotoxicity. One allograft exhibited primary nonfunction. Another is being lost after a steroid resistant rejection which occurred on minimal immunosuppression after EBV associated PTLD. Two patients with steroid responsive rejections continue without maintenance glucocorticoids after brief steroid pulses. One patient with FSGS and recurrence of proteinuria received plasmapheresis, 8 weeks of cyclophosphamide, and alternate day prednisone transiently. Two EBV naïve patients developed EBV associated PTLD: one > 1 year after transplantation associated with primary EBV infection, and another 4 months after transplantation with PTLD (lymphoma) in the hilum of the renal allograft with negative blood EBV PCR. PTLD in both patients was successfully treated with decreased immunosuppression, rituximab, antivirals, and tacrolimus changed to sirolimus. Infections included CMV enteritis (1), aplastic anemia with parvovirus B19 (1), and BK virus nephropathy (1). Seventeen percent required erythropoeitin or G-CSF transiently. Almost all patients remain without maintenance steroid therapy (92%). Renal allograft function is excellent, and cosmetic side effects are absent. “Catch up” linear growth beginning within the month after transplantation is the rule. Average weight gain is normal for growth. Hyperlipidemia is uncommon (here associated with sirolimus), and the incidence of hypertension remains low.

University of Utah School of Medicine

S21.2

THE PRO’S AND CON’S OF MTOR INHIBITORS IN PEDIATRIC RENAL TRANSPLANTATION AND C2 MONITORING IN THIS CONTEXT

Peter F. Hoyer and Udo Vester

Refined concepts to use the calcineurin-inhibitors cyclosporine or tacrolimus ensure better immunosuppression, but still are nephrotoxic and contribute to cardiovascular morbidity.
The two mTOR inhibitors sirolimus (rapamune^{R}) and everolimus (certican^{R}) are makrolid-derivatives, which inhibit growth factor (IL-2 & IL-15) dependent proliferation of T- und B-lymphocytes and myofibroblasts thru P70S6 kinase leading to arrest of cell cycle from G1 to S-phase. They have the potential to prevent acute und chronic rejection. They are true synergistic to cyclosporine. Major side effects encompass thrombocytopenia, hyperlipidemia and hypergonadotropic hypogonadism in elderly male transplant recipients. Sirolimus has been used as rescue therapy in pediatric organ transplantation and has allowed to reduce or to eliminate cyclosporine resulting in significant improvement of renal function. Due to its molecular structure, pharmacology of this drug in pediatric patients is still far from being satisfyingly predictive: consistency of intestinal absorption, interference with cyclosporine absorption, long half life, change of absorption over time and lack of a evidence based defined drug concentration need extensive studies before its general use may be recommended.
Everolimus is a hydroxyethyl derivate of sirolimus which has demonstrated in a pediatric phase II trial favourable absorption characteristics (steady state reached between days 3 and 5), shorter clearance as well as a significant correlation of trough levels with drug exposure (AUC) $r = 0.83$, $p < 0.0001$.
In a multicentre open-label study in pediatric *de novo* renal transplant patients everolimus was used in combination with cyclosporine (everolimus: dose 0.8 mg/m^2 (maximum 1.5 mg) BSA bid, cyclosporine: dosed to target trough level 50-80ng/ml after months 3). One year results demonstrate a low rejection rate (3/19), excellent GFR (86/ml/min/1.73m^2) and a good safety profile. The influence on testosterone production remains opens since study subjects are mostly not in the age to study.

Extensive studies in adult renal transplant recipients have led to the consensus statement that there is enough scientific data to validate C_{2h} monitoring. Neoral absorption during the first 4 hours post dose ($AUC_{0h\text{-}4h}$) represents the period of greatest variability among patients. Recently it was shown that the correlation between AUC and C_{2h} is nearly the same in different types of pediatric solid organ transplantation as well as in adult recipients. First single center studies demonstrate improved immunosuppression with employing C_{2h} targeted cyclosporine dosing. There is no reason to anticipate different outcome data compared to the excellent results obtained with C_{2h} guided treatment in adults. However, caution should be exercised for yet unsolved questions and uncertain late consequences. To date, the desired reduced target level for combined treatment with mycophenolate mofetil or mTOR inhibitors has not yet been defined. Using C_{2h} for cyclosporine, and trough concentrations for mTOR inhibitors may hamper to combine different drug monitoring concepts. Nevertheless this needs to be studied in order to combine different drugs and to define the lowest dose necessary in the view of minimizing side effects. This may be even more important in case of steroid avoidance.

