



INDIAN JOURNAL OF PRACTICAL PEDIATRICS



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OBITUARY

The team of Indian Journal of Practical Pediatrics submits its heartfelt condolences on the sudden demise of beloved past Editor in Chief Dr. M. Vijayakumar. He did his M.B.B.S, D.C.H., and M.D. (Pediatrics) at Stanley Medical College, Chennai. He obtained his D.M. in Nephrology from Madras Medical College, Chennai. He has also been awarded 'Fellow of Indian Academy of Pediatrics'.

He joined the Department of Pediatric Nephrology at the Institute of Child Health and Hospital for Children (ICH & HC), Madras Medical College, Chennai in 1988. He along with Prof. B.R. Nammalwar started training young pediatric post graduates in the technique of peritoneal dialysis and helped save many lives from acute renal failure even at a time pediatric intensive care was not that well developed. After taking voluntary retirement from government service, he was consultant nephrologist in Kanchi Kamakoti CHILDS Trust Hospital (KKCTH), Chennai for some time before starting the Department of Pediatric Nephrology at Dr Mehta's Children's Hospital, Chennai in 2008. He was the Head of the Department of Pediatric Nephrology and Program Director for Pediatric Nephrology Certificate course of Indian Society of Pediatric Nephrology (ISPN) and Fellowship Program of Pediatric Nephrology, from the Tamilnadu Dr.MGR Medical University, Chennai, till he became a victim of an abdominal malignancy which curtailed his work prematurely.

He was a teacher par excellence, an orator with clarity and a straight forward, sincere, hardworking but unassuming personality committed to his duties wherever he was. His contribution to teaching and community health services from Stanley Medical College, Madras Medical College and then at Dr.Mehta's Childrens Hospital is incomparable. He has been a great guiding force to his students and colleagues both in their professional and personal life. He has published 35 research articles both in National and International journals.

He was one of the editorial board members in Indian Journal of Practical Pediatrics when it was started in 1993 and his untiring work propelled him to become the Editor-in-Chief of the journal, between 1999 -2001. He has served as a reviewer in Indian Pediatrics and has also served in



the editorial board of Asian Journal of Pediatric Practice and Indian Journal of Nephrology. He is the author of the book "Principles and Practice of Pediatric Nephrology" along with Dr B R Nammalwar. He has also been a part of the Editorial Board of IAP Textbook of Pediatrics, 1999-2001.

He has served IAP as Executive Board Member of Central IAP, Office bearer of Tamil Nadu State IAP (IAP - TNSB), Secretary and Treasurer of IAP Subspecialty Chapter of Pediatric Nephrology. He started the IAP Chennai City Branch (IAP CCB) in 2003 and served as its President in 2003-04. He co-authored the book "Management Guidelines of Common Pediatric Problems" which generated funds for IAP CCB. He has been a faculty in many National / State / Zonal conferences of IAP. He was the Scientific Committee Chairman of PEDICON 2004 held at Chennai and his time management of the sessions throughout the conference became a benchmark for subsequent IAP conferences. He was one of the founder members of the Indian Pediatric Nephrology Group of IAP in 1988 and played an important role in the group and then in the Indian Society of Pediatric Nephrology. He had served as Honorary Secretary and Treasurer of this group and was the Organizing Secretary for Pediatric Nephrology Annual Conference at Chennai in 1991. He has been an expert member in all the guidelines formulated by this group from its inception and also a resource person in all educational activities of this group. He was also the Organising Chairman, ISPNCON 2012, National Conference of Indian Society of Pediatric Nephrology supported by International Society of Nephrology and International Pediatric Nephrology Association held in Chennai. He is survived by his wife, one son and daughter. With the passing away of Dr.M.V.K as he is fondly called, IAP has lost one of its great teachers and the country, an excellent pediatric nephrologist. We pray for his soul to rest in peace.

Team IJPP

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EDITORIAL

INTEGRATED APPROACH IN PEDIATRIC RENAL CARE

Pediatric nephrology is a developing subspecialty of pediatrics in India. The country's population is approximately 1.21 billion with 36% being children aged 19 years and below. The Indian Society of Pediatric Nephrology (ISPN) with more than 400 active members have been involved in clinical care and speciality training, thereby improving pediatric renal care. The major role in pediatric nephrology practice includes management of children with congenital anomalies of kidney urinary tract (CAKUT), glomerular (nephrotic and nephritic syndrome), tubular (renal tubular acidosis), interstitial (nephronophthisis) and metabolic (cystinosis) diseases.¹

Multidisciplinary approach and challenges

A substantial body of data indicates that hypertension, proteinuria and CKD in adulthood have childhood antecedents from as early as in utero and perinatal life there should be a healthy journey of kidneys from womb to tomb. This crucial journey of kid's kidney require a favorable intrauterine and extrauterine environment for growth, development and nourishment so that they graduate into healthy young adult kidneys at 18 years of age.² To meet the above needs, the care given to this population should be a co-ordinated multidisciplinary team approach that begins from the intrauterine period. The team includes geneticist, obstetrician, maternal-fetal medicine physicians, imaging specialist, pediatrician, pediatric nephrologist, pediatric urologist, intensivists, renal dietician, skilled pediatric nephrology nurse, dialysis staff, social worker, school teacher, psychologist, vascular surgeon, transplant coordinator and transplant surgeon and finally parents.³ The aim of this approach is essentially preventive by early identification of congenital anomalies, prevent renal injury in neonates, provide quality supportive care in AKI, prevent progression to CKD, minimize disease and treatment related burden upon patients' well-being. The key role played by some of the members of the team is highlighted below.

Clinical geneticist

In India, consanguineous marriage is common

especially in the rural areas leading to a high prevalence of inherited renal disorders. Pediatricians must emphasize the importance of genetic counselling for affected families, planning future pregnancy, including premarital counselling. More than 160 genes have been associated with hereditary nephropathies to date, which include genes involved in nephrogenesis, formation and function of the primary cilia, podocyte and tubular cell functions and complement regulation. Systematic screening of all known genes within each disease group by the next generation sequencing yields a genetic diagnosis in 15%-20% cases of severe kidney malformations, up to 30% cases of steroid-resistant nephrotic syndrome, 60%-70% cases of complement-mediated atypical hemolytic uremic syndrome and 50%-80% cases of hereditary tubulopathy.⁴

Maternal fetal medicine physician (MFMP)

MFMPs are able to diagnose and treat fetal complications in utero. Serial ultrasound can diagnose syndromic renal parenchymal diseases, renal malformation, degree of hydronephrosis, assess liquor volume and fetal urinary component to determine which fetuses may benefit from intervention. Fetal interventions in urinary system include vesicoamniotic shunting and fetal cystoscopic ablation of posterior urethral valve (PUV). In this era of antenatal diagnosis, fetal medicine physician plays a vital role in detecting CAKUT. CAKUT comprises of correctable anomalies like PUV, pelvic ureteric junction obstruction, ureterocele, etc. and uncorrectable problems like cystic kidney disease and renal dysplasia. Almost 40% of the pediatric surgical problems are contributed by CAKUT. Pediatric urologist in coordination with imaging specialist for early and accurate detection, and pediatric nephrologist for early and appropriate correction of metabolic abnormalities, will be able to achieve successful outcomes in children with correctable anomalies. For example, a PUV child with posterior urethral valve (PUV) if detected antenatally, counselled, primarily fulgurated in newborn period and supported well through the growth spurt, can have a better chance to prevent or postpone the progression to CKD.

India is the cradle of nearly 40% of all low birth weight (LBW) babies in the developing world.² A strong direct correlation between human birth weight and nephron

number has been reported.⁵ Low nephron number is a predisposition to adult onset of hypertension, cardio-vascular disease and CKD. As noted, the surrogate marker of low nephron number are low birth weight (LBW), preterm birth, short stature, low kidney volume and glomerulomegaly. High risk pregnancy is a risk factor for prematurity and/or LBW. We strongly believe that a MFMP must be involved in the care of high risk pregnancies which include maternal malnutrition, placental insufficiency, exposure to a maternal high fat diet, alcohol, overweight and obesity, young or old maternal age, multiple birth, diabetes, hypertension, associated complex medical conditions and infections.

Neonatologist

Neonatologist has a primary responsibility to recognize the special condition of the maturing kidney in healthy term and preterm baby associated with very low glomerular filtration rate which highly predisposes to develop AKI. The main causes for AKI at this young age are prerenal mechanisms which include hypotension, hypovolemia, hypoxemia, perinatal asphyxia, underlying cardiac failure and neonatal septicemia. Other causes include the administration of nephrotoxic antibiotics, angiotensin converting enzyme inhibitors and NSAIDs.

The immediate treatment consists of correcting abnormalities in fluid homeostasis, hyperkalemia, acidosis, hypertension, infection and avoid using nephrotoxic drugs or combination of drugs which may be nephrotoxic. Abundant epidemiologic data indicate that persons born at term but with relatively low birth weights may be at high risk for hypertension, albuminuria and CKD in later life. Animal studies have shown non-functional glomeruli in the preterm kidney is likely to have adverse consequences on renal function both in the neonatal period and in the long-term by reducing the functional reserve of nephrons. Direct measurements when pursued shows these infants growing as adults have fewer nephrons and thus a low cardiorenal endowment. It is the duty of the neonatologist to properly guide these children for a sequential follow up of kidney function and blood pressure throughout life.

Pediatrician

Neonates and children with AKI may have long-term sequelae that may lead to CKD. Pediatricians have the opportunity to identify the affected children and preempt the impact of CKD by initiating early therapy and timely involvement of pediatric nephrologist.⁶ Postnatally, the pediatrician should monitor low birth weight, preterm infants till adulthood to prevent overweight/obesity and

detect early signs of kidney injury (microalbuminuria/high BP).⁷ Children with antenatal ultrasound studies that indicate genitourinary anomalies, children with a family history of kidney disease and children with signs such as failure to thrive or a history of urinary tract infection, voiding dysfunction or an abnormal appearing urine should be examined. Initial screening would include a focused physical examination, BP measurement, formal urinalysis and a baseline renal function, followed by a more focused evaluation if indicated. If any of the above is abnormal, a pediatric nephrologist should be consulted.

Pediatric nephrologist

Pediatric nephrology deals with a completely different spectrum of renal diseases in children than that of adults. Apart from acquired renal diseases due to infections, drugs and others, it also deals with acute kidney injury (AKI) due to genetic abnormalities and chronic kidney disease (CKD) with a predominance of congenital and hereditary disorders. It is the prime responsibility of the pediatric nephrologist, to care for the kidneys during the tumultuous period from womb through diaper stage till their graduation.

The major challenge faced by the pediatric nephrologist is CKD. CAKUT accounts for the largest etiology of CKD which commonly includes renal hypoplasia/dysplasia and obstructive uropathy. Many pediatric glomerulopathies are caused by genetic or acquired defects of the podocytes, the unique cell type lining the glomerular capillaries. Less common but important causes of childhood CKD are inherited metabolic disorders such as hyperoxaluria and cystinosis, and atypical hemolytic uremic syndrome (HUS). An area of clinical care that remains a challenge to all pediatric nephrologists is pediatric dialysis and transplant. This is especially more challenging in adolescents and the above hurdles can be overcome with multidisciplinary approach.

A huge problem is precisely how one defines the needs for pediatric nephrology services in areas where there are no doctors. The future use of specifically trained pediatric nephrology extenders, such as advanced practice nurses and the use of computer-based continuing education seems essential.

Pediatric urologist

Unlike the adult urologist the pediatric urologist's involvement is born with the birth of the child in parallel with the pediatric nephrologist. In addition to the management of PUV as a neonate his relevance is interlaced with the growth of the child. It extends from the management of obstructive uropathy, neurogenic bladder,

dilatation of the upper urinary tract, vesicoureteric reflux, urinary stone disease, renal duplication, ureterocele, ectopic ureter, tumors, pediatric urological trauma in childhood and adolescent.

The unique needs of kids with renal disease include emphasis on growth and development, school attendance and performance, family dynamics, nutrition and physical, psychosocial and emotional adjustment of child and family to chronic disease.³ Treating children especially adolescents with CKD is an additional challenge. We need to prepare adolescents to face problems related to chronic disease as it affects them during a delicate period of intellectual and emotional development. This is possible with a team of specialists including a psychologist. It is also important that children have proper education, develop life skills and attitudes required for successful, independent adult life.

There is a rapid worldwide increase in the prevalence of obesity in adults and children. It appears to be an independent risk factor for CKD. Parents, teachers and treating pediatrician have the responsibility to identify children at risk and help them modify their lifestyle to encourage weight loss and live a healthy life.

Conclusion

The need of the hour for a better patient care is to establish combined clinics like “Nephro – Urology”, “Transplant” and “Transition” clinics. This helps us to formulate a structured treatment plan which improves patient care. The graduation day for young kidneys is the time when adult nephrologist takes over the care. This has to be a gradual transition which has to be undertaken over a period of years in transition clinics along with adult nephrologist.²

Early recognition and institution of preventive measures can reduce the morbidity, mortality and the economic burden due to CKD and other renal diseases. In a country like India, where health care delivery is disproportionate to the demand and dialysis and

transplantation care are not within the reach of economically compromised children, steps should be taken to prevent kidney diseases and the onset and progression of CKD in children.⁶ Educating and creating awareness among the primary care pediatricians on early identification of renal disease, its prevention and scientific therapy, will help to lower the morbidity, mortality in children with renal diseases. Team approach in taking care of children with renal ailment will improve their quality of life and will ensure longevity into adulthood.

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CLIPPINGS

High-sensitive CRP as a predictive marker of long-term outcome in juvenile idiopathic arthritis

This study attempted to assess whether C-reactive protein, including variation within the normal range, is predictive of long-term disease outcome in Juvenile Idiopathic Arthritis (JIA). The data demonstrated that baseline C-reactive protein concentrations above 10 mg/l are predictive of a poor outcome at 8-year follow-up. The study could not illustrate any predictive value of C-reactive protein variations within the normal range.

Alberdi-Saugstrup M, Zak M, Nielsen S, Herlin T, Nordal E, Berntson L, et al. High-sensitive CRP as a predictive marker of long-term outcome in juvenile idiopathic arthritis. Rheumatol Int 2017; 37(5): 695-703.

NEPHRO-UROLOGY

APPROACH TO A CHILD WITH GROSS HEMATURIA

***Sushmita Banerjee**
****Murari Bharadwaj**

Abstract: Hematuria defined as an abnormal number of red blood cells in urine, can be due to renal pathology, local infection or systemic disease. The primary physician may be able to arrive at a presumptive diagnosis in well over 50 % of children presenting with gross hematuria with a meticulous history, physical examination, and simple investigations. A pediatric nephrologist may be involved if these are inconclusive. A simple approach to the evaluation and management of pediatric patients with macroscopic/gross hematuria is discussed.

Keywords: Gross hematuria, Microscopic, Macroscopic, Investigations.

Hematuria is defined as an abnormal number of red blood cells (RBCs) in urine. Hematuria when visible can be red, dark or cola colored or brown and known as macroscopic hematuria. A small quantity of blood (1mL in 1000 mL urine) is enough to make the urine appear red. When it is not visible to unaided eye, it is microscopic hematuria. The incidence of gross hematuria in children is estimated to be 0.13% and accounts for 0.1% to 1.5% of pediatric acute care visits. More than half of the cases (56%) have an easily identifiable cause.¹ Fortunately the majority of patients can be diagnosed by simple tests and have treatable causes. However, a proportion of them will require more detailed investigations, specialist referral and advanced therapy.² Therefore knowledge of the etiologies and a scientific approach to the problem is essential (Fig.1). Hematuria is an important sign of renal or bladder disease, but proteinuria has a more important diagnostic and prognostic significance. A combination of proteinuria and hematuria carries a sinister prognosis. Gross hematuria is a more ominous feature than microscopic hematuria and is often due to an identifiable cause.

Etiology

A traditional way to classify the etiology of macroscopic hematuria is to divide them into 'renal and extra-renal cause' or 'glomerular and non-glomerular etiology^{3,4}' (Table I). The common causes include acute urinary tract infections (UTI), particularly cystitis, hypercalciuria or urolithiasis and trauma among the non-glomerular causes and post infectious glomerulonephritis (PIGN), IgA nephropathy (IgAN) and Alports syndrome (AS) among the glomerular causes.^{1,5,6} In a significant number of patients, no cause may be identified.^{5,6}

Gross hematuria is suspected when red or brown urine is present. However, red or brown urine can be hemoglobinuria due to intravascular hemolysis, myoglobinuria due to muscle injury or causes other than blood including pigments from drugs like phenazopyridine, rifampicin or food like beet root and aerated beverages. Rarely it could be due to metabolites associated with other clinical conditions such as porphyria (Box 1).

Box 1. Red or brown urine - causes other than blood

Medications - Chloroquine, phenazopyridine, doxorubicin, ibuprofen, nitrofurantoin, rifampicin

Food dyes - Beets, red dyes in food, blackberries

Metabolites - Bile pigments, porphyrins, melanin, homogentisic acid, methemoglobin, urates

Other - Myoglobin, carbon monoxide

Approach to diagnosis

Step 1: History and clinical examination

The features to be noted while evaluating a child with gross hematuria is given in Box 2. The common causes and clinical features of transient, recurrent or familial hematuria are given Table II and III respectively.

Step 2: Confirmation of hematuria

Urinary dipstick test for blood: Dipsticks are highly sensitive and can detect a very small amount of blood or RBCs in urine. Urinary dipsticks cannot be used to

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Table I. Macroscopic hematuria - etiology

Glomerular	Non-glomerular
Glomerulonephritis: PIGN, RPGN, MPGN, IgAN	Kidney and bladder infections-bacterial and viral
Renal vasculitides: HSP, SLE, ANCA, PIGN associated Hemolytic Uremic Syndrome	Hypercalciuria and nephrourolithiasis
Thin basement membrane disease	Bleeding diathesis
Alports syndrome	Renal vascular thrombosis
Systemic infections: malaria, leptospirosis, infective endocarditis	Tumours
	Trauma
	Exercise
	Obstructive uropathy
	Polycystic kidney disease
	Arterio-venous malformation
	Nutcracker syndrome
	Medications: NSAIDs, anticoagulants, cyclophosphamide, ritonavir, indinavir
	Infections: Tuberculosis
	Sickle cell disease acute papillary necrosis

PIGN: Post infective glomerulonephritis; RPGN: Rapidly progressive glomerulonephritis; MPGN: membranoproliferative glomerulonephritis; IgAN: IgA nephropathy; HSP: Henoch Schonlein purpura; SLE: Systemic lupus erythematosus; ANCA: Anti-neutrophil cytoplasmic antibodies.

Table II. Macroscopic hematuria - Etiology

Transient	Recurrent	Familial	Neonatal
Febrile illnesses, Trauma, Exercise, Infection	Hypercalciuria, Nephrolithiasis, IgA nephropathy, Benign familial hematuria, Alport's syndrome	Benign familial hematuria, Alport's syndrome, Nephrolithiasis, Hypercalciuria, Renal cystic disease, IgA Nephropathy	Renal vein thrombosis, Renal artery thrombosis, Obstructive uropathy, Urinary tract infection, Bleeding and clotting disorders, Trauma, bladder catheterization

distinguish between the presence of RBCs and free hemoglobin or myoglobin. Hence, the positive results of a dipstick test must be confirmed by microscopic examination – presence of RBCs confirms hematuria (Fig.1), absence should indicate tests for hemoglobinuria or myoglobinuria.

Urine microscopy: Hematuria is defined as > 5 RBCs / HPF in a freshly voided, centrifuged urine. A positive

dipstick reaction for blood, but an absence of RBCs and RBC casts in the urine suggest hemoglobinuria or myoglobinuria. The absence of hemoglobin, RBCs, or myoglobin should prompt a search for other causes of red urine (Box 1).

Step 3: Other urine tests

a) Phase contrast microscopy: The examination of the

Table III. Hematuria - Clues to diagnosis

Features	Diagnosis
Fever, dysuria, urinary frequency, loin or suprapubic pain	Cystitis / Urinary tract infection
History of renal calculi or severe renal colic	Renal stone disease
History of preceding sore throat or skin infection, edema, oliguria, hypertension	PIGN
Rash, arthritis, unexplained fever, edema, hypertension	Lupus nephritis
Palpable purpuric rash, abdominal pain	Henoch Schonlein purpura nephritis
Concurrent upper respiratory tract infection	IgAN
Hearing involvement, lenticonus	Alports syndrome
Sick child, fever, anemia, low platelets, abnormal coagulation profile	DIC
Low platelets, AKI and palpable abdominal mass	Renal vein thrombosis

Box 2. Gross hematuria – Features to be noted

- Is the hematuria transient, recurrent or persistent?
- Is it present throughout the stream or only at the beginning or at the end.
- Is it an isolated symptom OR associated with i) general symptoms such as malaise, fever, abdominal pain, edema of the limbs, decreased urine output, skin rash, purpura, joint pain, jaundice ii) system specific like respiratory, gastrointestinal, neurological iii) urinary tract problems such as dysuria, strangury, frequency and enuresis.
- Family history of consanguineous marriage, renal disease, eye disorders or deafness.
- History of food and drug intake, or any cause of muscle injury.
- Clinical examination for rashes, arthritis, edema, elevated blood pressure, cardiac hepatosplenomegaly, cardiac failure and ascites.
- Other system involvement.

RBCs under a phase contrast microscope can help to differentiate dysmorphic RBCs (glomerular disorders) from RBCs of normal shape⁷ (non-glomerular diseases in which dysmorphic RBC are less than 15%). The presence of acanthocytes in >5% of RBCs examined is diagnostic of glomerular hematuria. Acanthocytes are a subtype of dysmorphic erythrocytes with a characteristic appearance

that is due to the presence of one or more blebs protruding from a ring-shaped body (Fig.2).

b) Proteinuria: If significant proteinuria (>2+ on dipstick or protein/creatinine ratio >0.5) is present it suggests glomerular cause. Quantification of proteinuria by assessing protein/creatinine ratio, albumin/creatinine ratio (While protein/creatinine ratio is the standard for defining non-nephrotic vs nephrotic range of proteinuria in children, albumin/creatinine ratio is used to detect and prognosticate in chronic kidney diseases) or a timed urine collection is often important to assess the degree of glomerular damage.

c) Casts and crystals: Presence of RBC casts and proteinuria (> 2+) is pathognomic of glomerulonephritis. WBC casts indicate infection, while hyaline casts may be seen in different glomerulopathies. Crystalluria may suggest the presence of nephrolithiasis, but needs confirmation by further investigations.

d) Calciuria: Quantification of calciuria is indicated in the absence of other clinical and biochemical abnormalities. Hypercalciuria is defined as urine calcium/ creatinine ratio in: age <7 months: 0.8; 7-18 months: 0.6; 19 months-6 years: 0.4; >6 years 0.2 or >4 mg/kg/day in a 24 hours urine.

e) Urine culture and sensitivity needs to be done if child has UTI symptoms.

Step 4: Blood investigations and imaging

Some basic blood and imaging tests are required initially to determine which group of conditions the patient falls under. These should include:

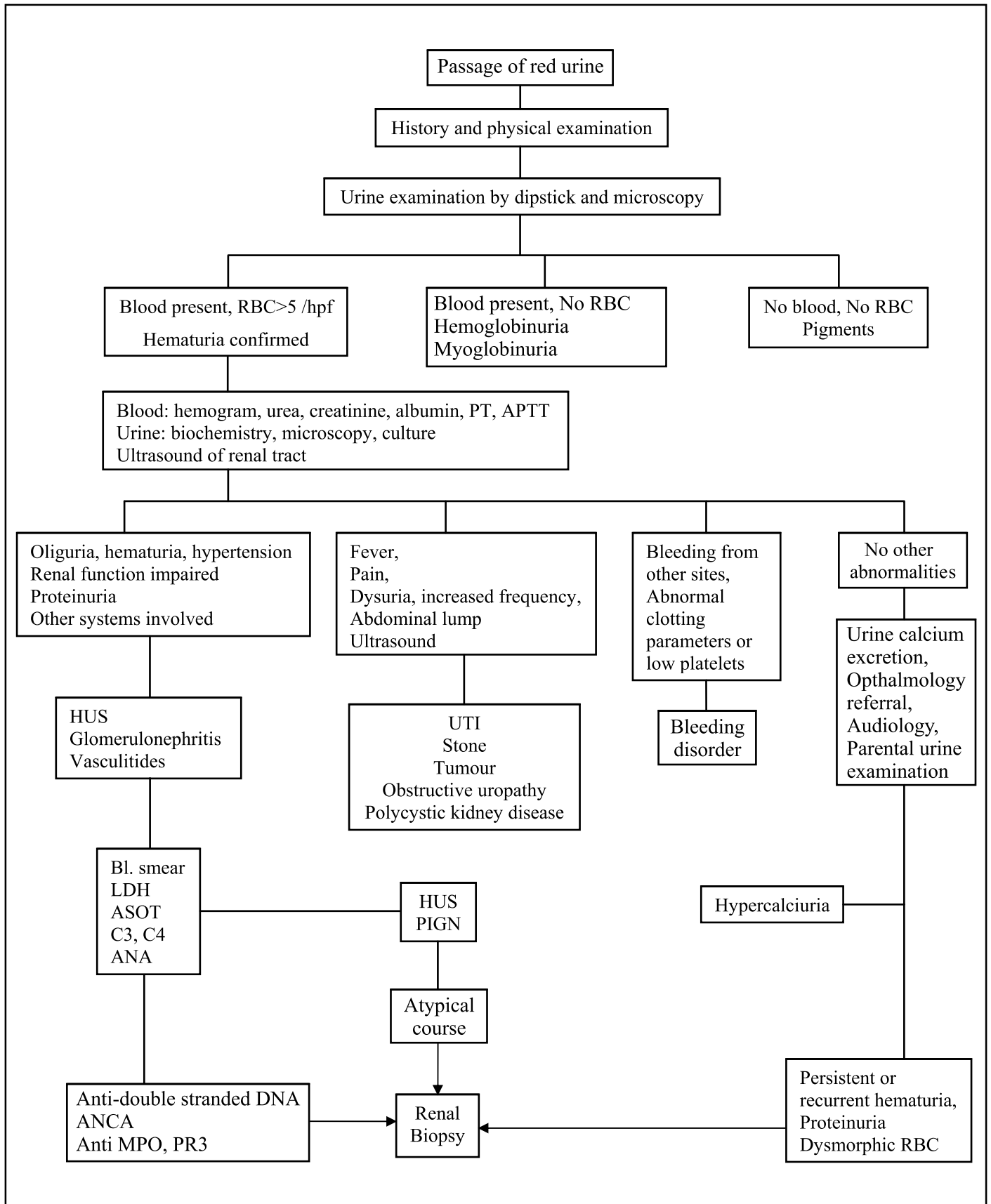


Fig. 1. Hematuria

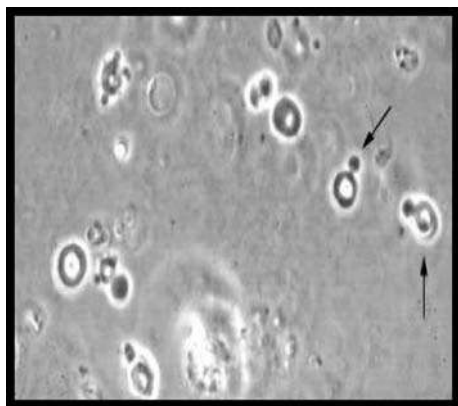


Fig.2. Urine deposits showing acanthocytes (arrows)

- a) Blood for hemogram, peripheral smear, blood urea, serum creatinine, electrolytes, albumin, and calcium. Anemia and thrombocytopenia, with fragmented RBCs on peripheral smear suggests hemolytic uremic syndrome (HUS). Moderate to high proteinuria, raised blood urea and serum creatinine with abnormal electrolytes is suggestive of glomerulonephritis.
- b) Normal hematological tests such as PT, APTT and platelet count will exclude bleeding disorders. If hemoglobinopathy is suspected, high performance liquid chromatography (HPLC) to exclude sickle cell disease should be performed.
- c) Ultrasonography of the urinary tract helps to exclude any structural abnormalities, nephro-uro-lithiasis or tumours, bladder infections or cystic kidney diseases.

Step 5: Further evaluation

Depending on the results of the tests given in step II, III and IV, further tests can be carried out based on possible etiologies.

- a) Glomerulopathies: Serological tests-ASO titre, other streptococcal antibody titres when available, ANA, C3, C4, anti-double stranded DNA, anti-neutrophil cytoplasmic antibody (ANCA) should be performed if a glomerulopathy is suspected. These investigation help to differentiate between different glomerulopathies, such as post streptococcal glomerulonephritis (PSGN), membranoproliferative glomerulonephritis (MPGN), SLE and other vasculitides. A renal biopsy may then be indicated to stage the disease and thereby guide therapy.
- b) Nephrourolithiasis: A detailed imaging including plain skiagram of the kidney, ureter bladder (KUB) region and non-contrast CT scan of the abdomen may be required to confirm the presence of stones. In children,

the presence of renal stone disease warrants a detailed metabolic work-up of blood and urinary solutes to determine the cause and guide treatment.

- c) Urological diseases, such as obstructive uropathies may require voiding cysto urethrography (VCU), dynamic isotope scintigraphy and urodynamic study in bladder dysfunction while tumours need biopsy and further investigation for staging. Cystoscopy may be rarely indicated if hematuria appears to be non-glomerular and is associated with bladder symptoms.
- d) Doppler studies and rarely angiograms may be required to diagnose conditions like renal vascular thrombosis or arterio-venous (AV) malformations.

In a small group of patients, all the above investigations will be normal. In such patients a renal biopsy is indicated if there is persistent gross hematuria, particularly if associated proteinuria more than 2+, RBC casts and the presence of dysmorphic RBCs. The differential diagnosis in this group is thin basement membrane disease, IgA nephropathy (IgAN) and Alports syndrome (AS). A family history of renal disease, eye and hearing tests along with a urinary screen may assist in differentiating between these conditions. Hematuria is almost never a cause of anemia. If there is anemia, systemic vasculitis, hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP) needs to be considered. Asphyxiated neonates and patients with hypercoagulability disorders such as nephrotic syndrome, sepsis, dehydration, protein S or C deficiency are at risk of renal vein thrombosis which can present as hematuria.

Treatment

Treatment depends on the etiology. UTI should be rapidly treated, initially with empiric antibiotics depending on local sensitivity patterns and modified, once the culture results are available.⁸ Supportive treatment with fluids, antipyretics and anti-emetics should be given as per need. Follow up investigations to exclude underlying structural or functional abnormalities of the renal tract are indicated.

Isolated hypercalciuria is managed by increasing fluid intake and restriction of salt intake. Rarely drug therapy with hydrochlorothiazide may be required. Primary causes like immobilisation, excessive calcium and vitamin D therapy and hyperparathyroidism should be excluded.⁹

The most common type of glomerulonephritis encountered in India is post infectious glomerulonephritis (PIGN). It may occur after streptococcal upper respiratory or skin infection, but may also occur after other bacterial or viral infections. Most patients require only supportive

therapy by way of fluid restriction, diuretics, anti-hypertensives and maintenance of electrolyte homeostasis.¹⁰ Patients with severe or atypical features should be referred early to a pediatric nephrologist. When there are atypical features, such as a nephritic-nephrotic syndrome, severe anemia or hypertension and progressive renal functional impairment, rapidly progressive glomerulonephritis should be suspected. This is a medical emergency as rapid end stage renal failure can ensue and a renal biopsy to look for crescentic glomerulonephritis should be performed. If confirmed, aggressive immunosuppressive therapy is warranted and all patients require long term follow-up. The other glomerulopathies causing hematuria, include HUS, MPGN, IgAN and the vasculitides. These conditions also require supportive and specific therapy in the long term.^{11,12,13}

Patients with renal stone disease need medical management according to specific metabolic diagnosis and surgical referral in the presence of symptomatic or obstructing stones.¹⁴ Similarly, children with obstructive uropathies, tumours, AV malformations, etc. require appropriate referrals for specific management.

Conclusion

Unlike microscopic hematuria, clinically important cause is much more common in macroscopic hematuria. The most frequent asymptomatic cause is hypercalciuria, while symptomatic causes include the renal stone disease, PIGN, IgAN and viral hemorrhagic cystitis. A step wise approach is essential to evaluate the cause of gross hematuria in children beginning with a complete history, thorough physical examination and a few basic tests. While acute conditions like UTI need prompt therapy, the focus should be on excluding major abnormalities such as underlying structural abnormalities, bleeding disorders, glomerulopathies, HUS, hypercalciuria, nephrolithiasis and tumors. Prompt and appropriate referral should be the priority in such cases.

Points to Remember

- *Gross hematuria may occur due to common and easily treatable causes or due to complex etiologies.*
- *Majority of children with gross hematuria can be diagnosed by basic lab and imaging studies, while a few patients require more specialized tests.*

- *A stepwise approach is required to elucidate the cause and plan specific management.*

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NEPHRO-UROLOGY

HYPERTENSION IN CHILDREN AND ADOLESCENTS

***Indira Agarwal**

Abstract: *Hypertension (HT) in children may remain undetected unless routinely screened for. Though majority of children are believed to have secondary HT, there is a rising incidence of primary HT not only due to increased survival rate of subjects with a very low birth weight but also life style changes namely inactivity and poor dietary habits, whose end product is obesity, especially in adolescent children. Essential or primary HT during childhood is associated with end organ damage and hence is not benign. Masked hypertension has an estimated prevalence of 7-9% in children and adolescents and has been associated with long term cardiovascular risks compared to sustained hypertension and higher left ventricular mass compared to normotensive children. Monogenic hypertension should be suspected in patients with family history of early onset, severe hypertension or death from premature cerebrovascular accidents and heart failure.*

Children requiring antihypertensive therapy often have secondary HT and 80-90% of them will have an underlying renal cause. Combination drug therapy for hypertension minimizes the side effects by allowing administration of lower dosage of different agents.

Keywords: *Hypertension, Children, End organ damage, Life style modification, treatment*

Hypertension (HT) in children may remain undetected unless routinely screened for. The prevalence of pediatric HT is reported to be 1-2%¹ in western literature and may often be identified on routine school examination. Essential or primary HT during childhood is also associated with end organ damage and hence is not benign.² Hypertensive children have high possibility of becoming hypertensive adults and will be at increased risk for cardiovascular

disease, chronic kidney disease and cerebrovascular accidents.³ The role of the pediatrician lies not only in management of these patients but also identification of these children at risk. Though majority of children are believed to have secondary HT, there is a rising incidence of primary HT due to increased survival rate of subjects with a very low birth weight and life style changes namely inactivity and poor dietary habits leading to obesity, especially in adolescent children. The importance lies in detecting HT early and initiating the necessary treatment measures before target organ damage occurs.

Definition

The definition of HT in children is arbitrary and is based on the normal distribution of blood pressure (BP) in healthy children, unlike, adults wherein it is associated with cardiovascular morbidity and mortality with certain level of BP.⁴ Normal blood pressure readings in children are based on sex, age, and height percentile. These charts with appropriate blood pressure ranges for children are available.^{4,5} Various definitions of terminologies are given in Table I.

Epidemiology

Blood pressure values increase progressively until the age of 17–18 years when adult values are reached. The increase is most rapid during the first weeks of life and during puberty. In the first years of childhood secondary forms prevail whereas with increasing age primary forms of hypertension become most frequent.⁶ The heritability of childhood HT is estimated to be about 50%.⁷ Eighty six percent of adolescents with primary HT have a positive family history for HT.⁸ Breastfeeding is associated with lower blood pressure levels in childhood. Obesity represents a strong risk factor for the development of childhood HT.

Classification

Primary HT is defined as HT for which a single underlying cause cannot be identified. This is the dominant form of HT above 12 years of age but also found in younger children. Such children tend to be obese, have hyperinsulinism or insulin resistance and ingest more salt than normotensive subjects.

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Table I. Classification of hypertension in children and adolescents

Category	0–15 years SBP and/or DBP percentile	16 years and older SBP and/or DBP values (mmHg)
Normal	<90 th	<130/85
High-normal (Pre hypertension)	≥90 th to <95 th percentile*	130–139/85–89
Hypertension	≥95 th percentile [§]	≥140/90
Stage 1 hypertension	95 th percentile to the 99 th percentile plus 5mmHg	140–159/90–99
Stage 2 hypertension	>99 th percentile plus 5mmHg	160–179/100–109
Isolated systolic hypertension (ISH) [@]	-	≥140/<90

* *Pre hypertension is considered to be an indication of heightened risk for developing hypertension*

§ *After measuring blood pressure on at least 3 separate occasions*

@ *European Society of Hypertension Guidelines for the Management of High Blood Pressure in Children and Adolescents has further classified HT in children 16 years or older as isolated systolic HT (ISH) in youth.*⁵

Secondary HT is defined as HT for which a cause can be identified. Children requiring antihypertensive therapy often have secondary HT; 80-90% of them will have an underlying renal cause. It can be caused by a variety of acute and chronic diseases which include structural, genetic and/or metabolic abnormalities. It may include coarctation of aorta, renal parenchymal disease (glomerulonephritis and scars) renovascular (renal artery stenosis) and endocrine causes (hyper or hypothyroidism).

