



Oral Communications 6 Pediatrics/Genetics/Electrolytes

December 6, 2025 (Saturday) 11:00~12:30

Venue : Room 6 (702)

Chair(s) Mignon McCulloch, Hsin-Hui Wang

11:00-11:09	Genetic Contributions, Phenotypic Characteristics and Follow-up Outcomes in Patients with Non-Neurogenic Neurogenic Bladder APCN20250291	Min-Hua Tseng Division of Nephrology, Department of Pediatrics, Chang Gung Memorial Hospital
11:09-11:18	Impact of Advanced Maternal Age on Renal Development and Adult Outcomes in Offspring: A Mouse Model Study APCN20250149	Rei Nakazato Department of Endocrinology and Metabolism, Renal Medicine, Nippon Medical School
11:18-11:27	T-Cell Efflux Dynamics: The Role of P-Glycoprotein and MRP-1 in Pediatric Steroid-Resistant Nephrotic Syndrome APCN20250837	Harshit Singh Department of Immunology, THSTI
11:27-11:36	IL-6 Transactivation is Critically Involved in C5a Related Renal Fibrosis APCN20250571	I-Jung Tsai Division of Nephrology, Department of Pediatrics, National Taiwan University Hospital
11:36-11:45	Exploring the Role of SGLT2 Inhibitors in Autosomal Dominant Polycystic Kidney Disease: A Systematic Review of Clinical and Preclinical Evidence APCN20251074	Muhammad Farid Rakhman Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya
11:45-11:54	Longitudinal Changes in Left Ventricular Mass Index and Blood Pressure Control in Children With Chronic Kidney Disease APCN20250515	You-Lin Tain Division of Pediatric Nephrology, Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital





11:54-12:03	Whole Genome Sequencing Identified Deep-Intronic COL4A5 Splice Variants in Two Pediatric Cases of Alport Syndrome Undetected by Targeted Exome Analysis APCN20250787	Asahi Yamamoto Department of Pediatrics, Kobe University Graduate School of Medicine
12:03-12:12	From Kidneys to the Brain: A Systematic Review and Meta-Analysis of Neurodevelopmental Outcomes in Neonates With Acute Kidney Injury APCN20251184	Astia Anelia Master of Biomedical Science Program, Faculty of Medicine, Nursing, and Public Health, Gadjah Mada University
12:12-12:21	Cumulative Nephrotoxic Drug Burden and Risk Stratification for Renal Tubulopathy in Pediatric Oncology: Beyond Platinum Compounds APCN20250776	Jhao-Jhuang Ding Division of Nephrology, Department of Pediatrics, Chang Gung Memorial Hospital and Chang Gung University
12:21-12:30	The Comparative Effectiveness of Mineralocorticoid Receptor Antagonists and Aldosterone Synthase Inhibitors in The Treatment of Essential Hypertension: A Systematic Review and Network Meta-analysis APCN20250817	Hadi Tehfe Division of Internal Medicine, Department of Medicine, University of Ottawa



Genetic Contributions, Phenotypic Characteristics and Follow-up Outcomes in Patients with Non-Neurogenic Neurogenic Bladder

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Abstract

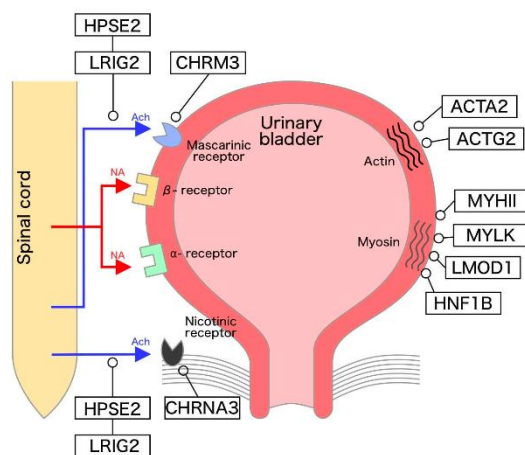
Background: Non-neurogenic neurogenic bladder (NNNB) represents a significant clinical challenge in children. This study investigated the clinical characteristics, urodynamic findings, genetic background, and management outcomes in Taiwanese patients with NNNB.

Methods: We analyzed 11 patients (6 females, 5 males) with NNNB from multiple Taiwanese medical centers. Evaluations included renal function assessment, urinary tract imaging, voiding cystourethrography, uroflowmetry, and genetic analysis.

Results: Median age 8 years (2-18). Underlying conditions: motility bowel disease, megacolon, prune-belly syndrome, intractable constipation; 2 with colostomy. Initial eGFR 44-102 ml/min/1.73m². Common findings: bladder wall thickening (6/11), emptying disorders (5/11), hydronephrosis (3/11). Vesicoureteral reflux in 4 patients (grades 1-4). Abnormal voiding in 8 patients; max flow 6.1-28 ml/sec. Genetic mutations in 7 (64%): ACTG2 (3), CHRNA3 (2), TP63, LRIG2. Management: spontaneous voiding (7), intermittent catheterization (3), indwelling catheter (1). UTI frequency: never to every 2-3 months. Over 5.5 years, two-thirds developed hydronephrosis; 3 reached advanced CKD (2 stage IV, 1 stage V)

Conclusion: Our study demonstrates significant clinical heterogeneity in NNNB with identifiable genetic mutations in approximately two-thirds of cases. ACTG2 and CHRNA3 mutations were most common, associated with severe bladder dysfunction and gastrointestinal motility disorders. These findings suggest important genotype-phenotype correlations that may guide personalized management approaches and genetic counseling.

Keywords : non-neurogenic neurogenic bladder, gene, phenotype, outcome



Oral Communications : Pediatrics/Genetics/Electrolytes

Abstract Submission No. : APCN20250149

Impact of Advanced Maternal Age on Renal Development and Adult Outcomes in Offspring: A Mouse Model Study

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Abstract

Background: The incidence of pregnancies at advanced maternal age (AMA), defined as maternal age of 35 years or older, is increasing worldwide, especially in developed countries, reflecting the growing social participation of women. According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, the perinatal maternal environment influences the risk of developing diseases later in life, with AMA being recognized as one factor that alters the intrauterine milieu. This study aims to investigate how the intrauterine environment associated with AMA impacts kidney development and adult phenotypes in offspring, using a mouse model of AMA.