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S21.3

TACROLIMUS PHARMACOKINETICS IN CHILDREN

Guido Filler, MD, PhD, FRCPC.

Tacrolimus, a hydrophobic macrolide lactone produced by Streptomyces tsukubaensis, is a potent immunosuppressive drug, which is commonly in use clinically as prophylaxis against organ rejection after paediatric renal transplantation. Its concentration can be analyzed in biologic fluids by HPLC, immunological and automated methods. Tacrolimus is known to exhibit low oral bioavailability and to have a wide range of variability in absorption, ranging from 4 to 89% with a mean of about 25% in kidney transplant recipients. Many factors account for the variable oral bioavailability, including ethnicity, age, and most importantly, the function of the small intestine. The multidrug efflux pump, MDR or P-glycoprotein (P-gp), is present at high levels in the villus tip enterocytes of the small intestine, the primary site of absorption for orally administered drugs. Other mechanism for the variability are thought to be due to the very low aqueous solubility of Tacrolimus, and variable metabolism via cytochrome P4503A4 (CYP3A4) in intestinal epithelium cells and hepatocytes. Tacrolimus is primarily eliminated by metabolism. Less than 1% of the administered dose is excreted in the bile or the urine.Concomitant drugs such as other macrolides or ketoconazoles also affect the metabolism. This variability mandates pharmacokinetic monitoring.
In children, the drug is rapidly absorbed with a median t_{max} of 90 to 120 minutes. The trough level correlates well with the area under the curve (AUC). There is no need for monitoring of the 2-hour concentration, in contrast to Cyclosporine Neoral. Descriptive Statistics of Pharmacokinetic Parameters of Tacrolimus in steady state in long-term stable renal pediatric transplant patients on MMF and Tacrolimus are given in the table. These are remarkably similar to those on Tacrolimus with concomitant Azathioprin. There appears to be no drug interaction between Tacrolimus and MMF. Patients taking a low dose of Sirolimus in combination with a standard dose Tacrolimus may require Sirolimus dose increments over time to maintain constant exposure to Sirolimus.
Target AUC and trough levels after pediatric renal transplantation have not been established. The manufacturer suggests a trough level of 10-20 ng/mL for the first 6 weeks and 5-15 ng/mL thereafter. Stable long-term patients frequently tolerate trough levels between 2.5-5 ng/mL. Using data from a large multi-centre randomised controlled clinical trial, a provisional target range will be discussed.

Parameter	C_{max} [ng/mL]	t_{max} [min]	C_{min} [ng/mL]	AUC [ng x h/mL]	Apparent Clearance [L/h]
Mean	17.3	93.3	7.1	120.6	27.6
STDev	5.7	44.3	2.5	30.4	18.5
% CV	0.3	47.5	35.6	25.2	67
Minimum	5	60	3.2	47.1	6
Maximum	31.4	180	13.7	180.3	72.3

StDev=Standard deviation; % CV = percentage variation coefficient

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S21.4

PHARMACOKINETICS AND PHARMACODYNAMICS OF EMERGING AGENTS IN PEDIATRIC RENAL TRANSPLANTATION

Robert Ettenger, MD

With current immunosuppressive strategies, the results of kidney transplantation have continually improved. New immunosuppressive agents and novel uses of currently available agents give promise that immunosuppressive regimens can be potentially more effective with less toxicity. This talk will focus on a number of such immunosuppressive agents. FTY 720 is a derivative of a Chinese herb ("Winter-worm, Summer Grass). This derivative has the effect of blocking egress of lymphocytes form lymph nodes and the thymus. This action results in peripheral lymphopenia. The retention of lymphocytes in the lymph nodes allows systemic immune reactions, but the peripheral lymphopenia blocks lymphocyte trafficking to areas of immune reactivity such as allografts. Mycophenolate mofetil (MMF) has become a popular agent for pediatric immunosuppression. Enteric coated mycophenolic acid (MPA) is a new formulation of MPA which may have reduced upper gastrointestinal side effects compared to MMF. In this discussion, the pharmacokinetics and pharmacodynamics of these 3 agents, and other new agents are discussed, with special emphasis on the pediatric data that are currently being generated, both at UCLA and at other centers.