White coat hypertension (WCH) is defined as a conditioned, transient, elevation of BP in a medical setting when the BP is normal at all other times. Its reported prevalence as measured by ambulatory blood pressure monitoring (ABPM) is 20-60% in adults and 28-88% in children. The mistaking of WCH for persistent hypertension may lead to unnecessary diagnostic studies and medication.⁹

Masked hypertension is defined as normal BP in the clinic and elevated BP out of the clinic setting. It has an estimated prevalence of 7-9% of children and adolescents. It has been associated with higher left ventricular mass compared to normotensive children. It also may portend long term cardiovascular risk compared to sustained hypertension.

Hypertensive crisis is diagnosed in those who present with severe hypertension (BP greater than the ninety-ninth percentile for age, height and gender) or with acute BP elevation requiring immediate attention and may be classified to have hypertensive urgency or emergency.

Hypertensive emergency is defined by elevations in systolic and diastolic BP associated with end-organ injury of the brain, heart, and/or kidneys. Clinical manifestations of hypertensive emergencies include hypertensive encephalopathy, congestive heart failure, pulmonary edema, acute renal failure, stroke, associated head trauma, myocardial infarction, adrenergic crisis, dissecting aortic aneurysm or eclampsia.

Hypertensive urgency is a situation in which the possibility exists for progression to a hypertensive emergency requiring a decrease in BP within 12 to 24 hours.¹⁰

Hypertensive encephalopathy typically presents with a prodrome lasting for at least 12 to 48 hours consisting of head-ache, altered mental status, visual impairment, seizures or focal neurologic deficits. The symptoms of hypertensive encephalopathy appear to be a result of disturbances in cerebral auto-regulation, which lead to altered cerebral blood flow and perfusion pressure.

Posterior reversible encephalopathy syndrome (PRES) is an MRI finding triggered by hypertensive crisis. It is associated with generalized tonic clonic seizures and may be seen in 50-60% of patients. Almost all demonstrate diffuse slowing by EEG. They have abnormal fundoscopy and left ventricular hypertrophy. The lesions may not be limited to posterior white matter and may not be completely reversible.

Etiology

Hypertension in childhood is considered to be secondary unless proved otherwise. In 95% of cases it may be renal or renovascular in origin. However with rising age, the likelihood of essential hypertension slowly increases and; this can be recognised only after excluding all other known causes. Evaluation involves taking a detailed history, doing a good clinical examination followed by an extensive laboratory and radiological evaluation. The causes of hypertension in children may best be categorized by age groups and will help to focus the investigations to these groups (Table II).

History

The basis of clinical evaluation is a through history elicitation from onset of symptoms, associated features, birth history, family and personal history, drugs, course of illness and assessment of end organ damage (Table III).

Clinical manifestations

Children with primary hypertension rarely have clinical evidence of the disease. Children with secondary hypertension are often symptomatic and present with clinical manifestations of underlying diseases which include edema, hematuria, oligoanuria, polyuria, stunted growth, failure to thrive, dissociation of four limb BP readings, unexplained anemia and easy fatigability. Not uncommonly elevation of blood pressure can lead to headaches, dizziness, visual changes, nausea, epistaxis, seizures and cardiac failure (Table IV).

Evaluation

Measurement of blood pressure on first visit to the clinician should be made routine, especially in all children more than 3 years of age. Exceptions would be younger children (<3 years) with history of major neonatal comorbidities who form a population at risk. Using correct cuff size and considering the concept of white coat hypertension before making the diagnosis of hypertension will avoid erroneous diagnosis.

Basic diagnostic studies

If hypertension is mild or moderate, diagnostic evaluation may continue while the child is being treated. However, if severe, emergency treatment must be undertaken before blood tests are performed. Certain basic diagnostic studies are done as a first step. If there are certain identifiable secondary causes, further tests may be carried out as warranted.

Step 1: Initial tests (Box 1)

Box 1. Initial investigations in the diagnosis of HT

- Complete blood cell count.
- Urinalysis for proteinuria, hematuria and cellular casts.
- Urine culture if UTI is suspected.
- Blood urea, S. creatinine, S. uric acid, S. sodium, potassium, chloride, bicarbonate for evaluating glomerular, tubular function, monogenic and endocrine disorders.
- Echocardiogram to evaluate left ventricular mass.
- Ultrasound with Doppler for evaluating renal parenchymal disease or renovascular disease.

If baseline evaluation is normal, primary hypertension is the likely diagnosis.

Step 2: Advanced investigations (Table V)¹²

In addition, it is also important to ascertain the duration of hypertension. This involves the assessment for presence of target organ damage. Long standing hypertension results in chronic complications and changes in the eyes (hypertensive retinopathy), heart (increased left ventricular mass, diastolic dysfunction), kidneys (microalbuminuria), brain and blood vessels (increased intimal and medial thickness). There is evidence that these can occur even in those with stage 1 hypertension.¹²

Monogenic hypertension

Monogenic hypertension should be suspected in patients with family history of early onset, severe hypertension or death from premature cerebrovascular accidents and heart failure. Both autosomal dominant and recessive patterns of inheritance are described. Monogenic hypertension can be divided into distal nephron or adrenal based disorders depending on the tissue where the mutative gene is primarily expressed. Low renin hypertension is common along with hypokalemia and alkalosis in all except Gordon's syndrome. Aldosterone levels are dependent on the effect of gene mutation. They are high in Gordon syndrome and glucocorticoid remediable hyperaldosteronism. Basic evaluation for suspected monogenic hypertension includes serum and urine electrolytes (sodium and potassium) and plasma renin activity and aldosterone. Diagnosis is confirmed by genetic studies.

Table II. Common causes of hypertension by age group in newborns, children and adolescents¹¹

Newborn - First year	1 to 6 years	6 to 10 years	10 to 18 years
Renal artery stenosis	Renal parenchymal disease	Renal parenchymal disease	Essential hypertension
Congenital renal abnormalities	Renovascular disease	Essential hypertension	Iatrogenic
Coarctation of the aorta	Coarctation of the aorta	Renovascular disease	Renal parenchymal disease
Bronchopulmonary dysplasia	Tumor	Coarctation of the aorta	Endocrine causes
Renovascular disease	Endocrine causes	Endocrine causes	Co-arctation of the aorta
Renal parenchymal disease	Iatrogenic	Tumor	
Iatrogenic	Essential hypertension		
Tumor			

Table III. Relevant history while evaluating the causes of HT in children

History	Relevance
Family history of hypertension, pre eclampsia, toxemia, renal disease, tumors	Important in essential hypertension, inherited renal disease and some endocrine diseases (e.g. Familial pheochromocytoma with multiple endocrine adenopathy II)
Family history of early complications of hypertension and/or atherosclerosis	Suggests likely course of hypertension and or presence of other coronary artery disease risk factors
Neonatal history	Use of umbilical artery catheter suggests need to evaluate renal vasculature and kidneys; prematurity, LBW predisposes to adult onset of HT and CKD.
Abdominal pain, dysuria, frequency, nocturia	May suggest underlying renal disease
Joint pains/swelling, facial or peripheral edema	Suggests connective tissue disease and/or other forms of nephritis
Weight loss, failure to gain weight, with good appetite, sweating, flushing, fevers, palpitations	In combination symptoms suggest pheochromocytoma
Muscle cramps, weakness, constipation	May suggest hypokalemia and hyperaldosteronism
Age of onset of menarche, sexual development	May be helpful in suggesting hydroxylase deficiencies
Ingestion of prescription and over-the-counter drugs, contraceptives, illicit drugs	Drug induced hypertension
Headaches, dizziness, epistaxis, visual problems	Nonspecific symptomatology, usually not etiologically helpful

Table IV. Relevant physical examination in HT in children

Physical Findings	Relevance
Pale mucus membranes, facial or pretibial edema	Renal disease
Pallor, evanescent flushing, increased sweating at rest, paroxysmal hypertension, tachycardia	Pheochromocytoma
Café au lait spots, neurofibromas	Von Recklinghausen's disease
Moon face, hirsutism, buffalo hump, truncal obesity, striae	Cushing's syndrome
Webbing of the neck, low hairline, wide-spaced nipples, wide carrying angle	Turner syndrome
Elfin facies, growth retardation	William's syndrome
Thyroid enlargement	Hyper or hypothyroidism
Absent or delayed femoral pulses, low leg pressure relative to arm BP	Aortic coarctation
Congestive cardiac failure with hypertension	Coarctation, pheochromocytoma, severe hypertension
Bruits over great vessels	Arteritis or arteriopathy
Abdomen – Epigastric bruit	Renovascular diseases isolated or associated with Williams or Von Recklinghausen's syndrome or arteritis
Unilateral or bilateral masses	Wilm's tumour, neuroblastoma, pheochromocytoma, polycystic kidneys, other tumours
Hypertensive fundoscopic changes, Bell's palsy Neurologic deficits (hemi paresis)	Chronic hypertension Chronic or severe acute hypertension with stroke

Management

Conventionally the diagnosis of HT can be made if blood pressure measurements are in the hypertensive range for sex, age, and height on three separate occasions. If the patient is hypertensive and symptomatic, immediate evaluation and treatment is required. If the patient is asymptomatic but found to be hypertensive, blood pressures can be checked again at least 1 week later to confirm the presence of HT. Readings obtained by oscillometric devices such as NIBP recording that exceed the 90th percentile should be confirmed by auscultation.

The need to start medication with antihypertensives depends on a number of factors. The cause of hypertension, its severity, risk factors and family history may be some of the factors which need to be considered.

Lifestyle and dietary recommendations to reduce high blood pressure values

Life style and dietary modifications are given in Box 2.

Non pharmacological intervention strategies are started in prehypertension while pharmacological strategies are used if BP is above 95th centile, in addition to non pharmacological measures. Indication for treatment of hypertension is stage 2 hypertension, which is 95 to 99th centile +5 mmHg. If there is target organ damage or underlying renal disease or any risk factor, one can start treatment at 95th centile also. Lifestyle changes are important at all times. Indications for pharmacological interventions and therapeutic goals are given in Box 3 and 4.

Therapy is initiated with one agent at an appropriate dose and the dose is increased until the desired blood pressure is achieved. If the highest dose is not effective or if there are side effects, a drug from a different class is added or substituted. Medications with a longer duration of action (once, twice daily dosing) are preferred for better compliance and less side effects. Combinations minimize the side effects by allowing administration of lower dosage of different agents. With combination therapy,

Table V. Advanced investigations to diagnose the etiology of HT

Clinical condition	Investigations
Glomerulonephritis	ASO, complement (C3,C4), ANA, ANCA, anti-dsDNA, renal biopsy
Chronic pyelonephritis	MCUG, DMSA scintigraphy
Renovascular HT	Renal angiography with measurement of renal vein renin, digital vascular imaging of renal arteries, captopril renography, CT of the kidneys (digital subtraction or conventional), MRI.
Coarctation	Echocardiography, angiography
Endocrine causes	Thyroxine, TSH, S. aldosterone, plasma renin activity, plasma and urinary cortisol, plasma and urine catecholamines, MIBG scan, CT/MR imaging of adrenals, measurement of other hormones in urine and plasma, free cortisol, 18-hydroxycorticosterone

ANA: antinuclear antibody, ANCA: antineutrophil cytoplasmic antibody, anti-dsDNA: anti-double stranded DNA antibody, DMSA: di mercaptosuccinic acid, MIBG: meta-iodobenzyl guanidine, MCU: Micturating cystourethrography

Box 2. Life style and dietary modifications

- Weight reduction and prevention of abnormal weight gain
- Regular physical exercise- aerobic exercise 40 min, 3-5 times/week and avoid more than 2hrs of daily sedentary activities (besides school hours)
- Dietary modification including prehypertensives
- Avoid intake of excess salt (more than 3 gms /day), sugar, excess soft drinks, saturated and trans fat, animal protein.
- Increase intake of vegetables, fruits, fiber, nonfat dairy Ca, K, Mg, Fe, unsaturated fatty acid
- Encourage breast feeding in neonates and infancy.
- Drink water liberally if no contraindications
- Avoid severe dietary restrictions, reduce portion size
- Family based interventions
- Develop health promoting reward system

Box 3. Indications for pharmacological interventions

- Diastolic hypertension
- Secondary hypertension
- Evidence of target organ injury
- Symptoms or signs related to elevated BP
- Blood pressure values that remain above the 95th percentile despite non- pharmacological measures

Box 4. Therapeutic goals

- Diastolic BP < 90th percentile
- 50th centile for those with associated morbidities
- Minimal side effects
- Use of least amount of drugs necessary to effectively reduce BP
- High degree of patient compliance

consideration must be given to combining drugs with complementary mechanism of action, e.g., angiotensin converting enzyme inhibitor (ACEI) with a calcium channel blockers (CCB) or thiazide diuretic, or vasodilator with diuretic or bblocker. Dose adjustment of antihypertensive medications need not be made more frequently than every 2-3 days.¹³

Antihypertensive drugs frequently used in children¹²

The choice of drug as first line therapy remains uncertain and may depend on the etiology of hypertension. Many causes of secondary hypertension in children are related to overproduction of renin and may thus be particularly responsive to the effects of ACEI or angiotensin receptor blocker (ARB) medications.¹³ There are currently no data available to support a particular class of drug for the treatment of primary hypertension in children. The choice of drug and the appropriate dosing is best left to the specialists. The drugs used in hypertensive emergencies and long term management of hypertension are summarized in Table VI and Table VII respectively.

Table VI. Drugs used in management of hypertensive emergencies

Hypertensive emergencies		
Drugs	Dose	Comments
Sodium Nitroprusside	0.3-8 µg/kg/min (in 5% dextrose) infusion	Onset 30 seconds, peaks 2min, disappears within 3 min
Nitroglycerine	0.5-5 µg/kg/min infusion	Onset 2-5 min, duration 5-10 minutes after stopping
Labetolol	0.25-3 mg/kg/hr; or bolus: 0.2-1 mg/kg/dose; may repeat q 5-10 min to maximum 40 mg	Onset 5-10 minutes, duration 3-6 hours Orthostatic hypotension
Nifedipine	0.25 mg/kg PO	Unpredictable and uncontrolled fall of BP

Table VII. HT - Long term management - Drugs

Long term therapy			
Class	Drug	Dose	Adverse effects and precautions
ACEi and ARB	Captopril, Enalapril, Losartan	0.3-6 mg/kg/day; tid 0.1-0.6 mg/kg/day; qd 0.7-1.4 mg/kg/day; qd	Avoid if GFR < 30 ml/min and in renal artery stenosis, dry cough
Calcium channel blockers	Extended release Nifedipine, Amlodipine	0.25-0.5 mg/kg/day;qd-bid 0.05-0.3 mg/kg/day;qd-bid	Swallowed as whole, headache, flushing, dizziness, headache, flushing
Beta-adrenergic blockers	Atenolol, Labetalol	0.5-1 mg/kg/day; qd-bid 1-3 mg/kg/day; bid	Decrease by 50% if GFR <50, sleep disturbances
Alpha1 blocker	Prazosin	0.05-0.5 mg/kg/day;bid-tid	First dose hypotension, syncope
Vasodilators	Hydralazine, Minoxidil	0.75 to 7.5 mg/kg/day; bid-qid 0.1-1 mg/kg/day,qd-bid	Headache, palpitation, fluid retention
Diuretics	Frusamide, Spironolactone, Metolazone, Hydrochlorothiazide	0.5-2.0 mg/kg per dose; qd-bid 1 mg/kg/day; qd-bid 0.2-0.4 mg/kg/day;qd 1-3 mg/kg/day qd	Monitor electrolytes, fluid status. hyperglycemia, hyperuricemia, hypokalemia (non potassium sparing diuretics), metabolic alkalosis, hypomagnesemia

qd – once daily, bid – twice daily, tid – thrice daily

ABCD strategy

‘A’. Drugs interfere with renin angiotensin aldosterone system (RAAS) and include the angiotensin converting enzyme inhibitors (ACEi) and the angiotensin receptor blockers (ARBs)

‘B’. Beta blockers (e.g. Propranolol or atenolol)

‘C’ inhibit the L type calcium channels in vascular smooth muscle cells- calcium channel blockers (CCB’s) like nifedipine and amlodipine. They are divided into two groups:

- Dihydropyridines-potent vasodilators with minimal effect on cardiac contractility or conduction (e.g- nifedipine and amlodipine)

- Non-dihydropyridines - diminish cardiac contractility and slow conduction

(verapamil, diltiazam- contraindicated in patients taking beta blockers or severe left ventricular dysfunction or atrio ventricular block)

'D' (diuretics - furosemide, hydrochlorothiazide) The latter has an advantage in primary hypertension without end organ damage but is more often used as an add on therapy to reduce salt intake. It can be combined with **A** drugs. **B + D** or **ACEI + ACB** combination is not recommended

Approach to treatment of hypertension¹²

Therapy is initiated with a calcium channel blocker (CCB), angiotensin converting enzyme inhibitor (ACEI) or β adrenergic blocker. If two drugs are required, the ACEI (or β -blocker) should be combined with a CCB. Unsatisfactory control of blood pressure requires the use of additional agents such as clonidine, labetalol, hydralazine or minoxidil.

Treatment of Hypertensive Emergencies involves a 25% reduction in BP during the initial hour after presentation and recommends not achieving a mean arterial pressure below the 95th percentile for age and height until 24 to 48 hours after presentation. Excessive reductions in mean arterial pressure must be avoided, because this can lead to diminished cerebral blood flow and syncope that may progress to infarction of the cerebral cortex, brainstem, or retina.

Conclusion

Identification of hypertension in children is important. Measurement of blood pressure in all children on first visit to the clinician should be made routine, especially in all children more than 3 years of age. Exceptions would be younger children (<3 years) with history of major neonatal comorbidities who form a population at risk. Appropriate screening and then referral is of utmost importance if facilities are limited. Lifestyle modification is an early intervention which can be highly beneficial in all stages. Good control of hypertension with minimum end organ damage should be the goal of every clinician.

Points to Remember

- *Measurement of blood pressure on first visit to the clinician should be made routine, especially in all children more than 3 years of age.*
- *Exceptions would be younger children (<3 years) with history of major neonatal comorbidities who form a population at risk.*

- *Using correct cuff size and considering the concept of white coat hypertension before making the diagnosis of hypertension will avoid erroneous diagnosis.*
- *Blood pressure readings recorded in child should be compared to appropriate blood pressure reference charts based on sex, age, and height percentiles.*
- *Clinical evaluation and appropriate investigations will help in the recognition of etiology in children with secondary hypertension.*
- *Therapy is initiated with one agent at an appropriate dose and the dose is increased until the desired blood pressure is achieved using ABCD strategy.*
- *Good control of hypertension with minimum end organ damage should be the goal.*

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CLIPPINGS

Ultrasound to improve the success rate of lumbar puncture in young infants

Ultrasound has been proposed as a means to increase the success rate of lumbar puncture (LP) in infants. A prospective, randomized, controlled trial in an emergency department (ED) was undertaken to determine whether ultrasonography-assisted site marking increases success for infant lumbar punctures. Infants younger than 6 months were randomized to either a traditional lumbar puncture arm or an ultrasonography-assisted lumbar puncture arm. Infants in the ultrasonography arm received bedside ultrasonography of the spine and the puncture space were identified and marked. The lumbar puncture was then performed by the predetermined ED provider. The primary outcome was successful first-attempt lumbar puncture. Subjects were considered to have a successful lumbar puncture if cerebrospinal fluid was obtained and RBC counts were less than 1,000/mm³. Sixty fur children were enrolled in each arm. The first-attempt success rate was higher for the ultrasonography arm (58%) versus the traditional arm (31%). Success within 3 attempts was also higher for the ultrasonography arm (75%) versus the traditional arm (44%). Ultrasonography-assisted site marking improved infant lumbar puncture success. This method can increase the CSF sample collection by LP with relatively less number of attempts in children where the CSF reports are crucial to decide treatment.

Neal Jeffrey T, Kaplan SL, Woodford AL, Desai K, Zorc JJ, Chen AE . The Effect of Bedside Ultrasonographic Skin Marking on Infant Lumbar Puncture Success: A Randomized Controlled Trial. Annals of Emergency Medicine 2017; 69(5): 610-619.e1.

NEWS AND NOTES

29th Annual Conference of Indian Society of Pediatric Nephrology

Pre-conference Workshop: 13 October, 2017-‘Critical Care Pediatric Nephrology and RRT’

Venue: Medanta, The Medicity, Gurgaon.

Main Conference: 14-15 October 2017 - Venue: Heritage Village Resort, Manesar, Haryana.

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NEPHRO-UROLOGY

RENAL IMAGING IN PEDIATRIC NEPHRO-UROLOGY-WHEN AND WHAT?

* **Arpana Iyengar**
****Thakur P**

Abstract: *Radio imaging, with advancements in technology plays an important role in screening, diagnosing and monitoring specific kidney diseases in the fetus, newborn and the growing child. The congenital anomalies of the kidney and urinary tract (CAKUT) such as renal agenesis, renal hypodysplasia, cystic kidneys, malformations and urinary tract obstruction can be diagnosed prenatally with the help of fetal ultrasonography though fetal MRI could be complementary in selected circumstances. Following birth though renal ultrasound is a useful diagnostic tool for majority of renal disorders, certain other additional imaging studies may be indicated in complex situations. Radio-nuclear imaging has revolutionized the radiological approach to aid clinical diagnosis in renal disorders. A combination of imaging studies may be required to reach precise diagnosis and facilitate certain surgical interventions. A basic knowledge of the utility and indications for various imaging modalities will go a long way in planning optimal management of patients with renal disease.*

Keywords: *Renal disease, Imaging, Radiology, Nuclear scan*

Radio imaging, plays an important role in screening, diagnosing and monitoring specific kidney diseases in the fetus, newborn and the child. This overview highlights aspects of imaging relevant to specific nephro – urological disorders, thereby attempting to give a clinical rather than a radiological perspective to the pediatrician. Box 1 gives the common pediatric renal disorders that need imaging modalities for evaluation.

Prenatal renal imaging

Prenatal kidney and urinary tract can be imaged as early as 14-16 weeks post-conception. Renal parenchymal differentiation is seen by 20 weeks of gestation. Routine prenatal ultrasonography (USG) and advanced ultrasound technologies (high resolution and 3 dimensional ultrasonography-3D-USG) results in a prenatal detection rate of ~89% of renal and urinary tract malformations.¹ Congenital anomalies of the kidney and urinary tract (CAKUT) that can be diagnosed prenatally are renal agenesis, renal hypodysplasia, cystic kidneys, malformations and urinary tract obstruction. It is critical to detect the amniotic fluid index (AFI) as a low AFI could point towards an underlying renal agenesis or obstructive renal hypodysplasia. Fetal magnetic resonance spectroscopy (MRS) has added diagnostic value in complex renal anomalies.² Fetal MRI has a 100% accuracy compared to a 55% accuracy rate for prenatal USG. Yet it should be mainly considered as a complementary study to prenatal USG and not as a replacement.

Evaluation of kidney size

Renal ultrasound provides renal length, diameter and renal volume. Large kidneys are seen with polycystic kidney disease (PKD), congenital nephrotic syndrome, infections, storage disorders and rarely with renal tumors. Small kidneys may point to the presence of renal hypodysplasia or scarred kidneys and advanced chronic kidney disease (CKD). It is helpful to monitor the growth of kidneys in children at risk for kidney disease. Table 1 enumerates the normal renal length from birth to 18 years.

Anomalies of fusion

Horse shoe kidney (HSK) is the most common fusion anomaly with an incidence of 1 in 600 and common in males. It is usually characterized by fusion of the lower poles across the midline by an isthmus lying anterior to the branching of inferior mesenteric artery (IMA) from aorta and rarely posterior to the aorta and inferior vena cava. In HSK, ascent into the abdomen is restricted by the IMA which hooks over the isthmus. Hence, HSKs are always low lying⁴. It is often associated with shorter vessels and ureter leading onto pelvic ureteral junction (PUJ)

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Box 1. Radio Imaging in common pediatric renal diseases

Structural evaluation

Kidney: Hypoplasia/ Dysplasia, Agenesis, Cysts, Solitary kidney, Ectopic kidney, Fusion anomaly, Nephrolithiasis, Renal mass/Abscess,

Collecting system: PUJO, VUR, VUJO, Megaureter, Duplex system, Urolithiasis, Infection (UTI)

Bladder : Neurogenic bladder, Cystitis, Valve bladder, Diverticulum/ Ureterocele, Calculi

Urethra : Posterior urethral valve

Vascular : RAS, RVT, Transplant kidney renal flow

Functional evaluation

Differential renal function

Guiding procedures:

Renal biopsies, Hemodialysis catheter insertion

PUJO: pelvi-ureteral junction obstruction, VUJO: vesico-ureteral junction obstruction, VUR: vesicoureteral reflux, UTI: urinary tract infection RAS: renal artery stenosis; RVT: renal vein thrombosis

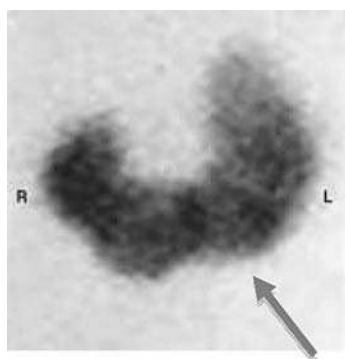


Fig 1. DMSA scan - Horseshoe kidney

Note two distinct renal masses (right and left moieties) lying vertically on either side of the midline and fused in their lower poles by an isthmus of functional parenchyma that crosses the median plane of the body.

obstruction, susceptibility to trauma, stones, renovascular hypertension and higher incidence of Wilm's tumour. USG is the first line tool for delineating the position of the kidneys and assessment of pelvicalyceal dilatation. The evaluation of the functioning renal parenchyma with its differential renal function of right, left moieties and isthmus is done with a dimercaptosuccinic acid (DMSA) scan (Fig.1). If there is any surgical intervention planned for PUJ obstruction, stones or renal tumour then further evaluation with contrast enhanced CT scan or magnetic resonance urogram (MRU) will give more anatomical information on the HSK, ureters and the feeding vessels.

Anomalies of position and rotation

Simple renal ectopy: It refers to a kidney that remains in the ipsilateral retroperitoneal space (Fig 2a). The most common position is in the pelvis or opposite the sacrum and below the aortic bifurcation diagnosed as pelvic or sacral kidney respectively. The lumbar or iliac ectopic kidney is one that is fixed above the crest of the ilium, but below the level of L2 and L3. Excessive cranial migration of the kidney results in a thoracic kidney or in a superior ectopic kidney lying below a thin membranous portion of the diaphragm. In general, the thoracic kidney functions normally, and most patients are asymptomatic. The thoracic kidney is detected on a routine chest radiograph as a suspected mass. The diagnosis of an ectopic kidney can be made by USG in most cases. Since vesico-ureteric reflux

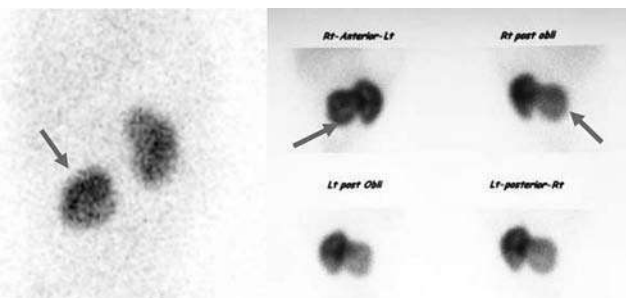


Fig 2a. Simple renal ectopy (Left kidney at lower position)

Fig 2b. Crossed fused ectopic right kidney (right kidney crossed over to left side as seen in anterior and posterior view pictures).

Table I. Renal length as per age³

Age	Mean length (cm)	Range (± 2 SD in cm)
Term newborn	4.48	3.86-5.10
2 months	5.28	3.96-6.60
6 months	6.15	4.81-7.49
1.5 years	6.65	5.57-7.73
2.5 years	7.36	6.28-8.44
3.5 years	7.36	6.18-8.54
4.5 years	7.87	6.87-8.87
5.5 years	8.09	7.01-9.17
6.5 years	7.83	6.39-9.27
7.5 years	8.33	7.31-9.35
8.5 years	8.90	7.14-10.66
9.5 years	9.20	7.40-11.00
10.5 years	9.17	7.53-10.81
11.5 years	9.60	8.32-10.88
12.5 years	10.42	8.68-12.16
13.5 years	9.79	8.29-11.29
14.5 years	10.05	8.81-11.29
15.5 years	10.93	9.41-12.45
16.5 years	10.04	8.32-11.76
17.5 years	10.53	9.95-11.11
18.5 years	10.81	8.55-13.07

(VUR) is frequently associated with an ectopic kidney, voiding cystourethrography (VCU) is recommended⁵. More recently, MRU has greatly enhanced the evaluation of these patients with additional information about the vascular supply.

Crossed fused ectopia: It is the second most common fusion anomaly after horseshoe kidney. Malrotation frequently accompanies renal ectopy, which creates a range of anomalies. The crossed ectopic kidney lies on the opposite side from the ureteral insertion of the bladder and occurs with fusion in about 85% and without fusion in about less

than 10%. Generally, it is difficult to distinguish between crossed renal ectopy with fusion and crossed renal ectopy without fusion by USG or by intravenous excretory urography (IVU). Any suspicion of crossed fused kidney by USG needs a DMSA scan (Fig.2b) to confirm the fusion anomaly. Vesicoureteral reflux (VUR) is the most common associated abnormality; hence VCU is warranted to establish the same. A contrast enhanced CT (CECT) and magnetic resonance urography (MRU) are occasionally needed to procure further details. MRU in particular can also provide information about the vascular supply, which is quite variable. MRU is the best diagnostic imaging if further anatomical detail is expected.

Parenchymal lesions

Multicystic dysplastic kidney (MCDK) is one of the most common prenatally detected anomalies presenting as a fetal anomaly or as an abdominal mass in neonates. Postnatal USG shows cysts of varying sizes with a small amount of abnormal appearing renal parenchyma. On the USG, every cyst will appear as a hypoechoic area with an imperceptible wall (Fig.3a). The contralateral kidney is normal except for compensatory hypertrophy. The dysplastic kidney mostly shrinks and disappears. If absent, hypo dysplasia must be suspected. Nephrectomy is needed if continuing growth or tumours are detected. It is required to confirm a normal contralateral renal unit and to rule out associated anomalies by USG, DMSA scan and a VCU. In patients with complex malformations, MRU is recommended. At times MCDK is difficult to differentiate from severe hydronephrosis when DMSA scan helps. It will show tracer uptake by the functional renal parenchyma even in severe hydronephrosis while there will be no tracer uptake in MCDK.^{4,6}

Autosomal dominant polycystic kidney disease (ADPKD): The diagnosis may be suspected on a plain X ray abdomen when the renal outlines are enlarged, multilobulated or difficult to discern, with associated displacement of bowel loops. USG is an excellent choice for imaging. On USG, the kidney may appear normal or may be bilaterally large with numerous cysts of varying sizes (Fig.3b). On initial examination, renal cysts will appear anechoic with well-defined imperceptible walls. Over years, cysts may grow in size and number and calcification may develop. CT is very sensitive to make the diagnosis of ADPKD and is also excellent at characterizing renal cysts (Fig.3c). On a CT scan, cysts appear as rounded structures and will have an attenuation near or equal to that of simple fluid.⁷ For monitoring disease progression and reliable measures of total kidney volume, MRI is an appropriate imaging



Fig.3a. USG - MCDK (cysts of varying sizes with abnormal parenchyma in between)



Fig.3b. USG - ADPKD (arrow showing numerous cysts of varying sizes)



Fig.3c. CT - ADPKD (arrow showing multiple small uniform cysts).

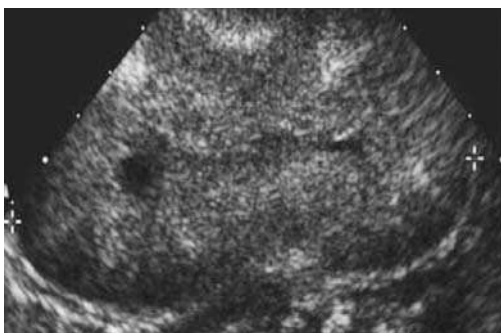


Fig.3d. USG - ARPKD (diffusely echogenic kidneys and loss of CMD)

approach as renal cysts could have better resolution. One should also look for the extra renal manifestations of ADPKD such as liver cysts, intracranial hemorrhage and valvular heart disease.⁷

Autosomal recessive polycystic kidney disease (ARPKD): The age of presentation is variable and is divided into perinatal, neonatal, infantile and juvenile forms. Antenatal USG shows bilateral, enlarged, hyperechogenic kidneys, placentomegaly and severe oligohydramnios. In postnatal USG the kidneys are smoothly enlarged, reniform and diffusely echogenic. This appearance is caused by the many interfaces between the radially arranged dilated ducts. There is loss of cortico-medullary differentiation, with a thin rim of hypoechoic parenchyma at the periphery that is presumed to be the compressed cortex (Fig 3d). Macrocysts may be evident and they tend to become larger and more numerous over time. CT scan will show smooth enlarged kidneys with low attenuation due to the large fluid volume in the dilated ducts. Intravenous contrast material shows a striated pattern of contrast media excretion. The striated appearance represents accumulation of contrast material in the dilated tubules. If renal function is considerably impaired, there may be poor opacification and excretion, making it difficult to visualize the kidneys. MRI has more diagnostic value for assessing the fetal kidneys.

Juvenile nephronophthiasis (NPHP): It is one of the most common genetic causes for end stage renal disease necessitating dialysis and renal transplantation in children and adolescents. Initially, USG in NPHP shows reduction in cortico-medullary differentiation. Subsequently the kidneys become slightly hyperechoic and renal size decreases, eventually leading to a contracted kidney, with detectable cysts in the cortico-medullary junction or subcapsular zone as the disease progress. CT scan may be helpful in detecting small medullary cysts earlier than USG.⁸ Rarely NPHP may develop liver fibrosis or dysplasia of the bile ducts similar to the changes seen in ARPKD.

Chronic pyelonephritis or renal scarring: It can be a sequelae of acute pyelonephritis or VUR and renal vein thrombosis.⁷ The development of permanent lesions leading to a scarred kidney is the consequence of delayed treatment of acute pyelonephritis. In boys with posterior urethral valves and VUR, similar lesions may represent segmental hypoplasia. USG may also demonstrate scars as thinning of the parenchyma and cortical irregularities. DMSA scan is the standard modality for diagnosis of scars with an increased sensitivity compared to USG. Scarring is usually well defined and appears as an area of photopenia with loss of cortical volume (Fig 4).⁸ MRI has shown improved clarity in demonstrating scarring and the collecting system.

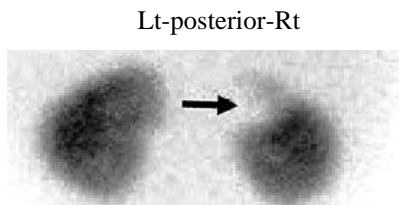


Fig.4. Scarring of right kidney - DMSA scan: photopenic area in upper pole of right kidney

Renal failure: In patients who present with unexplained renal failure, USG is the initial imaging modality. The role of this initial study is to rule out acute obstruction and distinguish features of chronic kidney disease (CKD) from acute kidney injury (AKI). CKD is characterized by small, hyperechogenic kidneys with thin cortex. In cases of prerenal azotemia, kidneys usually have a normal appearance whereas in cases of AKI there may be increased echogenicity.⁸ The exception to this is polycystic kidney disease, where kidneys are large despite CKD. Hydronephrosis may point out towards an obstructive etiology or VUR.

Renal calculi and nephrocalcinosis: Most calcium containing stones are radiopaque on plain X-ray abdomen. The exceptions to this rule are radiolucent stones like those with a predominant uric acid matrix component or those composed of the antiretroviral drugs like indinavir. As a primary diagnostic method, USG is the modality of choice for pediatric patients who present with findings consistent with renal stones (Fig.5a). USG has a high sensitivity for renal stones (up to 90%), although sensitivity for ureteral stones is lower. Despite such limitations, USG is a useful first line test in those children in whom stones are suspected. If stones are not seen on USG but suspicion remains high, by the presence of hydroureteronephrosis, obtaining a CT scan is reasonable. Nephrocalcinosis is typically detected by USG, although CT scan may be

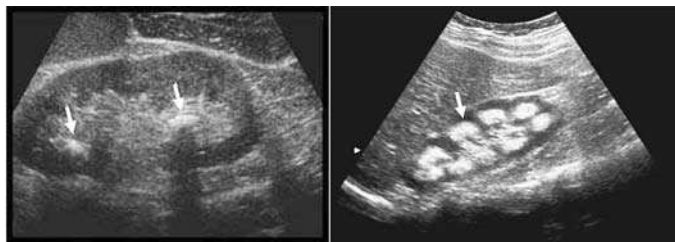


Fig.5a. USG - Renal calculi (Arrow - two hyper echoic dense spots followed by acoustic shadow)

Fig.5b. USG - Medullary nephrocalcinosis (Arrow - uniform dense areas corresponding to medulla of the kidney)

required occasionally. Cortical nephrocalcinosis such as that seen in primary hyperoxaluria may appear, as bright echogenic kidneys. Medullary nephrocalcinosis such as in renal tubular acidosis, is seen as echogenic renal pyramids (Fig.5b).⁷

Renal tumor: In most of renal neoplasms (Wilms's tumor lymphoma and pheochromocytoma) in children, an ultrasound is the first imaging modality to know the renal origin of an abdominal mass, nature, extension of renal tissue around the mass (claw sign) (Fig.6a). Doppler USG may also determine the extension of tumor to renal vein or IVC. Once the preliminary USG suggests the presence of tumor, a contrast enhanced CT Scan is the modality of choice for staging of tumor⁷ with additional information on capsule invasion, adherence to adjacent structures, vasculature, regional nodes, para-aortic nodes, invasion of IVC/renal vein with tumor, thrombus, liver and systemic involvement (Fig.6b). This aids in planning preoperative chemotherapy followed by surgery with postoperative chemotherapy schedules and follow-up regimen.