Methods: Male offspring born to Jcl:ICR female mice aged ≥ 6 months, mated with 10- to 16-week-old ICR males, were assigned to the advanced maternal age (AMA) group, while those born to 10- to 12-week-old Jcl:ICR females constituted the control group. In both groups, phenotypic analyses were performed from birth to adulthood, including measurements of body weight (BW), kidney weight, and blood pressure (BP). Additionally, comprehensive evaluations of kidney morphology, function, renal gene expression (via bulk RNA sequencing), and metabolomic profiles were conducted.

Results: The AMA group exhibited significantly lower birth weights compared to controls; however, catch-up growth was observed by 4 weeks of age. By 8 weeks, these offspring displayed significantly higher body weights and elevated systolic blood pressure. Although kidney weights did not differ between groups at 8 weeks, histological analysis revealed a significantly lower cortical glomerular density and increased individual glomerular tuft area in the AMA group. At birth, the expression of genes associated with ureteric bud branching was significantly reduced. Furthermore, gene set enrichment analysis (GSEA) of renal RNA sequencing data at 8 weeks demonstrated substantial downregulation of gene sets related to mitochondrial function and oxidative phosphorylation, alongside significant upregulation of angiogenesis-related gene sets. Metabolomic profiling of the kidneys revealed increased activity in purine, amino acid, and nucleotide metabolism, with elevated levels of AMP and IMP in the AMA group, suggesting a compensatory response to mitochondrial dysfunction and ATP depletion.

Conclusion: Advanced maternal age impairs nephron development and mitochondrial function in offspring, accompanied by alterations in the renal metabolomic profile that may contribute to glomerular hypertrophy and adult-onset hypertension. These findings support the DOHaD hypothesis and underscore maternal aging as a potential risk factor for future chronic kidney disease in offspring.

Keywords : Advanced Maternal Age (AMA), DOHaD Hypothesis, Kidney Development

Oral Communications : Pediatrics/Genetics/Electrolytes

Abstract Submission No. : APCN20250837

T-Cell Efflux Dynamics: The Role of P-Glycoprotein and MRP-1 in Pediatric Steroid-Resistant Nephrotic Syndrome

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Abstract

Background

Idiopathic nephrotic syndrome represents the most common type of primary glomerular disease in children. Glucocorticoids remain the mainstay of therapy. However, 60-80% of patients become resistant to steroid. Overexpression of P-glycoprotein (P-gp) and Multidrug resistance associated protein 1 (MRP-1) might be responsible for steroid resistance due to their ability to modulate the pharmacokinetics of steroids. We aimed to investigate the role of P-gp and MRP-1 in resistance to steroids.

Aim

To evaluate the differential alteration of P-gp and MRP-1 on CD4+ and CD8+ T-cell subsets in steroid resistant as well as steroid sensitive patients.

Methods

After ethical approval, all paediatric patients who matched the inclusion criteria were recruited. P-gp and MRP-1 expression were evaluated on whole blood and functional activity on peripheral blood mononuclear cells (PBMCs) in steroid sensitive nephrotic syndrome (SSNS) (n=40, male 29, mean age=7.54±3.5) and steroid resistant nephrotic syndrome (SRNS) (n=40, male 24, mean age=8.43±3.8) patients. SSNS patients were in sustained remission for at least 6 months without steroid. All definitions are as per the criteria of ISKDC.

P-gp and MRP-1 expression were analyzed by Flow Cytometry. The absolute values were calculated using formula (% of positive cells × Relative Fluorescent Intensity (RFI)), Multi resistance activity factor (MAF) for each transporter, was calculated using formula (MAFMDR1=100×(FMDR1-F0)/FMDR1). All data are expressed as mean±s.d.

Results

Among 80 patients, demographic significant difference were in S.Albumin (SSNS=2.87±.98, SRNS=2.27±.79, p=0.012) and proteinuria (SSNS=14.38±3.09, SRNS=273±183.45, p<0.001). The % of P-gp and MRP-1 positive cells were significantly higher in SRNS as compared to SSNS (11.07±4.17 v/s 5.80±2.77, p<0.001); (15.32±6.80 v/s 7.75±3.53, p<0.001). Absolute P-gp and MRP-1 expression was significantly high in SRNS (67.01±24.01 v/s 33.58±22.40, p<0.005); (68.04±21.40 v/s 39.20±19.07, p<0.005) respectively.

P-gp expression on CD4+ and CD8+ cells were significantly high in SRNS (6.48±1.93 v/s 3.01±1.06, p=0.008) ; (6.92±1.09 v/s 2.12±0.91, p<0.001) respectively. MRP-1 expression on CD4+ and CD8+ cells were significantly higher in SRNS (10.74±5.33 v/s 3.86±1.11, p=0.043) ; (5.36±0.79 v/s 1.70±0.63, p<0.001) respectively. Functional activity of P-gp and MRP-1 was significantly increased in SRNS as compared to SSNS (47.10±19.10 v/s 93.94±33.07, p<0.001); (87.49±36.72 v/s 52.10±32.83, p<0.001) respectively.

Conclusion

We conclude that overexpression of P-gp and MRP-1 on CD4+ and CD8+ cells may contribute to resistance to corticosteroids in idiopathic nephrotic syndrome in children.

Keywords : Nephrotic Syndrome, Steroid Resistance, P-glycoprotein

Oral Communications : Pediatrics/Genetics/Electrolytes

Abstract Submission No. : APCN20250571

IL-6 transactivation is critically involved in C5a related renal fibrosis

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Abstract

Background

Idiopathic nephrotic syndrome (INS) is a common pediatric kidney disease caused by breakdown of the glomerular filtration barrier. Pathologically, mesangial hypercellularity is recognized as a variant of minimal change disease (MCD). Our prior cohort studies revealed elevated serum C5a levels during INS relapse, and in a mouse model, recombinant C5a was shown to induce substantial proteinuria and renal fibrosis. In mouse model, recombinant C5a induced profound proteinuria and renal fibrosis. Interestingly, recombinant C5a did not induce renal fibrosis in IL-6 knockout mice. Despite IL-6 did not significantly elevate in patients with immune-mediated kidney diseases, we hypothesized IL-6 might play critical role in kidney tissue fibrosis via local activation of classical or trans-signaling pathway in kidney autoimmune and inflammatory diseases.