Mattel Children's Hospital at UCLA

S22.1

DIALYSING NEWBORNS WITH END-STAGE RENAL FAILURE

Malcolm G Coulthard

Dialysing children with ESRF is burdensome, and not always appropriate. Infants present even greater difficulties. This is partly because of simple scale, and partly because their physiological variables change disproportionately.

Physiological proportions Unlike older children, GFR in newborns varies with weight, whereas fluid requirements vary with surface area. The surface area to weight ratio is higher in babies; it is nearly 3x the adult ratio at term, and double that at 1 kg. Infants with ESRF who maintain a urine output merely require dialysis to remove biochemical waste, as in older children. By contrast, oliguric babies also need large volumes of fluid removed, since their nutrition consists of milk.

Peritoneal dialysis Babies that void typically require peritoneal dialysis to improve growth, or produce stability of their plasma sodium concentrations. Other biochemical concentrations (eg: urea, potassium, phosphate, bicarbonate) can usually be controlled relatively easily in babies by adjusting the constituents of their milk, which is typically tube fed.

Oliguric babies require dialysis earlier to prevent fluid overload. Restricted volumes limit the extent to which manipulations can be made by adjusting feeds. Their ultrafiltration must be closely controlled because these volumes are inevitably relatively large (eg: about 12% of body weight daily at term). The risk of inducing hypovolaemia (or longterm fluid overload attempting to avoid this) is substantial.

Conventional haemodialysis Poiseuille's law dictates that with decreasing size, haemodialysis access availability falls disproportionately to the dialysis requirement. This makes a 1 kg baby 800% harder to haemodialyse than an adult. For all patients, single lumen access produces substantially higher blood flows than double lumen lines. This counter-intuitive fact must be utilised when treating babies.

All conventional haemodialysis circuits necessitate blood priming for small infants. When an infant's circulation mixes with this, it may cause hyperkalaemia, acidosis, and hypocalcaemia unless the blood is highly modified. Furthermore, the dependence of the circuit blood flow on its access rate promotes clotting within the circuit. This excludes conventional haemodialysis in very small infants.

Syringe-driven dialysis We have developed an automated haemodialysis machine which overcomes these problems for babies down to 1 kg. The circuit blood flow is independent of the sampling rate, and it is too small to need priming. A baby that produced urine would require overnight treatments thrice weekly, but an anuric baby would need nightly treatment. It could provide a useful temporary role, but its use as a primary technique would be controversial.

S22.3

COMPLEXITIES OF CONSENT WITHIN A MORAL AND LEGAL FRAMEWORK

Christopher Boundy

Obtaining consent to treatment within the context of managing an infant with end stage renal failure can present some interesting challenges for the clinician.

Often referred to as "informed consent", it can be the warrant that authorises the subsequent actions of an entire clinical team involved in the management and care of an ESRF infant.

To be valid, the consent must signify a patient's agreement to allow medical professionals to provide treatment and to take actions that are lawful, and consistent with proper professional medical practice.

In a hospital setting, the consent *form* is a written acknowledgement. It signifies that the patient (and in the case of an infant, the parent(s) or legal agent) has agreed to a particular course of action, or set of actions, by medical personnel in response to the patient's perceived medical situation.

What the consent *form* most often will not (or cannot) do is reflect the full scale and dimension of the information exchange between clinicians and parents.

Ideally, consent involves the parents' affirmation of a clinical decision that is made in respect of proposed treatment, following a candid exchange which involves the medical facts, the clinical options, and the parents' wishes on behalf of the infant. This necessitates a relationship of trust.

One view is that in jurisdictions which allow litigation based upon issues of clinical negligence, there is already an impediment to establishing candour and trust as between doctors and patients. As against this, common law accountability can be seen as encouraging health professionals to give due and proper consideration to the clinical decisions that may have profound and far reaching effect(s).

In an emergency situation (imminent risk to life or health) there is statutory provision in South Australia for a medical practitioner to administer treatment to an infant, even despite refusal of consent by parents, so long as the treatment is considered to be in the best interest of the infant's health and well being.