Disease of collecting system

Anomalies at any level of the collecting system are observed as urinary tract dilatation. Often they are detected during fetal life. The role of imaging is to determine the

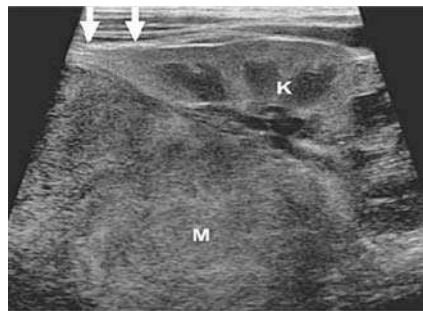


Fig.6a. USG - Wilm's tumor [Arrow showing circumscribed mass (M) arising from kidney (K)]

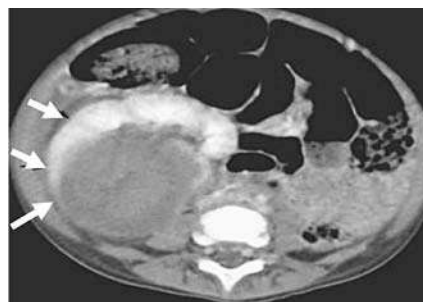


Fig.6b. Axial CT - Wilm's tumour (arrow Claw sign - compressed normal renal tissue as whitish area)

site and severity of dilatation, differentiate between obstructive and non-obstructive dilatation and provide information on the renal parenchyma. USG should be performed first as it helps to plan subsequent work-up. USG is very efficient to demonstrate dilatation of the urinary tract and the level of obstruction, but cannot differentiate between obstructive and non-obstructive dilatation. Additionally, USG provides information on the renal parenchyma. MRU can help in visualization of both the parenchyma and collecting system. It provides morphological assessment of the very dilated urinary tract, ectopic ureteral insertion, ureteric stenosis and assessment of renal parenchyma damage. Use of gadolinium-enhanced sequences provides information on both morphology and function.⁷

Any information on the position of the functioning parenchyma warrants static nuclear imaging and hence a DMSA scan is indicated in cases of MCDK, HSK, pelvic or thoracic kidney, crossed fused ectopia, duplex kidney

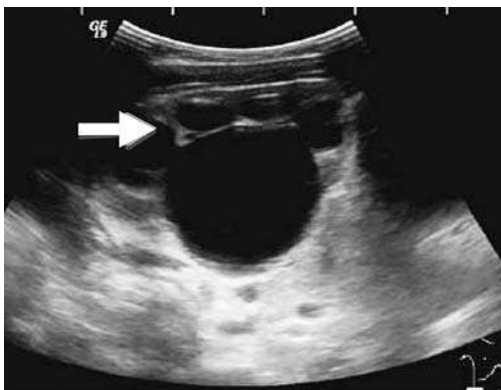


Fig.7. USG - Hydronephrosis (Dilated renal pelvis and calyces)

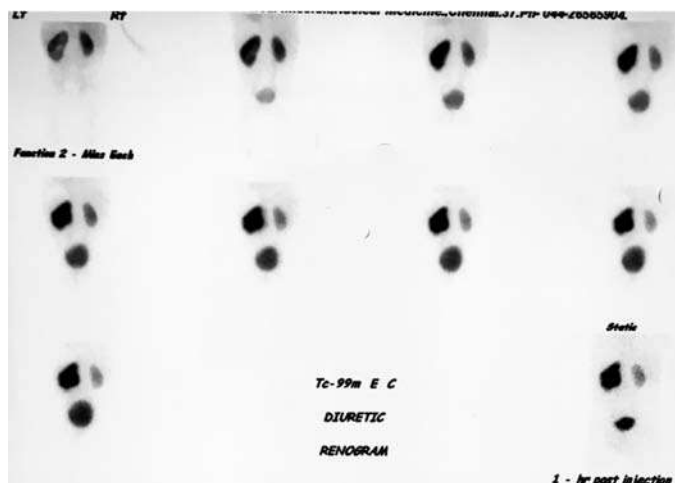


Fig.8a. EC + furosemide isotope study - Left urinary tract obstruction (delay in isotope clearance at 1 hour in left kidney)

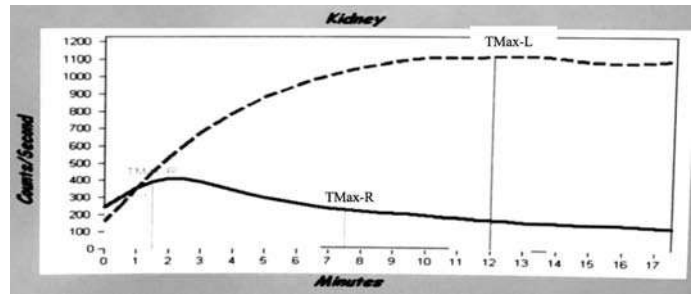


Fig 8b. Typical obstructive pattern of PUJO (progressively rising graph of the left kidney (L) even at the end of 20 mins while the graph representing the drainage system of the right kidney (R) has sloped down indicating its free clearance from the right kidney)

and scarring. The dynamic isotope study - diethylenetriamine pentaacetic acid (DTPA) / ^{99m}Tc-ethylene dicysteine (EC) scan should be undertaken for obstructed systems like PUJ obstruction and obstructive megaureters. This gives information in detail on three phases namely vascular, intrarenal and excretory phase of the kidney.

Hydronephrosis: It refers to dilatation of renal pelvis and calyceal system caused by obstruction at the pelvi-ureteric junction or a refluxing system. USG is the primary investigation for demonstration of dilatation of the urinary tract.⁸ Dilatation is best evaluated on an anteroposterior measurement of the renal pelvis on a transverse scan of the kidney (Fig.7). In the newborn, a pelvic diameter greater than 7 mm and in older children, a diameter above 10 mm should be considered as abnormal. USG is the best screening tool to differentiate between hydronephrosis and hydroureteronephrosis wherein the ureter/ureters are also dilated. PUJ obstruction is the commonest cause of hydronephrosis in children. The best functional evaluation of renal function and of the degree of renal obstruction is obtained by isotope studies with furosemide injection. DTPA / EC scan can provide information on delay in the drainage pattern of kidney by an obstructive curve which is the major deciding factor for surgical management (Fig 8a and 8b).

Antenatal hydronephrosis (ANH): It is the most common renal abnormality on fetal USG.⁸ Different grading systems exist. The commonly used grading system of ANH during 2nd and 3rd trimester is given in Table II.⁹ A frequently used classification is the one proposed by Society for Fetal Urology (SFU).¹⁰ Severe degrees of hydronephrosis (SFU grades 3–4) and an anterior-posterior renal pelvic diameter (APD) of >12 mm on a third trimester USG are highly predictive of a significant postpartum pathology.

Table II. Antenatal hydronephrosis (ANH) staging⁹

ANH classification	APD	
	2 nd trimester (mm)	3 rd trimester (mm)
1. Mild	≤7	≤9
2. Mild / moderate	<10	<15
3. Moderate	7-10	9-15
4. Moderate / severe	≥7	≥9
5. Severe	≥10	≥15

Postnatally, a renal USG must be performed at 48 hours of life for measurement of AP diameter after ensuring adequate hydration. In case the initial postnatal USG is reported to be normal, a 2nd USG should be done at 4 weeks of postnatal life.⁸ Hydronephrosis resolves in most patients with unilateral or bilateral hydronephrosis with APD <10 mm documented postnatally during the first 2-years of life. The policy to follow these neonates with sequential USG to monitor for resolution of hydronephrosis seems satisfactory and radiologic investigations or antibiotic prophylaxis is usually not necessary. A VCU must be performed in patients with unilateral or bilateral hydronephrosis with renal pelvic APD >10 mm. Infants with APD >10 mm who do not show VUR should undergo diuretic renography.

Pelviureteric junction obstruction (PUJO): It is diagnosed in young infants who present with antenatal hydronephrosis and can be asymptomatic. Older children present with symptoms of abdominal pain or infection. The decision to operate in the antenatal and asymptomatic group is more difficult and warrants repeated radiological evaluation. The antero-posterior measurement of the renal pelvis is best measured by USG of the kidney. In the newborn, a pelvic diameter >7 mm and in older children >10 mm is considered abnormal. VUR and obstruction may coexist in the same collecting system and hence VCU would be indicated. Once VUR is excluded, infants with moderate to severe hydronephrosis with caliectasis will need ongoing monitoring and functional assessment by ⁹⁹Tc - MAG₃ or EC to evaluate the differential function and wash out time⁸ (Fig.8a and 8b). MRU has been used in patients with obstructive uropathy in situations where the diuretic renogram is ambiguous.

Vesicoureteric junction obstruction (VUJO): It is characterized by an obstruction at the distal end of the ureter

and results in a hydroureteronephrosis. Diagnosis of VUJO is usually achieved by USG. With the conservative approach, repeated follow-up studies using USG are essential.⁸

Duplex collecting system: Antenatally they are demonstrated by the presence of two collecting systems particularly if one is dilated. After birth, duplex collecting system can be inferred on ultrasound when the renal sinus echo complex is interrupted by a band of renal cortical tissue. Often USG demonstrates the two renal poles and ureterohydronephrosis involving one or both moieties. The presence of duplex collecting system may be associated with obstruction (usually of upper moiety) and /or VUR, usually of lower moiety.⁷ Further confirmation can be done with a VCU and MRU to delineate the anatomy of ureteral duplication before planning for surgery.⁸

Ureterocele: Ureteroceles are cystic dilatations of the submucosal or intravesical portion of the ureter. Ureterocele can be associated with the upper pole of a duplex kidney. Ureteroceles are visualized on USG examination as a cystic structure within the bladder. VCU is essential to evaluate the lower urinary tract for a ureterocele, where it may appear as a smooth, round filling defect along the base of the bladder the “cobra head” sign.⁸ Alternately they are also well visualized on IVU and MRU.

Bladder abnormalities

USG and VCU are the standard imaging modalities for patients with a neurogenic bladder, valve bladder, ureteroceles, bladder diverticulum and bladder stones. Bladder wall thickening consistent with high bladder pressure can be quantified by an ultrasound. Bladder wall thickness varies minimally with age, with a mean of 3 mm when the bladder is full and 5 mm when empty.

Vesicoureteric reflux: VCU is the gold standard dynamic study for diagnosing VUR or for the workup of an antenatal diagnosed fetal uropathy. VUR is graded as per the International Reflux Study In Children - Grade I VUR limited to the ureter, Grade II VUR upto the renal cavities without dilatation, Grade III VUR into the renal cavities inducing dilatation of the calyces, Grade IV Moderate to marked dilatation of the ureter and pelvis and calyceal system and Grade V Marked tortuosity and dilatation of the ureter and pelvis and calyceal system (Fig.9).¹⁰ Renal ultrasound lacks the adequate sensitivity and specificity for diagnosing VUR, although high grade VUR is more likely if hydronephrosis is present.⁸ Reflux of contrast within the vagina during the micturition phase of the VCU is commonly observed and should not be regarded

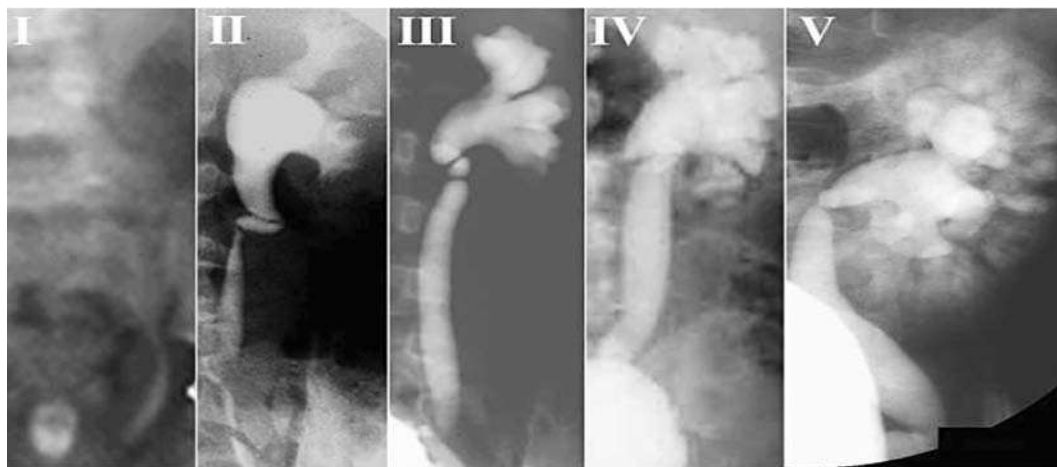


Fig.9. International grading system of VUR.⁹

as a sign of ectopic insertion or of fistula. In the direct radionuclide cystography the radiopharmaceutical is injected directly into the bladder with USG monitoring. It is more sensitive than conventional VCU for the demonstration of VUR at lesser irradiation levels. However, it does not provide information about the bladder or the urethra and misses intrarenal reflux and grade I VUR. It is indicated for follow-up of patients with previously diagnosed VUR and for screening of siblings of patients with VUR. In the indirect radionuclide cystography the isotopic tracer is injected intravenously and the presence of VUR is evaluated in the late phase of this examination, after micturition. This technique requires good cooperation from the child and is not suitable for children under the age of five years.

Posterior urethral valve (PUV): Is the most common cause of urinary outflow obstruction in a male child. VCU is the definitive test for the diagnosis of PUV and for assessing severity of obstruction. Dilated posterior urethra, narrow anterior urethral stream, with or without impression of

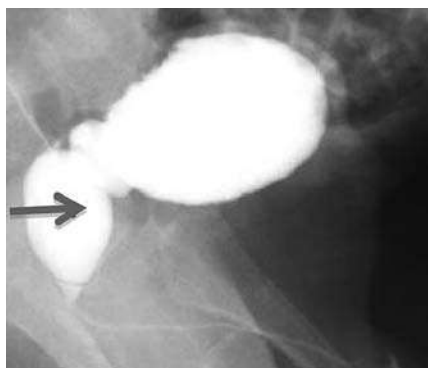


Fig.10. VCU-PUV: Dilated posterior urethra, regular bladder wall and multiple diverticulae.⁸

valves, trabeculated bladder, diverticulae if any, with or without VUR are the vital findings obtained from a VCU (Fig.10). Other urethral abnormalities such as anterior urethral valve, urethral duplication, and urethral diverticulum are also best visualized on VCU.⁸

Conclusion

Imaging modalities have emerged as a vital service to aid the clinician in diagnosis and treatment planning of renal disorders. However, it becomes imperative to ensure that these highly skilled tools are utilized appropriately and effectively. Hence, optimum knowledge regarding the principles and concepts of these tools become critical.

Points to remember

- *Advanced ultrasound technologies can easily pick up anomalies of size, position as well as fusion anomalies. CT Scan is the preferable modality for the delineation of associated malformations and vessel anatomy*
- *As ectopic kidney is frequently associated with vesicoureteric reflux (VUR), voiding cystourethrography (VCU) is recommended.*
- *For antenatally detected hydronephrosis renal ultrasound must be performed at 48 hours of life for measurement of AP diameter of renal pelvis after ensuring adequate hydration.*
- *Renal ultrasound can detect dilatation of the urinary tract and the level of obstruction but cannot differentiate between obstructive and non-obstructive causes.*
- *DMSA is the standard modality for the detection of renal parenchymal scars.*

- *The dynamic isotope study DTPA / 99mTc-ethylene dicysteine (EC) scan should be undertaken for evaluation of obstructed system.*
- *VCU is the imaging modality of choice to detect posterior urethral valves and also to stage vesicoureteral reflux.*

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CLIPPINGS

Tight glycaemic control in critically ill children.

The multicentre trial assigned critically ill children with confirmed hyperglycemia into one of the two groups. The glycaemic control at 80–110mg/dl and 150-180 mg/dl were the target range in two groups. Continuous glucose monitoring was undertaken. The primary outcome was the number of intensive care unit -free days. In the intention-to-treat analysis, the median number of ICU-free days did not differ significantly between the lower-target group and the higher-target group (19.4 days [interquartile range {IQR}, 0 to 24.2] and 19.4 days [IQR, 6.7 to 23.9], respectively P=0.58). In per-protocol analyses, the median time-weighted average glucose level was significantly lower in the lower-target group than in the higher-target group (p<0.001). Patients in the lower-target group also had higher rates of health care-associated infections than those in the higher-target group (P=0.04), as well as higher rates of severe hypoglycemia, defined as a blood glucose level below 40 mg / dl (P=0.03). No significant differences were observed in mortality, severity of organ dysfunction, or the number of ventilator-free days. Critically ill children with hyperglycemia did not benefit from tight glycaemic control targeted to a blood glucose level of 80 to 110 mg per deciliter, as compared with a level of 150 to 180 mg /dl.

Michael S.D. Agus, David Wypij, Eliotte L. Hirshberg, Vijay Srinivasan, Vincent Faustino, Peter M. Lockett, et al. Tight Glycaemic Control in Critically Ill Children. N Engl J Med 2017; 376:729-741, DOI: 10.1056/NEJMoa1612348.

Blood glucose variability and outcomes in critically ill children.

This study was planned to determine the incidence of hyperglycemia (blood glucose [BG] ≥ 150 mg/dL), hypoglycemia (BG < 60 mg/dL), and variability (presence of hypoglycemia and hyperglycemia) in critically ill pediatric population in the 1st week of Intensive Care Unit (ICU) stay and their link with death, length of ICU stay and organ dysfunction. Data reported a frequent incidence of glucose disorders in critically ill children. It was also observed that an association existed between Blood Glucose variability and multiorgan dysfunction and increased ICU stay.

Naranje KM, Poddar B, Bharguvanshi A, Lal R, Azim A, Singh RK, Gurjar M, Baronia AK. Blood glucose variability and outcomes in critically ill children. Indian J Crit Care Med 2017; 21:122-126.

NEPHRO-UROLOGY

ACUTE INTERMITTENT PERITONEAL DIALYSIS IN AKI

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****Liji R**

Abstract: *Acute kidney injury is seen in about one fourth of children admitted to PICU and can affect the prognosis in sick child. Different renal replacement therapy (RRT) modalities include acute intermittent peritoneal dialysis (AIPD), intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT). Early initiation of RRT has improved the outcome in AKI. There is no consensus regarding most appropriate modality or timing for initiation of RRT. APD is most often the modality of choice in developing countries as it is widely available. In recent years, especially in developed countries, hemodialysis and CRRT are being increasingly utilized in pediatric AKI. Pediatricians have greater experience and comfort level using PD as it is technically simple, inexpensive and widely available with minimal infrastructure requirements. In this review, role of APD in Pediatric AKI with emphasis on technical aspects, possible advantages, efficiency and limitations in comparison to other modalities will be discussed.*

Keywords: *Pediatric acute kidney injury, Renal replacement therapy, Acute peritoneal dialysis, Intermittent hemodialysis*

Acute kidney injury (AKI) occurs in 3-5% of hospitalized children and more so in PICU (20-30%). It is an independent risk factor for morbidity and mortality in critically ill patients.¹⁻⁴ Acute kidney injury (AKI) is the abrupt decline in kidney function, resulting in inability of kidneys to maintain internal homeostasis.⁵ There is retention of urea and other nitrogenous waste products and dysregulation of extracellular volume, acid base and

electrolytes. Term AKI has largely replaced acute renal failure (ARF), as it clearly defines renal dysfunction as a continuum rather than the discrete finding of failed kidney function. The term ARF is now reserved for severe AKI, requiring RRT. According to Kidney Disease: Improving Global Outcomes (KDIGO), AKI is defined by any of the following:

- Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 micromol/L) within 48 hours or
- Increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days or
- Urine volume < 0.5 mL/kg/h for six hours.⁶

Epidemiology of AKI

Pediatric AKI is common in children from developing world due to increased incidence of infections especially gastroenteritis, sepsis, malaria, envenomation and exposure to various nephrotoxins. Poor socioeconomic status, overcrowding, lack of access to health care and late referral contribute to the poor outcome in community acquired AKI in the developing world.⁷ The overall mortality in community acquired AKI with failure is as high as 40%-50%. AKI is more common in PICU where it is often multifactorial in etiology and mortality is as high as 70%-80%.^{8,9}

Renal replacement therapy (RRT)

Early institution of RRT significantly improves the outcome in kidney failure. RRT modalities can be classified into a) intracorporeal b) extracorporeal and c) renal transplant. Peritoneal dialysis (PD) is intra-corporeal therapy whereas intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), slow low efficiency dialysis (SLED) and slow continuous ultra-filtration (SCUF) are the different extracorporeal therapies. APD is most often the modality of choice as it is widely available compared to IHD and CRRT.¹⁰ In pediatric AKI, there are no definite guidelines on the appropriate modality, time of initiation, dose or duration of RRT. Choice of modality in children depends on the goals of therapy (fluid or solute removal or both), disease characteristics, hemodynamic stability, weight, vascular access, expertise,

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Box 1. Indications of RRT

Fluid overload more than 15%

Oliguria unresponsive to diuretics

Anuric AKI

Fluid overload more than 10% and increasing ventilator requirements

For provision of adequate nutrition

Need for provision of blood products or of large volume medication if fluid overload already >10%

Azotemia

Life-threatening metabolic derangements like hyperkalemia or acidosis refractory to medical management

availability and cost.¹¹ Specific indications for RRT are given in Box 1.

Peritoneal dialysis, the first RRT for AKI has been widely used in children of all ages and remains the preferred modality in younger children and neonates.^{12, 13} As technology advanced, more IHD and CRRT have almost replaced PD especially in developed countries. However, access to electricity, clean water supply and facilities for water treatment are lacking in developing countries. Also dialysis centers are mainly located in major cities and towns. Pediatricians have greater experience and comfort level using PD. Extracorporeal RRT is complex, expensive, often beyond the finances and logistics in resource poor countries where technical expertise and expensive machinery are often the limiting factors.¹⁴ Hence, acute PD is the modality of choice especially for community acquired AKI in developing countries as it is widely available, cost effective and requires minimal infrastructure.^{10, 14, 15}

Physiology of PD

Peritoneum is a thin semi-permeable membrane composed of loose connective tissue, blood vessels and nerves. It lines the walls of the peritoneal cavity and covers all organs. Peritoneal cavity acts as the dialysis system and peritoneum serves as dialysis membrane. It is an optimal dialyzer as its surface area is same as body surface area. Diffusion and osmosis are the major mechanisms of solute and water transport. Diffusion is the movement of solute from an area of higher concentration to an area of lower concentration across a semipermeable membrane. Osmosis

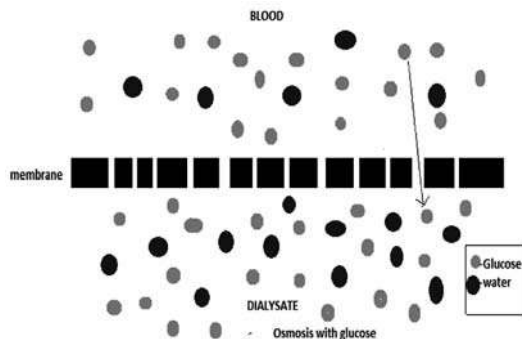


Fig. 1. Osmotic ultrafiltration with glucose in PD

is water movement from an area of lower solute concentration to an area of higher solute concentration (Fig.1). Glucose is the osmotic agent used and by increasing glucose concentration, fluid removal (ultrafiltration) can be increased.

Acute PD can be performed either manually or via an automated device. Depending on the dynamics of fluid instillation into the peritoneal cavity, there are five types of acute PD - acute intermittent PD (AIPD), continuous flow PD (CFPD), continuous equilibration PD (CEPD), tidal PD (TPD) and high volume PD (HVPD). AIPD is the most commonly used one. In TPD, a constant “tidal” volume of 10 to 50 percent of the inflow volume is left in the peritoneal cavity during each cycle after initial fill with a large volume dialysate. The urea clearance will be better in TPD and CFPD.^{3, 7}

Peritoneal access

Establishing a good peritoneal access is the corner stone of successful PD. A catheter is placed in the lower abdomen and dialysis fluid is introduced into the peritoneal cavity. Inflow line, dialyzer (peritoneum) and outflow line (effluent) constitute the circuit (Fig.2). Gravity aids in the inflow and outflow.

In APD, catheter can be quickly and safely placed as a bedside procedure under sedation and local anesthesia by a trained clinician under strict aseptic precautions. PD is safe even in hemodynamically unstable children and small infants. Semi-rigid polyurethane acute stylet catheter or a single cuffed Tenckhoff catheter may be used.³ Disposable stylet catheter consists of two parts - a plastic catheter with multiple small holes on its distal 8 cm and a metal stylet that protrudes from the end of the catheter providing a sharp cutting tip to penetrate the abdominal wall.¹⁶ Pediatric catheters are used for children below 25kg. Neonatal or infant PD catheters are also available.^{17, 18}

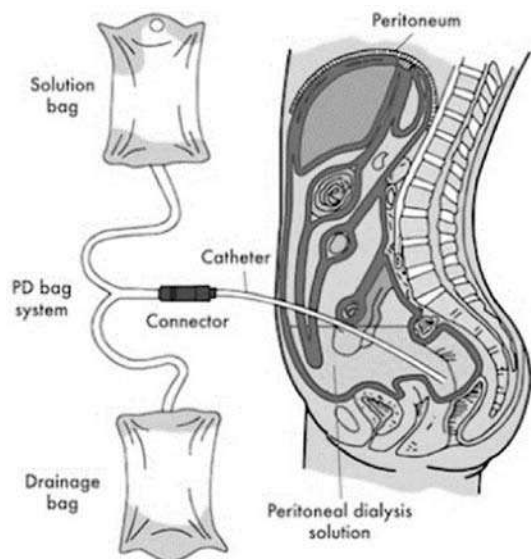


Fig.2. Peritoneal dialysis circuit (Reference for figure)

Most preferred site for PD catheter insertion is in the midline or lateral to rectus sheath, one inch below the umbilicus. Instruments required include pediatric PD catheter with stylet, Y connection set, IV cannula 22 Gauge, intravenous (IV) fluid set, number 11 surgical blade, PD fluid bottles and drain bag (urobag) (Fig.3). If colon is loaded enema is given. Catheterize and empty the bladder. Sedate the child and monitor vitals. Locate the site in the midline or lateral to the rectus 2-3 cm below the umbilicus. Prepare the area with alcohol and povidone iodine. Drape from xiphisternum to mid-thigh. Give local anesthetic. Create a fluid reservoir by instilling 20-30 ml/kg of dialysis fluid using an IV cannula and drip set connected to PD fluid bottle. Free flow of fluid in drip chamber indicates



Fig.3. Consumables for acute PD (PD Catheter, Y connection set, PD Fluid, Urocom/measured volume urobag)

correct position in the peritoneal cavity. Remove the cannula. A small nick is made at this site piercing skin and subcutaneous tissue using No.11 blade. Insert PD catheter with a 'cork-screw' motion till a give-away feel is obtained as the parietal peritoneum is pierced. Withdraw the stylet so that its cutting tip is about 2 cm within the sheath, tilt the catheter and proceed towards the pelvis, iliac fossa or para colic gutter. The stylet is removed and the primed fluid in the peritoneum is drained out. The speed and quantity of fluid drained confirms the success of the procedure. Then connector tube is attached to the proximal end of the PD catheter and other end of the tube is connected to the Y connection set. Ensure patency. A purse string suture is put on the skin around the catheter and suture thread is wrapped around above the bead so as to anchor and secure the catheter (Fig.4) After catheter placement PD is started as per the prescription.¹⁶

Acute PD prescription

Standard PD prescription has following components-



Fig.4. Bedside catheter insertion for acute peritoneal dialysis

session length, number of exchanges, dialysate composition, glucose concentration, potassium concentration, exchange volume, inflow-outflow periods, dwell time, dialysate additives and monitoring. Duration of dialysis and number of exchanges or cycles are decided based on clinical condition and anticipated disease course. One cycle involves fill, dwell and drain. Prescribed amount of dialysis fluid is allowed to flow in (fill), allowed to remain in the peritoneum for specified length of time (dwell). Dialysate and any extra fluid are then allowed to flow out (drain). In manual PD, hourly cycles are planned with 10 minutes fill, 30 minute dwell and 20 minutes drain. Usually one dialysis session is 48-72 cycles.¹⁹ Fill volume at the start of dialysis is 10-20 ml/kg and may be increased to 30-40 ml/kg as tolerated. Ultra filtration (UF) depends on dwell volume, dwell time and dialysate glucose concentration. Solute clearance depends on dwell volume and dwell time. Based on the clinical condition, indication for dialysis and clearance requirements, dialysate composition is decided. Commercially available PD fluid is commonly used. The standard PD fluid composition is given in Table I.³ PD fluid can also be prepared in the unit under strict aseptic precautions. Intravenous fluids like normal saline, Lactated Ringer's solution and 5% dextrose in water can be suitably modified to prepare fluids freshly for the PD exchanges (Table II).³ In severe fluid over load, pulmonary edema, hyperkalemia, hyper catabolic states and in neonates, shorter cycles with 20 minutes dwell is given. In infants peritoneal surface area per unit weight is twice that in adults. Frequent, continuous low volume (10-20 mL/kg or 300-600 mL /m²) exchanges in infants will prevent dialysate leakage and lung compression.^{20, 21}

Table I. Composition of PD fluid³

Solute	Standard fluid
Sodium(mmol/L)	132–134
Potassium (mmol/L)	0–2
Calcium (mmol/L)	1.25–1.75
Magnesium(mmol/L)	0.25–0.75
Chloride(mmol/L)	95–106
Lactate (mmol/L)	35–40 or HCO ₃ ⁻ -34
Glucose (gm/dL)	1.5–4.25
pH	5.2-5.5
Osmolality	344

Hypertonic exchanges and short dwell is preferred in severe fluid overload.^{3, 22} The percentage of hypertonic PD fluid can be titrated by addition of dextrose. For example to prepare 4.0% hypertonic PD fluid, 50 ml of 50% glucose is added to 950 mL standard PD fluid. Bicarbonate based PD fluid is preferred in liver failure as the metabolism of lactate is impaired.^{3, 6, 23, 24} Bicarbonate based PD fluid is prepared by mixing 500 ml normal saline with 250 ml of a prepared solution (220 ml of 5% dextrose and 30 ml of 8.4% sodium bicarbonate). It does not contain calcium and phosphate. Phosphate can be added in the form of potassium acid phosphate. Calcium should be administered separately as an infusion of 0.5 - 1.0 mmol/kg/day. Drugs can be added to the dialysis solution under sterile precautions. Commonly used dialysate additives are potassium, insulin, heparin and antibiotics. Potassium chloride (3-4 mmol/L) is added if serum potassium is below 3.5mEq/L. In hyperglycemia, insulin is added (4 units/L). Heparin (200 - 500 units/L) prevents fibrin clot formation and subsequent catheter block in case of bleeding.

Manual PD requires constant supervision to ensure proper inflow, accurate dwell and drain times. Hourly inflow, outflow, total inflow, outflow and net ultrafiltration are tabulated in the monitoring chart (Table III). Daily intake and output charting and monitoring of weight is mandatory in acute PD. Blood urea and electrolytes should be checked at least twice daily.

Contraindications

PD is absolutely contraindicated in diaphragmatic defects, recent abdominal surgery, abdominal wall cellulitis, pleuro-peritoneal communication, high intra-abdominal pressure compromising pulmonary function, severe respiratory failure, ARDS, severe volume overload and fecal peritonitis.^{21, 22} Slow efficiency of the procedure with potentially unpredictable fluid removal and solute clearance makes it suboptimal in hyper catabolic AKI. High glucose content of the PD fluid causes hyperglycemia. Increased carbon dioxide production during PD will exacerbate respiratory failure in children with compromised lung function.¹⁵

Complications

Can be serious and potentially life threatening. Risk of bowel perforation during insertion and high risk of peritonitis beyond 72 hours of initiating PD are the common complications. Turbid effluent having more than 100 cells/HPF with more than 50% neutrophils is diagnostic of peritonitis. Rapid flushes followed by intraperitoneal antibiotics is the treatment. Maintaining sterile precautions

Table II. Local preparation of PD fluid³

Type of fluid	Na+	K+	Ca 2+	Mg	Cl-	HCO ₃ -	Lactate	pH	Osmolality
Hartmann's solution	131	5	2.0		111		29	7.0	278
Ringer's Lactate	131	5	1.8		112		28	6.5	279
Plasmalyte B	130	4	0	1.5	110	27		7.4	273
½ Normal saline	77				77			5.0	154

- 1L Plasmalyte + 30 ml 50% dextrose (15gm) gives a solution with following concentrations Glucose 1.45% Na 126mmol/L, K 3.8mmol/L, HCO₃ 27 mmol/L, Mg 1.45mmol/L, Osmolality 342.
- 1L Ringer Lactate + 30 ml 50% dextrose (15gm) gives a solution with following concentrations Glucose 1.45% Na 127mmol/L, K 3.8mmol/L, Lactate 27 mmol/L, Ca 1.36 mmol/L, Osmolality 346.

This is similar to lactate based PD solutions

- 1L ½ Normal saline + 40 ml 50% dextrose (20gm) + 40 ml 8.5% Sodium bicarbonate (40mmol) + 60 ml 3% Na Cl (30mmol) will give a solution with following concentrations Glucose 1.7%, Na 130mmol/L, HCO₃ 35mmol/L, Osmolality 340.

Table III. PD Monitoring chart

No of cycle	Time	Fluid in	Fluid out	Balance (In - Out)	Cumulative balance	Remarks

during the placement of PD catheter and by preventing contamination during exchanges helps to reduce incidence of peritonitis.^{3,16} Prophylactic antibiotics when used in conjunction with sterile technique decreases the incidence of peritonitis.³ Mechanical complications include pain, over distension with splinting of diaphragm, lung atelectasis, aspiration pneumonia, hydrothorax, herniation, external leakage and catheter malfunction causing incomplete drainage. Inadequate drainage may occur due to improper catheter placement, block by fibrin, blood clot or omental wrapping. Common metabolic complications include hyperglycemia, hypernatremia, hypokalemia and protein losses often exceeding 5 g/day.^{18,19}

Flexible soft single cuffed swan neck catheters are more comfortable with less risk of injury to the bowel or intra peritoneal organs and lower risk of peritonitis as the cuff prevents bacterial migration. Though expensive, longer life of this catheter makes it an attractive option in conditions like hemolytic uremic syndrome (HUS) where recovery may be delayed.^{3,16, 17, 18}

PD vs extracorporeal RRT

PD is the modality of choice in pediatric AKI in developing countries. PD results in better hemodynamic stability especially in critically ill infants and children as the fluid and solute removal is gradual.²¹ Vasudevan et al in their survey on the choice of RRT modality in pediatric AKI in India reported PD as the predominant modality.¹² There is less risk of cardiovascular instability with hypoperfusion and exacerbation of ischemic AKI.¹⁴ As there is no need for systemic anticoagulation, PD is ideal for children with coagulation failure. Prophylactic PD catheter placement and early PD is proved to be beneficial post cardiac surgery in small neonates and infants.²⁴ PD is more physiological and as solute removal is gradual there is less potential for disequilibrium syndrome. Continuous glucose absorption provides nutritional benefits to the critically ill.⁷ In sepsis associated AKI (SA-AKI) there may be clearance of toxic cytokines as peritoneal membrane has large enough pores and this may help in reducing the vasopressor needs.^{18, 19} Major limitation of PD is slow

Table IV. Comparison of different RRT modalities

Modality	Advantages	Disadvantages
Peritoneal Dialysis	Minimal equipment needs Minimal training needed Simple procedure Feasible in small infants Bedside PD catheter placement No need for vascular access No Need for anticoagulation Feasible in hemodynamic instability Faster renal recovery Higher large solute clearance than with IHD Gradual & continuous solute and water clearance Less nursing effort	Less efficient Variable ultrafiltration (UF) Less small molecular clearance Not effective in hypercatabolic ARF Less effective in Pulmonary edema, Hyperkalemia Poisoning Drug overdose
Intermittent Hemodialysis (IHD)	Short treatment times Accurate UF	Need for vascular access Need for anticoagulation Hemodynamic instability
CRRT	Accurate UF Continuous treatment	Need for vascular access Need for anticoagulation Close supervision and nursing care

clearance of uremic toxins and variable ultrafiltration. Clearance of low-molecular weight toxins is lower while large solute clearance is better with PD compared to HD. Extracorporeal RRT generates inflammatory mediators, rapidly decreases osmolality and blood volume, diminishing renal perfusion and retarding renal recovery. PD is favored in the neonates in view of difficulty in establishing vascular access, thermodynamic instability and low tolerance to volume shifts.^{20, 21} There are no large randomized clinical trials comparing the three modalities (PD, HD, and CRRT) for treatment of children with AKI. Though CRRT is superior to PD in terms of fluid balance, solute clearance, and ability to provide adequate nutrition, the overall outcome is not superior.^{21,25} The small comparative studies suggest no significant differences in mortality between peritoneal dialysis and extracorporeal blood purification in AKI.^{22,25} Comparison of different RRT modalities is given in Table IV.