Methods

This study aimed to elucidate the precise role of IL-6 in C5a-induced renal fibrosis using soluble glycoprotein 130 knock-in (sgp130KI) and IL-6 knockout (KO) transgenic mouse models. To identify the IL-6-producing cell type, primary cultures of mouse mesangial cells, kidney endothelial cells, and podocytes were treated with recombinant C5a. Mouse renal fibroblasts were treated with IL-6 and IL-6R-alpha protein to verify the IL-6 trans-signaling pathway on type I collagen and fibronectin expression. Level of IL-6, type I collagen, and fibronectin were determined by ELISA. IL-6 trans-signaling pathway in C5a-induced renal fibrosis was clarified in sgp130KI mice.

Results

The results indicated that C5a may induce IL-6 expression in mesangial cells, but not in kidney endothelial cells or podocytes. Furthermore, the combination of IL-6/ IL-6R-alpha significantly enhanced the expression of type I collagen and fibronectin expression in renal fibroblasts in vitro. The phenomenon of C5a-induced renal fibrosis was significantly attenuated in both sgp130 KI mice and IL-6KO mice.

Conclusions

Our study conclusively demonstrates that IL-6 transactivation plays a critical role in C5a-related renal fibrosis in vivo and in vitro. These insights are pivotal and may inform the development of novel therapeutic strategies for managing renal function impairment associated with renal fibrosis in INS, including conditions such as focal segmental glomerulosclerosis (FSGS).

Keywords : C5a, IL-6, kidney fibrosis

Exploring the Role of SGLT2 Inhibitors in Autosomal Dominant Polycystic Kidney Disease: A Systematic Review of Clinical and Preclinical Evidence

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Abstract

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a leading cause of end-stage renal disease. While SGLT2 inhibitors are established in chronic kidney disease, their efficacy and safety in ADPKD remain uncertain. **Objective:** This systematic review aims to evaluate the efficacy, safety, and mechanistic effects of SGLT2 inhibitors in patients with ADPKD, based on current clinical and preclinical evidence.

Methods: A systematic search of PubMed, Embase, ClinicalTrials.gov, Google Scholar, and ScienceDirect up to June 2025 identified studies evaluating SGLT2 inhibitors in ADPKD. Two reviewers independently screened and extracted data from eligible clinical and preclinical studies.

Results: Out of 95 records, five studies met inclusion criteria: three clinical studies (n=27, n=7, n=20), one large retrospective cohort (n=2,640 SGLT2i users among 31,070 PKD patients), and one preclinical animal study. Dapagliflozin improved annual eGFR slope from -5.65 ± 9.57 to $+2.57 \pm 7.88$ mL/min/1.73 m²/year (p=0.002) in a randomized crossover trial, and slowed eGFR decline from -2.7 to -1.9 mL/min/1.73 m²/year in a retrospective study. SGLT2i use was associated with reduced risks of dialysis (HR 0.657), acute kidney injury (HR 0.896), and mortality (HR 0.840) in a large cohort. However, effects on kidney volume and cyst growth were inconsistent: dapagliflozin plus tolvaptan reduced 6-month TKV growth (-0.44% vs. $+5.04\%$, p=0.01), while other studies reported annual htTKV increases and significant short-term volume gains. Preclinical data indicated increased cyst burden with SGLT2i. Adverse events were consistent with known safety profiles.

Conclusions: SGLT2 inhibitors may slow eGFR decline in ADPKD, particularly with tolvaptan, but effects on cyst growth are mixed, and long-term safety remains unclear. Use in ADPKD should be cautious and ideally within clinical trials.

Keywords : Autosomal dominant polycystic kidney disease; ADPKD; SGLT2 inhibitors; dapagliflozin; kidney function; total kidney volume; cyst growth.

Study (Year)	Sample Size/ Population	Intervention	Follow-up Duration	Common Adverse Events (AEs)	Serious AEs / Discontinuations	Statistical Notes
Uchiyama et al. (2025)	27 ADPKD patients on tolvaptan	Dapagliflozin 10 mg + Tolvaptan	6 months per phase	Transient eGFR dip; urinary tract infections in 2 patients (7.4%)	None	No significant difference vs. control (P > 0.05)
Yoshimoto et al. (2024)	7 ADPKD patients	Dapagliflozin (likely 10 mg)	Median 20 months	Mild genital infection in 1 patient (14.3%)	None	No formal statistical testing due to small sample size
Morioka et al. (2023)	20 ADPKD patients	Dapagliflozin 10 mg	~3 months	Transient polyuria and thirst in 3 patients (15%)	None	No serious AEs reported
Yu et al. (2024)	2,640 SGLT2i users with PKD + T2DM	SGLT2 inhibitors (various)	Not specified	No increased diabetic ketoacidosis or severe hypoglycemia	None reported	Lower AKI incidence (HR 0.896; P = 0.01); mortality reduced (HR 0.840; P = 0.002)
Kapoor et al. (2015)	PCK rat model	Dapagliflozin	6 weeks	Increased albuminuria	N/A (animal study)	Significant adverse renal effects (P < 0.05)

Table 3. Safety and Adverse Events in Included Studies

Longitudinal Changes in Left Ventricular Mass Index and Blood Pressure Control in Children With Chronic Kidney Disease

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Abstract

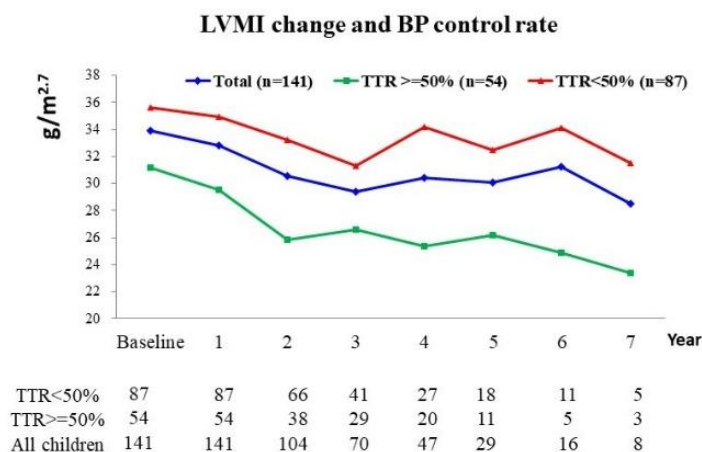
Introduction: Children with chronic kidney disease (CKD) are at high risk of developing left ventricular hypertrophy, an early marker of cardiovascular disease (CVD) in the pediatric population. This study evaluated the impact of blood pressure (BP) control—measured by the proportion of time within the target range (TTR)—on longitudinal changes in left ventricular mass index (LVMI) in children with CKD.