This type of legislative provision ultimately allows the medical practitioner to act (in the infant's best interest) in an emergency, in a non-consensual setting; but at the risk of impoverishing the relationship of trust with the parents.

When the situation is non-urgent, a contemporary view is that emphasis should remain on achieving a mutuality of support for treatment decisions involving infant patients.

In the process of gaining parental support, consent discussions with health professionals may encompass issues such as the quality of life of the infant. These discussions may also be influenced by what the medical professional is prepared to canvass within his or her own perspective of what constitutes ethical medical conduct.

Using a case study, this paper looks at some of the prevailing influences in matters of consent in a first world medical setting.

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S22.4

MANAGEMENT OF ESRF IN THE INFANT

Third World Perspective: What is the status of the child? What lessons and strategies come from the 3rd world experience?

F Eke

There is likely underreporting of end stage renal failure (ESRD) in the third world. Very few countries have Registries and the following table is a guideline

Country	Child P/million	No. expected with ESRD/pmp/yr	Children's ESRD Program	Total P/ million	Adults. with ESRD/pmp/yr	Adult ESRD Program/pmp	.Adult Program started	Budget/ Capita/ annum
India			NIL	1 billion	100	0.9		$6
Kenya	8		NIL	20	90	0.2	1984	
Nigeria	48	7.5	NIL	120	200	0.1	1981	$9
Sudan					100	0.2	1986	
USA		178.5	150	180		178.5	1950	>$2,000

Table Contrasting 3rd world countries & USA: p=population; pmp=per million population. The high cost of renal replacement therapy (RRT) must be met by the patients and their families. In most African countries, children are discriminated against partly due to social norms.

Other cultural and ethical considerations facing the Paediatric Nephrologist include "non-existent" cadaver donor programs. Many countries have no legislation on brain death and where enacted, hospitals lack the infrastructure and the networking required to obtain and use the kidneys. Live organ donation is acceptable to 47% of the population. Cultural and religious beliefs regard organ donation as mutilation of the body

Tropical nephrotoxins result in toxic nephropathies, acute or CRF. Traditional medicines, a mixture of herbs with botanical nephrotoxins (impila, cat's claw) plus unknown chemicals, and administered through all available orifices are prescribed by traditional healers and thought to be a combination of ignorance, poverty, lack of medical facilities, lax legislation, and widespread belief in indigenous systems.

Infants with CRF present late. Ultrasonography rarely detects congenital anomalies due partly to lack of experienced staff.

Infection rates are high right from infancy with AIDS, tuberculosis, Hepatitis B & C, and malaria. Malnutrition, poor sanitation, lack of trained staff and facilities for at risk babies in "special care units", frequent power outages, poor staff motivation and remuneration leading to frequent Industrial actions and emigration of trained staff compound the problems.

Economic and manpower factors dictate a conservative approach to the therapy of ESRF.

Selecting patients for RRT, when the criteria for choice is not entirely medical is an unenviable task. Focusing on prevention of ESRF by a systematic screening and treatment programs, education, and greater Government funding for the wider availability of transplantation appear to be the better option.

S23.1

THE MOLECULAR BIOLOGY OF PHYSIOLOGICAL AND PATHOLOGICAL BONE TURNOVER

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Bone matrix comprises mineralised osteoid, which contains type I collagen and a number of non-collagenous proteins. In mature bone, new osteoid is laid down by osteoblasts following osteoclastic resorption of existing matrix, in a process referred to as bone remodelling. However, the molecular regulation of the processes of bone turnover, which result in a biomechanically appropriate bone architecture, are not well understood. Nor are the mechanisms of pathological bone loss observed, for example, in renal disease. We have sought to elucidate these mechanisms by combining methods to quantitatively describe bone structure and bone turnover parameters with molecular analyses, from the same bone samples. This method, which we have termed *molecular histomorphometry,* represents a powerful new approach to linking the expression of particular genes with their putative role in bone remodelling. Our data, relating to the human bone microenvironment, obtained from this approach will be discussed in the context of understandings obtained from *in vitro* investigation of human bone cells. For example, the combination of histomorphometric and molecular analyses in bone from the proximal femur has revealed strong associations between the RANKL mRNA levels and trabecular bone volume (BV/TV), erosion surface (ES/BS), and osteoid surface (OS/BS). The significance of this result is that RANKL has emerged as the central molecular activator of osteoclast formation and resorptive function. *In vitro* studies have shown that RANKL expression by human osteoblasts is essential for the development of osteoclasts. Thus, the osteoblast lineage of cells appears to sequentially promote osteoclast resorption and then bone formation, providing a link between bone resorption and formation. Our data suggest that it is the immature cells of the osteoblast lineage that respond to pro-resorptive signals with induction of RANKL expression. In addition, the microenvironment in which this occurs is likely to be important, since inflammatory mediators, such as IL-1 and TNF? can inhibit the maturation of human osteoblasts, perhaps explaining the disturbed bone metabolism and bone loss in some inflammatory conditions, such as rheumatoid arthritis. The potential signalling between the resident cells in bone (osteoblasts and osteocytes), and the osteoblasts and osteoclasts involved in a resorption/repair cycle, will be discussed, because it is the breakdown of the equilibrium between bone resorption and formation that characterises skeletal pathology.