Conclusion

AKI is common in developing countries and is an important cause of morbidity and mortality. Timely initiation of RRT in AKI is crucial in optimizing the outcome. But there is no consensus regarding the optimal time of initiation or mode of RRT in AKI in children. Acute PD is now the modality of choice in children in developing countries as it is simple, gentle, continuous and efficient form of RRT readily available at affordable rates.²⁶

Points to Remember

- *AKI is an important cause of mortality in critically ill children.*
- *Timely initiation of RRT improves the outcome in AKI.*
- *Acute PD is the modality of choice in community acquired AKI especially in resource limited settings.*

- *PD provides gradual, continuous fluid, electrolyte and solute clearance and corrects acid base imbalance, maintaining hemodynamic stability in critically ill with AKI.*
- *In AKI, there is no significant difference in mortality between PD and extracorporeal blood purification.*

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NEPHRO-UROLOGY

HYPERCALCIURIA SYNDROME AND NEPHROLITHIASIS

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Abstract: *In children, renal stone disease is on the rise. The clinical presentation varies depending upon age with hematuria being a common finding. Ultrasound is the first imaging modality of choice in children. The most common cause is metabolic disorder which requires complete evaluation before initiating treatment. Once the etiological diagnosis is confirmed, specific therapy should be initiated based on the type of stone along with non-pharmacological treatments like increased water and reduced salt intake. Long term therapy is required with proper counseling and follow up in order to prevent further stone formation. This review discusses various aspects of pediatric nephrolithiasis.*

Keywords: *Hypercalciuria, Nephrolithiasis, Nephrocalcinosis, Renal calculi, Urolithiasis, Management*

In pediatric population, kidney stone disease has shown a significant increase in both incidence and prevalence in the recent past.¹ Chronic kidney disease (CKD) is a long term complication of renal stone disease (RSD) and is under recognized with delay in diagnosis, inappropriate therapy and rare inherited disorders causing progression to CKD. The goal of the pediatric nephrologist and pediatric surgeon is to eliminate the burden of kidney stones, prevent complication, recurrence and progression to CKD. Nephrolithiasis describes stone residing in kidney. Nephrocalcinosis comprises deposits of calcium salts in the tubules, tubular epithelium and /or the interstitial tissue of the kidney.² Urolithiasis includes stones formed in the kidney but localized anywhere in urinary tract including primary bladder stones. Hypercalciuria can progress to nephrocalcinosis (NC) or urolithiasis.

Epidemiology

Urolithiasis and NC affect children of all ages.³ NC primarily appears during the first year of life which may be due to the underlying genetic tubulopathies and/or metabolic disorders.

Etiology

Most common cause for renal stones in children is an underlying metabolic disorder with high risk of recurrence and progression to NC.⁴ Hence, early diagnosis of metabolic abnormalities and appropriate management is imperative to prevent stone recurrence. Risk factors for urolithiasis/NC include genetic abnormalities in renal tubular epithelial transport, metabolic disturbances, anatomical abnormalities and urinary tract infection in most of these children.

Environmental factors mainly reflected by diet have definitively contributed more to the increasing incidence of stone disease in adults and may gain importance in pediatric population in near future, in view of increasing number of children with obesity or metabolic syndrome.⁵

Mechanism of stone formation

In majority of cases, kidney stones are thought to grow attached to stone precursor lesions??nidus, preceded by urinary supersaturation of the stone forming minerals or ions. Randall was the first to describe the stone precursor renal papillary lesion referred to as Randall's plaques and plugs.

Three pathways of stone formation have been proposed on the basis of recent studies. First, kidney stones can form and grow attached to preformed subepithelial interstitial plaques of calcium phosphate (Randall's plaques) on the renal papillae. The second pathway involves deposition of crystals in the renal tubules (Randall's plugs), primarily in the inner medullary collecting ducts (IMCD) and ducts of Bellini and finally stones do form by free solution crystallization of stone forming salts.⁶

Urinary macromolecular inhibitors of stone formation include the glycoproteins, uropontin, nephrocalcin and Tamm-Horsfall protein (THP) or uromodulin. These proteins are responsible for the bulk of inhibitory

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activity of calcium oxalate crystallization in human urine. Urinary citrate, pyrophosphate and magnesium are important low molecular weight urinary crystal inhibitors.⁷

Risk factors

1. Hypercalciuria

Hypercalciuria has been defined in children with urinary calcium excretion of more than 4 mg/kg/day. In children the presenting symptoms may include hematuria, flank pain, abdominal pain, voiding dysfunction and urolithiasis. Additionally hypercalciuria has been associated with recurrent urinary tract infections (UTIs) and decreased bone mineral density.⁸

Genetics: In children with hypercalciuria, the prevalence of nephrolithiasis in the family is 46-69%.⁹ A positive family history appears to be the single most important risk factor.⁸ The frequently observed familial clustering of calcium urolithiasis is most compatible with an autosomal dominant transmission.⁸ A number of candidate genes have been suggested in pathogenesis of hypercalciuria, such as soluble adenylate cyclase, calcium sensing receptor (CASR), vitamin D receptor, chloride channel-5, sodium phosphate co-transporter-2 and claudin-16.¹⁰ Currently the hypercalciuric trait is suspected to be polygenic and requires the interaction of genetic and environmental factors.⁸

Classification: The development of hypercalciuria involves interactions between the gastrointestinal tract, bone and kidney and a complex interplay of hormones, such as parathyroid hormone (PTH), calcitonin and 1,25-dihydroxyvitamin D

The classification suggested by Pak ["absorptive" hypercalciuria (with three types), "resorptive" hypercalciuria and "renal" hypercalciuria] is controversial and of little assistance in clinical practice. Three mechanisms has been postulated in idiopathic hypercalciuria: increased intestinal absorption of calcium, defective reabsorption of calcium by the renal tubule and increased bone resorption. Overexpression of the vitamin D receptor (VDR) and deficiencies in renal tubule enzymes may also be involved.¹¹

Dietary factors affecting urine calcium excretion include the intake of animal proteins, sodium, potassium, phosphorus and calcium.⁷ High sodium intake in clinical trials has been found to increase urinary calcium excretion in both adults and children. Tubular reabsorption of calcium is inhibited by urinary sodium and an increase in sodium intake leads to an increase in urinary calcium excretion.⁷

2. Hyperoxaluria

2a. Primary hyperoxaluria: All currently known three types primary hyperoxaluria (PH) are rare autosomal recessive diseases of the glyoxylate metabolism. In primary hyperoxaluria type I (PH I), low or absent activity of liver-specific peroxisomal alanine: glyoxylate aminotransferase (AGT) causes massive hyperoxaluria.¹² PH I is the most frequent subtype, and the underlying AGXT gene comprising 11 exons is located on chromosome 2q36-37. Diagnosis is mostly based on complete AGXT sequencing and more than 150 mutations have been identified throughout the gene. There is a presentation heterogeneity ranging from infantile end-stage renal disease (ESRD) to a late onset or oligosymptomatic course in advanced adulthood. As most patients will develop end stage renal disease (ESRD) over time, early diagnosis is mandatory.¹³

Primary hyperoxaluria type II (PH II) is characterized by increased urinary excretion of oxalate and L-glyceric acid caused by glyoxylate reductase/hydroxypyruvate reductase (GRHPR) deficiency.¹³ The clinical course of PH II is generally more benign, but symptoms may be clinically indistinguishable from PH I.

Primary hyperoxaluria type III (PH III) is due to mutations in the HOGA1 gene that encodes the liver-specific mitochondrial 4-hydroxy-2-oxoglutarate aldolase (HOGA) enzyme, which is involved in the metabolism of hydroxyproline.¹⁴ PH III accounts for about one-half of the remaining 10% of patients who do not have either type I or II disease.

2b. Secondary enteric hyperoxaluria: Secondary hyperoxaluria is frequently found in patients with chronic inflammatory bowel disease (e.g. Crohn's) or with malabsorption syndromes (cystic fibrosis, celiac disease, abetalipoproteinemia). Hyperoxaluria resulting from based on increased intestinal oxalate absorption after bariatric surgery is clearly associated with stone formation. Normally, oxalate will bound to calcium to form insoluble calcium oxalate in intestine, which is not absorbed. In patients with enteric hyperoxaluria, calcium binds to fatty acids, instead of oxalate and thus more soluble oxalate is available for absorption.¹⁵

3. Hypocitraturia

Urinary citrate is an important urinary crystal inhibitor, hence adequate urinary citrate excretion is of paramount importance in the prevention of urinary supersaturation and nephrolithiasis (Table I and II). Low urinary citrate excretion is characteristic of the complete form of distal renal tubular acidosis.¹⁵

Table I. Normal urinary values in spot urine samples

Parameter	Age	Value (mg/mg creatinine)
Calcium	<7 mo	<0.86
	7-18 mo	<0.60
	19mo-6 years	<0.42
	>6 years	<0.20
Oxalate	<6 mo	<0.29
	6 mo -2 years	<0.20
	2-5 years	<0.11
	6-12 years	<0.06
Citrate	<5 years	>0.42
	>5 years	>0.25
Cystine	All ages	<0.075
Uric acid	>2 years	<0.56 per GFR (ratio × plasma creatinine)

4. Cystinuria

Cystinuria is the cause in upto 10% of all urinary stones in children. Cystinuria is caused by a defective transport of dibasic amino acids (cystine, lysine, ornithine and arginine) through the epithelial cells of the renal tubule and the intestinal tract, but only cystine is insoluble enough to form stones. Cystine solubility will increase threefold at pH >8.¹⁵

5. Hyperuricosuria

Uric acid stones are rarely found in children. Hyperuricosuria results from high-purine diets, myeloproliferative disorders, tumor lysis syndrome or enzymatic defects. Many drugs, e.g. probenecid, high-dose salicylates, or contrast media, also increase uric acid excretion. However, low urine pH and low urine volume are far stronger risk factors for stone formation than hyperuricosuria per se.¹⁵ Some rare inherited disorders like Lesch-Nyhan syndrome and glycogenosis type 1a will also cause hyperuricosuric nephrolithiasis.

6. Urinary tract infections

Infectious stones are mainly composed of struvite (magnesium ammonium phosphate), but often also contain carbonate apatite, the crystallization of which is favored

Table II. Normal urinary values in 24- hours urine collection

Parameter	Age	Values
Calcium	All ages	<4 mg/kg
Oxalate	All ages	<0.5 mmol (<45 mg)/1.73 m ²
Citrate	All ages, Male	>1.9 mmol (365 mg)/1.73 m ²
	All ages, Female	>1.6 mmol (310 mg)/1.73 m ²
Cystine	<10 years	<55 μmol (13 mg)/1.73 m ²
	>10 years	<200 (48 mg) should we add / 1.73 m ² for cystine and creatinine
	Adults	<250, (60 mg)
Uric acid	All ages	<815mg/1.73 m ²
Creatinine	3-5 years	12-20 mg
	6-13 years	15-25 mg
	14-18 years, male	18-27 mg
	14-18 years, female	17- 24 mg
Magnesium	All ages	>0.04 mmol (0.8 mg)/kg

by a high urinary pH (>7.0). Urease-producing bacteria are responsible for the formation of struvite calculi. Urea is hydrolyzed to ammonium ions, which results in a high urinary pH. Many gram-positive and gram-negative bacteria produce urease, with proteus species being the predominant organisms. In one-third of patients, there is a primary anomaly of the urinary tract. Stones may also occur during secondary infection on a nidus of different composition, e.g., cystine or calcium oxalate. It is therefore important not to miss an underlying metabolic disorder. Urinary stasis increases the risk of crystallization.¹⁵

7. Medication and intoxication

About 1–2% of all kidney stones are drug related. Medication increasing the excretion of lithogenics (e.g. loop diuretics, calcium/vitamin D supplementation) or reducing the excretion of inhibitory substances (carbonic-anhydrase inhibitors, topiramate), will increase the risk of stone formation. For example, hypercalciuria induced by loop diuretics was reported as one major risk factor in NC of prematurity.¹⁵

Intoxication with ethylene glycol will cause severe hyperoxaluria which results in acute kidney injury due to calcium oxalate crystal agglomeration in the renal parenchyma. Indinavir, a protease inhibitor is also implicated in stone formation.¹⁵

Clinical presentation

Most kidney stones in children are calcium based as reported in several pediatric series.¹⁶ Calcium oxalate is most common and accounts for 40% to 60% of cases of pediatric nephrolithiasis while calcium phosphate accounts for 10% to 20%. Mixed stones composed of both calcium oxalate and calcium phosphate constitute 10% to 25% of cases of pediatric nephrolithiasis. Magnesium ammonium phosphate (struvite or infection-related) stones are seen in 17% to 30% of cases.¹⁶ The presentation of nephrolithiasis in children is variable, depending on the age of the patient. Severe colicky abdominal pain is common in adolescents and school-aged children. Nonspecific symptoms of abdominal pain, nausea, vomiting and irritability, rather than the typical renal colic, are seen in younger children. Hematuria is a common presenting symptom. In children younger than 5 years, kidney stones are frequently discovered following a urinary tract infection or as an incidental finding.

Evaluation

The goal of evaluation is to identify modifiable risk factors and abnormalities for which targeted therapy can

be prescribed to decrease recurrence and complications of nephrolithiasis.

a. Medical history and examination: The medical history should focus on diet, fluid intake, medications, family history and presence or absence of specific disorders that can lead to nephrolithiasis. A detailed dietary history should be obtained, including information regarding the amount of fluid and dietary sodium intake. The ketogenic diet is a risk factor for formation of uric acid stones and may be associated with hyperuricosuria, hypocitraturia and low urine pH. Excessive animal protein intake has been associated with increased urinary excretion of calcium and uric acid and decreased urinary excretion of citrate, resulting in calcium oxalate and uric acid stones.

Medications and supplements associated with nephrolithiasis include vitamin D, calcium supplements, vitamin C, diuretics (furosemide and acetazolamide), seizure medications (felbamate, topiramate and zonisamide), steroids, uricosuric drugs and antibiotics (indinavir sulfate and ceftriaxone sodium). Features in patient's history suggestive of a possible hereditary etiology would include (a) infantile or early childhood presentation (b) parental consanguinity (c) positive family history with unexplained renal insufficiency (d) recurrent kidney stones (e) signs and symptoms of tubular dysfunction with associated polyuria, acidosis, rickets, growth retardation, renal insufficiency, nephrocalcinosis and dysmorphism. Specific disorders or conditions predisposing a patient to nephrolithiasis would include urinary tract obstruction, vesicoureteral reflux, inflammatory bowel disease, short gut syndrome, cystic fibrosis, seizure disorder and immobilization. Key elements of the physical examination include documentation of blood pressure, growth parameters, bony deformities, abnormal calcifications, rickets, abnormal genitalia and immobility.¹⁶

b. Laboratory evaluation: Results of urinalysis provide information regarding specific gravity, urine pH and the presence of hematuria or pyuria. Tubular dysfunction may be present if the results of urinalysis show glucosuria and proteinuria. A diagnosis of infection accompanying acute kidney stone episodes may be supported by the presence of pyuria, urinary symptoms and fever. Urine should be obtained for culture as part of the evaluation for nephrolithiasis. Microscopic analysis can demonstrate the presence of cystine crystals in cystinuria. Low-molecular-weight proteinuria in boys with kidney stones or nephrocalcinosis can establish the diagnosis of Dent disease.

Kidney stone material should be analyzed by X-ray

crystallography or infrared spectroscopy. Kidney stone composition can narrow the differential diagnosis and help tailor evaluation and management. Metabolic evaluation should incorporate measurement of electrolytes, uric acid, calcium, magnesium and phosphorous. Serum creatinine levels should be measured to assess renal function. Parathyroid hormone and 25-hydroxy vitamin-D level should be documented in hypercalcemia to rule out hyperparathyroidism and vitamin D toxicity respectively.¹⁶

Metabolic stones are more common in children hence, 24-hour urine collection is the mainstay of workup. When patients are unable to give 24-hour urine samples, spot urine samples can be collected, especially in young patients who are not toilet trained. Normal values for spot urine samples and 24-hour urine collection are given in Table I and II respectively.^{17,21}

c. Imaging: In adults, CT without contrast is the gold standard for diagnosing nephrolithiasis and urinary tract calculi because of its high sensitivity and specificity. In children, radiation exposure has been a major concern, resulting in recommendations supporting the initial use of renal ultrasound (US) with or without radiographs to limit radiation exposure.¹⁶ In a recent study by Smith-Bindman et al,¹⁸ no difference in serious outcome arising from a missed or delayed diagnosis was demonstrated between the use of US and CT as the initial imaging study in adults with suspected nephrolithiasis. This finding, together with the lower cumulative radiation exposure over 6 months from multiple imaging tests that followed the initial use of US, supports the conclusion that US can be considered as an initial imaging study of choice. Some pitfalls in the renal ultrasonography of neonates and especially preterm infants, have to be noted. Tamm Horsfall protein (THP) deposits within the renal calyces may look like nephrocalcinosis. THP deposition however disappears within 1-2 weeks and follow-up will show completely normal kidneys. Many stone types can be visualized using KUB radiography; however cystine and struvite stones often are poorly visible on KUB radiography and uric acid rich matrix stones are not visible at all.

Management

a. Acute management

Renal calculi are generally nonobstructing and acute decompression is not indicated. Obstructed ureteral calculi require acute decompression with a ureteral stent. A percutaneous nephrostomy tube is preferred when there is a calculus at pelvic ureteric junction leading to obstructed pyelonephritis, acute kidney injury or intractable pain.

Effective management of pain with analgesic is important. Renal and ureteral stones pass spontaneously in children 32% to 50% and 41% to 63% of the time, respectively, so most cases can be managed successfully by watchful expectancy.¹⁶ Medical expulsive therapy is a well-established treatment for ureteral calculi in adults that uses α -blockers (tamsulosin, terazosin, doxazosin, prazosin) or calcium channel blockers (nifedipine) to relax ureteral smooth muscle, resulting in increased rates of stone passage, decreased time to stone passage, and improved analgesia. Mokhless et al. reported no adverse symptoms when tamsulosin 0.4 mg was prescribed for children older than 4 years old and 0.2 mg was prescribed for children 4 years old or younger.¹⁹ Stone passage may take 4 to 6 weeks and confirmation of passage by either repeated imaging or visualization of the passed calculus is mandatory.

b. Non-pharmacological intervention

i) Fluids: The universal and probably most important component of kidney stone treatment is increased urine volume, thereby decreasing solute concentration and consequently, supersaturation. Lande, et al, studying 32 children with urolithiasis, showed that urine flow of >1 ml/kg per hour, almost eliminated the risk of supersaturation for calcium oxalate, calcium phosphate and uric acid, thus protecting from kidney stones formation.²⁰

ii) Diet: Urinary calcium excretion is significantly affected by sodium, protein, potassium, phosphorus and calcium in the diet. There is a reproducible linear positive correlation between urinary sodium and calcium excretion in both stone formers and normal individuals. Hence, "sodium restriction", in essence, should reflect changing the habits of high sodium intake to that of optimal sodium intake. The Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences, states that the optimal daily intake of sodium at ages 4-8 years is 1.2 g and at ages 9-18 years, is 1.5 g, and the upper limit values (namely maximal amounts not to pose health risks) are 1.9 g and 2.3 g, respectively.²² On the other hand, high potassium intake decreases urine calcium excretion. The optimal daily potassium intake, provided mostly in the form of fruit, vegetable and dairy products, is 3.8 g at age 4-8 years and 4.5g at age 9-18 years.²² In hypercalciuric stone formers, another important aspect of decreasing urine calcium is by changing the diet to be less acidic, by reducing animal-protein intake.²¹ A dietary restriction of calcium is not recommended in children with hypercalciuria, as it puts the growing child at risk for negative calcium balance and poor bone mineralization and also increases urinary

excretion of oxalate from increased gastrointestinal absorption of oxalate.⁸

c. Pharmacological intervention (Table III)

i) Calcium stones, hypercalciuria and hypocitraturia:

Potassium citrate has the dual advantage of decreasing urine calcium and increasing urine citrate in patients with calcium stones and hypocitraturia. Furthermore, it improves the bone mineral status of these patients. Alkaline pH increases risk of calcium phosphate stone formation therefore urine pH should be maintained between 6.3-6.5 with citrate therapy.⁷ Thiazides are time-proven preparations for the treatment of hypercalciuria. Thiazides decrease urine citrate excretion, probably by inducing hypokalemia and hence it is advantageous to use a combination of thiazides plus K-sparing diuretics such as amiloride.²¹

ii) **Primary hyperoxaluria:** In type 1 primary hyperoxaluria, 30–50% of patients lower their urine oxalate in response to treatment with pyridoxine. In recent years it has become evident that it is the patient's genotype that dictates such response, seen with the commonest mutant allele, G630A.²¹ Pyridoxine is effective in individuals both homozygous and heterozygous for these alleles, though the specific mechanism of the vitamin's action under these circumstances is yet unknown. A novel approach to the treatment of hyperoxaluria might be achieved with oral intestinal colonization with *Oxalobacter formigenes*, which

not only degrades intestinal oxalate but also enhances colonic secretion of endogenously produced oxalate, resulting in decreased blood and urine oxalate levels.²¹ In patients who develop chronic renal failure and ESRD, aggressive dialysis, followed by liver and kidney transplantation, is currently the best available approach.

iii) **Absorptive hyperoxaluria:** The treatment of this condition involves correction of the basic GI tract anomaly, restricted dietary oxalate intake, and increased calcium intake.

iv) **Cystinuria:** The goal of treatment is to keep cystine soluble at a concentration below 250 mg (1 mmol/L). This means that a patient who excretes 750 mg (3 mmol) cystine per day needs to have a urine volume of 3 litres in order to maintain the urinary cystine soluble. As cystine solubility increases in alkaline urine, urine pH should be kept between 7.0 and 7.5 with the help of alkalinizing agents like potassium citrate.

D-penicillamine and tiopronin are sulfhydryl compounds which cleave cystine into two cysteine-disulfide moieties that are 50-times more soluble than cystine. Although treatment with D-penicillamine is effective, it carries a high incidence of serious side effects. If used for long-term, it should be supplemented with pyridoxine (25-50 mg/day) because of the anti-pyridoxine effect of the medication. Tiopronin, is preferable because

Table III. Medications commonly used in the treatment of urolithiasis

Drug name	Dosage (oral)	Formulations	Indications
Potassium citrate	0.5 – 1.5 mEq K/kg per day. 2 divided doses (tablets) and 3 divided doses (liquid)	Tablet: 5 mEq K, 10 mEq K. Solution: 2 mEq K/ml	Hypocitraturia, hypercalciuria, hyperuricosuria, cystinuria
Hydrochlorothiazide	1-2 mg/kg/day in (HCTZ)	Tablet: 12.5 mg, 25 mg. 1-2 divided doses	Hypercalciuria, hyperoxaluria
Allopurinol	10 mg/kg per day. Single or 2–3 divided doses	Tablet: 100 mg, 300 mg.	Hyperuricosuria
Pyridoxine (vitamin B6)	25–200 mg/day, once daily (titrated to effect with urine oxalate levels)	Tablet: 40 mg, 100 mg	Primary hyperoxaluria
Captopril	0.5-1.5 mg/kg per dose, 2-4 times per day	Tablet: 12.5 mg, 25 mg.	Cystinuria
Tiopronin	15 mg/kg/day, 3 divided doses	Tablet: 100 mg	Cystinuria
D-Penicillamine	30 mg/kg/day, 4 divided doses	Capsule: 150 mg, 250 mg	Cystinuria

Table IV. Surgical treatment modalities for pediatric urolithiasis

Treatment	Indication	Stone-free rate %	Limitations	Complications
Extracorporeal shock wave lithotripsy	Smaller stones in ureter and kidney	80-83	Lacks direct visualization of stone, high retreatment rate	Steinstrasse [#] , perirenal hematoma
Ureteroscopy	Smaller stones in ureter and kidney	85-88	Adult-sized instruments, surgical expertise needed	Infection, ureteral obstruction, ureteral stricture
Percutaneous nephrolithotomy	Larger stones, abnormal anatomy	70-97	Adult-sized instruments, surgical expertise needed, higher complication rate	Bleeding (8%-16% require blood transfusion), urine leak, urinary obstruction, sepsis
Open pyelolithotomy	Larger stones	79-98	Invasive, long postoperative convalescence	As for any open surgery
Minimally invasive pyelolithotomy	Larger stones	No data	Surgical expertise needed, learning curve	As for any minimally invasive surgery

#Steinstrasse (German word for “stone street”) is a collection of stone fragments that become obstructed within the ureter following lithotripsy.

of lower incidence of side effects. Captopril, which is a sulfhydryl agent, has been used with mixed results in cystinuria.²¹

v) Uric acid stones: The formation of uric acid stones is due to either high rates of urinary urate excretion or persistently low urine pH, or a combination of the two. The first line of treatment is urine alkalinization, optimally by potassium citrate. In case there is a need to lower urate excretion, dietary purine restriction is indicated and if needed allopurinol can be added.

vi) Infection related urolithiasis: Struvite stones can develop very rapidly and, at times, form a cast in the pelvicaliceal system, known as “staghorn calculus”. One of the essential management strategies in infection-related stone is to sterilize the urinary tract. Alkaline urine promotes formation of these stones hence needs to be avoided. Prevention of recurrence of such stones requires correction of the underlying anatomic abnormality and protection from infection.²¹

D. Surgical management

Surgical options for children with kidney stones, including indications and complications, are summarized in Table IV.¹⁶

Conclusion

It is important for every primary care pediatrician to know the fact that renal stone disease occurs in children. If not properly investigated and treated it can lead on to chronic kidney disease and its attendant complications. Managing these children with help from pediatric nephrologists in a proper way would not only reduce the morbidity but also mortality due to renal stone disease.

Points to Remember

- *Metabolic cause is the commonest etiology of nephrolithiasis in children, predominantly hypercalciuric calculi.*
- *Clinical presentation varies depending on the age of patient.*
- *Ultrasound should be considered as the initial diagnostic modality of choice and metabolic workup with blood and urine is mandatory.*
- *Adequate water intake, proper dietary advice along with drug therapy will decrease the rate of stone formation in children prone for nephrolithiasis.*

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NEPHRO-UROLOGY

CONUNDRUM OF VESICoureTERIC REFLUX, SCARRING/HYPODYSPLASIA AND ANTIBACTERIAL PROPHYLAXIS FOR URINARY TRACT INFECTION

***Pankaj Hari**

Abstract: *Primary vesicoureteric reflux (VUR) has been regarded as an important risk factor for urinary tract infection (UTI) and end stage renal disease. Almost one-third of children diagnosed to have VUR following UTI have renal scarring. It is debated whether scarring in VUR is entirely due to UTI or maldevelopment of kidney called "hypodysplasia". As opposed to previous assumption, the risk of end stage renal failure and hypertension is fairly small with post UTI scarring. The efficacy of antibiotic prophylaxis has been variable for prevention of UTI in children with VUR. Meta-analysis suggests that it might be of some benefit in preventing UTI but not renal scarring but also reveals a definite increase in bacterial resistance with antibiotic prophylaxis. Because of questionable efficacy and potential risk, use of antibacterial prophylaxis should be based on risk-stratification rather than mere presence of reflux.*

Keywords: *Vesicoureteric reflux, Prevention, Antimicrobial resistance.*

Vesicoureteric reflux (VUR) is the retrograde passage of urine into the upper urinary tract during detrusor contraction at micturition. In the absence of lower urinary tract outlet obstruction and neurogenic bladder, it is considered to be "primary". Primary VUR has been regarded as an important risk factor for urinary tract infections and post infection scarring. About 7-17% of ESRD has been reported to be associated with primary VUR.¹⁻³

The precise prevalence of primary VUR is debated. While traditionally its prevalence was assumed to be around 1%⁴, studies suggest that it would range from 10-40%.^{5,6}

VUR is most often diagnosed on evaluation following one or multiple urinary tract infections. About one-third of children when evaluated for UTI have VUR⁵, whereas 16% of antenatally diagnosed hydronephrosis is due to VUR.⁷ In addition it may be diagnosed in children evaluated for chronic kidney disease, hypertension, renal stones and rarely for proteinuria. A meta-analysis of studies that screened for VUR showed a prevalence of 27% in siblings and 34% in offspring.⁷ There is a strong association of bladder bowel dysfunction and VUR and UTI.⁸ VUR has a high chance of spontaneous resolution. A population-based prospective long-term follow-up study showed that the median time to resolution was 38 months for low grade and 156 months for grade (IV-V) reflux.⁹

VUR has been shown to be associated with renal scarring referred to as reflux nephropathy. Traditionally, this scarring was attributed to UTI. Treatment strategies for VUR include surgical reimplantation of ureters or endoscopic injection at the ureterovesical junction or medical treatment consisting of low dose antibacterial prophylaxis with the aim of preventing UTI and the consequent scarring. However, it is debated whether scarring in VUR is entirely due to UTI or maldevelopment of kidney called hypodysplasia. This review will focus on the contribution of UTI in scarring in primary VUR and the efficacy of antibacterial prophylaxis in its prevention.

Renal scarring

Children with higher grades of VUR are associated with more renal damage at diagnosis than those with Grade I or II VUR.^{3,8,10,11} This renal scarring has been referred to as reflux nephropathy and is histologically characterized by chronic tubulointerstitial inflammation and fibrosis. Renal scarring has been demonstrated in older studies by using intravenous pyelography, while the recent studies have used dimercaptosuccinic acid (DMSA) scan. The latter is more sensitive than intravenous pyelography, however it can also detect uptake defects which are due to pyelonephritic inflammation and not true parenchymal loss; the former is transient and can be differentiated reliably from permanent scar on follow-up scans.

Almost 30-40% of children diagnosed to have VUR following UTI have renal scarring.⁵ The rate of baseline

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Table I. Renal scarring in primary VUR

	Congenital hypodysplasia	Post infection scar
Cause	Developmental anomaly	Infection
Gender preponderance	Boys	Girls
Extent	Global	Focal
Grade of VUR	High	Low
Prevalence of bladder bowel dysfunction	Low	High
Risk of hypertension, ESRD	High	Low
Preventable	No	Yes

scarring in patients with VUR has been variable. Since most patients of VUR are diagnosed following one or more episodes of UTI, it was assumed that scarring in these patients was due to infection. However patients have been diagnosed with renal scarring in the absence of history of UTI.¹² The mechanism of this form of renal scarring is unclear and it has been suggested to be of congenital origin (hypodysplasia). Most researchers now agree that two different kinds of parenchymal defects - congenital hypodysplasia and post infectious scar are associated with vesicoureteric reflux (Table I).

Congenital hypodysplasia

There is evidence that primary VUR can be associated with renal parenchymal damage in the absence of urinary tract infection. Overall 22% of neonates found to have primary VUR when evaluated for antenatal hydronephrosis had parenchymal damage in the absence of any evidence of urinary tract infection.⁷ Similarly as much as 14% of asymptomatic siblings of children with VUR who on screening were found to have VUR had renal scarring.

Some of the investigators claim that much of the scarring associated with VUR leading to end stage renal failure is congenital hypodysplasia⁶ while scars formed following UTI are generally small and innocuous (Table I). Majority of congenital hypodysplasia associated with VUR is seen as large areas of parenchymal damage or small poorly functioning kidneys on DMSA scan. Such damage is seen predominantly in boys with high-grade reflux.¹¹

It is postulated that congenital dysplasia associated with VUR may be a result of developmental anomaly that leads to abnormal formation of ureterovesical junction and the kidney such that there is histological evidence of focal

or diffuse dysplasia. Abnormal ureteric budding is proposed to be a key factor in the pathogenesis of VUR. Since the interaction of ureteric bud with the metanephric blastema is important in nephrogenesis, variations in genes associated with ureteric budding pathway have shown to be associated with renal dysplasia.¹³ This suggests that the association between primary VUR and dysplastic kidney could be of genetic origin and leads to a debate about sterile reflux causing renal scarring. Old studies in minipig model of surgically induced VUR have reported that sterile reflux alone was sufficient to cause scarring.^{14,15} However, a recent study in mice model with naturally occurring VUR showed that renal scarring does not develop with sterile reflux in the absence of infection.¹⁶ However, severe renal damage could be progressive even after the reflux has resolved and is possibly due to autologous tubular antigens, hyperfiltration of intact nephrons, reaction to Tamm-Horsfall protein and superoxide production.

Post infection scarring

VUR promotes the ascent of bacteria from the bladder into the renal pelvis resulting in pyelonephritis. Pyelitis refers to the inflammation induced by neutrophil influx in the submucosa of the pelvis and collecting system while nephritis refers to extensive renal parenchymal inflammation including tubules and interstitium. Reactive oxygen metabolites released by neutrophils in response to the bacterial infection have been shown to induce renal scarring or fibrosis in animal models.¹⁷ Animal studies using mice models with naturally occurring reflux have shown that sustained infection with uropathogenic *E. coli* is required to induce scar formation in VUR.¹⁶ Post infection scarring has been commonly reported in girls, in contrast to congenital dysplasia that occurs more often in boys (Table I).¹⁸

Most randomized trials have shown that the risk of new scar formation in children with VUR who are not treated with antibiotic prophylaxis, followed up in controlled environment, has been fairly low ranging from 2% to 8%^{8,10,11,18,19} except in the Swedish trial where it was found to be 32%.¹⁹

The long-term consequences of post infection scarring are difficult to assess due to lack of well-designed studies. The risk of end stage renal failure following urinary tract infection is estimated to be quite low at 1 per 10000 cases.²⁰ A prospective follow-up of Gothenburg cohort using ambulatory blood pressure monitoring found no difference between occurrence of hypertension in children with or without renal scarring.²⁰ The risk of pregnancy related complications in women with renal scarring was reported to be high in one study and similar to women without scarring in another. Thus, as opposed to previous assumption, it appears that post infection scarring leads to fewer complications in children and adults.

Antibacterial prophylaxis in VUR

A Cochrane review concluded that there was no difference in the incidence of UTI and renal scarring in children treated with either surgery or long-term antibiotic prophylaxis.²¹ Being non-invasive the latter became the corner stone of therapy for VUR. A decade ago, Williams

et al., in a systematic review found that the evidence to support long-term antibiotic prophylaxis for prevention of UTI was weak.²²

Antibacterial prophylaxis and recurrent UTI

In the last decade, several randomized controlled trials have compared antibiotic prophylaxis with no treatment or placebo for prevention of UTI in children with and without VUR.^{10, 18, 22, 23-26} Initial studies involving children with absent or lesser grades of VUR demonstrated no difference in rates of recurrent UTI in the treatment versus no treatment groups.^{19,25} Garin et a.,¹ found that as compared to untreated children the risk of pyelonephritis was higher in those treated with antibiotic prophylaxis.¹⁹ Though statistically insignificant, Pennesi et al also found a trend favoring more UTI in children on antibiotic prophylaxis.²⁵ The Swedish Reflux Study reported on 203 children aged 1 to 2 years with grade III-IV dilating VUR, who were randomized to antibiotic prophylaxis, surgical correction or observation.¹⁸ A reduced rate of recurrent UTI was found in girls in the treatment groups compared with observation. No treatment benefit was observed in boys. However, these trials were not placebo-controlled and did not report adherence to treatment. Thus these studies are considered to have high risk of bias and their results circumspect.

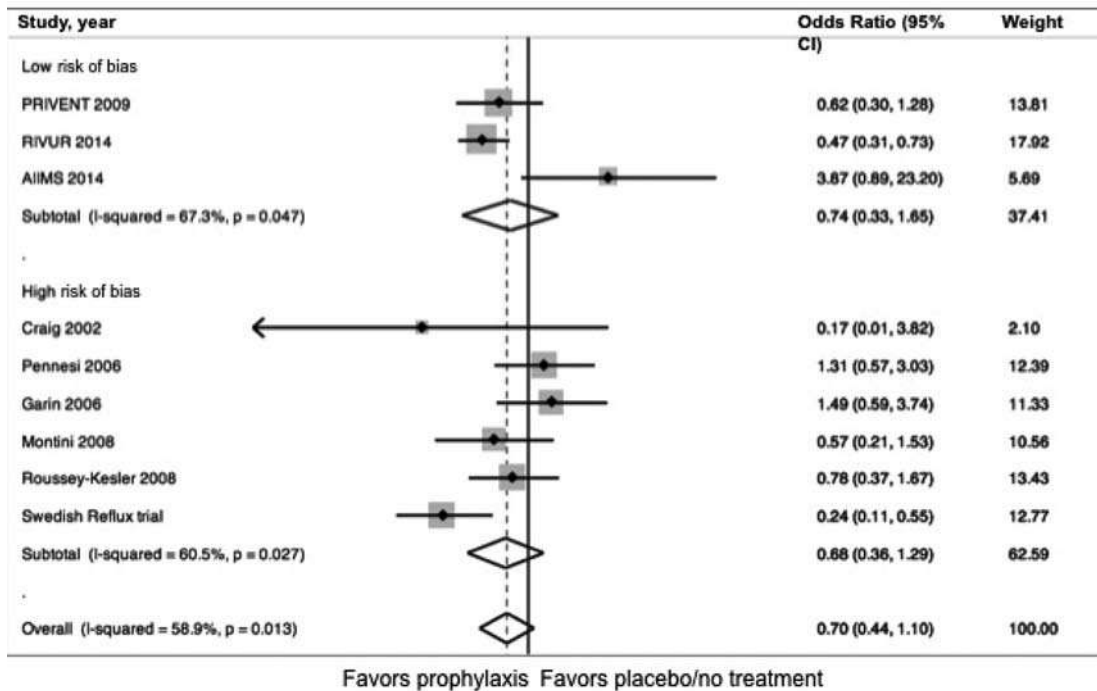


Fig. 1. Meta-analysis of symptomatic UTI in children with VUR treated with prophylaxis

(Note that after excluding the trials with high risk of bias there was no difference between antibiotic prophylaxis and placebo)

There are three well designed, randomized, placebo-controlled trials published till date that are considered to have low risk of bias. The first study (PRIVENT trial)¹⁰ involving 576 children with absent or any grade of reflux demonstrated a marginal benefit of 6% with antibiotic prophylaxis. The largest study (RIVUR trial) showed that antibiotic prophylaxis reduced recurrences of UTI by 50%.⁸ Prophylaxis was more effective in children with febrile UTI and in those with bladder-bowel dysfunction (BBD). Results of subgroup analysis of RIVUR trial with reasonable number of subjects and event rates showed that effect of prophylaxis was not significant in grade III-IV VUR and in absence of BBD. Thus it seems that prophylaxis was beneficial to a distinct patient-population comprising of girls with low-grade reflux and BBD. The only trial on VUR from Asia has been from India, which interestingly showed a higher risk of symptomatic UTI in children with VUR treated with trimethoprim-sulfamethoxazole as compared to placebo.¹¹ This was possibly due to eradication of the protective periurethral flora leading to colonisation and later infection with drug resistant bacteria in the antibiotic treated patients.