Methods: This prospective cohort study followed children under 18 years of age with CKD for up to 8 years at a medical center in Kaohsiung, Taiwan. Participants were stratified into two groups based on BP control: intensive (TTR $\geq 50\%$) and non-intensive (TTR $< 50\%$). The primary outcome was annual change in LVMI measured via echocardiography. Linear mixed-effects models adjusted for age, sex, estimated glomerular filtration rate (eGFR), and comorbidities were used for analysis.

Results: Among 141 children (59% male, mean age 9 years), 556 LVMI measurements were collected over a median follow-up of 3.02 years. The mean BP TTR was 35% (± 33.5). The intensive group (n=54) showed a greater annual reduction in LVMI ($-0.95 \text{ g/m}^2.7$ per year; 95% CI: -2.1 to 0.19) compared to the non-intensive group (n=87; $-0.1 \text{ g/m}^2.7$ per year; 95% CI: -0.93 to 1.73) (Fig 1). This suggests that better BP control is associated with reduced progression of left ventricular hypertrophy and risk of CVD.

Conclusion: Sustained BP control within the normotensive target range is associated with a greater reduction in LVMI over time in children with CKD, highlighting the importance of intensive BP management in reducing long-term cardiovascular risk.

Keywords : children, chronic kidney disease, left ventricular mass index, blood pressure control, cardiovascular risk



Whole Genome Sequencing Identified Deep-Intronic COL4A5 Splice Variants in Two Pediatric Cases of Alport Syndrome Undetected by Targeted Exome

Analysis

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Abstract

Introduction:

Alport syndrome is a hereditary glomerular disorder caused by pathogenic variants in COL4A3, COL4A4, or COL4A5, which encode type IV collagen. It is characterized clinically by hematuria, progressive kidney dysfunction, sensorineural hearing loss, and ocular abnormalities. While targeted exome sequencing is widely used for genetic diagnosis, its limitation lies in its inability to detect deep-intronic variants that can affect gene splicing. Here, we report two pediatric cases of Alport syndrome in which whole genome sequencing (WGS) successfully identified deep-intronic COL4A5 splice-altering variants that were not detected by targeted exome sequencing.

Methods:

The first case was a 16-year-old girl who presented with recurrent gross hematuria from infancy. A kidney biopsy performed at age two showed lamellation of the glomerular basement membrane and a mosaic pattern of $\alpha 5$ collagen staining, suggestive of X-linked Alport syndrome. The second case was a 3-year-old girl who also had recurrent gross hematuria from infancy, along with persistent proteinuria (urinary TP/Cr ~ 1) and normal kidney function. Her kidney biopsy revealed a similar $\alpha 5$ mosaic pattern. In both patients, targeted exome sequencing was performed to analyze COL4A3, COL4A4, COL4A5, and approximately 140 additional genes associated with hereditary kidney diseases, but no pathogenic variants were detected.

Results:

Whole genome sequencing revealed deep-intronic COL4A5 variants in both patients: c.276+1306G>A in the first case and c.3791-1066A>G in the second case (NM_000495.5). Functional assessment using a minigene assay demonstrated that each variant led to the insertion of a cryptic exon into the COL4A5 mRNA transcript. These results confirmed that both variants caused aberrant splicing, providing a molecular diagnosis consistent with Alport syndrome.

Conclusion:

These two cases highlight the diagnostic utility of whole genome sequencing for detecting deep-intronic pathogenic variants in patients with clinically suspected Alport syndrome. When targeted exome analysis is negative but histological or clinical findings strongly support the diagnosis, whole genome sequencing followed by functional validation should be considered to achieve a definitive genetic diagnosis.

Keywords : Alport syndrome, COL4A5, deep-intronic variant, whole genome sequencing, minigene assay

Oral Communications : Pediatrics/Genetics/Electrolytes

Abstract Submission No. : APCN20251184

From Kidneys to the Brain: A Systematic Review and Meta-Analysis of Neurodevelopmental Outcomes in Neonates with Acute Kidney Injury

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Abstract

Background: Neonatal acute kidney injury (AKI) remains an underreported contributor to long-term neurodevelopmental impairment. The neonatal period is critical for neurogenesis, myelination, and cortical connectivity. AKI during this phase can impair brain development by reducing cerebral perfusion, inducing inflammation, and accumulation of metabolic waste. These processes may result in lasting cognitive consequences. To date, this is the first systematic review and meta-analysis to investigate neurodevelopmental outcomes following neonatal AKI.

Methods: A systematic search of PubMed, Scopus, and Web of Science identified 4,780 records. After screening, 12 studies (2014–2024) were included, encompassing 2,602 neonates. Inclusion criteria were studies reporting head circumference (HC), Bayley Scales of Infant Development, neurodevelopmental impairment (NDI), cerebral palsy, or brain MRI outcomes in neonates with AKI. Risk of bias was assessed using ROBINS-I. Meta-analysis was performed using a bivariate random-effects model (REML) in R Studio and heterogeneity was assessed using I^2 .

Results: Neonates with AKI had significantly lower birth weights than those without AKI (Mean Difference [MD] = -79.13 g; 95% CI: -150.34 to -7.93), suggesting that low birth weight may predispose to AKI due to immature renal and circulatory systems. Head circumference (HC) was consistently smaller in the AKI group from birth to 24 months, with the largest gap at 24 months (MD = -1.94 cm; 95% CI: -2.69 to -1.19). A reduction of ≥ 1 cm in head circumference is clinically meaningful and may reflect significant loss in brain volume, potentially affecting long-term neurodevelopment. AKI was associated with an increased risk of delay across Bayley domains: cognitive (RR = 1.35), language (RR = 1.23), and motor (RR = 1.18), with overall risk elevated significantly (RR = 1.24; 95% CI: 1.02–1.51). At 20–24 months, AKI was significantly linked to higher NDI rates (RR = 1.84; 95% CI: 1.11–3.04) and cerebral palsy (RR = 2.36; 95% CI: 1.07–5.21). Brain MRI revealed abnormalities in 63% of neonates with AKI (95% CI: 51%–74%), involving superficial/deep gray matter, white matter, basal ganglia, thalamus, cerebellum, and delayed myelination or infarction consistent with moderate to severe encephalopathy.