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S23.2

AN ADYNAMIC OSTEODYSTROPHY AND PTH RESISTANCE ASSOCIATED WITH A LDLR-/- MOUSE IS WORSENED IN AN ABLATION MODEL OF CKD AND SUCCESSFULLY TREATED WITH EXOGENOUS BMP-7.

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An osteodystrophy has not been defined in an animal model of the metabolic syndrome with hypercholesterolemia, insulin resistance, obesity, vascular calcification and chronic kidney disease (CKD). We hypothesized the vascular calcification seen in these animals may be associated with alterations in bone remodeling, and changes in Pi. 10 wk old low density lipoprotein receptor deficient (LDLR-/-) mice were shammed or subjected to electrocautery of one kidney followed by nephrectomy, then randomized into groups: Sham/Chow, Sham/Fat (15%), Sham/F/ BMP-7 (10 mcg/kg q week), CKD/Fat, CKD/ F/BMP-7. The mice fed a high fat diet developed hyperglycemia, hypercholesterolemia and aortic calcification. All groups were maintained on their regimens for 12 wks prior to calcein labeling and histomorphometry of femurs. BUN levels were equally high in the CKD groups; iPTH levels were high only in the CKD/Fat animals. Despite high iPTH levels 173±186 pg/ml in CKD vs 33±26 pg/ml in sham ($p<0.05$), the underlying osteodystrophy in both of the LDLR-/- high fat groups was consistent with an adynamic bone disorder (decreased OV/TV, ObN, MS/BS, and BFR/TV). BMP-7 did not affect the iPTH level (161±239) but normalized the osteodystrophy, by improving ObN, MS/BS, and BFR. LDLR-/-/CKD animals also had hyperosteoidosis, but no significant peritrabecular fibrosis. These findings were inconsistent with secondary HPTH. Pi levels were reduced from 16.4±0.4 mg/dl to 10.1±0.4 mg/dl with BMP-7 treatment ($p<0.01$) (Sham Pi 9.9±0.6). This study demonstrates altered bone remodeling and relatively high iPTH levels in LDLR-/- animals with CKD fed a high fat diet consistent with an adynamic bone disorder and PTH resistance. Identical surgery on C57Bl6 animals resulted in a high turnover osteitis fibrosa due secondary hyperparathyroidism at lower iPTH levels. Both osteodystrophies were reversed with BMP-7 treatment, without change in iPTH. The hyperphosphatemia observed in the LDLR-/- fat mice may have been caused by the ABD and diminished exchangeable Pi and may have contributed to the calcification observed. Improving the mineralizing and bone formation parameters with BMP-7, normalized Pi and decreased vascular calcification. Thus, the ABD is associated with vascular calcification, and a skeletal anabolic treated both the ABD and vascular calcification.

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S23.3

DOES THE PREVENTION OF HYPERPARATHYROIDISM MODIFY GROWTH VELOCITY?