Meta-analysis including all the randomized controlled trials published till date shows that there might be a marginal benefit of antibiotic prophylaxis in preventing symptomatic UTI (Fig.1). However, when studies with high risk of bias are excluded from the analysis there is no difference between antibiotic prophylaxis and placebo (Fig.1).

Antibacterial prophylaxis and post infection renal scarring

The risk of post infection scarring in most controlled trials has been below 10%. Most studies including the RIVUR trial and the Indian study except the Swedish study failed to show a significant difference in the occurrence of new or progression of existing renal damage.^{8,10,11,18,19,24,25} However, all trials till date were primarily designed to examine the recurrences of UTI rather than renal scarring. Since the rate of acquired renal scarring is considerably small it is practically impossible to conduct a trial aiming to study renal scarring as an outcome as the required number of subjects to be studied will be in thousands.

Why is efficacy of antimicrobial prophylaxis inconsistent?

Published cohorts of children with VUR on antibiotic prophylaxis differ in baseline characteristics and methodology. The differences in efficacy of antimicrobial

prophylaxis might be due to differences in the phenotypes of VUR studied such as gender, severity of VUR, scarring and presence of bladder bowel dysfunction. There are gender differences in VUR according to the geographical regions. More than 90% of patients in studies from US have been girls⁸, while proportions of girls ranged from 52% to 65% in studies from Europe²³ and Australia.¹⁰ In contrast, boys make most of VUR diagnosed in India (67%)³ and Japan (83%).²⁶

Most patients in the US study had grade I-III reflux and scarring was present in less than 5%.⁸ While patients in Indian study were mostly boys with severe renal scarring, other studies have also had 35-40% boys and 40-57% scarring at baseline.^{8,10,11,18,19,24,25} A majority of renal scarring in severe grades of reflux as seen in Indian study would represent renal dysplasia. This study suggested that antibiotic prophylaxis is not useful in cohorts comprising of predominantly boys with high grade VUR and baseline renal scarring. This is somewhat similar to findings of Swedish trial where boys with III-IV VUR and baseline scarring did not benefit from antibiotic prophylaxis as opposed to girls.¹⁸

Increasingly, VUR is increasingly recognized as a heterogeneous condition with regional and genetic differences.⁶ Differences in demographic and clinical characteristics could explain variability in the effectiveness of antibiotic prophylaxis in various studies. This could be due to genetic heterogeneity of the populations and would also explain the differences in the responses to the medical treatment. Thus combining data of different phenotypes of VUR in meta-analyses to derive treatment recommendations is incorrect.²⁷

How safe is antibacterial prophylaxis

While antimicrobial prophylaxis may prevent UTI in children with VUR, this benefit may be mitigated by rise in microbial resistance. All studies that have described antimicrobial resistance to the prophylactic drug in subsequent symptomatic UTI in the randomized controlled trials of antimicrobial prophylaxis in VUR showed that the incidence ranged from 16 to 36%.^{8,10,18,23,24} Overall estimated risk of prophylactic drug resistance in the repeat UTI was three fold higher with use of antibiotic prophylaxis.²⁸ This increase in multidrug resistant UTI is problematic as antibiotic choice of these infections is challenging. Resistant infections are twice as likely to be associated with greater morbidity and mortality and are also associated with increased healthcare costs.²⁹

Recommendations for antibacterial prophylaxis

Although generally safe and well tolerated, antibiotic prophylaxis besides costs can potentially increase the risk of antibiotic resistant infections in children receiving them. Further, its benefit in reducing renal scarring has not been demonstrated. Therefore while prophylaxis might reduce morbidity related to UTI, this would be at the cost of increased antimicrobial resistance and it will not reduce renal scarring and its consequences (hypertension and renal failure). Because of questionable efficacy and potential risk, a prudent way forward will be that the use of prophylaxis be based on risk-stratification rather than mere presence of reflux.³⁰

Conclusion

Renal damage in primary VUR is either due to renal hypodysplasia or post UTI scarring. While the former is generally severe and associated with hypertension and ESRD, these risks are fairly low with the latter. While evidence suggests that antibacterial prophylaxis might reduce morbidity by preventing UTI at the cost of increased antimicrobial resistance, it will not reduce renal scarring and therefore its consequences (hypertension and renal failure).

Points to Remember

- *Almost 30-40% of children diagnosed to have VUR following UTI have renal scarring.*
- *Renal scarring associated with vesicoureteric reflux is of two types: Congenital hypodysplasia and post infectious scar.*
- *Risk of hypertension and end stage renal disease following post infectious scar is low.*
- *Controlled trials have shown that antibacterial prophylaxis might be of some benefit in preventing UTI but not renal scarring and is associated with an increase in bacterial resistance.*

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CLIPPINGS

Fruit Juice in Infants, Children and Adolescents: Current Recommendations.

This article highlights the odds of fruit juice intake among infants and children. Unless clinically indicated they do not recommend introduction of juice in the diet of infants before 12 months. They recommend 4 ounces/day in toddlers 1 through 3 years of age, and 4 to 6 ounces/day for children 4 through 6 years of age. For children 7 to 18 years of age, juice intake should be limited to 8 ounces or 1 cup of the recommended 2 to 2.5 cups of fruit servings. Children should be encouraged to eat whole fruit to meet their recommended daily fruit intake. Toddlers should not be offered juices at bed time. Consumption of unpasteurized juice products should be strongly discouraged in infants, children, and adolescents. Grapefruit juice should be avoided in any child taking medication that is metabolized by CYP3A4. Pediatricians should advocate for a reduction in fruit juice in the diets of young children and the elimination of fruit juice in children with abnormal (poor or excessive) weight gain. Pediatricians should support policies to seek reduce the consumption of fruit juice and promote the consumption of whole fruit by toddlers and young children.

Melvin B. Heyman, Steven A Abrams. Policy Statement, Fruit Juice in Infants, Children, and Adolescents: Current Recommendations. From the American Academy of Pediatrics. Pediatrics, 2017; 139 (6): e20170967; DOI: 10.1542/peds.2017-0967.

NEPHRO-UROLOGY

PATHOGENESIS AND THERAPY OF NEPHROTIC SYNDROME

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Abstract: *Nephrotic syndrome is an important chronic disease of childhood, with a steroid sensitive course in most patients. Research on pathogenesis has emphasized the importance of T lymphocyte dysregulation and vascular permeability factors that alter podocyte function and glomerular permselectivity. Mutations in genes that encode important podocyte proteins and therapeutic targets within podocytes have been identified. A hypothesis unifying available evidence on pathogenesis is yet to be proposed. An important proportion of patients have difficult disease course, characterized by frequent relapses, steroid dependence or steroid resistance, requiring therapy with alternative immunosuppressive agents. Clinical studies support the use of levamisole, cyclophosphamide, mycophenolate mofetil, calcineurin inhibitors and rituximab in patients with frequent relapses or steroid dependence. The management of steroid-resistant nephrotic syndrome is difficult and patients failing to achieve remission show progressive renal damage. Prospective studies in patients with frequent relapses and steroid resistance are the basis of current guidelines while ongoing studies will help to identify and formulate effective and safe therapies.*

Keywords: *Calcineurin inhibitors, Focal segmental glomerulosclerosis, Minimal change disease, Podocyte, Rituximab.*

Nephrotic syndrome is characterized by massive proteinuria, hypoalbuminemia (albumin <2.5 g/dL), hyperlipidemia and edema.¹ Data from single, multicenter or nationwide studies show that the incidence of nephrotic

syndrome varies from 2-7 and prevalence 14-16 per 100000 children.² More than 90% cases are primary (idiopathic) and a secondary cause (e.g., amyloidosis, lupus, Henoch Schonlein purpura) is rare. Most (~80%) children with idiopathic nephrotic syndrome show remission following therapy with oral corticosteroids.³ The prognosis in these cases are favorable, in contrast to patients who do not respond to such treatment, termed 'steroid resistant'. In this article, we summarize the current knowledge on the pathogenesis and management of steroid sensitive and steroid resistant nephrotic syndrome.

Pathology

Histological studies by the International Society for Kidney Disease in Children (ISKDC) show that almost three-quarter patients have insignificant glomerular changes on light microscopy (minimal change disease). While immunofluorescence examination is usually normal, ultrastructure reveals effacement of podocytes with disruption and disorganization of actin filaments. About 40-70% patients with steroid resistant and 5-10% cases with sensitive nephrotic syndrome have focal segmental glomerulosclerosis (FSGS), with sclerosis involving a segment of the glomerular tuft. FSGS is classified, into five morphologic variants, based on location of sclerosis: tip lesions, cellular variant, perihilar lesions, collapsing FSGS and FSGS not otherwise specified.⁴ There is evidence that renal outcomes are adverse and favorable in patients with collapsing and tip FSGS, respectively.^{5,6} Collapsing glomerulopathy, characterized by segmental and/or global collapse of glomerular capillary tufts and podocyte hypertrophy is associated with HIV, heroin intake and parvovirus infection.⁷ About 10-15% of patients with steroid resistance show features of membranoproliferative glomerulonephritis, membranous nephropathy or IgA nephropathy. Certain syndromic forms of nephrotic syndrome are associated with diffuse mesangial sclerosis, in which progressive mesangial sclerosis causes the glomerular tuft to contract into a dense mass.

Pathogenesis

The glomerular filtration barrier consists of capillary endothelial fenestrations, glomerular basement membrane (GBM) and interdigitating podocyte foot processes.

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Most studies show that the podocytes are critical in maintaining the selective filtering function.

Genetics: Use of high-throughput next-generation sequencing shows defects in genes encoding the slit diaphragm or cytoskeletal proteins of podocytes in 80-100% cases with congenital nephrotic syndrome (onset <3 months age), and 50-60% of infantile-onset, 65-70% of familial and 25% of sporadic steroid resistant disease.⁸⁻¹⁰ Mutations in many genes are recognized, including those encoding structural elements of the slit diaphragm or the podocyte cytoskeleton (NPHS1, NPHS2, CD2AP, TRCP6 and ACTN4), proteins deposited in the GBM (LAMB2), mitochondrial genes (COQ2), or transcription factors (WT1, LMX1B), with wide spectrum of illness.²

Homozygous or compound heterozygous mutations in NPHS1 and NPHS2 are the chief causes of early onset nephrotic syndrome.⁸ Other genes implicated in childhood are: Wilms' tumor 1 (WT1), laminin β 2 (LAMB2), phospholipase C ϵ (PLCE1), myosin (MYO1E)¹¹, cubilin (CUBN)¹² and rhoGDI α (ARHGDI A).¹³ Heterozygous mutations in α -actinin 4 (ACTN4), transient receptor potential cation channel subfamily C member 6 (TRCP6) and inverted formin 2 (INF2) present with later onset FSGS; INF2 mutations are seen in patients with concomitant Charcot Marie Tooth disease.¹⁴ The risk of developing FSGS with high-risk haplotypes in MYH9 or APOL1 genes needs to be ascertained across ethnicities.^{15,16} Although most patients with inherited forms of steroid resistance do not respond to immunosuppressive agents, partial response to calcineurin inhibitors is reported.^{17,18} While disease due to genetic defects does not recur in the allograft, exceptions may occur.¹⁹

Immune dysfunction: There is evidence of immune dysfunction in patients with steroid sensitive disease. Altered cell mediated immunity and T helper type 2 (Th2) polarization is proposed to release an uncharacterized circulating factor that increases glomerular permeability. Evidence favoring Th2 bias includes association with atopy, high plasma IgE, decreased induction of Th1 specific transcription factor T-bet and induction of c-Maf, a Th2 specific transcription factor.²⁰ Recent studies suggest that the steroid sensitive illness is associated with an imbalance between T helper 17 cells, upregulated in many autoimmune disorders and regulatory T (Treg) cells.²¹⁻²³ Deficiency or dysfunction of Treg cells^{24,25} may allow activation of effector T cells to secrete factors that mediate glomerular permeability²⁵ or increase oxidant production.²⁶ Conversely, stimulation of Treg cells, shown to cause remission in experimental models of nephrotic syndrome,²⁷ follows measles²⁸ as well as B cell depletion with

rituximab,^{26,29} both of which induce prolonged remission in patients with minimal change disease.

The rapidity with which relapses follow infections indicates involvement of the innate immunity. It is proposed that pathogen triggered activation of toll like receptors induces nuclear factor kappa β (NF- κ B) signalling or alters its regulatory feedback leading to activation of innate immune responses and/or polarization towards the Th2 phenotype. The beneficial influence of saquinavir, a protease inhibitor that blocks NF- κ B activation, supports this hypothesis.³⁰

CD80 is normally expressed on antigen presenting cells and engages either CD28 on effector T cells or cytotoxic T-lymphocyte-associated (CTLA)-4 on Treg cells.³¹ In vitro models of nephrotic range proteinuria show increased podocyte expression of CD80.³¹ A 'two-hit' hypothesis proposes that podocyte CD80 expression, by a virus or cytokine, remains upregulated due to inadequate censoring by Treg cells or podocytes.^{32,33} Studies report increased urinary CD80 in patients with minimal change disease and not FSGS.³⁴⁻³⁶ Finally, increased podocyte CD80 expression and proteinuria in patients with recurrent FSGS or minimal change disease were attenuated by the CTLA-4 agonists, abatacept and belatacept.^{37,38}

Circulating factors: The soluble mediator hypothesis, supported by recurrence of nephrotic range proteinuria immediately post-transplant in 20% - 40% of patients with idiopathic FSGS,³⁹ induction of proteinuria and podocyte foot process effacement in rats, or increase in vascular permeability in guinea pigs⁴⁰ by supernatants from T-cells of patients with nephrotic syndrome, is an accepted paradigm for disease pathogenesis. Proposed circulating factors include interleukin (IL)-13,⁴¹ cardiotrophin like cytokine-1,⁴⁰ tumor necrosis factor α ,⁴² hemopexin⁴⁰ and c-mip (c-Maf inducing protein).⁴³

The debate on the identity of the elusive circulating factor was stimulated by findings of Wei et al, who described high levels of soluble urokinase plasminogen activating receptor (suPAR) in Caucasians with primary and recurrent FSGS, and showed that membrane bound suPAR activated podocyte β 3 integrin signaling, foot process effacement and histology resembling FSGS.⁴⁴ Further studies showed that serum levels of suPAR were elevated in two well characterized cohorts of children and adults with primary FSGS,⁴⁵ distinguished FSGS from minimal change disease,⁴⁴ primary from secondary FSGS,⁴⁶ recurrent from non-recurrent disease,⁴⁴ and declined with mycophenolate mofetil⁴⁷ and plasmapheresis.⁴⁸ Recent studies contest these findings⁴⁹⁻⁵¹ and suggest that blood

levels relate more closely to reduced glomerular filtration and systemic inflammation than to renal histology.^{49,52}

Recent studies link a hyposialylated form of podocyte glycoprotein angiopoietin-like 4 (ANGPTL4) to proteinuria in experimental models⁵³ and soluble ANGPTL4 to proteinuria and hypertriglyceridemia.⁵⁴ Modification of ANGPTL4 at alipoprotein lipase interacting site⁵⁵ and administering oral N-acetyl-D-mannosamine, a precursor of sialic acid,⁵⁶ reduced proteinuria without inducing hypertriglyceridemia, suggesting that sialylation of ANGPTL4 is a potential antiproteinuric intervention. Serum and urinary levels of microRNAs (miRNAs), short noncoding RNA molecules that regulate gene expression, are altered in nephrotic syndrome and relate to underlying histology or degree of tubulointerstitial injury.⁵⁷ Blood levels of mir-186,⁵⁸ miR-192 and miR-205 might differentiate FSGS from minimal change disease.⁵⁹

Podocytes are recognized as a target for antiproteinuric interventions.⁶⁰ Incubation of podocytes with steroids enhances nephrin transport, reduces actin disruption and increases polymerization, prevents upregulation of miRNA-30 and enhances their recovery.^{61,62} Calcineurin inhibitors stabilize podocytes by stabilizing the expression, distribution or phosphorylation of nephrin, synaptopodin, cofilin-1 and TRPC6.⁶³ Rituximab is proposed to bind to podocyte sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b), preventing disruption of actin cytoskeleton and podocyte apoptosis by plasma from patients with FSGS.⁶⁴

Evaluation

Majority of patients with idiopathic nephrotic syndrome have steroid sensitive illness. The course varies with 35% - 40% having a single episode or 1-2 relapses and 55% - 60% showing multiple relapses that occur infrequently or frequently. Nephrotic range proteinuria is presence of 3-4+ protein by dipstick on first morning urine sample for 3 consecutive days, spot protein/creatinine ratio >2mg/g, or protein excretion >40 mg/m²/hr. Investigations at the onset include: (i) urinalysis, (ii) blood levels of urea, creatinine, albumin, cholesterol and (iii) complete blood counts. Additional investigations, apart from a tuberculin test and chest X-ray, are rarely required. Most patients do not require a kidney biopsy. A biopsy is required at onset if a cause other than minimal change disease is suspected, such as: (i) age at onset <1 yr or >16 year, (ii) gross or persistent microscopic hematuria, or low C3; (iii) renal failure not attributable to hypovolemia; (iv) suspected secondary cause; and (v) sustained severe hypertension. A renal biopsy is considered later (i) for steroid resistance,

(ii) if therapy with calcineurin inhibitors is planned. The specimen is examined by light, immunofluorescence and electron microscopy.

The diagnosis of steroid resistance is based on demonstration of non-response (3-4+ proteinuria, edema or hypoalbuminemia) despite therapy with prednisolone in adequate doses for 4-8 weeks.⁶⁵⁻⁶⁷ Recent recommendations suggest awaiting remission for 6-8 weeks while tapering corticosteroids; the use of pulse steroids to confirm resistance is not recommended.⁶⁶ Patients with steroid resistant nephrotic syndrome require: (i) 24 hour quantitation of proteinuria, (ii) estimation of glomerular filtration rate and (iii) renal biopsy. Those with the collapsing variant of FSGS are screened for anti-HIV and anti-parvovirus B19 IgM antibodies. Testing for inherited mutations is not currently recommended due to variable availability and high cost of testing, low prevalence of defects and unclear association with response to therapy.^{8,66} Screening for genetic mutations is recommended for patients with family history of similar renal disease, those presenting within the first 3-6 months of life and those not responding to therapy with steroids and calcineurin inhibitors.

Management - Steroid sensitive nephrotic syndrome (SSNS)

International collaborative efforts by the ISKDC⁶⁸ and Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN)⁶⁹ have helped to refine the treatment of nephrotic syndrome. Randomized controlled trials (RCT) using corticosteroids and non-corticosteroid medications,^{70,71} form the basis for recommendations by the Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group^{72,73} and the Indian Society of Pediatric Nephrology⁷⁴ (Table I). A number of RCTs have recently been published on therapy of nephrotic syndrome.⁷⁵⁻⁸⁴ Corticosteroids should be dosed by surface area rather than by weight, since underdosing by the latter might result in delayed response or risk of subsequent relapses⁸⁵

Initial episode: Although the ISKDC proposed that initial prednisolone therapy comprise of 4-weeks daily and 4-weeks intermittent therapy,⁶⁸ refinements were proposed over the last four decades. Ever since an APN supported RCT showed reduced relapse rates on prolonging initial therapy from 8 to 12-weeks,⁶⁹ experts have suggested that extending therapy to 24-weeks was even better. Results from a meta-analysis showed that, compared to 3-months, therapy, 6-months therapy led to reduced risk of frequent relapses (relative risk, RR 0.55; 95% confidence interval, CI 0.39,0.80) and reduced number of annual relapses (mean difference -0.44; 95% CI -0.82,-0.07).⁷⁰

Table I. Guidelines for management of steroid sensitive nephrotic syndrome

	Indian Society of Pediatric Nephrology (ISPN) 2008⁷⁵	Kidney Disease: Improving Global outcomes (KDIGO)2012⁶⁷
Initial episode	Prednisolone Daily: 2 mg/kg (max. 60 mg) for 6 wk Alternate days (AD): 1.5 mg/kg (max. 40 mg) for 6 weeks; discontinued without taper	Prednisolone Daily: 60 mg/m ² for 4-6 week AD: 40 mg/m ² for 2-5 months, tapered Total duration: ≥12 weeks
Relapse; infrequent relapses	Prednisolone Daily: 2 mg/kg until remission [#] ; then AD: 1.5 mg/kg for 4 week; discontinued	Prednisolone Daily: 60 mg/m ² till remission [#] AD: 40 mg/m ² for ≥4 week
Frequent relapses, steroid dependence	Long term prednisolone: Treat relapse as above, then administer therapy on AD at a dose of 0.5-0.7 mg/kg for 9-18 months Corticosteroid sparing agents: Prednisolone threshold >0.5-0.7 mg/kg or if steroid toxicity Levamisole: 2-2.5 mg/kg AD for 1-2 year Cyclophosphamide ^{\$1} : 2 mg/kg/d for 12 week Chlorambucil: Not recommended Calcineurin inhibitors ^{\$2} : Cyclosporine 4-5 mg/kg, tacrolimus 0.1-0.2 mg/kg daily x 1-2 year; levels if non-compliance, toxicity, unsatisfactory response Mycophenolatemofetil: 800-1200 mg/m ² daily for 1-2 year Mizoribine: Not mentioned Azathioprine: Not mentioned Rituximab: Not mentioned	Long term prednisolone: AD for ≥3 months in lowest dose Administer dose daily during respiratory tract & other infections Administer daily, in lowest dose to maintain remission without major adverse effects, if AD therapy is ineffective Corticosteroid sparing agents: Use if steroid toxicity Levamisole: 2.5 mg/kg AD for ≥1 year Alkylating agents: For frequent relapses; may use in steroid dependence; avoid second course; initiate therapy in remission Calcineurin inhibitors: Cyclosporine or tacrolimus for ≥1 year; latter preferred if unacceptable cosmetic side effects with cyclosporine; monitor levels during therapy Mycophenolate mofetil: 1200 mg/m ² daily for ≥1 yr Mizoribine: Suggest that not be used Azathioprine: Recommend that not be used Rituximab: If failing other agents, serious adverse effects

[#]Urine protein trace or nil or urine protein to creatinine ratio <200 mg/g (<20 mg/mmol) for 3 consecutive days

^{\$}Prefer in ¹patients with significant steroid toxicity, severe relapses with hypovolemia or thrombosis, poor compliance or difficult follow up; ²patients who continue to show steroid dependence or frequent relapses despite treatment with agents listed previously

(Adapted from: Sinha A, Menon S, Bagga A. Nephrotic syndrome: State of the art. *Curr Pediatr Rep* DOI 10.1007/s40124-014-0066-4)

Three recently published, well designed RCTs contest this view (Table II).⁷⁵⁻⁷⁷ Results from these studies that enrolled almost 600 patients emphasize that prolongation of initial therapy to 6-months is not useful in modifying the course of the disease, or reducing subsequent need for corticosteroids and other agents. One study showed that the benefit of extended initial therapy was limited to the

period while steroids were being administered.⁷⁵ Since the intent of intensive initial therapy is to alter the disease course rather than delay the time to first relapse, lower rates of relapses during steroid tapering do not appear to be a valid outcome. Given the current data and risk of adverse effects due to steroid intake, prolongation of initial therapy beyond 12-weeks⁶⁹ is perhaps not required. Results

Table II. Important recently published randomized controlled trials in nephrotic syndrome

Author, year (ref)	Type; N	Comparison groups	Follow up	Results (Comparisons of group 1 with 2)
First episode of steroid sensitive nephrotic syndrome				
Sinha, 2014 ⁷⁶	Placebo controlled; 181	Prednisolone: 3 vs. 6 months	12 months	Similar frequency of relapses (mean difference 0.28; 95% CI 0.75, 0.19) and proportions in sustained remission (37.5% vs. 46.7%; P=0.21) or frequent relapses (39.8% vs. 38%; P=0.81); similar HR for first relapse and for frequent relapses
Yoshikawa, 2014 ⁷⁷	Open label; 255	Prednisolone: 2 vs. 6 months	24 months	Similar time to frequent relapses (HR 0.86; 90% CI 0.64, 1.16) and first relapse (HR 0.97; 95% CI 0.72, 1.31); similar frequency of relapses and adverse events; lower cumulative prednisolone dose over 2-yr for 2- vs. 6-months (P<0.0001)
Teeninga, 2013 ⁷⁸	Placebo controlled; 150	Prednisolone: 3 vs. 6 months; identical cumulative dose	Median 47 months	No difference in proportions with relapse (77% vs. 80%), frequent relapses (45% vs. 50%), need for immunosuppressive medications (50% vs. 59%) or adverse events; similar time to frequent relapses (log rank P=0.91)
Frequent relapses, steroid dependence				
Gulati, 2010 ⁷⁹	Open label; 100	Low-dose prednisolone daily for 7 days during infections vs. alternate days	12 months	Reduced frequency of relapses (difference 0.9 episodes/patient/yr; 95% CI 0.4, 1.4) & infection associated relapses (difference 0.7 episodes/patient/yr; 95% CI 0.3, 1.1); 59% reduction when adjusted for infections (rate ratio 0.41; 95% CI 0.3, 0.6)
Gellerman, 2013 ⁸⁰	Open label, crossover; 60	Mycophenolate mofetil vs. cyclosporine (12 months each)	24 months	Higher frequency of annual relapses during the first (P=0.03) but not second year (P=0.14); lower proportion in sustained remission (64% vs. 85%; P=0.06); shorter time to relapse during the first (P<0.05) but not second year (P=0.36)
Iijima, 2014 ⁸¹	Placebo controlled; 52	Rituximab vs. placebo, 4 doses weekly	12 months	Median relapse-free period significantly prolonged (267 vs. 101 days); HR for relapse 0.27 (95% CI 0.14, 0.53; P<0.001)
Ravani, 2011 ⁸²	Open label; 54	Rituximab (one dose), low dose CNI & prednisolone vs. CNI & prednisolone	3 months	70% lower proteinuria (95% CI 35%, 86%); lower proportion with relapses (18.5% vs. 48.1%; P=0.029); higher proportion drug free (62.9% vs. 3.7%; P<0.001)
Steroid resistance				
Gipson, 2010 ⁸³	Open label; 138	Oral dexamethasone, mycophenolate mofetil & prednisolone vs. cyclosporine & prednisolone	Therapy 52 weeks; followup 26 weeks	Partial or complete remission in 33% vs. 46% (P=0.11; OR 0.59, 95% CI 0.30, 1.18); similar preservation of remission after stopping treatment (OR 1.21, 95% CI 0.56, 2.66); similar proportions progressed to kidney failure or died (P=0.56)
Gulati, 2011 ⁸⁴	Open label; 131	Tacrolimus & prednisolone for 12 months vs. IV cyclophosphamide & prednisolone for 6 months	12 months	Higher proportion in complete remission (52.4% vs. 14.8%) and complete or partial remission (82.5% vs. 45.9%) (adjusted HR 2.61; 95% CI 1.59, 4.26; P<0.001); fewer treatment failures (52.4% vs. 14.8%) (all P<0.001); higher proportion in sustained remission (73.1% vs. 42.9%; P=0.002); high odds of favorable outcome
Magnasco, 2011 ⁸⁵	Open label; 31	Rituximab (2 doses), CNI & prednisolone vs. CNI & prednisolone	3 months	No significant change in proteinuria at 3 months (difference -12%; 95% CI -73%, 110%; P=0.77)

CI confidence intervals; CNI calcineurin inhibitors; HR hazards ratio; IV intravenous; OR odds ratio; vs. versus
Adapted from: Sinha A, Menon S, Bagga A. Nephrotic syndrome: State of the art. *Curr Pediatr Rep* DOI 10.1007/s40124-014-0066-4

from a British study comparing 2- and 4-months initial corticosteroid therapy (NCT00308321) are awaited.

Management of frequent relapses: Therapy for relapses comprises of daily prednisolone until remission followed by alternate days for 4 weeks. There is no evidence that prolonged therapy for a relapse determines the long-term outcome of the illness. Patients with two or more relapses in 6-months or ≥ 4 in one year are classified as frequent relapsers. Steroid dependence is defined by occurrence of at least two relapses while receiving a reduced dose of prednisolone or within 2-weeks of its stoppage. Frequent relapses and steroid dependence are more common in patients with age at onset less than 3 years, delayed time to initial remission, brief corticosteroid therapy at onset and short duration of initial remission.^{68,86-88}

Prolonged therapy with high-dose prednisolone is associated with significant toxicity, including behavior problems, cataract, glaucoma, hypertension, avascular hip necrosis and diabetes. Relapses are associated with significant complications, including infections, thrombosis and dyslipidemia. Hence, patients with frequent relapses or steroid dependence are treated with long-term alternate day steroids, or alternative steroid sparing agents to maintain remission while limiting exposure to steroids. Since few RCT have compared the relative efficacy of these medications, most guidelines do not specify the order or choice of therapy^{67,73,74} (Table II).

Long term, alternate day steroids: Prednisolone is tapered to the lowest dose required to maintain the patient in remission without significant adverse effects. A dose of 0.3-0.7 mg/kg given on alternate days for 6-18 months is effective in reducing relapses or maintaining remission in 30-40% patients. Since relapses are precipitated following minor infections, three studies have examined the role of short-term (5-7 days) daily administration of steroids in reducing infection related relapses.^{78,89,90} While all studies found an effect of this intervention on relapse rates, one had enrolled a small number of patients⁸⁹ and another did not examine long-term benefits.⁹⁰ A well powered RCT showed that daily administration of small dose of prednisolone, during intercurrent infections, independently reduced annual relapse rates by 59% (95% CI 0.4, 0.7) without increase in steroid toxicity; 6 patients were required to be treated to prevent occurrence of frequent relapses in one.⁷⁸ KDIGO suggests that the frequency of administration of prednisolone be increased from alternate day to daily during episodes of fever and/or upper respiratory tract infection.⁷³ Based on the hypothesis that suppression of hypothalamo-pituitary axis is a risk factor for relapses, few reports suggest that compared to therapy on alternate days,

prednisolone intake at low doses daily may reduce the frequency of relapses.^{91,92} Evidence from a RCT comparing daily low dose with standard alternate day prednisolone is awaited (CTRI/2012/12/003194). Meanwhile, KDIGO guidelines suggest therapy with low-dose daily prednisolone if alternate-day treatment is not effective.⁷³ The role of zinc supplements in reducing the frequency of relapses is unclear.^{93,94}

Corticosteroid sparing agents: The additional use of an alternative agent should be considered in patients with: (i) prednisolone threshold (for maintaining remission) higher than 1.0 mg/kg on alternate days or (ii) features of corticosteroid toxicity (growth failure, hypertension, cataract).^{67,73,74} The agents used are listed below and in Fig.1 and Table I. Based on findings of a meta-analysis that mizoribine and azathioprine are no more effective than placebo or prednisolone alone in maintaining remission,⁷¹ these agents are not recommended for management of frequent relapses or steroid dependence.

Levamisole: This is an effective steroid sparing agent, especially in patients with mild dependence. Results from five RCTs at a dose of 2-2.5 mg/kg on alternate days for 4-12 months, shows 57% reduction in the risk of relapses (RR 0.43; 95% CI 0.27,0.68).⁷¹ Levamisole is associated with few adverse effects (neutropenia, seizures, cutaneous vasculitis, hepatotoxicity). Since levamisole does not reduce steroid requirement substantially, patients with high threshold or marked steroid toxicity do not do well, and require the use of potent agents. Results from two RCTs comparing levamisole to placebo (ISRCTN23853712) and mycophenolate mofetil (CTRI/2012/02/002394), respectively are expected in near future.

Alkylating agents: Meta-analysis of five RCT (n=134 patients) comparing cyclophosphamide or chlorambucil and prednisolone to prednisolone alone show that these agents reduce the risk of relapse at 6-12 months (RR 0.43; 95% CI 0.31, 0.60) and 12-24 months (RR 0.20; 95% CI 0.09, 0.46).⁷¹ Adverse effects are common including leukopenia, hemorrhagic cystitis, alopecia, nausea and vomiting; with prolonged use, gonadal toxicity and malignancies. While the efficacy of the two agents is similar, therapy with chlorambucil is avoided due to high toxicity, including seizures. The efficacy of IV and oral cyclophosphamide is perhaps similar; the former might be a choice if there are concerns about compliance with oral therapy. Benefits of therapy with cyclophosphamide are better in patients with frequent relapses compared to steroid dependence, and in older (>7 years) than younger patients.^{67,73}

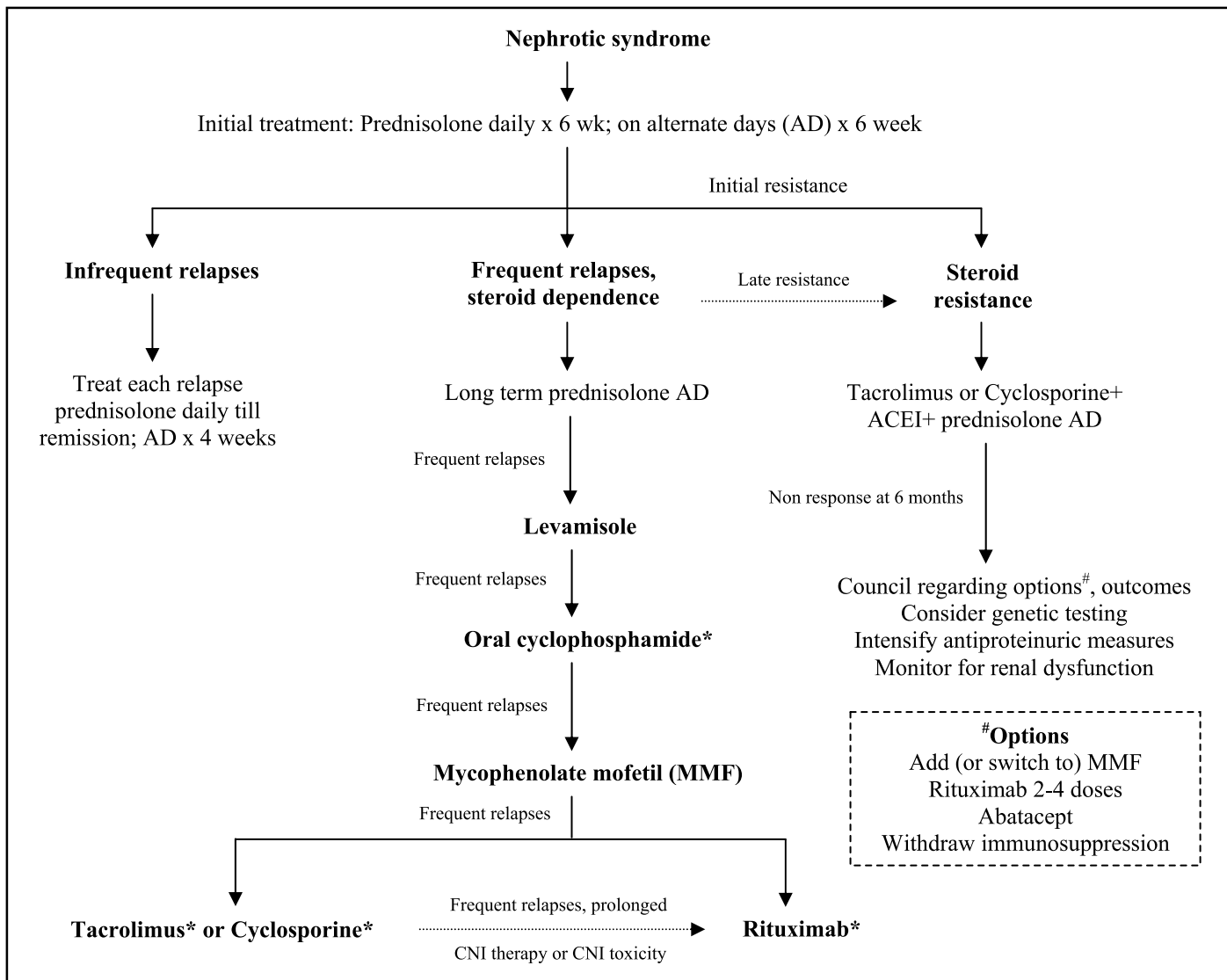


Fig.1. Immunosuppressive agents in frequent relapses or steroid dependent nephrotic syndrome

The agents listed are usually recommended in order from top to bottom. Agents marked with asterisk (*) are preferred in patients with significant steroid toxicity (cataracts, severe stunting, obesity) or if relapses are associated with severe complications, e.g., thrombosis, severe infections. Patients with steroid resistance should receive treatment with a calcineurin inhibitor (CNI) along with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker and tapering doses of prednisolone. Since response to other immunosuppressive strategies is less satisfactory and non-response to CNI is associated with adverse outcomes, further immunosuppression should be considered following counseling regarding efficacy, safety and costs of various options, including withdrawing immunosuppression.