Conclusion: Neonatal AKI is not just an acute and reversible event. Beyond its acute course, it carries significant long-term risks to brain development. These findings emphasize the importance of early detection, neuroprotective strategies, and urgent longitudinal research to close critical gaps in neonatal care.

Keywords : Neonatal Acute Kidney Injury; Neurodevelopment; Head Circumference; Neurodevelopmental Impairment; Bayley Scales; Brain MRI; Cerebral Palsy

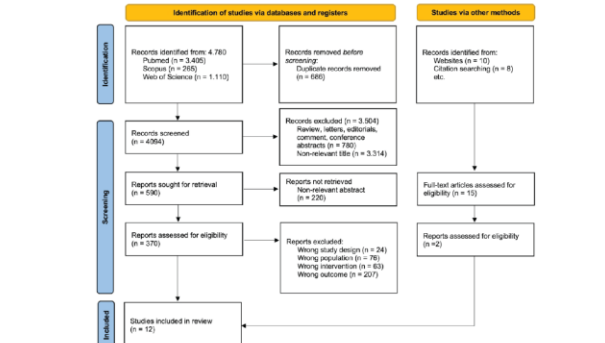


Figure 1. PRISMA 2020 flow diagram. The literature search was conducted across PubMed, Scopus, and Web of Science databases, resulting in a total of 4,780 records. After screening, 12 studies were included that reported on neurodevelopmental outcomes in neonates with acute kidney injury (AKI).

Table 1. Baseline characteristics of neonatal patients with AKI and non-AKI

No.	Year	Country	Study Design	n patient AKI	n patient Non-AKI	AKI Diagnosis	AKI Etiology	AKI Staging	Follow Up Duration
1	Opeta_2024	India	cross-sectional	74	348	42	Modified KDIGO	-	at admission
2	Chen_2023	Taiwan	longitudinal follow-up cohort retrospective	154	578	732	Modified KDIGO	Stage 1 = 162 Stage 2 = 42 Stage 3 = 19	6, 12, 24 months
3	Chowdhary_2017	USA	retrospective cohort	223	178	401	Modified KDIGO	-	9 months
4	Turner_2024	USA	multi-center prospective cohort	12	45	57	Modified KDIGO	-	at admission
5	Yen_2024	Taiwan	retrospective case control	51	103	154	Modified KDIGO	-	6, 12, 24 months
6	Pande_2024	USA	observational retrospective cohort	62	141	203	Modified KDIGO	-	20 months
7	Pande_2022	USA	retrospective cohort	62	141	203	Modified KDIGO	-	20 months
8	Gallo_2021	Belanda	retrospective cohort	42	0	42	NIHDK	-	24 months
9	Sarkar_2014	USA	observational retrospective cohort	34	54	88	Modified KDIGO	-	7-10 days
10	Cavallin_2020	India	observational retrospective cohort	10	91	101	Modified KDIGO	-	Stage 1 = 8 Stage 2 = 2
11	Mouqdad_2022	Saudi Arabia	retrospective case control	36	80	116	Modified KDIGO	-	12, 24 months
12	Maqsood_2017	USA	retrospective case control	110	113	222	Modified KDIGO	-	Stage 1 = 87 Stage 2 & 3 = 21

KDIGO: Kidney Disease: Improving Global Outcomes
NIHDK: National Institute of Diabetes and Digestive and Kidney Diseases

Table 2. Baseline characteristics of age, birth weight, and birth head circumference in AKI and non-AKI neonates

No.	Author Year	n AKI	n Non-AKI	Age at AKI (weeks)	Birth Weight of AKI Patient (grams)	Birth Weight of Non-AKI Patient (grams)	Birth Head Circumference of AKI Patient (cm)	Birth Head Circumference of Non-AKI Patient (cm)	
1	Opeta_2024	74	348	44	3,338.6 (490)	2,238.5 (519.7)	2,094.1 (64.47)	24.02 ± 1.96	
2	Chen_2023	154	578	70	25.8 (weeks)	859.5 (500)	1023 ± 500	23.5	
3	Chowdhary_2017	223	178	20	26.0 ± 2.2 (weeks)	744 ± 156	744 ± 156	23.1 ± 2.2	
4	Turner_2024	12	45	27	30	38.75 (weeks)	3305 ± 650	3410 ± 560	-
5	Yen_2024	51	103	32	32.6 ± 3.2 (weeks)	1,880 ± 890	1,910 ± 890	29.6 ± 4.1	
6	Pande_2024	62	141	20	28.5 ± 1.5 (weeks)	3,100 ± 600	3,100 ± 600	31.0 ± 4.3	
7	Pande_2022	62	141	20	28.5 ± 1.5 (weeks)	3,100 ± 600	3,100 ± 600	31.0 ± 4.3	
8	Gallo_2021	42	0	40	40 (weeks)	841	690-841	-	
9	Sarkar_2014	34	54	39	39.1 (weeks)	3,290 ± 118.5	3,290 ± 118.5	-	
10	Cavallin_2020	10	91	22	28.5 ± 1.5 (weeks)	990 ± 74.75	1055 ± 299.26	-	
11	Mouqdad_2022	36	80	26.2 ± 2.2 (weeks)	761 ± 147	813 ± 127	23.2 ± 1.7	23.7 ± 1.5	