Lesley Rees

It is generally accepted that PTH levels should be 1 to 2 times the upper limit of normal (ULN) for patients in CRF, and 2 to 4 times on dialysis. This is based on adult data, which have shown that levels <2 x ULN are associated with adynamic bone disease (ABD). Also, ABD has been associated with poor growth in dialysed children. However, potential risks of ABD, which is associated with an increased incidence of fractures (in adults) and a decreased ability to handle a calcium load, need to be balanced against those of persistently high PTH levels, which cause progressive parathyroid hyperplasia, high turnover bone disease and may culminate in parathyroidectomy. Most importantly, PTH is an independent risk factor for vascular disease.
For 20 years it has been the policy of Great Ormond Street Hospital Renal Unit to maintain PTH levels as far as possible within the normal range throughout the course of CRF into ESRF in order to prevent escape of the parathyroid gland from normal control mechanisms. When the GFR is <60 mls/min/1.73m^2 dietary phosphate is restricted, followed by the introduction of calcium based phosphate binders, aiming to maintain the serum phosphate below the 50th centile for age. In the majority of patients small quantities of 1-α calcidol are also necessary.
This policy allows normal growth and bone density: of 99 children aged 0.5-6 years with at least 2 years of follow-up, mean (range) GFR 22 (0-40) ml/min/1.73m^2, change in Ht SDS was +0.3 ($p=0.004$), and DEXA age matched SDS +0.02 (–2.3 to 2.8).
One reason why measured PTH levels may need to be above normal is that current 'intact' PTH assays measure both 1-84 PTH and long carboxyl-terminal PTH (C-PTH) fragments, overestimating actual PTH levels. C-PTH has an inhibitory effect upon the actions of 1-84 PTH, probably mediated at a separate C-terminal receptor. New assays that measure only 1-84 PTH allow calculation of C-PTH. The ratio of 1-84 PTH:C-PTH may correlate with bone turnover.
Of 241 children with CRF and 53 controls, the 1-84 PTH:C-PTH ratio was significantly lower than controls in dialysis patients and with a GFR <30mls/min/m^2. It was comparable to controls when the PTH was normal and significantly lower with PTH levels below and above the normal range. In 194 children followed for 1.1 (0.5-1.7) years, better growth was associated with a higher 1-84 PTH:C-PTH ratio.

S23.4

NON-INVASIVE ASSESSMENT OF BONE QUALITY IN CHILDREN WITH RENAL DISEASE

Mary Leonard

During childhood and adolescence, skeletal growth is characterized by gender-, maturation-, and race-specific increases in cortical dimensions and trabecular density. At least 90% of peak bone mass is acquired by 18 years of age, and 25% is acquired during the two-year period surrounding peak height velocity. Despite the widespread use of phosphate binders and vitamin D analogs to treat renal osteodystrophy, fracture rates in young adults on dialysis are markedly increased. The growing skeleton may be particularly vulnerable to the structural effects of renal osteodystrophy during critical growth periods.
The 2000 NIH Osteoporosis Consensus Development Conference defined osteoporosis as compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects bone density and bone quality. Bone quality refers to architecture, turnover, damage accumulation (e.g., microfractures) and mineralization. Renal disease may adversely affect bone density and each component of bone quality. Non-invasive imaging techniques are needed to characterize accurately the effects of renal disease and its therapies on bone density and bone quality. DXA is, by far, the most widely used technique for measuring bone mass in renal disease. However, DXA is a projectional technique in which three dimensional objects are analyzed as two dimensional, and bone is presented as the combined sum of cortical and trabecular bone mineral content within the projected bone area, concealing distinct structural characteristics. Because trabecular and cortical bone behave differently in response to increased parathyroid activity (increase and decrease, respectively), DXA is especially limited in the assessment of renal osteodystrophy. The poor correlation between DXA results and fracture risk in renal disease highlights the limitations of this technique.
In contrast, quantitative computed tomography (QCT) describes volumetric bone density, measures bone dimensions, and distinguishes between cortical and trabecular bone. QCT estimates of bone architecture reflect the flexural and torsional strength of bone. QCT findings in the vertebrae in patients with renal disease confirm histomorphometric data; trabecular density is increased in high-turnover bone disease and decreased in low-turnover disease.
Recent advances in high resolution imaging technologies, such as micro magnetic resonance, enable three dimensional representation of trabecular bone microarchitecture, and structural parameters such as trabecular thickness and network connectivity. Our preliminary studies suggest this technique captures the microarchitectural changes that compromise bone strength in renal disease. These techniques have the potential to improve detection of renal patients at risk for fracture, and to guide clinical studies of new therapies.