(Adapted from: Sinha A, Menon S, Bagga A. Nephrotic syndrome: State of the art. *Curr Pediatr Rep* DOI 10.1007/s40124-014-0066-4)

Mycophenolate mofetil (MMF): MMF inhibits inosine monophosphate dehydrogenase, limiting T and B lymphocyte proliferation and cytokine gene expression. Over the last decade, several uncontrolled retrospective and prospective studies reported that MMF (dose 600-1000 mg/m²/day or 20-25 mg/kg/day) has

steroid-sparing effects and reduces relapse rates without significant toxicity in patients with frequent relapses or steroid dependence.^{95,96} Side effects are few and include leukopenia, abdominal pain and diarrhea. A recent multicenter, open-label, crossover study in 60 children showed no difference in the proportions in sustained

Table III. Guidelines in management of steroid resistant nephrotic syndrome

	Indian Society of Pediatric Nephrology, 2009⁶⁸	Kidney Disease: Improving Global outcomes (KDIGO), 2012⁶⁹
Definition	Lack of remission [#] despite treatment with prednisolone at 2 mg/kg/day for 4 week; exclude systemic infections	Lack of remission [#] despite treatment with prednisolone for 8 week, (2 mg/kg/d for 4 week; 1.5 mg/kg on alternate days for 4 week)
Evaluation	Essential Kidney biopsy Serum creatinine, albumin Not essential Screening for genetic mutations: Familial or congenital forms; patients with initial resistance	Essential[not graded] Kidney biopsy Estimated GFR; spot protein to creatinine (Up/Uc) or 24-hour protein Not essential Screening for genetic mutations
Therapy	Choice based on physician preference and medication costs (i) Calcineurin inhibitor (CNI) - cyclosporine or tacrolimus: efficacy 50-80% (ii) Cyclophosphamide: efficacy 40-60% for IV and 25% for oral therapy (iii) IV methylprednisolone, oral cyclophosphamide: efficacy 30-50%	Immunosuppressive regimens: CNI [1B] with low dose prednisolone: Efficacy 69-86% Patients without remission to CNI at 6 months Mycophenolate mofetil efficacy ~33% High-dose corticosteroids efficacy ~47% Combination of agents: Do not use cyclophosphamide or rituximab
	Non immunosuppressive therapies ACE inhibitors or ARB HMG CoA reductase inhibitor: if dyslipidemia >6 months	Non immunosuppressive therapies ACE inhibitors, ARB: Use in all patients; proteinuria reduction 33-62%
Response to therapy (assess at 6-months)	Both complete and partial remission acceptable Complete remission: trace/negative protein; Up/Uc<0.2 mg/mg Partial remission: 1-2+ proteinuria; Up/Uc 0.2-2 Nonresponse: 3-4+ proteinuria; Up/Uc >2; blood albumin <2.5 g/dl	Both complete and partial remission acceptable Complete remission: proteinuria <0.3 g/24-hour (Up/Uc <300 mg/g or <30 mg/mmol) Partial remission: proteinuria >0.3 but <3.5 g/24-hour; decrease in proteinuria by ≥50%
Duration of therapy	Discontinue CNI if no remission at 6 months Continue CNI for 2-3 year if complete/partial remission Continue longer if nephrotoxicity ruled out on repeat biopsy	Discontinue CNI if no remission at 6 months Continue CNI for ≥12 months if complete/partial remission at 6 months
Monitoring	During therapy with CNI Trough cyclosporine 80-120 ng/ml; tacrolimus 5-8 ng/ml eGFR: Maintain ±20% of baseline Rebiopsy: if therapy >2-3 year; suspected nephrotoxicity	Relapse after achieving remission: (i) Treat with oral corticosteroids (ii) Use previously successful medication (iii) Use alternative agent to minimize cumulative toxicity

[#]Urine protein trace or nil or urine protein to creatinine ratio <200 mg/g (<20 mg/mmol) for 3 consecutive days

ACE angiotensin converting enzyme; ARB angiotensin receptor blockers; eGFR estimated glomerular filtration rate

Adapted from: Sinha A, Menon S, Bagga A. Nephrotic syndrome: State of the art. *Curr Pediatr Rep* DOI 10.1007/s40124-014-0066-4

remission during 1year therapy with cyclosporine (85%) and MMF (64%), but the time to first relapse was longer with cyclosporine therapy (Table II).⁷⁹ Adverse effects were comparable but therapy with MMF was associated with higher levels of cystatin clearance, estimated GFR and hemoglobin thereby suggesting that MMF is a useful agent particularly due to lack of nephrotoxicity. There is evidence

that therapy with MMF should be monitored by drug levels; targeting area under the curve >45 mg/L/hour ensures results that are equivalent to calcineurin inhibitors.^{79,97} KDIGO suggests the use of MMF for 12-24 months, in patients with steroid dependent nephrotic syndrome.⁷³

Calcineurin inhibitors (CNI): Cyclosporine A (CsA) and

tacrolimus maintain remission and enable steroid sparing in 60-90% patients with steroid dependent nephrotic syndrome who fail treatment with alkylating agents.^{98,99} The efficacy of these agents relative to placebo or to each other has not been examined. While 2 RCT found that efficacy of CsA was comparable to alkylating agents (RR 0.91; 95 % CI 0.55, 1.48), patients relapsed when therapy with the former was discontinued.^{71,73} Information on tacrolimus use is limited to non-randomized studies, but the agent is preferred due to lack of cosmetic adverse effects (hirsutism, gum hyperplasia).⁹⁹ With either agent, therapy should be given for at least 12 months with monitoring of drug levels (target trough 4-7 ng/mL for tacrolimus; 80-150 ng/ml for CsA).⁷³ Chief adverse effects include acute and chronic nephrotoxicity (both agents), hypertension and hyperlipidemia (chiefly CsA), and diarrhea, hypomagnesemia and hyperglycemia (chiefly tacrolimus).

Rituximab: Multiple case series, summarized in a review,¹⁰⁰ have reported benefits of B cell depletion with rituximab in patients with difficult-to-treat steroid dependent nephrotic syndrome. Treatment with one or more doses of rituximab results in remission lasting 3-12 months, with 25-83% patients showing sustained remission. A large series, on 101 patients with steroid dependence, found that therapy with rituximab was associated with 81.8% reduction in relapse rates,¹⁰¹ comparable to 62-95% in previous reports.¹⁰⁰ Controlled studies on the efficacy of rituximab are limited to three recent studies, one showing superior efficacy of rituximab when compared to placebo,⁸⁰ one showing non-inferiority of rituximab plus low doses of CNI and prednisolone to standard therapy with CNI and prednisolone in maintaining short-term remission and allow their temporary withdrawal⁸¹ (Table II) and a single limb study showing steroid sparing with improved growth velocity in patients with difficult steroid dependence.¹⁰² A retrospective case control study showed that 2-doses of rituximab were as effective as 12-months' treatment with tacrolimus.¹⁰³ Adverse effects range from common events like infusion reactions, to rare occurrence of leukopenia, acute lung injury and progressive multifocal leukoencephalopathy.¹⁰⁰

Clinical practice guidelines suggest that treatment with rituximab be considered in patients with steroid dependent nephrotic syndrome who fail to respond to conventional agents, including CNI, and/or have serious adverse effects of therapy.^{67,73} The beneficial response may be sustained by further administration of 1-2 doses of rituximab, every 6-12 months for 2-3 years. Increasing reports on efficacy and safety of rituximab are likely to result in the preferential

use of this agent compared to calcineurin inhibitors and/or MMF.

Management of steroid resistant nephrotic syndrome

Therapy of patients with steroid resistant nephrotic syndrome is difficult, with variable response to immunosuppression, adverse effects of prolonged therapy and risk of progressive renal damage. Table III and Fig. 1 summarise guidelines on the evaluation, management and definitions of response.⁶⁵⁻⁶⁷ The aim of therapy is to induce and maintain remission of proteinuria, while avoiding medication related adverse effects. Patients are monitored closely until response to therapy is demonstrated, and then every 3-4 months.^{65,72} While complete remission is associated with high rates of renal survival,¹⁰⁴ even partial remission is associated with satisfactory outcomes, compared to those with non-response.¹⁰⁵

Immunosuppressive protocol

Most regimens use a combination of an immunosuppressive agent with prednisolone given on alternate days, and an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB).^{65-67,106}

Calcineurin inhibitors (Cyclosporine A (CsA), tacrolimus): Following evidence from RCTs showing efficacy for CsA (5 studies) and tacrolimus (2 studies) in inducing and maintaining remission in 46-100% patients, therapy with calcineurin inhibitors is considered 'first line' for patients with steroid resistance.^{66,67,106} While the National Institute of Health (NIH) multicenter RCT, which enrolled adults and children with FSGS, showed relatively low rates of remission with either CsA (45.8%) or combination of MMF with pulse dexamethasone (33%)($P=0.11$),⁸² a randomized trial from India showed significantly higher rates of complete or partial remission using tacrolimus (82.5%) compared to IV cyclophosphamide (45.9%) in children with steroid resistant FSGS or MCD ($P<0.001$) (Table II).⁸³ The reasons for variable outcomes relate to differences in definitions of steroid resistance, histology or prevalence of inherited defects. CsA and tacrolimus showed comparable efficacy and low rates of adverse effects in another RCT.¹⁰⁷

Examination of renal histology is advised in patients receiving prolonged therapy (2-3 years); specific features of nephrotoxicity include nodular arteriolar hyalinosis and striped interstitial fibrosis.⁶⁵ Risk factors for nephrotoxicity include prolonged duration of therapy (>2-3 years) and persistent heavy proteinuria (>1-3months).¹⁰⁸ The decision

to continue calcineurin inhibitor therapy should be reviewed in patients showing non-response to proteinuria despite 6 months of therapy.

Consensus is lacking on the optimal duration of treatment with calcineurin inhibitor. While guidelines suggest continuing therapy for 12 months or longer in patients who show complete or partial remission (2C),⁶⁵⁻⁶⁷ in practice the agent is continued for 2-3 years, followed by one of the following: (i) taper to the lowest effective dose, and continue for another 1-2 years; (ii) exclude nephrotoxicity on renal histology, and continue therapy; (iii) switch treatment to a less toxic agent, e.g. MMF or rituximab.

Cyclophosphamide: Meta-analyses show that the proportions of patients with remission is similar between patients treated with oral cyclophosphamide and prednisolone compared to those receiving prednisolone alone (RR 1.06; 95% CI 0.61, 1.87).¹⁰⁶ The efficacy of IV cyclophosphamide (administered monthly at 500 mg/m² for 6 pulses) was not superior as compared to oral cyclophosphamide with (RR 3.13; 95% CI 0.81,12.06) or without IV dexamethasone (RR 1.13; 95% CI 0.65,1.96).¹⁰⁶ Contrary to results of a recent RCT,⁸³ tacrolimus and IV cyclophosphamide had similar rates of complete or partial remission at 6 months (66.7% vs. 55.6%; P=0.77) and 12 months (77.3% vs. 66.7%; P=0.97) in Chinese adults with steroid dependent or resistant FSGS.¹⁰⁹ Given the overall limited efficacy in pediatric patients and risk of significant toxicity, KDIGO and Canadian guidelines suggest not using cyclophosphamide for patients with steroid resistance.^{66,67} However, the relatively low cost of IV cyclophosphamide still allows it to be an option in resource limited settings.⁶⁵

Pulse corticosteroids with oral cyclophosphamide: Pulses of IV methylprednisolone or dexamethasone have been used in combination with oral cyclophosphamide with modest efficacy. However, patients are at high risk of steroid toxicity, systemic infections, hypertension and electrolyte abnormalities.¹⁰⁶ This protocol is no longer recommended for management of steroid resistance.⁶⁵⁻⁶⁷

Mycophenolate mofetil (MMF): MMF has been tried with limited success in patients with steroid resistance, including in a recent randomized trial.⁸² Its use may be considered in patients who have achieved remission with calcineurin inhibitors, and may help mitigate medication dependence and toxicity.^{65,67,110}

Rituximab: Despite initial interest,¹¹¹ the efficacy of rituximab in inducing remission in patients with steroid and CNI-resistant nephrotic syndrome appears limited.¹⁰⁰

Experience on treatment with rituximab in various series, summarized in a recent review,¹⁰⁰ shows that the agent induces complete remission in 0-27.3% and partial remission in 21.2-37.5% patients at 4-8 weeks. A RCT on 31 children with steroid and CNI-resistant nephrotic syndrome failed to show benefits of additional rituximab therapy in ameliorating proteinuria at 3 months and 6 months.⁸⁴ Review of experience at our centre in 58 patients with steroid- and CNI-resistance confirms limited efficacy, with complete and partial remission in 12.1% and 17.2% patients, respectively.¹⁰¹ Similar to previous findings,¹⁰⁰ response to rituximab was better in patients with prior response to CNI and unsatisfactory in those with FSGS. Therapy with rituximab is likely to maintain remission, reduce relapse rates and enable patients to withdraw corticosteroids and calcineurin inhibitors.¹⁰¹

Other agents: In patients with steroid- and CNI-resistance, guidelines suggest the use of MMF (2D), high-dose steroids (2D) or combination of calcineurin inhibitors and MMF (2D).⁶⁶ Therapies that been examined, in anecdotal reports, include the combination of CsA and MMF,¹¹² abatacept,³⁷ lipid column apheresis,¹¹³ galactose,¹¹⁴ protease inhibitor: saquinavir,³⁰ TNF blockade: etanercept⁴² and ACTH.¹¹⁵ These agents require careful evaluation in prospective studies.

Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blockers: Therapy with ACE inhibitors (enalapril 0.3-0.6 mg/kg/day, ramipril 6 mg/m²/day) is associated with decrease in proteinuria and control of hypertension. Adverse effects include dry cough, hyperkalemia and decline in renal function and therapy is discontinued if hyperkalemia develops or estimated GFR falls to <30 mL/minute/1.73 m². Angiotensin receptor blockers (e.g. losartan, valsartan) may be used in case of persistent dry cough with ACE inhibitors, or as add-on therapy for better antiproteinuric effect. A recent RCT on 268 children showed that losartan and enalapril reduce proteinuria by 30.0% and 40.5%, respectively.¹¹⁶ While there are limited studies on the combined efficacy of ACE inhibitor and ARBs in children, meta-analyses of RCT in adult patients underscore the significant risk of adverse events (hyperkalemia, hypotension, nephrotoxicity) with dual blockade of the renin angiotensin aldosterone axis.¹¹⁷

Vitamin D: A systematic review of six RCT(n=688 adults) showed that vitamin D analogs (paracalcitol, calcitriol) reduce residual proteinuria (weighted mean difference - 16% vs. 6%, P<0.0001) with high odds of achieving ≥15% proteinuria reduction from baseline (OR 2.7; 95% CI 1.8, 4.1; P<0.001).¹¹⁸ Therapy was associated with the risk of

hypercalcemia (RR 4.8; 2.2, 10.4),¹¹⁹ and there was no evidence that the intervention retards the decline of kidney function.^{118,119}

Outcomes

Most patients with steroid sensitive nephrotic syndrome show satisfactory renal outcomes. Morbidity due to infections has declined with their prompt diagnosis and use of vaccines; steroid toxicity remains a major concern in patients with frequent relapses or steroid dependence. Follow up of the initial ISKDC cohort revealed that almost 80% patients were in sustained remission at 8 years from diagnosis;⁶⁸ however, other series suggest that 27-42% patients continue to relapse into adulthood.^{120,121} Ten year follow-up of patients who received CsA for frequent relapses in a randomized study showed that 17.4% and 50% continued to suffer infrequent or frequent relapses, respectively, into adulthood.¹²² Relapses recurred in adulthood in 16.4% patients, chiefly among patients with frequent relapses.¹²³

Outcomes in patients with steroid resistance are less satisfactory. Patients with minimal change disease demonstrate higher rates of remission and better prognosis than those with FSGS; however, the chief factor predicting renal outcome is the response of proteinuria to therapy rather than histology. Renal survival varies from 72-94% at 5 years, with resistance to calcineurin inhibitors and presence of FSGS predicting adverse outcomes.^{124,125} A recent study on 29 patients with late steroid resistance followed for a mean of 7 year reported that 66% patients were in complete or partial remission and <10% showed end stage renal disease.¹²⁶

Recurrence of FSGS after renal transplantation

Almost 30% of patients with idiopathic FSGS undergoing transplantation develop recurrence of FSGS in the first allograft, with risk of delayed allograft function and loss (30-50% at 5 years).³⁹ Recurrence of proteinuria occurs within hours to days after the transplant, and is characterized by progressive hypoalbuminemia and foot process effacement on electron microscopy. After loss of the first allograft, the risk of recurrence of FSGS in subsequent kidney transplants is 80–100%. Features that are associated with recurrence include: (i) white ethnicity, (ii) disease onset in childhood (<15 year), (iii) late rather than initial resistance, (iv) non-genetic forms of disease, (v) mesangial proliferation, (vi) progression to end stage disease within 3 years from onset and (vii) nephrectomy of native kidneys prior to transplant.^{128,129} Disease recurrence is attributed to circulating permeability

factors, with a potential role for increased levels of suPAR, TNF- α and proteases that phosphorylate vasodilator stimulated phosphoprotein (VASP).^{42,44} A panel of antibodies against 7 antigens (CD40, PTPRO, CGB5, FAS, P2RY11, SNRPB2, APOL2) predicts FSGS recurrence with more than 90% accuracy.¹²⁹

Despite the risk of recurrence, live donors are preferred in view of better overall outcome. Pre-transplant plasmapheresis is a widely used strategy to decrease the risk of recurrence.¹²⁷ Peri-transplant administration of rituximab is recommended, since it is believed to stabilize the podocyte cytoskeleton.⁶⁴ Therapy for patients with recurrent FSGS include one or more of the following: (i) intensive and prolonged plasmapheresis;¹³⁰ (ii) rituximab (375 mg/m²/week for 2-4 weeks);¹³¹ (iii) immunosuppression, including high dose CsA, cyclophosphamide (2-2.5 mg/kg/day for 3 months) instead of MMF; (iv) IV immunoglobulin (500 mg/kg/dose once a week) and (v) ACE inhibition. Results of treatment with IV abatacept have been unsatisfactory. Patients with refractory illness might be offered intensive lipid apheresis, using specially designed columns,¹³² with almost one-half of patients showing complete or partial response.

Points to Remember

- *Nephrotic syndrome is a chronic disorder of childhood characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia and edema*
- *Ninety percent are idiopathic with majority being steroid responsive with favourable prognosis in contrast to those with steroid resistant course.*
- *Minimal change disease is the most common histologic variant in steroid sensitive nephrotic syndrome followed by focal segmental glomerulosclerosis.*
- *Genetic mutation screening is recommended for congenital nephrotic syndrome, steroid resistant nephrotic syndrome and in those with positive family history.*

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NEPHRO-UROLOGY

RENAL RICKETS – PEDIATRICIAN'S PERSPECTIVE

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Abstract: Rickets is one of the most important causes of metabolic bone disease. Majority of them are due to vitamin D and calcium deficiency. When it is refractory to the conventional treatment with vitamin D and calcium supplementation, renal causes, hepatic causes and vitamin D metabolism disorder are to be thought of. In renal osteodystrophy (ROD) the bone changes are primarily due to disorders of phosphorus and calcium homeostasis. As kidney function deteriorates along with abnormalities in vitamin D, parathyroid metabolism, bone turnover, mineralization, volume, linear growth and strength, ROD develops which is currently labelled as 'chronic kidney disease -mineral and bone disorder' Early focused evaluation and intervention will greatly prevent the morbidity and lead to better quality of life .

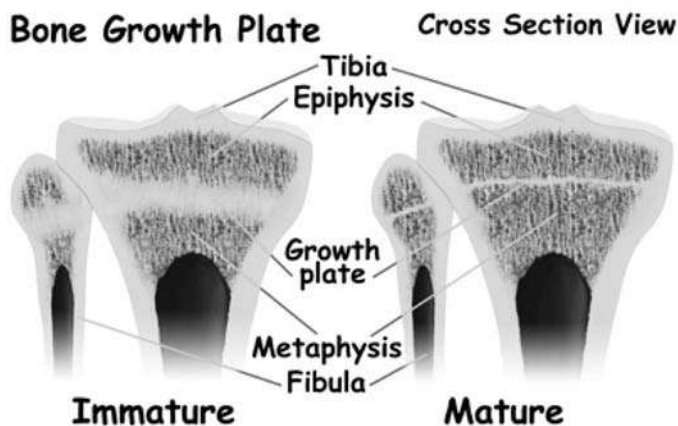
Keywords: Renal rickets, Renal tubular acidosis, Hypophosphatemic rickets, Vitamin D dependent rickets.

Disorders affecting bone mineralization are called rickets and osteomalacia. When the problem occurs prior to fusion of growth plate affecting both the growth plate and bone matrix it is called as rickets. After the fusion of growth plate when defective mineralization occurs only in bone matrix it is termed as osteomalacia. Bone is made up of living cells embedded in a mineralized organic matrix. Bone matrix is the intercellular substance made up of a mixture of organic component, collagen and inorganic components predominantly calcium and phosphate. Rickets is the end result of many etiologies and the term renal rickets is imprecisely employed to include different types of renal disorders having defective mineralization as a common factor (Fig.1).

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SOURCE: ORTHOPODHome » Orthopedic Topics » Children's Orthopedics » Blount's Disease. Blount's Disease A Patient's Guide to Blount's Disease in Children and Adolescents

Fig.1. Various components of bone ends

Classification

Rickets can be broadly classified into renal or non-renal rickets (Table I)¹ based on etiology and also according to the predominant type of mineral deficiency as calcipenic or phosphopenic rickets (Table II).² Calcipenic rickets is caused by Vitamin D deficiency or calcium deficiency, which is commonly due to insufficient intake or vitamin D deficiency or decreased absorption of calcium even in the presence of adequate serum vitamin D levels. Phosphopenic rickets is caused by renal phosphate wasting. Calcipenic rickets is often but not always associated with low serum calcium levels, while phosphopenic rickets is always characterized by low serum levels of phosphorus.

Clinical features

Rachitic changes usually manifest at the sites of rapid bone growth such as distal forearm, knee and costochondral junctions.

Head: Delayed closure of the fontanelles/wide open fontanelle, parietal and frontal bossing with caput quadratum, craniotabes (soft skull bones).

Chest: Enlargement of the costochondral junction along the anterolateral aspects of chest described as "rachitic

Table I. Classification of rickets based on etiology

<p>Non – renal rickets</p> <ol style="list-style-type: none"> 1.Nutritional 2.Gastrointestinal causes: <ol style="list-style-type: none"> a) Malabsorption eg Celiac disease b) Hepatobiliary disorders eg Wilson disease, neonatal cholestasis 3.Medications e.g. anticonvulsant therapy, 4.Oncogenic –Mesenchymal tumors 5.Rickets of prematurity 6. Vitamin D dependent rickets type II (VDDR type II) <p>Renal rickets</p> <ol style="list-style-type: none"> 1. Chronic kidney disease. (Renal Osteodystrophy) 2.Hereditary hypophosphatemic rickets <ol style="list-style-type: none"> a) X-linked hypophosphatemic (XLH) rickets b) Autosomal dominant hypophosphatemic rickets c) Autosomal recessive hypophosphatemic rickets d) Hereditary hypophosphatemic rickets with hypercalciuria 3.Distal renal tubular acidosis 4.Fanconi syndrome <ol style="list-style-type: none"> a) Primary b) Secondary (Cystinosis, tyrosinemia, Wilson's disease, Lowe syndrome) 5.Vitamin D dependent rickets type I (VDDR type I)

Table II. Classification of rickets based on mineral deficiency

<p>Calcium deficiency with secondary hyperparathyroidism</p> <ol style="list-style-type: none"> 1.Vitamin D deficiency 2.Malabsorption disease 3.Hepatic disease 4.Anticonvulsant therapy 5.Renal osteodystrophy 6 VDDR Type 1 and 2 <p>Primary phosphate deficiency with no secondary hyperparathyroidism.</p> <ol style="list-style-type: none"> 1.Familial hypophosphatemia 2.Fanconi syndrome 3. Renal tubular acidosis (Type I) 4. Oncogenic hypophosphatemia 5. Phosphate deficiency due to malabsorption and low phosphate intake

rosary”, Harrison sulcus is the groove seen at lower margin of thorax caused by muscular pull of diaphragmatic attachments to lower ribs, sternum may be pulled into a pigeon-chest deformity.

Trunk and abdomen: Kyphoscoliosis, pot belly and visceroptosis

Limbs: Widening of wrist, genu valgum or knock knee deformity, genu varum or bow legs, or double malleoli at ankle may be seen. Upper limbs are predominantly involved in calcipenic rickets, probably because of early onset prior to weight bearing by legs. Lower extremities tend to be predominantly affected in heritable forms of phosphopenic rickets.

Radiology of rickets

Early changes are seen better in the growth plate of ulna in the wrist and fibula in the lower limbs. They are indicated by widening of physis (growth cartilage) and loss of delineation or definition at the zone of provisional calcification which lies at the epiphyseal-metaphyseal interface. Cupping and splaying of the metaphysis, delayed appearance or reduced size of epiphyseal centres or osteopenia of shaft are other radiological features. Deformities and pathological features can occur in advanced forms of rickets (Fig 2,3,4,5).

Clinical approach to rickets (Fig.6)

Step 1. Diagnosis of rickets. Common presentations are delayed walking, bony deformities or rarely hypocalcemia leading to stridor or seizures. Not uncommonly rickets is recognized from the radiological findings when a child presents with cardiac failure due to vitamin D deficiency, cardiomyopathy or unrelated problems like recurrent respiratory symptoms.⁴ A common mimic of rickets is metaphyseal dysplasia where serum levels of calcium, phosphorus and vitamin D are normal even though their radiological findings may be confused with that of rickets.³ Hypophosphatasia is another close differential diagnosis of rickets where conspicuous laboratory finding is low serum alkaline phosphatase, which is never seen in rickets.

Step 2. Nutritional vs non nutritional rickets: Always consider nutritional rickets as the first possibility, as the incidence of hypovitaminosis D is increasing all over the world irrespective of the economical status. The disease is characterized by deformities of the long bones, enlargement of the wrists and costochondral junctions, hypotonia and in infants, craniotabes and delayed fontanelle closure. Rickets can also be associated with hypocalcemic seizures and cardiac failure. First presentation is typically at 6-24 months of age, although hypocalcemia/hypocalcemic seizures may be evident in neonates and younger infants.⁴

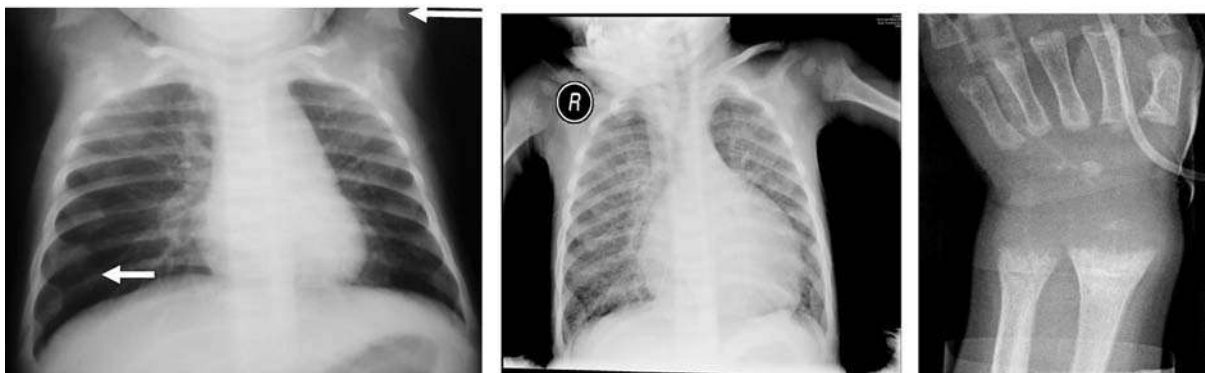


Fig.2, 3 & 4. Radiological changes in rickets - Humerus - upper end, hand bones -lower end and ribs - enlarged anterior ends (white arrow)



Fig.5. X-ray wrist - Appearance of healed rickets

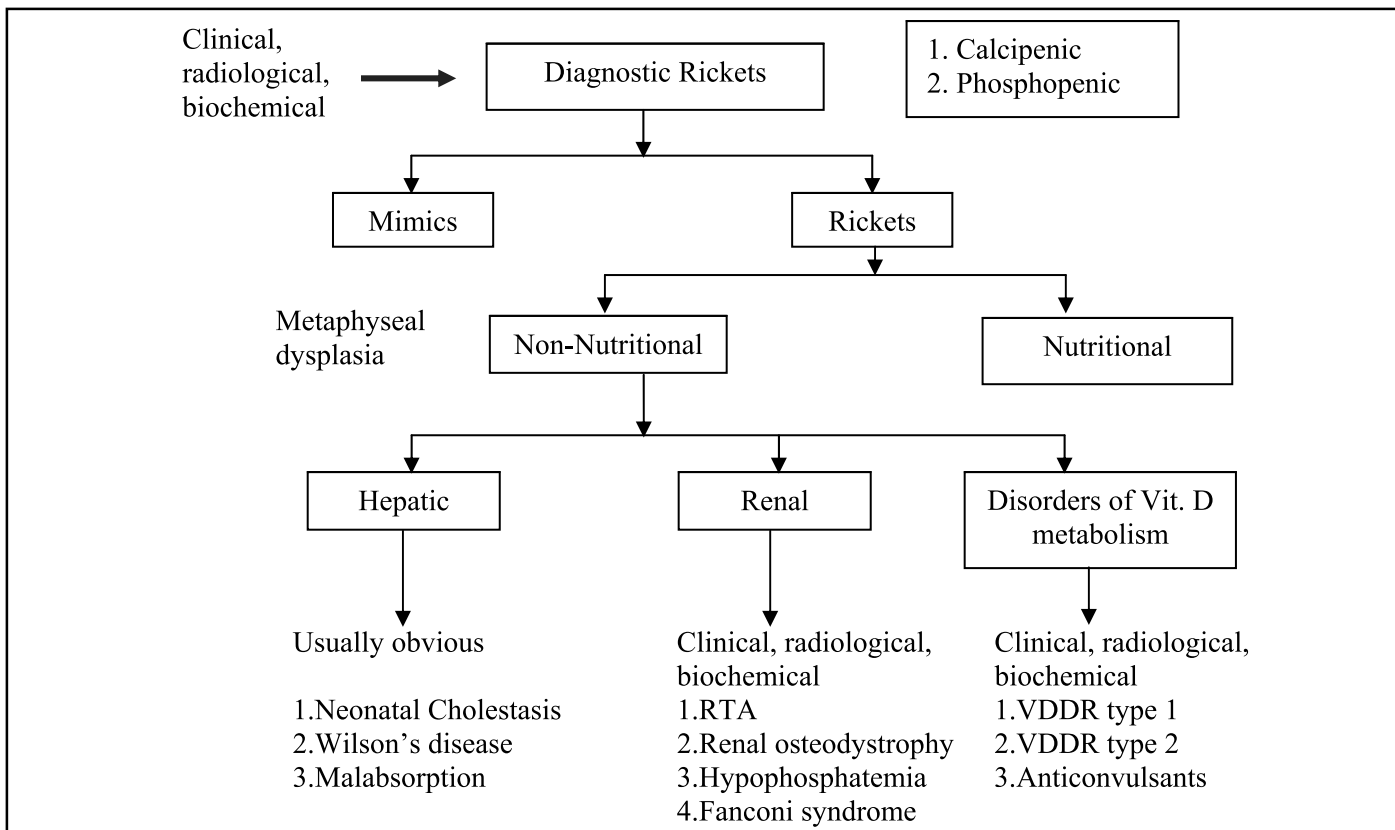


Fig.6. Clinical approach to rickets

One should consider the possibility of non nutritional rickets if the age of the child is beyond the classical age group i.e less than 6 months or above 3 years and in the presence of clinical signs of non nutritional rickets. Family history of similar illness, global developmental delay, presence of failure to thrive, stunted growth, cataract, icterus or alopecia will suggest the diagnosis of non nutritional etiology. When facilities for further investigations are not available, in the presence of clinical features of rickets, it may be presumed to be nutritional and treated accordingly with vitamin D and calcium supplements. Serum alkaline phosphatase can be taken as surrogate marker for vitamin D deficiency.⁵ If there is non-healing after 2-4 mega doses of vitamin D along with calcium, the diagnosis of non –nutritional rickets can be made and child has to be evaluated further to find the cause.

Stage 3. Causes of non-nutritional rickets: In addition to the usual clinical features the possibility of non nutritional rickets is high in the presence of the following constellation of clinical features (Table III).

Laboratory evaluation⁷

To identify rickets: X-ray of ends of long bones, serum calcium, serum phosphorous and alkaline phosphatase.

To identify hepatic etiology: Liver function tests, stool for

fat globules for chronic or cholestatic liver diseases and malabsorption.

To identify renal causes Urine pH, glycosuria, proteinuria, pyuria, electrolytes, amino acids, spot protein, creatinine, calcium, phosphorus, arterial blood gases, blood urea, serum creatinine, electrolytes, calcium (ionised calcium should ideally be measured because this is the biologically active component and is more accurate than “corrected” calcium levels derived from total calcium concentration), serum magnesium, phosphate, alkaline phosphate, serum parathyroid hormone (PTH) levels are needed. Ultrasonography of urogenital tract, maximum tubular reabsorption of phosphorus (TRP), the maximal tubular reabsorption of phosphorus per glomerular filtration rate (TmP/GFR) are the other investigations. In disorders like hypophosphatemic rickets patients have decreased proximal renal tubular reabsorption of phosphate and increased urinary excretion. Hence the TRP as well as the maximum tubular phosphate reabsorption is reduced.

Calculation of TRP: The normal value of the tubular reabsorption of phosphate (TRP) is >80% and is calculated as follows: $TRP = 1 - [(Up/Pp) \times (P_{crea}/U_{crea} \times 100)]$. In children between 2 and 15 years of age the normal values of TmP/GFR vary from 3.5-7.5 mg/dl. This value is calculated as per the following formula: $TmP/GFR = Pp -$

Table III. Clinical signs as an indication for underlying disease

Clinical signs	Possible cause of rickets
Consanguineous parents, positive family history rickets	Familial hypophosphataemic rickets or VDDR type 1 or 2
Chronic hepatocellular failure, obstructive jaundice	Hepatic dysfunction
Chronic diarrhea with loose, fatty and foul smelling stools	Malabsorption syndromes
Alopecia	VDDR type 2
Predominant lower limbs deformity, frequent dental abscesses and decay	Hypophosphatemic rickets
Cataract	Wilson's disease
Failure to thrive, polyuria, metabolic acidosis, hypokalemia, nephrocalcinosis	Renal tubular acidosis
Hepatosplenomegaly, hypoglycemia and hyperlipidemia	Tyrosinemia, Glycogen storage disorders like Von Gierke's disease and Fanconi-Bickel syndrome ⁶
Presence of acidotic breathing, hypertension, anemia with or without edema	Chronic kidney disease (CKD)

$[(Up \times P_{crea})/U_{crea}]^8$ [Pp Up, Pcrea, and Ucrea refers to the concentrations of phosphate (p) and creatinine in plasma (P) and urine (U)]. Serum 25 hydroxy vitamin D and 1,25 hydroxy vitamin D levels are done to identify the vitamin D metabolism disorders.

Renal rickets: The kidney has an important role in the maintenance of 'bone health'. Normal bone growth and mineralization require a finely tuned interaction of vitamin D, calcium and phosphate, the two major constituents of the crystalline component of bone, parathyroid hormone and a physiological 'internal milieu'. Perturbations in any one component can cause bone changes to be diagnosed as rickets. The kidney plays a major role in maintaining calcium and phosphorus balance, metabolism of vitamin D and pH of blood. Renal rickets includes bony changes that simulate changes due to vitamin D deficiency, renal dysfunction, tubular reabsorption disorders and uncommonly due to 1,25 hydroxylase enzyme functional deficiency in the proximal tubules (Box 1) (Fig.7).