Table 3. Follow-up head circumference measurements in AKI and non-AKI neonates

No.	Author Year	n AKI	n Non-AKI	HC 0 day (cm)	HC 6 months (cm)	HC 9 months (cm)	HC 12 months (cm)	HC 24 months (cm)
1	Chen_2023	24.02	21.8	21.8	21.8	21.8	21.8	22.9
2	Chowdhary_2017	1.96	2.45	1.68	2.165	2.45	2.45	2.31
3	Yen_2024	29.3 ± 4.3	29.6 ± 4.1	42.0 ± 1.6	40.5 ± 2.2	44.7 ± 4.6	43.5 ± 2.2	47.3 ± 1.8
4	Maqsood_2017	23.7 ± 1.5	22.7 ± 1.91	32.3 ± 2.5	33.8 ± 3.24	-	-	-

Table 4. Prevalence of Bayley Scale, Neurodevelopmental Impairment (NDI), and Cerebral Palsy in AKI and non-AKI neonates

No.	Author Year	n AKI	n Non-AKI	Cognitive	Motor	Language	Neurodevelopmental Impairment (NDI)	Cerebral Palsy
1	Opeta_2024	74	348	43/41 (58.1%)	28/82 (34.1%)	39/141 (27.6%)	28/82 (34.1%)	28/82 (34.1%)
2	Chen_2023	48/141 (33.3%)	27/62 (43.5%)	29/141 (20.6%)	17/62 (27.4%)	7/141 (4.9%)	38/62 (61.3%)	38/62 (61.3%)
3	Chen_2023	44/80 (55.0%)	19/21 (90.5%)	18/21 (85.7%)	5/21 (23.8%)	5/21 (23.8%)	18/44 (40.9%)	18/44 (40.9%)
4	Yen_2024	56/103 (54.3%)	29/103 (28.2%)	56/103 (54.3%)	29/103 (28.2%)	56/103 (54.3%)	29/103 (28.2%)	29/103 (28.2%)
5	Gallo_2021	42	0	Term: 0/20 Preterm: 0/20	Term: 0/20 Preterm: 0/20	Term: 0/20 Preterm: 0/20	Term: 0/20 Preterm: 0/20	Term: 0/20 Preterm: 0/20

Table 5. Characteristics of brain imaging results and accompanying symptoms in AKI neonates

No.	Author Year	n AKI	n Non-AKI	Tools	Seizure Prevalence in AKI	Encephalopathy (by EEG)	MRI Lesion Detail
1	Opeta_2024	74	422	MRI on a 1.5 Telsa	10/12 (83.3%) in AKI	Seizure = 5/74 (6.7%) Focal (n=5) Deep (n=2) Wk = 2/74 (2.7%) Cerebral hematomas = 38/74 (51.3%) Basal ganglia = 20/74 (27%) Basal nuclei and cortex, more extensive MRI = both	Superficial (GM = 37/74 (50%) Deep (GM = 24/74 (32.4%) WM = 2/74 (2.7%) Cerebral hematomas = 38/74 (51.3%) Basal ganglia = 20/74 (27%) Basal nuclei and cortex, more extensive MRI = both
2	Sarkar_2014	34	88	Brain MRI	Seizure in abnormal MRI = 17/34 (50%)	NIHDK Sumat Stage: Severe = 5/6%	MRI stage 2A: IGV/bleeds = internal capsule = infarction MRI stage 2B: IGV/bleeds = internal capsule = infarction and cerebral lesion. No lesion data provided
3	Turner_2024	12	57	Brain MRI	Not studied	Not studied	Cerebellar signal (p=0.04), cerebellar volume (p=0.001), high cerebellar score (p=0.001), myelination delay (p=0.04)
4	Pande_2022	62	203	Not studied	Retrospective data	AKI: 4/62 (6.4%) Non-AKI: 6/203 (3%)	Not studied
5	Mouqdad_2022	36	116	Brain MRI with 1.5 T scanner	Not studied	Not studied	Cerebellar signal (p=0.04), cerebellar volume (p=0.001), high cerebellar score (p=0.001), myelination delay (p=0.04)

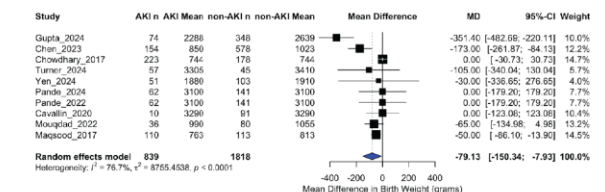


Figure 2. Forest plot of mean birth weight (grams) in neonates with and without acute kidney injury (AKI). This forest plot illustrates that neonates with AKI had a significantly lower mean birth weight compared to those without AKI (Mean Difference [MD] = -79.13 grams; 95% Confidence Interval [CI], -150.34 to -28.93; $p < 0.05$). Low birth weight may act as a risk factor for AKI due to immature renal function and hemodynamic instability.

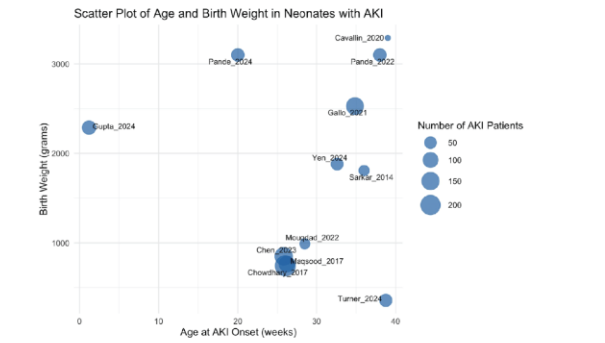


Figure 3. Scatter plot of the relationship between age at onset of AKI and birth weight in neonates. Each dot represents a single study, with the size of the bubble reflecting the number of neonates with AKI reported in that study.

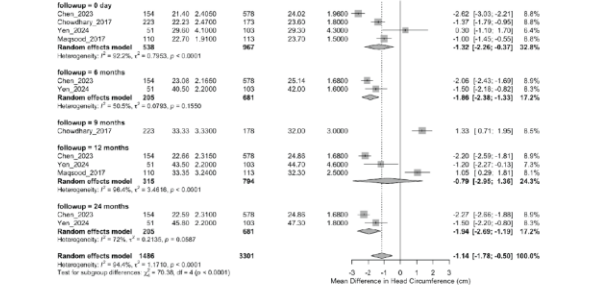


Figure 4. Forest plot of mean differences in head circumference (HC) between neonates with and without AKI across multiple follow-up points (from day 0 to 24 months). Neonates with AKI consistently exhibited smaller head circumferences compared to their non-AKI counterparts, beginning from birth (MD = -1.32 cm up to 24 months of age (MD = -1.94 cm), with a significant heterogeneity ($\chi^2 = 70.38$, $p < 0.0001$). This indicates a persistent and progressive adverse impact of AKI on brain growth. A reduction of approximately 1 cm in HC is associated with increased risk of motor, intellectual, or neurological developmental impairments as referenced by WHO.