Renal rickets with hyperphosphatemia, hypocalcemia with secondary increased PTH activity

1. Chronic kidney disease: In mild to moderate CKD there is decreased serum 1,25 (OH)₂ vitamin D and increased

Box 1. Pointers to the diagnosis of renal rickets

- Failure to thrive, recurrent vomiting, polyuria, lethargy, acidotic breathing
- Hypertension, anemia with or without edema
- Positive findings in urine analysis.
- Abnormalities in electrolytes, blood urea and creatinine
- Renal abnormalities in ultrasound abdomen

PTH levels. The circulating levels of 1,25 (OH)₂ vitamin D in CKD are low .due to reduced volume of functional kidney mass and reduced 1- α -hydroxylase enzyme activity in the proximal tubules. This results in decreased intestinal calcium absorption and low serum ionic calcium levels which stimulates the release of PTH. With further reduction in glomerular filtration rate, below 30-35ml/min/1.73m², the phosphorus excretion dips down. Hyperphosphatemia causes suppression of 1- α -hydroxylase activity and increased stimulation of PTH release. Over time, this chronic hypocalcemia, hyperphosphatemia, and low circulating 1,25 (OH)₂ vitamin D levels result in autonomous increased PTH release. This combination of chronic metabolic acidosis, hypovitaminosis D, hypocalcemia, hyperphosphatemia and excessive PTH

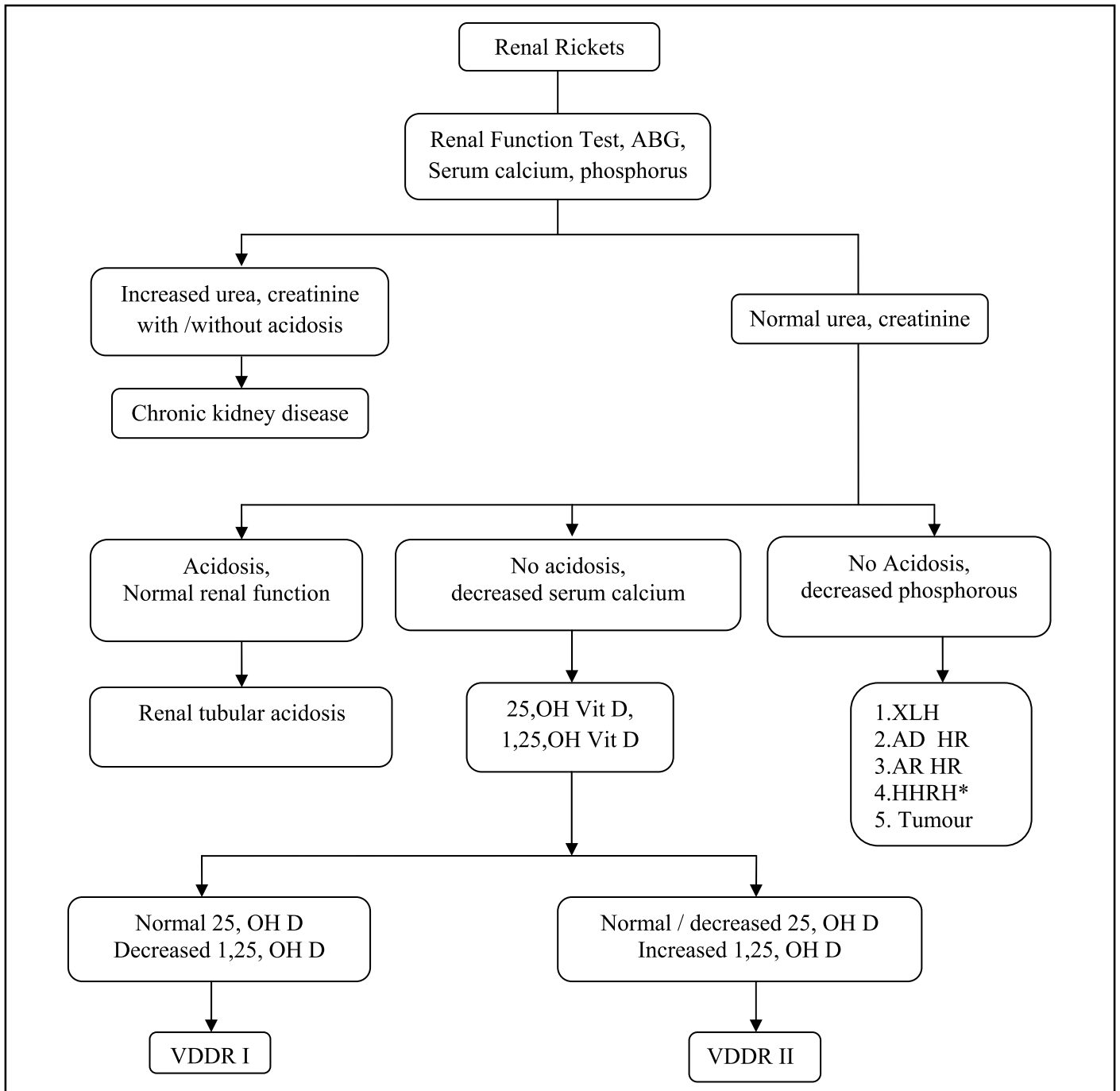


Fig.7.Approach to renal rickets

(* HHRH –Hereditary hypophosphatemic rickets with hypercalciuria)

activity causes bone changes termed as ‘renal osteodystrophy’ (ROD), but erroneously termed as rickets in clinical practice. Renal osteodystrophy is the only type of rickets with a high serum phosphate level. The cause, pathogenesis, bone histology and management of ROD are at variance with the classical rickets. The increased osteoclastic bone resorption with fibrous replacement and extensive bone marrow fibrosis results in the most common abnormality the osteitis fibrosa cystica. Bone resorption

occurs because of increased osteoclastic activity which affects all bone surfaces at different skeletal sites unlike rickets where it is confined to growth plate. It may be subperiosteal, intracortical, endosteal, trabecular, subchondral, subligamentous or subtendinous. Loss of lamina dura of the teeth, a feature of ROD, is due to bone resorption.⁹ One should be aware that ROD is an abnormality of bone turnover, mineralization, volume, linear growth, and strength presently renamed as ‘metabolic

bone disease' which is part of a broad spectrum of disorders of phosphorus/calcium mineral metabolism that occur in CKD termed as 'CKD-mineral and bone disorder.

Management is focused on overcoming phosphate retention and vitamin D deficiency which initiates hyperparathyroidism in addition to dialysis and other supportive management for CKD.

Phosphate restriction: In addition to phosphate restricted diet, phosphate binders are very useful in the prevention of phosphate absorption from the gastrointestinal tract. Calcium based phosphate binders are very safe and effective such as calcium carbonate, calcium acetate and calcium gluconate. Calcium citrate has to be avoided because of its potential to increase aluminum absorption. In the presence of high serum calcium levels, calcium containing phosphate binders may cause soft tissue calcification. Newer non calcium non aluminum phosphate binding drugs like Sevelamer are used in these situations.

Vitamin D supplement: Vitamin D has a renoprotective effect in CKD.¹⁰ There are specific indications and dosage schedules in various stages of CKD based on serum calcium, phosphorous, vitamin D and PTH levels. In short the aim is to correct this deficiency by administration of a vitamin D preparation such as cholecalciferol in sufficient dosage to raise 25-hydroxyvitamin D levels above 30 ng/ml.¹¹

Renal rickets with hypophosphatemia, normocalcemia with normal PTH activity

Hereditary hypophosphatemic rickets consists of a group of inherited disorder in which the primary problem is the phosphate wasting rather than true vitamin resistance alone.¹² The term "vitamin D-resistant rickets" should not be used because this disorder is not characterized by vitamin D resistance. There are two types of phosphate wasting a) secondary to fibroblast growth factor 23 and b) due to a primary renal tubular defect.

i) Phosphate wasting may be secondary to increased fibroblast growth factor 23 (FGF23) signaling, which is a circulating factor secreted by osteoblasts, odontoblasts, and osteocytes. The secreted FGF23 inhibits the sodium phosphate co transporter NaPi-IIa and NaPi-IIc and prevents 1,25-(OH)₂ vitamin D production. This causes diminished renal and digestive absorption of phosphate. NaPi-IIb is mostly expressed in small intestine and in a number of other organs including testis, lung, liver and lactating mammary glands. These hereditary forms include a) X-linked hypophosphatemic rickets (XLHR) due to loss-of-function mutations in Phosphate regulating

endopeptidase on X chromosome (PHEX), an endopeptidase encoded by a gene localized on the X, b) autosomal dominant hypophosphatemic rickets (ADHR) and c) autosomal recessive hypophosphatemic rickets (ARHR).

ii) Phosphate wasting may be due to a primary renal tubular defect due to molecular defects of the sodium-phosphate transporter NaPi-IIa, NaPi-IIc and several other tubular function resulting in hypercalciuria: such as hereditary hypophosphatemic rickets with hypercalciuria (HHRH), Dents disease, Toni-Debre-Fanconi and Lowe syndromes. In these conditions there is diminished capacity to transport phosphate from the glomerular filtrate to the blood circulation. In response to hypophosphatemia, FGF23 secretion is suppressed resulting in increased 1,25 (OH)₂ vitamin D production with increased absorption and excretion of calcium.¹²

1) Rickets due to increased fibroblast growth factor 23: X-linked hypophosphatemic rickets (XLHR) is an X-linked dominant disorder and is the most common form of rickets and accounts for 80% of hereditary phosphate wasting disorders. The gene responsible was identified on chromosome Xp 22.1 and was named PHEX. PHEX is expressed mostly in bones and teeth. A large number of mutations in PHEX can cause XLHR and there is no obvious correlation between genotype and phenotype. Products of PHEX gene degrade and inactivate FGF23, a hormone-like substance that promote phosphate excretion and impair bone mineralization. In XLHR, inactivating mutations of PHEX result in failure to inactivate FGF23 resulting in elevated levels of FGF-23 resulting in unregulated loss of phosphate. Child with XLHR does not develop tetany or myopathy which is seen in hypocalcemic rickets. Growth retardation is marked in untreated males, who seldom reach a height of 110 cms. Presence of clinical and radiological features of rickets differentiates this from physiological bowing of legs. Serum phosphorous levels are usually less than 2.5 mg/dL, but levels may be as high as 4 mg/dL in infants, which may be attributed to low GFR. Main biochemical feature of XLHR is the low tubular reabsorption of filtered phosphate (TRP) in the presence of low serum phosphate. Normal range of TRP is 80-95% and in patients with XLHR it is reduced to 40-70%. Oral administration of phosphate and 1,25 (OH)₂ vitamin D are the important steps to achieve normal longitudinal growth rate and normal serum alkaline phosphatase (SAP) levels rather than normalizing serum phosphate levels. The recommended oral phosphate preparation consists of the solution of 136 g of dibasic sodium phosphate and 58.5 g phosphoric acid (85%) in a liter of water.

One milliliter of solution contains 30 mg of elemental phosphorus. Prepared oral formulations are available for ready use. The recommended dose of phosphate varies from 30-90 mg/kg/day, with an average of 60 mg/kg/day divided into four doses. Some authors have recommended lower initial doses, 20-40 mg/kg/day. From a practical point of view, if a phosphate solution is used, one can start with 5 ml (150 mg) four times a day (600 mg/day) doses and then increase the dose to 10 ml (300 mg) or 15 ml (450 mg), four times a day to achieve a total dose of 1-2 g/day. The main problems that arise are the frequency with which the doses should be administered during the day and the diarrhea that develops in the first week. This treatment should be continued until growth has concluded. Subsequently, it should be individualized during adulthood. It is recommended that treatment with phosphate solution be administered simultaneously with $1\alpha, 25(\text{OH})_2\text{D}$. It is convenient, at the beginning, to start with low doses of active vitamin D and gradually increase the dose. The recommended dose is between 0.02-0.03 $\mu\text{g}/\text{kg}/\text{day}$.⁸ Nephrocalcinosis and hyperparathyroidism are the two important complications of therapy that need close monitoring. Adjuvant therapy with hydrochlorothiazide is noted to give benefit to control hypercalciuria.

Autosomal dominant hypophosphatemic rickets is characterized by rickets, hypophosphatemia, hyperphosphaturia, fatigue, bone pain and lower limb deformities in face of inappropriately low or normal vitamin D_3 levels. Clinical features are similar to XLHR. Autosomal dominant hypophosphatemic rickets results from missense mutations in FGF23 gene on chromosome 12p13. Mutations in FGF23 gene causes the FGF-23 molecule to be resistant to cleavage by proteolytic activity, resulting in high circulating levels of the hormone. Accumulating FGF23 inhibits renal phosphate reabsorption and $1\text{-}\alpha\text{-hydroxylase}$ enzyme synthesis.¹³ Phosphate wasting defect may disappear after puberty. The treatment is similar to XLH treatment.

Autosomal recessive hypophosphatemic rickets (ARHR) type 1 occurs due to loss of function mutations in Dentin matrix protein 1(DMP1), a noncollagenous bone matrix protein expressed in osteoblasts and osteocytes. This protein has a role in osteocyte proliferation and in the down regulation of FGF23.¹⁴ Affected individuals exhibit elevated serum levels of FGF-23, renal phosphate wasting and inappropriately normal levels of $1,25(\text{OH})_2\text{D}$. It is caused by mutations in the gene that encodes DMP1 that normally suppresses FGF-23 secretion.¹³

Autosomal recessive hypophosphatemic rickets type 2 is a rare form of renal tubular phosphate wasting disorder

due to loss of function mutations of the ecto-nucleotide pyrophosphatase/pyrophosphodiesterase 1 gene (ENPP1). The mutated ENPP1 gene, causes hypophosphatemic rickets resulting from elevated FGF23 levels and reduced inorganic pyrophosphate levels, a physiologic inhibitor of calcification. It presents a wide spectrum of phenotypes, ranging from lethal generalized arterial calcification of infancy to hypophosphatemic rickets with hypertension. Hearing loss is a feature of the disease entities and was merely regarded as a complication rather than a part of the disease.¹⁵ Clinical manifestations, biochemical findings, and management of patients with ARHR are similar to those with XLHR.

2) Rickets due to a primary renal tubular defect:

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH) is an autosomal recessive form that is characterized by reduced renal phosphate reabsorption, hypophosphatemia and rickets. It can be distinguished from other forms of hypophosphatemia by increased serum levels of $1,25(\text{OH})_2$ vitamin D resulting in hypercalciuria. HHRH is caused by homozygous or compound heterozygous mutations in the SLC34A3 gene encoding a sodium-dependent phosphate transporter namely sodium-phosphate cotransporter $\text{NaP}_i\text{-IIc}$.¹⁶ However experimental studies showed absence of rickets and only hypophosphatemia, hypercalciuria and elevated $1-25(\text{OH})_2$ vitamin D with this mutation.¹⁷ Rickets or osteomalacia, hypercalciuria and nephrolithiasis are the common features. This condition differs from XLHR, ADHR, ARHR in that only phosphate transport is affected and plasma $1,25(\text{OH})_2$ vitamin D concentration is normal or appropriately elevated for the degree of hypophosphatemia. Hypercalciuria is due to high $1,25(\text{OH})_2$ vitamin D levels and secondarily increased calcium absorption in intestine. Unlike XLH and ADHR, phosphate supplementation alone can cause a complete remission of HHRH, whereas the addition of vitamin D can create complications, such as hypercalcemia, nephrocalcinosis and renal damage. Serum phosphate levels are normalized but osteomalacia is not cured. Biochemical, radiological and ultrasonographic monitoring is needed on long-term follow-up.

Dent disease is an X-linked recessive disorder of the proximal tubules that is diagnosed based on the presence of all three of the following criteria: Low-molecular-weight (LMW) proteinuria, hypercalciuria and at least one of the following: nephrocalcinosis, kidney stones, hematuria, hypophosphatemia or renal insufficiency and rickets. The exact mechanism for this and the low molecular weight proteinuria is still not fully understood. Dysfunctions in tubular phosphate reabsorption via the sodium-phosphate

cotransporter, endocytotic reabsorption of the vitamin D+vitamin D-binding protein complex mediated by megalin and cubilin, and acid-base dysregulation are factors that cause these findings. In most cases, it is due to mutations that inactivate a voltage-gated chloride channel named *CLC5* encoded by a gene *CLCN5* at Xp 11.22. In some it is associated with mutations in the *OCRL1* gene, which is also mutated in the oculocerebrorenal syndrome of Lowe located on chromosome Xq25.^{18,19} Loss of function mutations (A type of mutation in which the altered gene product lacks the molecular function of the wild-type gene) in the renal voltage-gated chloride channel *CLC5* causes a proximal tubular defect and leads to the hypercalciuria and nephrolithiasis of Dent's disease.¹⁹ Clinical manifestations include bone pain and difficulty in walking due to rickets, or symptoms of renal stones such as abdominal pain and hematuria. These features are predominant in males from early childhood. By late childhood a few exhibit renal insufficiency and ESRD by 30 and 40 years of age. Laboratory evidence of LMW proteinuria, aminoaciduria, phosphaturia, glycosuria, uricosuria, kaliuresis and impaired urinary acidification are present with rickets or renal stones. LMW proteinuria excretion includes α 1 and β 2 microglobulins, retinol-binding protein (RBP), Clara cell protein and vitamin D binding protein and is found in about 99% of the affected males. β 2 microglobulin is usually measured but RBP is more sensitive and specific. Glomerular sclerosis may be one of the causes for renal failure. For unclear reasons, some patients have no signs of bone disease and achieve normal height.

Treatment of hypercalciuria is done with dietary sodium restriction and thiazide diuretics that stimulate the reabsorption of calcium in the distal convoluted tubule (DCT) where *CLC-5* is not expressed. Dietary calcium restriction is not recommended because it may exacerbate the risk of bone disease. Oral phosphate therapy and active vitamin D supplementation result in improvement of bone disease. Monitoring the serum calcium, phosphorous and alkaline phosphatase along with random urine Ca/Cr estimation is needed frequently to avoid exacerbating hypercalciuria via increased intestinal calcium absorption. Dialysis and transplantation are routinely offered to these patients if they develop stage V CKD. The disease apparently does not recur after kidney transplantation.

Renal rickets with acidosis and without renal failure

Type I (distal) renal tubular acidosis (dRTA) is a disorder associated with the failure to excrete H^+ ions from the distal renal tubule. The acidification of urine in the distal tubule primarily depends on acid-base exchange

transporters in intercalated cells. The α -intercalated cell is responsible for H^+ ion secretion by a vacuolar H^+ -ATPase and also by a H^+ - K^+ -ATPase. Mutations of the gene encoding the B1 subunit of the renal H^+ -ATPase cause autosomal recessive dRTA and sensorineural deafness. Intracellularly formed HCO_3^- leaves these acid secreting cell by the Cl^- - HCO_3^- exchange, facilitated by an anion exchanger AE1. Mutations of the gene encoding the chloride bicarbonate exchanger AE1 that transports bicarbonate to the blood from acid-secreting cells causes autosomal dominant distal RTA. It is characterized by hyperchloremic metabolic acidosis, an abnormal increase in urine pH, reduced urinary excretion of ammonium and H^+ ions, and transient mild deterioration in renal function. Hypercalciuria is common in dRTA because of bone resorption, which increases as a buffer against metabolic acidosis. This can result in intractable rickets. Most patients with dRTA have hypokalemia because the inability to excrete H^+ ion is compensated for by increased K^+ secretion. The clinical manifestations are short stature, failure to thrive, recurrent vomiting, dehydration, and irritability.²⁰

Clinical and biochemical features: Recurrent vomiting, polyuria with acidotic breathing, positive family history of muscle weakness due to hypokalemia and features of rickets are the clinical features of this group. Biochemical characteristics are metabolic acidosis with normal anion gap, hypokalemia, and raised serum chloride, hypercalciuria and hypocitraturia causing nephrolithiasis and nephrocalcinosis, along with normal blood urea and serum creatinine.

Patients with dRTA require an alkaline dose of 1-3 mEq/kg/day, requiring dose adjustments until the hypercalciuria and hypocitraturia are normalized. The total dose is divided in order to be administered three or four times daily, and a higher nighttime dose is recommended. Citrate is useful in the presence of hypocitraturia in conjunction with hypercalciuria as in some cases of dRTA. Potassium citrate is preferred instead of sodium citrate because the latter favors hypercalciuria. Citrate is converted to bicarbonate in the liver on entering the Krebs cycle. Alkalinization of the urine reduces reabsorption of citrate and increases solubility of cystine, calcium oxalate and uric acid, with a tendency to reduce the development of nephrolithiasis and nephrocalcinosis. However, care must be taken not to over-alkalinize urinary pH because it may favor the precipitation of calcium phosphate. Rapid correction of the hyperchloremic metabolic acidosis can lead to the development of hypocalcemia or hypokalemia, mainly when potassium salts are not administered concomitantly.

Toni-Debre-Fanconi syndrome or Fanconi syndrome (FS) is a rare disorder of proximal tubular function that results in excess amounts of glucose, bicarbonate, phosphates, uric acid, potassium, sodium and certain amino acids being excreted in the urine.²¹

Fanconi syndrome can be hereditary or acquired. Among the hereditary causes such as galactosemia, hereditary fructose intolerance, tyrosinemia, Wilson's disease, Lowe syndrome, glycogenosis, mitochondrial cytopathies, cystinosis is the commonest. A good number of children develop the full picture of FS without any identifiable cause and are said to have idiopathic or primary FS. Autosomal dominant, autosomal recessive and X-linked pattern of inheritance are seen in primary FS and even sporadic cases are being documented. Possible mechanism includes widespread abnormality of most or all the proximal tubule carriers (specialized facilitated diffusion systems for the sugar and aminoacids). (a) It could be a defect in sodium binding to the carrier or insertion of the carrier into the brush border membrane, (b) 'Leaky' brush border membrane, (c) 'Leaky' type junction, (d) Inhibited or abnormal Na⁺, K⁺, ATPase pump and (e) impaired mitochondrial energy generation. Metabolic abnormalities include hyperaminoaciduria, glucosuria, hypophosphatemia, hypokalemia, proteinuria and acidosis. Clinical features include rickets, osteomalacia, growth retardation, polyuria and dehydration. Usually GFR is normal in childhood. A few develop stage V CKD 10-30 years after initial presentation.

Symptomatic treatment with attention to various abnormalities caused by the tubular defect is mandatory, like attention to phosphate wasting and concentration defect. Replacement of fluids, bicarbonates and potassium along with oral phosphates as discussed in the hypophosphatemic rickets along with vitamin D supplements as 1,25(OH)₂ vitamin D, forms the principles of treatment. Role of growth hormone has been emphasized in a few studies. Transplantation when done had recurrence of the disease in a few without rejection indicating there could be some extra-renal cause of idiopathic FS.

Renal rickets with hypocalcemia (Secondary hyperparathyroidism)

Vitamin D-dependent rickets type 1 (VDDR 1) is the first identified inborn error of vitamin D metabolism. This condition, which is also known as pseudo deficiency rickets, is an autosomal recessive disorder. It is caused by a mutation in the 1-alpha hydroxylase gene that causes impaired 1-alpha hydroxylation of 25-hydroxyvitamin D

in the renal proximal tubule. The defect is located on chromosome 12q13.3.

Clinical features: Hypocalcemic symptoms manifest during the first few months of life and the affected children may also have enamel hypoplasia and oligodontia. Usual symptoms are failure to thrive, tremulousness and convulsions. Because of severe muscle weakness and bone pain, they mostly lay supine and hence gross skeletal abnormalities are not present in this age. However if treatment is delayed, they will develop severe deformities of long bones and spine with generalized muscle weakness resembling myopathy.^{22,23}

Laboratory evaluation: In these infants, the serum levels of 25 (OH)₂ vitamin D will be normal and serum 1,25(OH)₂ vitamin D levels will be low indicating defective hydroxylation. But in an infant with vitamin D deficiency, serum 25 (OH)₂ vitamin D level in baby is low. Sometimes, mother also might have vitamin D deficiency.

Treatment: Treatment with calcitriol 0.25-2.0 mcg per day till radiological healing occurs. After this maintenance dose is given as 0.25-1.0 mcg /day depending on the severity and body weight along with calcium supplementation of 30-75 mg/kg/day of elemental calcium. Side effects of calcitriol is hypercalcemia, hypercalciuria, nephrocalcinosis and intraocular calcifications. Hence periodical monitoring every three months with urinary calcium/creatinine ratio and serum creatinine during each visit and annual renal ultrasound and ophthalmologic consultation should be done. During therapy serum calcium should be kept at lower limit of normal, normal phosphate and high normal levels of PTH.^{22,24}

Hereditary resistance to vitamin D -HRVD (Formerly known as VDDR – type 2)

(Theoretically VDDR type II may not be categorized as renal rickets but it is included here mainly to show the differentiating features of both the types)

Vitamin D-dependent rickets type II (VDDR II) is caused by the autosomal recessive inheritance of a mutation in the vitamin D receptor (VDR) gene (12q12-q14). The defective gene product causes end-organ resistance to active 1,25(OH)₂ vitamin D and primarily not due to renal dysfunction or renal tubular disorder

Etiopathogenesis: The disease is characterized by end-organ resistance to 1,25(OH)₂ D, due to mutations in the gene encoding the vitamin D receptor thereby preventing the action of 1,25(OH)₂ D despite high serum levels of 1,25(OH)₂ D.

Clinical manifestation: Features vary widely with the type of mutation. They appear normal at birth, but develop rickets within the first 2 years of life. Alopecia is seen in approximately two-thirds of patients because of lack of vitamin D receptor activity in keratinocytes.⁷

Laboratory investigation: Biochemical features of calcipenic rickets will be seen in addition to very high levels of $1,25(\text{OH})_2\text{D}$.

Treatment: Management of HVRD involves heroic attempts and therapeutic trials of unusually high doses calcitriol and calcium for 3-5 months. Initial dose of $1,25\text{D}$ is 6 mcg/day along with calcium supplementation. It is gradually increased to very high doses up to 60 mcg/day and calcium up to 3g per day aiming at radiologic healing and normocalcemia. This therapy also needs intensive weekly monitoring of calcium, $1,25(\text{OH})_2\text{D}$ levels, phosphate and PTH levels. Resistant patients are tried with long term infusion of intravenous calcium into central vein and changed to oral calcium once radiographic healing has occurred²⁵ (Box 2).

Box 2. Renal rickets in nutshell²

- Rickets with renal failure: Renal osteodystrophy
- Rickets with acidosis but without renal failure: Proximal RTA, distal RTA and Fanconi syndrome
- Rickets without acidosis or renal failure: Familial hypophosphatemic rickets, VDDR type 1 and VDDR type 2

Conclusion

The kidney plays a pivoting role in orchestrating many factors that contribute to bone health. It begins with the production of $1,25(\text{OH})_2$ vitamin D, the bioactive form of vitamin D, which directs the serum calcium phosphorus homeostasis and regulates PTH activity. The end result of loss of functional renal mass (CKD/hypodysplasia) or hereditary abnormalities of vitamin D metabolism is ROD or vitamin D dependant rickets respectively. If the proximal tubules fails to reabsorb adequate amount of phosphorus, either as a primary transport defect or secondary to extraneously produced inhibitors, it is termed as hypophosphatemic rickets. Finally if the distal tubules fail to maintain the 'internal milieu' because of dysregulation of acid base balance it also results in the development of rickets. Hence it can be summarized that good kidneys mean good bones.

Points to Remember

- *Rickets is commonly caused by vitamin D deficiency and responds to vitamin D and calcium supplements. If there is no response, then renal causes should be suspected.*
- *If facilities are available, laboratory investigations can identify various causes of renal rickets even prior to starting therapy.*
- *A normal serum creatinine rules out renal osteodystrophy.*
- *The presence of metabolic acidosis indicates renal tubular acidosis.*
- *The absence of acidosis indicates either hypophosphatemic rickets or VDDR.*
- *Hypophosphatemic rickets shows renal phosphate loss, whereas VDDR Type 1 can be made out by demonstrating normal or high serum $25(\text{OH})$ vitamin D and low $1,25(\text{OH})$ vitamin D levels.*
- *Management of renal rickets is more complex involving infrequently used drugs and should be coordinated with pediatric nephrologist.*

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NEWS AND NOTES

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NEPHRO-UROLOGY

NOCTURNAL ENURESIS

***Kalaivani G**
****Prabha S**

Abstract: *Primary nocturnal enuresis is one of the most common chronic ailment in children. Bowel control is achieved before bladder control and girls acquire bladder control before boys. By the age of five years of age 90%-95% are continent during the day and 80%-85% are continent by night. Enuresis is complete evacuation of bladder and is mostly functional.*

Keywords: *Primary nocturnal enuresis, Behavioural, Desmopressin.*

The International Children's Continence Society (ICCS) follows Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and International Classification of Diseases (ICD) criteria which require age above 5 years for the symptom of incontinence and further defines nocturnal enuresis as an intermittent incontinence with more than one episode per month and at a frequency of 3 episodes over 3 months during periods of sleep.¹

Enuresis (bedwetting) is a socially stigmatizing and stressful condition which affects around 15% to 20% of the five-year olds.² of whom 60% are boys with a positive family history in 50%. Nocturnal enuresis (NE) with daytime incontinence is seen in 20% of children. It ceases spontaneously in approximately 15% of affected children.¹ Risk factors for nocturnal enuresis are males, first born in large families, family history of enuresis, late toilet training, working mothers and lower socioeconomic status.

Classification

1) Mono symptomatic nocturnal enuresis (MNE): In MNE there is no lower urinary tract symptoms (LUTS) and bladder dysfunction. This is further classified as primary and secondary based on the onset and the causes are given in Table I.

Table I. Primary and secondary enuresis - causes

Primary enuresis	Secondary enuresis
Idiopathic	Dysfunctional voiding
Disorder of sleep arousal	Overactive bladder(OAB)
Nocturnal polyuria	Neurogenic bladder
Small bladder capacity	Urethral obstruction
Behavioral problems	Psychological
Cystitis	Ectopic ureter
Constipation	Seizures
	Obstructive sleep apnea
	Diabetes mellitus
	Acquired diabetes insipidus
	Acquired urethral obstruction

Primary nocturnal enuresis (75%) (PNE) is the presence of enuresis in a child above 5 years old who has never achieved an asymptomatic period (>6 months) of consistent nighttime dryness. Bedwetting persists from early age and they have never attained bladder control due to delayed maturation of voiding mechanism. Spontaneous resolution is seen in 75% of them.

Secondary nocturnal enuresis (25%) (SNE) is the presence of enuresis in a child above 5 years who has achieved an asymptomatic period (>6 months) of consistent nighttime dryness in the past. Secondary enuresis is most commonly triggered by an unusually stressful event, significant enough to cause psychosocial regression or due to an underlying cause like recurrent urinary tract infection (UTI) or renal abnormality.

2) Non-mono symptomatic enuresis: Enuresis in children with other lower urinary tract symptoms (LUTS) like increased frequency, urgency and lower urinary tract pain. Day time enuresis is the hallmark of non-mono symptomatic enuresis. This also is classified based on the onset as primary and secondary.¹

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Etiopathogenesis

Nocturnal enuresis is a triad involving three organs: polyuria (kidneys), detrusor overactivity (bladder) and higher arousal thresholds (brain).³ Usually underlying structural abnormalities are not found. Though the exact cause is unknown, there are various postulations given for nocturnal enuresis.

Genetic: A family history of nocturnal enuresis is found in most children. One study has shown that in families where both parents had enuresis, 77 % of children had enuresis. But if only one parent had enuresis, 44 % of children were affected; But if neither parent had enuresis only 15% of children had enuresis.² Heredity as a causative factor of primary nocturnal enuresis has been confirmed by the identification of a major dominant gene located on chromosome 13(ENUR1) and (ENUR2) on chromosome 12.⁴

Delayed maturation of central nervous system: Delayed functional maturation of the central nervous system reduces the child's ability to inhibit bladder emptying at night. The child's bladder will fill, but the sensory output due to stretching of the bladder is not perceived. Hence central cortical control over the emptying reflexes of the full bladder are not adequately inhibited during sleep leading to nocturnal detrusor overactivity.⁵

Sleep fragmentation: Parents of children with nocturnal enuresis complain of deep sleep and difficulty in waking them up due to a high degree of sleep fragmentation associated with increased cortical arousals and periodic limb movements during sleep (PLMS).⁶ Nocturnal enuresis is associated with upper airway obstruction causing snoring and sleep apnea. Surgical relief of obstruction by tonsillectomy, adenoidectomy or both diminished nocturnal enuresis by 76%. Sleep EEG showed increased slow brain wave activity.⁷ Additionally in children with snoring (adenotonsillar hypertrophy) or obstructive sleep apnoea (OSA) a constant arousal stimuli from the obstructed airways paradoxically increases the arousal threshold thereby producing a negative intrathoracic pressure which stimulates increased secretion of atrial natriuretic peptide (ANP) leading to polyuria.⁸

Nocturnal polyuria: Secretion of vasopressin (anti-diuretic hormone) increases urine concentration and reduces urine output at night. Anti-diuretic hormone (ADH) has a circadian rhythm with optimum secretion during night. Nocturnal enuresis occurs due to blunted circadian rhythm. Normal children have normal vasopressin throughout the night but enuretics have reduced plasma vasopressin

between 10 pm and 6 am resulting in increased nocturnal diuresis with a low urine osmolality. Hence, the use of desmopressin (DDAVP) may help them. But about 20-60% of children will not respond. DDAVP resistant MNE is defined as a reduction of less than 50% of the number of enuretic nights.

Children with NE produce excessive amounts of relatively dilute urine in the night due to altered diurnal rhythm of vasopressin secretion. This is reflected in the assessment of bladder capacity. The expected bladder capacity (EBC) for the age is calculated as age (years) + 2 x 30 = ml of urine and 390 ml above 12years.⁹ When EBC is >130% it is defined as nocturnal polyuria. Hence the combination of increased fluid intake in the night with reduced production of ADH contributes to increased dilute nocturnal urine output and nocturnal enuresis.

Biological: Research suggests that bladder capacity remains same during day and night and there is functionally a small bladder capacity. When the bladder capacity is < 70% it indicates reduced bladder volume. In NE there is a combination of functionally reduced bladder capacity, lack of inhibition of bladder emptying during sleep, bladder overactivity and nocturnal polyuria resulting in enuresis.

Behavioral: Behavioral disturbances also play a major role in PNE. Primary nocturnal enuresis can occur due to neurobiological dysfunction like attention deficit hyperactivity disorder (ADHD) and autistic spectrum.¹⁰ History of bed wetting is a very strong clue to the diagnosis of ADHD. Secondary enuresis occurs due to stressful situations like parental divorce, birth of a sibling, sexual abuse or school trauma leading to anxiety, social withdrawal and low self esteem. Besides this, the differences in sleeping practices of our children co-sleeping with parents till early adolescence and in sleep hygiene also make this benign condition disturbing for the whole family and the child.¹¹

Clinical evaluation

Evaluation of enuresis usually requires a complete history and a focused physical examination. Past history of recurrent UTI, constipation, age of toilet training (PNE is more common in late trainers) should be obtained. Family history of urological and psychological problems must be looked for. History of difficulty in paying attention in school and concentrating on academics, impulsive behavior, fidgetiness and temper tantrums must be enquired. The child's habits like consuming more fluids in the night which may contribute to nocturnal enuresis should be noted. History of constipation and encopresis to check

Table II. Evaluation and inference

Evaluation	Relevance
History	
Weight loss, polydipsia, polyuria	Diabetes mellitus, diabetes insipidus, chronic kidney disease
Medications (selective serotonin reuptake inhibitors valproic acid)	Bladder inhibition
Obstructive sleep apnea	Impaired arousal
Micturition Bed wetting frequency, day time incontinence, previous dry nights	Primary voiding disorders like detrusor sphincter dyssynergia, hypercalciuria, urinary tract infection
Weak stream, urinary urgency, frequency, abdominal pain/seizures, gait abnormality, constipation	obstructive uropathy like posterior urethral valves, neurogenic bladder
Physical Examination	
Continuous urinary dribbling	Ectopic ureter
Distended bladder	Obstructive uropathy, neurogenic bladder
Fecal impaction, abnormal reflexes, lumbo sacral lesions, relaxed anal sphincter	Neurogenic bladder
Behavioral problems	ADHD, other psychological problems

on the bowel habits should be enquired. Voiding history like volume, number of voids and interval between voids and frequency in relation to meals, school breaks and play activities will give a clue to the cause of enuresis. Urine color, hematuria, dysuria and urgency should be enquired.

Examination: Vital signs including blood pressure, blood pressure and growth assessment must be done. Abdominal examination for renal masses, distended bladder, fecoliths and undergarments for wetness (Table II). Urinary stream has to be observed to detect whether it is weak, slow or intermittent. Bladder distension tenderness should be noted along with examination of lumbosacral spine or looking up for anorectal anomalies. Complete nervous system examination including perineal reflexes should be examined. Rectal examination would give information on the tone, diameter (constipation) and chronic bladder distension.

Investigations

Urinalysis should include the first void morning sample for urine specific gravity urine osmolality and pus cells. Urine must be examined for glucosuria, hypercalciuria and proteinuria. Basic tests like blood urea, serum creatinine, serum electrolytes serum calcium, serum

uric acid, blood sugar and serum osmolality must be done. All children with enuresis must undergo an ultrasonogram of kidneys, ureters and bladder for structural anomalies along with bladder wall thickness and post void residual urine (PVR). X ray lumbosacral spine would help in screening for spinal dysraphism.

Micturition cystourethrogram is done if vesicoureteral reflux or neurogenic bladder is suspected. Magnetic resonance imaging (MRI) may show delay in maturation of neuronal circuits in prefrontal cortex if present, while spinal MRI can document spinal dysraphism and a tethered cord if present in case of neurogenic bladder. Uroflowmetry is to be done to observe for any interruption in urinary stream and urodynamic studies if voiding dysfunction is suspected are the other investigations which help during the evaluation of enuresis. Deep sleepers and children who snore may require a polysomnography to rule out obstructive sleep apnea.