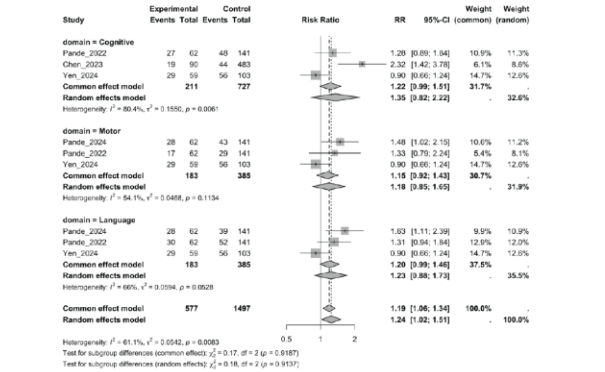


Figure 5. Forest plot of developmental delay based on the three domains of the Bayley Scales of Infant Development (Cognitive, Motor, and Language) in neonates with AKI versus non-AKI. Neonates with AKI showed a significantly higher risk of developmental delay compared to those without AKI (Relative Risk [RR] = 1.24; 95% CI: 1.02–1.51), particularly in the cognitive domain (RR = 1.35; 95% CI: 0.92–2.22; $P = 80.4%$). The underlying mechanisms include impaired cerebral perfusion, accumulation of nephrotoxic metabolites, systemic inflammation, and electrolyte imbalances, all of which can disrupt normal brain maturation.

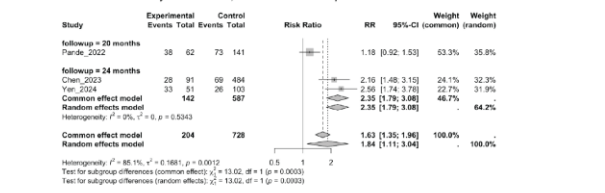


Figure 6. Forest plot of neurodevelopmental impairment (NDI) at 20-24 months of age in neonates with versus without AKI. This plot demonstrates that NDI was significantly more prevalent in neonates with AKI compared to non-AKI peers (RR = 1.84; 95% CI: 1.11–3.04), indicating that the risk of long-term neurodevelopmental sequelae becomes increasingly evident with age.

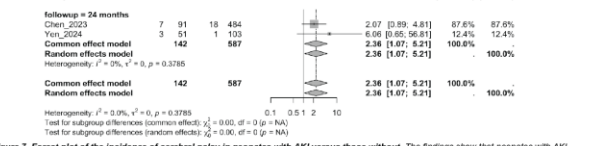


Figure 7. Forest plot of the incidence of cerebral palsy in neonates with AKI versus those without. The findings show that neonates with AKI had more than twice the risk of developing cerebral palsy compared to non-AKI neonates (RR = 2.36; 95% CI: 1.07–5.21). The development of cerebral palsy may result from hemodynamic instability, release of proinflammatory cytokines, increased blood-brain barrier permeability, and electrolyte/metabolic disturbances leading to neural tissue injury. Given its permanent nature, early detection and management of AKI is crucial.

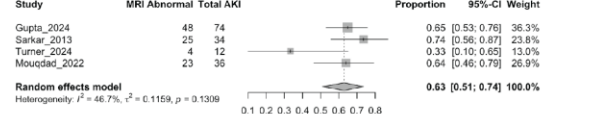


Figure 8. Forest plot of the proportion of abnormal brain MRI findings in neonates with AKI. The pooled proportion of abnormal brain MRI findings was 63% (95% CI: 46.7%–79.5%), indicating that more than half of neonates with AKI exhibit detectable structural brain abnormalities on MRI.

Cumulative Nephrotoxic Drug Burden and Risk Stratification for Renal Tubulopathy in Pediatric Oncology: Beyond Platinum Compounds

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Abstract

Introduction: Platinum-based chemotherapy is essential in pediatric oncology but carries significant nephrotoxicity risk. While acute kidney injury has been extensively studied, the specific patterns and independent predictors of tubular dysfunction have received minimal attention. This study represents the first comprehensive analysis to identify independent risk factors for renal tubulopathy in pediatric cancer patients receiving platinum-based chemotherapy, focusing on drug interactions per the NINJA (Nephrotoxic Injury Negated by Just-in-time Action) list.

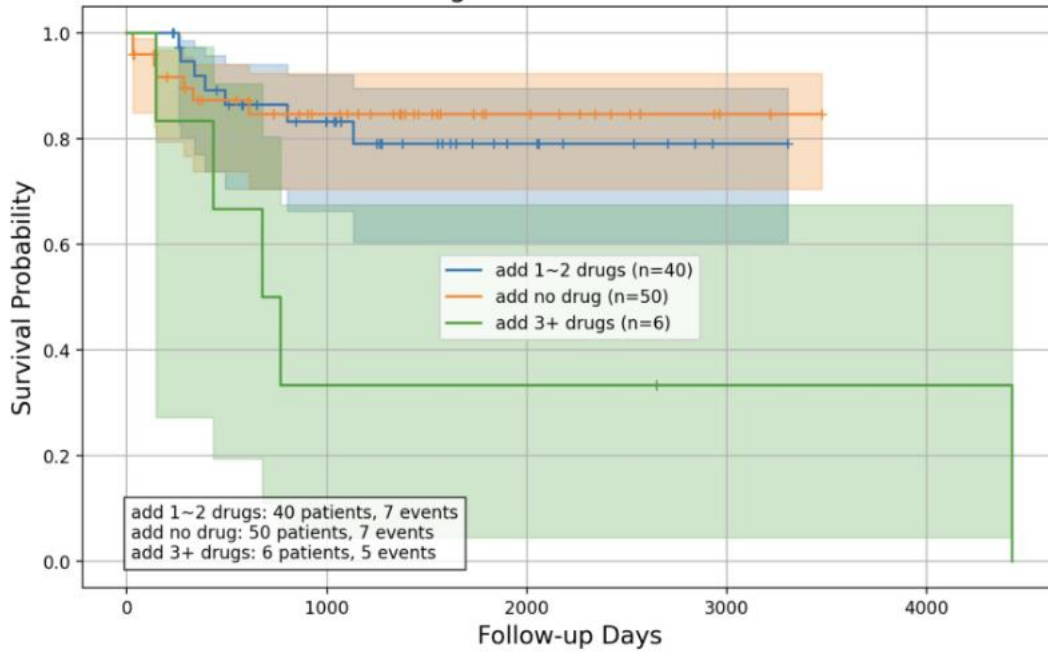
Methods: We conducted a retrospective cohort study of pediatric cancer patients (age <18 years) who received platinum-based chemotherapy at Chang Gung Memorial Hospital from 2007-2022. Renal tubulopathy was defined as renal tubular acidosis, normoglycemic glucosuria, tubular proteinuria, or renal electrolyte wasting occurring on ≥ 2 occasions. Drug exposures were quantified as cumulative doses (chemotherapy) or duration in weeks (supportive medications). Cox proportional hazards models adjusted for age and sex were used to identify independent risk factors.

Results: Among 135 patients (mean age 5.20 ± 5.78 years), 14.1% developed tubulopathy at mean 2.26 ± 3.22 years post-treatment. Common malignancies included retinoblastoma (25.2%), germ cell tumor (20.7%), and neuroblastoma (17.0%). Patients developing tubulopathy had higher exposure to cisplatin (0.43 ± 0.43 vs 0.17 ± 0.25 g/m², $p < 0.001$), carboplatin (2.67 ± 2.38 vs 1.36 ± 1.40 g/m², $p < 0.001$), and ifosfamide (44.90 ± 44.62 vs 12.99 ± 30.10 g/m², $p < 0.001$). Kaplan-Meier survival analysis revealed striking differences in tubulopathy-free survival: patients receiving ≥ 3 additional nephrotoxic drugs had only 33% survival at 5 years versus 80% for 1-2 drugs and 87% for no additional drugs (log-rank $p < 0.001$). (Figure 1) Multivariate analysis identified NSAIDs (HR 1.708, 95% CI 1.319-2.214, $p < 0.001$), aminoglycosides (HR 1.615, 95% CI 1.182-2.205, $p = 0.003$), and ifosfamide (HR 2.216, 95% CI 1.517-3.237, $p < 0.001$) as independent risk factors. Methotrexate showed protective effect (HR 0.630, 95% CI 0.450-0.882, $p = 0.007$). Cumulative nephrotoxic drug burden significantly correlated with tubulopathy incidence ($r = 0.2429$, $p = 0.0044$).

Conclusion: Beyond platinum compounds, concomitant NSAIDs, aminoglycosides, and ifosfamide significantly increase tubulopathy risk through synergistic mechanisms. The protective association with methotrexate likely reflects mandatory hydration protocols. Given the chronic, often irreversible nature of tubulopathy and its impact on childhood development, these findings underscore the urgent need for evidence-based nephroprotective strategies and enhanced renal monitoring protocols in pediatric oncology to preserve lifelong kidney health.

Keywords : renal tubulopathy, carboplatin, cisplatin, nephrotoxicity, pediatric oncology, drug interactions, NINJA

Drug Count and Survival



The Comparative Effectiveness Of Mineralocorticoid Receptor Antagonists And Aldosterone Synthase Inhibitors In The Treatment Of Essential Hypertension: A Systematic Review And Network Meta-analysis

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Abstract

Introduction

Mineralocorticoid-receptor antagonists (MRAs) are the preferred fourth-line therapy for resistant hypertension. Second-generation aldosterone-synthase inhibitors (ASIs) have recently emerged, but no head-to-head trials compare these classes. We performed a network meta-analysis of randomized controlled trials (RCTs) to compare the antihypertensive efficacy and risk of hyperkalaemia of MRAs and ASIs in adults with primary (non-secondary) hypertension.

Methods

MEDLINE, Embase, Cochrane CENTRAL, MEDLINE-In-Process, Scopus, and Web of Science were searched from inception to May 2025. Two reviewers independently screened citations, selected RCTs enrolling adults with primary hypertension—including low-renin essential hypertension, a phenotype enriched for primary aldosteronism—and extracted study data in duplicate. Risk of bias was assessed with the Cochrane tool; certainty of evidence with GRADE. Primary outcomes were change in systolic (sBP) and diastolic blood pressure (dBP) and incidence of hyperkalaemia. We preferentially analysed ambulatory BP monitoring (ABPM) data, followed by home BP (HBPM), automated office BP (AOBP), and manual office BP (OBPM). Random-effects network meta-analyses generated pooled mean differences (MDs) and relative risks (RRs).

Results

Thirty-nine RCTs (8 053 participants) evaluated spironolactone, eplerenone, esaxerenone, ocedurenone, lorundrostat, and baxdrostat. Across three complementary BP analyses (ABPM/HBPM-only, AOBP/OBPM-only, and hierarchical), no agent lowered sBP or dBP more than another (e.g., largest absolute MD for sBP -2.1 mm Hg, 95 % CI -5.8 to 1.5). Hyperkalaemia was infrequent overall. Eplerenone may reduce the risk of hyperkalemia versus spironolactone (RR 0.24, 95 % CI 0.06–1.03) (low certainty). However, the effect of eplerenone compared to ocedurenone (RR 0.26, 0.04–1.98), lorundrostat (RR 0.14, 0.01–1.60), esaxerenone (RR 0.29, 0.07–1.19) and baxdrostat (RR 6.43, 0.27–152.00) is very uncertain (all very low certainty). Results were low- to very-low-certainty, chiefly owing to imprecision and risk of bias.

Conclusion

Current evidence suggests equivalent BP-lowering effectiveness among MRAs and second-generation ASIs in primary hypertension. Eplerenone may confer a lower—though imprecisely estimated—risk of hyperkalaemia compared with other agents and could be preferred in patients at heightened risk. All evaluated MRAs and ASIs remain reasonable options for managing hypertension without an identifiable secondary cause.

Keywords : Hypertension, Mineralocorticoid Receptor Antagonists, Aldosterone Synthase Inhibitors