Treatment

Urotherapy or psychotherapy based on conservative cognitive behavioral treatment focussing on life style therapy and lower urinary tract rehabilitation is done by training the child to get control over their voiding. It is

Table III. Voiding diary

Name : Age : DOB: Record date: Urinary complaints: Age of toilet training: Infection Wetting (day/night) Burning Frequency Number of daytime voids/24h 1-3 4-6 7-10 Volume of voided urine(bladder capacity) Maximal interval between the voids LUTS Bowel problems: Number of bowel movements/day/week Soiling	Time	Day 1	Day 2	Day 3
	10 pm			
	11 pm			
	12 mid night			
	1.00am			
	2.00 am			
	3.00 am			
	4.00 am			
	5.00 am			
	6.00 am			
	7.00 am			
	Day time voids			

done by intensive voiding re-education on normal bladder function, normal voiding patterns, voiding behavior and voiding diaries. It also includes the advice on fluid intake, diet and bowel habits. Great support should be provided to child and family during training.¹ Voiding diary is a significant simple tool used to assess nocturnal enuresis. It is helpful in identifying children with non monosymptomatic enuresis. Frequency, volume charts and mobile apps can also be used (Table III).

i) Fluid intake: Drinking fluids should be maximum in the daytime, 40% in the morning, 40% in the afternoon and restricted to 20% after 5.00 pm.

ii) Voiding: Timed voiding every 3-4 hours, double voiding if large post void residue (4-6 years PVR 30ml and 7-10 years is 20ml) and voiding before bedtime. While voiding child should relax, use optimal posture and take time to empty the bladder completely.

iii) Bowel management: Train the child for regular bowel movements at the same time daily and correction of constipation by laxatives.¹²

iv) Diet: Sugar, dairy products, chocolates, citrus fruits, juices and caffeine intake are diuretic diets which increases nocturnal enuresis, hence these should not be offered after 6.00pm. Ensure high fibre intake of 15-20 g daily with five servings of fruits.¹²

Non pharmacological therapy

Motivational therapy is a form of behaviour modification focusing on positive reinforcement and it should be the first-line approach to treat children, especially in the age group of 5-7 years. It involves reassuring the parents and the child, removing the guilt associated with bed-wetting and providing emotional support to the child. Children with NE should be helped to understand about the condition and motivated to cooperate for the treatment.

Positive reinforcement is to set up a diary and chart (Table III). Dry nights would be rewarded with stars or stickers. Negative reinforcement like punishments or criticism should be avoided.⁵ Resolution rate for children has been estimated to be 25%-70% with a relapse rate of 5%.¹ If therapy is not successful within three to six months, alternate treatment should be offered. Self hypnotherapy is to help the child psychologically and motivate to arise to void at night when the bladder is full.⁵

Bladder training program

Bladder retention training: Functional bladder capacity may be decreased in children with NE causing premature bladder emptying during night. Bladder retention training during day may increase bladder capacity at night by advising child to hold urine for increasing periods of time for 6 months.

Physiotherapy: Tonicizing abdominal wall and pelvic floor muscles, pelvic floor relaxing exercises and improving posture for micturition have been shown to give good results.¹³

Behavioral condition therapy

Enuretic alarm: If urotherapy is not successful by six weeks interventions like the addition of an enuresis alarm is indicated. When the child voids in bed, a moisture-sensing device called moisture alarm (bell & pad) placed near the genitals is activated and triggers the alarm. This evokes a conditioned response of waking and inhibiting urination. Extra fluid is given at bedtime after successfully becoming dry and intermittent reinforcement before stopping treatment is highly effective. If there is no response by two weeks, alternate methods are to be considered. Disadvantages are some parents and children decline to co-operate and the alarm fails to awaken the child when they are in non-rapid eye movement (NREM) sleep. Disrupted sleep for the family members can occur.¹⁴

Arousal training: This therapy focuses on the sequence of events like waking up the child, getting up, turning off alarm, attending restroom, emptying the bladder completely and reattaching the enuresis alarm.

Biofeedback therapy: It is by using an objective measure like visualizing uroflow curve during micturition and learning to correct flow curve and also check the post void residue. EMG shows children how far they have progressed in achieving a goal like pelvic floor relaxation during voiding and complete voiding without any residual urine.¹⁵

The importance of constipation or fecal retention as a contributing factor has to be recognized and treated appropriately.

Pharmacotherapy

Pharmacotherapy is advised for children above 6 years after a detailed history and clinical examination (Table IV). It is best to remember that drugs do not cure NE; they provide only a stop gap measure until the affected children are able to wake on their own at night to void.

a) Desmopressin (DDAVP) is a synthetic vasopressin analogue acting on V2 receptors in the kidney. One spray in each nostril (which can be increased to two sprays in each nostril) for 3-6 months, shows a rapid response in one to two weeks. It is effective in 10%-50%, but 60% relapse on stopping treatment. Main adverse effects are dry mouth and constipation.¹⁶

Desmopressin melt - a fast melting orally lyophilized tablet, is also recommended for children specially below 12 years.^{17,18} It decreases urinary output in well hydrated children with PNE. A dose range of 120-240 µg controls diuresis during the night. If there is no response doses can be increased. Advantages are that it is not affected by nasal congestion or GI transit and fluid intake is not required (as it melts). It is given 30-60 min before bedtime.

b) Imipramine (tricyclic antidepressant): Current theories are that nocturnal enuresis are CNS related or due to local bladder effects. Imipramine facilitates urine storage by decreasing bladder contractility and increasing outlet

Table IV. MNE drugs

Drug	Action	Dose	Duration	Adverse effects
Desmopressin	ADH action	0.12-2.4 mg/day	4weeks, tapered & stopped 3wks later high relapse rate	Hyponatremia - so restrict fluids
Oxybutinin	Anticholinergic	< 5 years - 0.2mg/kg/day >5 years- 2.5-5mg 8-12 hourly	3-6months	Drymouth,palpitation,constipation, blurring of vision
Tolterodine	Anticholinergic	0.5mg/kg 12 hourly	3-6months	Dry mouth less
Imipramine	Antipsychotic, Anticholinergic	1-2.5mg/Kg/day	3-6months high relapse rate	Anxiety, palpitations, mood changes
Clonidine	Alpha blocker	0.04 mg/kg/day	Response by 4wks for 3-6months	Hypotension, headache, dizziness

Table V. Definitions of treatment out comes¹

Response	Reduction of wet nights
Initial success	
Complete response:	100%
Partial response	50-99%
No response	<50%
Long-term success	
Relapse	More than one symptom recurrence per month
Continued success	No relapse in 6 months after interruption of treatment
Complete success	No relapse in two years after interuption of treatment

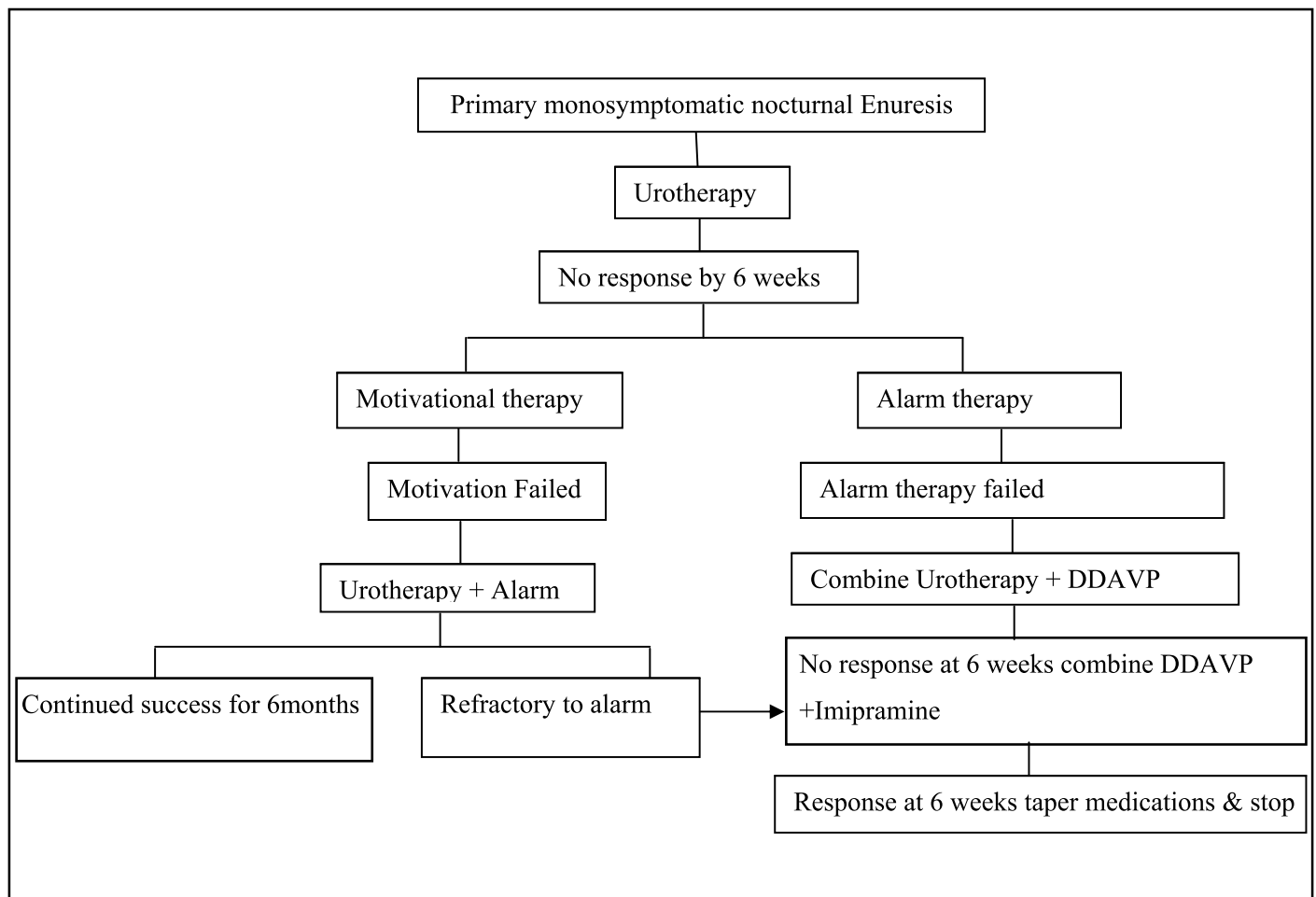


Fig.1. Algorithm for management of monosymptomatic nocturnal enuresis

resistance. It inhibits reuptake of norepinephrine or serotonin at presynaptic neuron.¹⁹

c) Oxybutinin (anticholinergic): Most enuretics have a small functional bladder capacity. This drug is indicated for children with symptoms of urgency and frequency. It allows bladder to relax and store more urine.

d) Tolterodine is a competitive muscarinic receptor antagonist for overactive bladder. Unlike oxybutynin it is more selective for urinary bladder over salivary glands. Hence, lesser side effects.

e) Flavoxate (Urispas) is for symptomatic relief of incontinence. As an anticholinergic it has direct effect on the muscle. It counteracts smooth muscle spasm of urinary tract.

Surgical management

Ectopic ureter and obstructive sleep apnea are the only two conditions which respond to specific surgical intervention.

Management of primary nocturnal enuresis may involve one or a combination of interventions. Education and motivational therapies usually are tried initially. More active intervention is warranted when social pressures increase and self-esteem is affected as the child grows older. When monotherapy fails combinations were found to be useful. Alarm and desmopressin above 5-7 years or desmopressin and imipramine can be combined. For drugs a combination therapy of imipramine with oxybutynin was reported to be more effective and also had significantly lower relapse rates of 20% than imipramine monotherapy. Treatment outcome is defined by standard criteria (Table V).

Treatment – relapse / refractory

Relapse: It is defined by more than one wet night per month after a period of dryness.¹ Treatment of relapse varies depending upon the initial management. Underlying causes like overactive bladder, diabetes mellitus, occult constipation and faulty use of alarm must be ruled out.

Refractory enuresis: When motivated children and families do not respond to treatment with an enuresis alarm for three months with maximum dose of desmopressin (0.4 mg) it is called refractory enuresis. Atomoxetine, a norepinephrine reuptake inhibitor at a dose of 0.5mg/kg /day to a maximum dose of 1.4mg/kg/day (100mg/day) has been found useful in refractory enuresis due to ADHD.²⁰ Clonidine, an α_2 adrenoceptor agonist in a dose of 4 μ g/kg before bedtime reduced enuretic nights in four weeks, But mechanism of

action is not known. However referral to a Pediatric nephrologist is warranted¹

Differential diagnosis

Polyuric conditions like diabetes mellitus, diabetes insipidus, non oliguric renal failure, UTI, urge incontinence due to bowel bladder dysfunction and pollakiuria should be differentiated from nocturnal enuresis.

Prognosis

Majority of primary nocturnal enuresis has a 15% spontaneous resolution every year with education and reassurance. Treatment should be individualized based on specific situation of the individual child and family patients. Persuasion and reward plays an important role in therapy.²¹

Conclusion

MNE is not benign as previously assumed. A step wise approach to management of MNE is given in Fig.1. Due to its increased comorbidity with neuropsychological dysfunction and disrupted sleep they need to be identified and managed appropriately as they are reversible if promptly diagnosed and treated.

Points to Remember

- *Primary monosymptomatic enuresis is defined by discrete episodes of urinary incontinence during sleep in children above 5 years of age who have never achieved a satisfactory period of night time dryness, with no history of lower urinary tract symptoms or bladder dysfunction.*
- *Management of primary nocturnal enuresis may involve one or a combination of interventions. Education and motivational therapies are the initial treatment of choice.*
- *Active interventions are warranted as the child gets older, when social pressures increase and when self esteem is affected.*
- *Enuresis alarms and desmopressin are effective interventions for nocturnal enuresis in children and families who desire active treatment.*
- *Enuresis alarms are the most effective long term therapy and have few adverse effects, but requires a long term commitment (usually three to four months).*
- *Oral desmopressin works best for children with nocturnal polyuria and normal functional bladder capacity. It is the initial active therapy for children and families who seek short term improvement of enuresis.*

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NEPHRO-UROLOGY

RENAL NUTRITION IN EARLY CHRONIC KIDNEY DISEASE (CKD)

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Abstract: Renal nutrition in early chronic kidney disease (CKD) is focused on the importance of dietary modifications and supplements for children with CKD stage 2-4. Poor nutrition often complicates CKD. Conversely, reduction of renal function frequently leads to abnormalities of nutritional intake or metabolism, resulting in a complex inter-relationship of renal function and nutrition. The guidelines are provided by Kidney Disease Outcomes Quality Initiative (KDOQI) for pediatric age group with early CKD. Early evaluation, proper intervention, judicious use of nutritional supplements according to blood chemistry level is the corner stone. Children should be allowed to take daily recommended intake (DRI) of carbohydrates, healthy fats, unrestricted vegetarian proteins and fiber according to their age group. Timely nutritional intervention will provide long term benefits for disease modification, improve growth potential, maintain muscle mass and reduce infection rates.

Keywords: Chronic kidney disease, Nutrition, Children, Diet

Nutrition is the science that interprets the interaction of nutrients and other substances in food in relation to maintenance, growth, reproduction, health and disease of an organism. It includes food intake, absorption, assimilation, biosynthesis, catabolism and excretion.¹ The most important window for optimizing growth is during the first two years of life. Nutrition has key role in overall growth, development and also for renal maturity. Even maternal malnutrition can lead to increase in apoptosis of mesenchymal cells of the very early metanephrons and reduce expression of peri-ureteric genes

Prox-1 and Cofilin-1.² Any ground lost during perinatal or early infantile period is often difficult to recover. Hence, an early detailed nutritional evaluation and support is essential.

Chronic kidney disease (CKD) itself is a catabolic disease and additional factors like cachexia (loss of body mass that cannot be reversed nutritionally), elevated resting metabolic rate, baseline malnutrition (quality and quantity of food is not sufficient to meet individual's requirements), anorexia (loss of appetite and early satiety), depression, growth hormone resistance, metabolic abnormalities like- acidosis / uremia and high levels of cytokines such as IL-6/ TNF-alfa can contribute to significant nutritional deficiency.

According to Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, CKD is defined by structural or functional abnormalities of kidney with or without decreased glomerular filtration rate (GFR) that is manifested by either pathological abnormalities or other markers of kidney damage including abnormalities in the blood, urine or in imaging studies. Staging of renal failure is mentioned in Table I.

Table I. Chronic kidney disease - Stages

Stage	Description	GFR (mL/min/1.73m ²)
1	Kidney damage with normal or GFR	≥90
2	Mild GFR	60-89
3	Moderate GFR	30-59
4	Severe GFR	15-29
5	Kidney Failure	<15 (or dialysis)

Evaluation of growth and nutritional status evaluation

KDOQI³ guidelines of 2008 expanded target population for CKD stage 2-4 and transplant. All these guidelines are based on practical experience rather than evidence.⁴ There are significant challenges in evaluating nutritional status in CKD mostly due to presence of edema.

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No single measure can provide true assessment of nutrition. Following are some surrogate markers:

1) Anthropometric assessment: Height, weight and head circumference (for <3 years) should be plotted on percentile charts; and values expressed in terms of SD (standard deviation). Body mass index [(BMI) (kg/m²)] is more prognostic because extremes are associated with increased mortality. Wong et al., suggested that adjusted relative mortality rate of children with end stage renal disease (ESRD) is 60% higher at BMI SD of +/- 2.5 as compared with an ideal BMI SD of 0.5.⁵ Skin fold thickness and mid arm circumference do not hold any value due to confounding factors like edema, regional fat distribution and age related variations.

2) Dietary assessment: Prospective diet diary for 3 days and retrospective recall are most commonly used methods.³ It should be done at monthly interval for infants and 3-4 monthly for children.

3) Serum albumin: Malnutrition related low serum albumin (<2.9 gm/dL) is consistently associated with high mortality. However, hypoalbuminemia may be seen due to factors other than nutritional, such as protein loss in nephrotic syndrome and peritoneal dialysis, GI losses and systemic inflammatory conditions (such as SLE).

4) Others: Dual energy X-ray absorptiometry (DEXA) scanning can be used to estimate lean body mass, fat mass and bone mineral density. However, lean body mass may not be accurately determined in presence of fluid overload. Other tools such as bioelectrical impedance, total body potassium and in vivo neutron activation are seldom used in clinical practice.

Energy requirement and recommendation

Requirement of calories for children with CKD stage 1-4 is equal to RDA (Recommended Daily Allowances) for the same chronological age group. In children with malnutrition it should be 125% of RDA; additional calories are required for ongoing losses like vomiting or dehydration. Of this energy intake, 55-60% of calories should be derived from carbohydrates, 30% from fats and 10% from proteins.

Adequate calorie intake has several implications, 1) preventing the breakdown of protein for gluconeogenesis, 2) avoiding the loss of growth potential (even catch-up growth can be achieved in children less than 2 years of age), 3) decrease in the number of hospitalizations and 4) reduction in the rates of peritonitis.

Estimated energy requirement (EER) (kcal/day) can be calculated based upon child's age and weight. Equations accepted by Food and National board are complicated.⁶ Another simple equation for calorie requirement is based on Holliday and Segar's formula.⁷

0-10 Kg: 100 cal/kg

10-20 Kg: 1000cal + 50 cal/kg for each kg over 10 kg

>20 kg: 1500 Cal+20 cal/kg for each kg over 20 kg

Route of administration and various options

Encouragement for oral feeds is optimal but can be challenging and stressful for parents with infants. When energy intake remains low despite use of diet manipulation and oral supplements, enteral feeding is recommended. Nasogastric tube, gastrostomy, gastro-jejunosomy and jejunostomy tube feedings have all been successful to provide additional nutritional, fluid and medication intake. Poor oral intake, recurrent nausea, vomiting and poor weight gain are major indications for enteral feeding. Tube feedings not only improves caloric and nutrient intake, but also reduces the stress that accompanies forceful oral feeding to meet nutritional requirement. Night time continuous feeding with daytime hunger and oral route are preferred options. Parenteral nutrition is rarely required in early CKD.

Use of corn oil or canola (mustard) oil is also low cost, good alternative. Graded increases in calories help to avoid side effects like increased bowel frequency. For older children, use of margarines or oils, cream and other fats, sugar and syrups can be used for additional calorie intake. If formula feeds are preferred it is safe to choose those with dense calories and low minerals.

Protein: Children need to be in positive nitrogen balance to support growth. Optimal protein requirement for children with CKD stages 1 through 5 have not been determined. Start with RDA as for healthy children and increase subsequently based on proteinuria, glucocorticoids, acidosis, dialysis, peritonitis and catabolism. Reducing dietary protein intake with CKD has not been shown to slow the progression of CKD. In fact, it may worsen the malnutrition associated with CKD and hence, protein restriction is not recommended.³

For children with CKD Stage 2-4, a minimum of 0.8-1.1 gm/kg/day of protein is required to maintain growth. For CKD stage 2-3 protein requirement is 100%-140% of RDA and for stable Stage 4 it is 120%-140% of RDA.³ Progressive CKD is generally associated with a reduction in spontaneous dietary intake of both protein and energy.

In a study comparing 50 children with CKD stages 3 to 4 with healthy controls, protein intake was found to be 33% lower and energy intake was 10% lower in patients with CKD.⁹

When spontaneous energy intake tends to be critically low, e.g. less than 80% to 85% of the RDA, dietary protein intake in those with CKD is far in excess of the average requirements, typically 150% to 200% of the RDA. Herein protein intake is restricted to 0.8-1.1 gm/kg. According to KDOQI guidelines, implementation and maintenance of a strict low-protein diet requires a major lifestyle change that may not be acceptable to many families. Hence, moderate protein restriction aiming at 100% to 140% of the DRI in CKD stage 3 and 100% to 120% of the DRI in CKD stages 4 to 5 considered as reasonable compromise. First class protein or complete proteins derived from meat, fish and eggs have a good balance of the essential amino acids and are in similar proportions to those found in human tissues, muscles and organs. Vegetarian protein is derived from plant protein. Age wise protein requirement is shown in Table II.³

Carbohydrate: Healthy distribution of calories from carbohydrates should be 45%-65%.³ There is no evidence to suggest that macronutrient distribution in children with CKD should be different from that in the general population. Average intake (AI) for infants between 0-6 months is 60 g/d of carbohydrate and for 7-12 months 95 g/d of carbohydrate. RDA for age 1-18 years is 130 g/d of carbohydrate for both girls and boys.⁵ Use of complex carbohydrate in the place of simple sugars is recommended. Certain medications such as steroids and tacrolimus can cause glucose intolerance in 5-20% of patients that may require medical intervention. Regular check of blood and urine sugar is mandatory for all children on treatment.

Fat: High fat food and added fats to feeding as a concentrated source of calories (9 Kcal/gm of fat) for children with poor weight gain is recommended. Due to disproportion of micro and macro nutrients there is increased risk for cardio vascular disease (CVD). Both traditional (like dyslipidemia, hypertension, obesity, poor physical activities, genetics, etc..) and nontraditional factors (uremia, uremia related anemia, inflammation, prothrombotic factors, high homocystine, vascular calcification and volume overload, etc..) can predispose these children for CVD.

Practical consideration: Use of “heart healthy” fats (high in mono-saturated fatty acids and omega 3 fatty acids) like margarines or oil from corn, canola, safflower, soy, olives or peanuts can be used. Therapeutic life style changes and unrestricted physical activities are recommended. Use of omega 3 fatty acids (cold water fish, canola oil, walnuts, flax seeds, etc..) at least twice a week in diet is helpful to slow progression towards ESRD (specially in IgA nephropathy).¹⁰

Fibers: Hypercholesterolemia and constipation can be treated effectively with help of natural fibers (like cranberries/cereal cookies/shredded cabbage/fig fruit added to salad, etc) or synthetic fibers.¹¹ Few other alternatives are ispaghula, isabgol, organic psyllium whole husk etc. These fibers are generally available as conjugation with potassium or phosphorus, dose and interval with medication has to be adjusted.

Vitamins: Routine supplementation of fat soluble vitamins likes A, D, E, K is not recommended in children with CKD because of their impaired excretion and concerns about their accumulation.¹² Hypervitaminosis A can lead to anemia, hyperlipidemia, hypocalcemia, headache, alopecia

Table II. Protein requirement according to age and CKD stage

Age	DRI (g/kg/d)	CKD Stage 3 (g/kg/d) (100%-140% DRI)	CKD Stage 4 (g/kg/d) (100-120% DRI)
0-6months	1.5	1.5-2.1	1.5-1.8
7-12 months	1.2	1.2-1.7	1.2-1.5
1-3 years	1.05	1.05-1.5	1.05-1.25
4-13 years	0.95	0.95-1.35	0.95-1.15
14-18 years	0.85	0.85-1.2	0.85-1.05

DRI: Daily recommended intake

Table III. Dose of Vitamin D (cholecalciferol)

Vitamin D status*	Calcidiol(ng/mL) (25-OH cholecalciferol)	Vitamin D2 Dose (to be given orally)
Severe deficiency	<5	Initial dose:8000 IU/day or 50000 IU/week × 4 weeks then:4000IU/day or 50000IU twice monthly× 2 months
Mild deficiency	5-15	4000IU/day or 50000IU every other week ×3 months
Insufficiency	16-30	2000IU/day or 50000IU every 4 weeks ×3 months

IU – International Unit

**Hold vitamin D if calcium ≥ 10.2 mg/dl or if phosphorus exceeds the upper limit for age and Calcidiol is normal*

and bone disease. In contrast, vitamin K deficiency is more likely due to widespread use of antibiotics and poor intake.

Vitamin D is important not only for bone mineral health but also for its role in immune system, cardiac function and anti-cancer effects. Serum 25- hydroxyvitamin D level has to be measured once per year for children with CKD 2-5.³ According to serum levels specific supplements are to be administered. In deficiency states, supplementation with inactive form (cholecalciferol) is recommended as mentioned in Table III.³

In children with early CKD, supplementation with water soluble vitamins is required especially for folic acid that prevents hyperhomocysteinemia. According to KDOQI guidelines the following is the RDA of vitamins (Box 1). Use of multi vitamin preparations should be used cautiously due to presence of fat soluble vitamins. Excessive use of vitamin C can lead to hyperoxaluria and increase risk of renal stone disease / nephrocalcinosis especially in predisposed children.

Calcium and phosphorus: Hypocalcemia is very common in children with CKD due to insufficient oral intake, low intestinal absorption (due to impaired endogenous production of calcitriol) and high phosphorus levels. 100% of the DRI for calcium (60-100mg/kg/day) is a starting point in children with CKD. Depending on serum calcium levels and adjusted values for low serum albumin level, oral supplements have to be scaled up. The safe upper limit of dietary calcium intake in healthy individuals older than 1 year is 2,500 mg/d. For children this is approximately 2 times the RDA. Calcium salts are used in empty stomach as a source of calcium and after meals as a phosphate binder. Therapy with active vitamin D (calcitriol) is generally required in early stage of CKD to boost intestinal calcium absorption. Dose of calcitriol is 15-30 ng/kg/day. In children

Box 1. RDA of vitamins

Vitamin B:

B1- 1mg/day

B2 -1 to 2 mg/day

Biotin- 20 mcg/day

B6 - 1.5 to 2 mg/day

Pyridoxine -1 mg/day

Pantothenic acid -5 mg/day

Folic acid – 80 mcg/day for infants, 200 mcg/day for children up to 5 years and 400 mcg/day for >5 years age

Vitamin C:

15mg/day for infant and 60 mg/day for children

the dose for <10kgs- 0.25 mcg twice a week, between 10-20 kg- 0.25 mcg on alternate days and >20kgs- 0.25 mcg daily.

Serum calcium phosphorus product has to be maintained $<65 \text{ mg}^2/\text{dl}^2$ to maintain PTH levels in target reference range and prevent metastatic calcifications. Age specific normal range for calcium and phosphorus are mentioned in Table IV.³ In case of high serum phosphorus and high calcium levels non-calcium containing phosphorus binders like sevelamer bicarbonate can be used.

Trace elements like zinc, copper and l-carnitine are also required especially to maintain GI mucosal health and for therapy of refractory anemia.

Table IV. Age-specific normal ranges of blood ionized calcium, total calcium and phosphorus

Age	Ionized calcium (mmol/L)	Calcium (mg/dL)	Phosphorus (mg/dL)
0-5 month	1.22-1.40	8.7-11.3	5.2-8.4
6-12 month	1.20-1.40	8.7-11.0	5.0-7.8
1-5 year	1.22-1.32	9.4-10.8	4.5-6.5
6-12 year	1.15-.32	9.4-10.3	3.6-5.8
13-20 year	1.2-1.30	8.8-10.2	2.3-4.5

Low phosphorus formula are recommended to lower phosphorus load. Limit foods that are high in phosphorus like milk, dried beans, peas, nuts, whole grain products, butters, chocolates etc. There are very limited brands of formula milk with low phosphorus available in India. Cow's milk has 96mg phosphorus /100 mL, as compared to human milk with 15mg/100mL and Similac^R 60/40 with 18mg/100mL of phosphorus. High phosphorus containing packed milk or regular formula feed are not advisable for children with progressive CKD.

Pediasure^R is most commonly used high energy formula, but it has a protein of 14.1mg/100ml and phosphorus of 240 mg/100mL. Specific renal formulas for children are not available in India. Hence, we could suggest use of adult formulations like Nepro HP^R, Renalcal^R and Nutrenal^R that are not only calorie dense, but also low in phosphorus and potassium.

Sodium: Sodium intake is necessary for maintenance of intra-vascular volume and blood pressure. Most families consume between 15-20 grams of salt per day against the adult human body needs of ~ 4-6 gram/kg/day of sodium chloride. Requirement of sodium depends on native kidney disease (tubular or glomerular). Children with glomerular diseases usually need salt restriction to 2 gm/kg/day to assist in edema control as well as blood pressure management. In contrast, certain salt wasting states such as obstructive uropathy, renal dysplasia and tubular disorders (Bartter syndrome) require much higher sodium intake compared to healthy children. Salt can be provided as 3% NaCl solution orally in infants less than 6-8 months age or added to solid foods in older infants and children.

When low salt diet is recommended, it is preferable to prepare homemade baby food without salt. The entire family should switch to low salt diet for better compliance and positive impact on child's health (the children should not feel that they are sick and provided with separate food).

It is good to avoid canned foods. To compensate for low salt, taste can be enhanced by adding spices, herbs, lemon juice or vinegar. Some dietary indiscretions should be permitted as long as it is limited to small quantities.

Potassium: Potassium is the major intracellular cation and is required for muscle and nerve function. Hyperkalemia is often asymptomatic. Restriction of dietary potassium depends upon blood potassium level and is usually not necessary until the GFR falls below 25% of normal. Children started on angiotensin converting enzyme inhibitor, tacrolimus and beta-blockers may require restriction at earlier stages of CKD and many a times, discontinuation of the medications if plasma potassium remains greater than 5.5 mEq/L. Common practice is to limit potassium intake to 1-3mmol/kg/day for infants and toddlers and to 50-100 (2-4 grams) per day in children and adolescents. Food rich in potassium and poor in potassium is given in Box 2.¹³

Box 2. Potassium content in foods	
Foods rich in potassium	Foods poor in potassium
Coconut water, Banana, Sweet lime, Custard apple, Guava, mangoes, Papaya, Dried fruits, Potatoes, Chocolates, Tomato products Salt substitutes	Apples Grapes Cherries Popcorn Raisins Nuts White rice

If dietary restriction is not sufficient to reduce plasma potassium concentration, potassium binders (such as sodium or preferably, calcium-potassium exchange polystyrene resins) can be used. Approximately 3-5 grams of binder can be added to 100 mL formula or expressed

Box 3. Common foods	
Common foods to include	Common foods to avoid
Home made low salt/ low fat vegetarian diet, All pulses/ whole grains Egg Fish Raisins Fig Walnuts, Flax seeds	Meat, mutton and chicken Dark green leafy vegetables like palak Coconut water Sweet lime Custard apple (high in potassium) Fried and packed foods (chips, samosa, chats) Excess of dairy products

breast milk and kept aside for 30-40 minutes. Subsequently, the milk is filtered, the supernatant with bound potassium is discarded and filtered milk can be administered orally. In older children on solid diet, the water used for boiling vegetables is discarded potassium is leached out during boiling and fresh water used to make the final preparation.

Vegetarianism: Modification for source of protein to vegetarian sources is recommended.¹⁴ Health benefits of vegetarian diet for CKD stage 1-4 includes improvement in lipid profile, reduction in proteinuria and a reduced postprandial glomerular filtration rate that will reduce hyperfiltration injury to glomeruli. There is no restriction in vegetarian protein or egg protein intake. A practical list of foods to be included/avoided is given in Box 3.

Conclusion

Appropriate nutritional management is helpful for disease modification, improve growth potential, maintain muscle mass and reduce infections. Diet has to be tailored on an individual basis depending on age, nutritional status, type of renal disease, estimated GFR and type of renal replacement therapy planned, medication, psychological and financial status and cultural practice. Multidisciplinary team approach should include a renal dietitian. In addition to medical management, supplementation of multivitamins, calcium and trace elements is essential. Low salt, low fat vegetarian diet for the entire family is recommended. Counseling of family members and ongoing education regarding diet will help improve compliance and thereby, the nutritional status of the child.

Points to Remember

- ***Nutrition plays a key role in the overall growth and development and also for renal maturity. The most***

important window for optimizing growth is during the first two years of life.

- ***Besides anthropometric and nutritional assessment, serum albumin (in the absence of urinary losses) also provides information about nutritional adequacy.***
- ***In children with CKD, reducing dietary protein intake has not shown to slow the progression of CKD and in fact, can be detrimental to growth.***
- ***Intake of vegetarian sources of protein is recommended.***
- ***Reduced intake of foods that are high in sodium, phosphorus, and potassium such as junk food, processed fast food, canned fruit-juice, etc. is recommended.***

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CLIPPINGS

Health Effects of Overweight and Obesity in 195 Countries over 25 Years – The Global Burden of Disease (GBD) 2015 Obesity Collaborators

The rising pandemic of obesity has received major attention in many countries. The effects of this attention on trends and the disease burden of obesity remain uncertain. Data from 68.5 million persons were analysed to assess the trends in the prevalence of overweight and obesity among children and adults between 1980 and 2015. Using the Global Burden of Disease study data and methods, the burden of disease related to high body-mass index (BMI), according to age, sex, cause, and BMI in 195 countries between 1990 and 2015 was also quantified.

In 2015, a total of 107.7 million children and 603.7 million adults were obese. Since 1980, the prevalence of obesity has doubled in more than 70 countries and has continuously increased in most other countries. Although the prevalence of obesity among children has been lower than that among adults, the rate of increase in childhood obesity in many countries has been greater than the rate of increase in adult obesity. High BMI accounted for 4.0 million deaths globally, nearly 40% of which occurred in persons who were not obese. More than two thirds of deaths related to high BMI were due to cardiovascular disease. The disease burden related to high BMI has increased since 1990; however, the rate of this increase has been attenuated owing to decreases in underlying rates of death from cardiovascular disease.

It was concluded that the rapid increase in the prevalence and disease burden of elevated BMI highlights the need for continued focus on surveillance of BMI and identification, implementation, and evaluation of evidence-based interventions to address this problem.

GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. DOI: 10.1056/NEJMoa1614362.

Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults

A multinational, prospective study involving patients admitted to pediatric intensive care units to define the incremental risk of death and complications associated with severe acute kidney injury. *Kidney Disease: Improving Global Outcomes* criteria was used to define acute kidney injury.

A total of 4683 patients were evaluated; acute kidney injury developed in 1261 patients (26.9%) and severe acute kidney injury developed in 543 patients (11.6%). Severe acute kidney injury conferred an increased risk of death by day 28 after adjustment for 16 covariates; death occurred in 60 of the 543 patients (11.0%) with severe acute kidney injury versus 105 of the 4140 patients (2.5%) without severe acute kidney injury (P<0.001).

Acute kidney injury is common and is associated with poor outcomes, including increased mortality, among critically ill children and young adults.

Kaddourah, A Basu, RK, Bagshaw, SM, Goldstein SL. N Engl J Med 2017; 376:11-20 DOI: 10.1056/NEJMoa1611391.

NEPHRO-UROLOGY

BLADDER BOWEL DYSFUNCTION - A PRACTICAL APPROACH

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Abstract: *Bladder Bowel Dysfunction (BBD) is an increasingly seen clinical entity consequent of present evolving family, social and cultural traditions, feeding patterns and environmental factors. Voiding dysfunction commonly denotes lower urinary tract symptoms (LUTS) in the form of an overactive or an underactive bladder. BBD is often interchanged with voiding dysfunction but needs more qualification. BBD includes LUTS with bowel symptoms: urinary incontinence, dysuria, urinary tract infections (UTI), urinary frequency, infrequent voiding along with constipation and encopresis. This article aims in briefing the pathophysiology identification and the practical approach to this condition in pediatric office practice.*

Keywords: Bladder bowel dysfunction, Lower urinary tract symptoms, Urinary tract infection, International children's continence society, Urotherapy.

Bladder bowel dysfunction (BBD) is a broad spectrum of lower urinary tract symptoms (LUTS) and bowel dysfunction in the form of constipation / encopresis in children. BBD was previously referred to as dysfunctional voiding and/or dysfunctional elimination syndrome (DES). It is primarily an exclusion diagnosis from any anatomical or organic functional abnormality of urinary / GI system (s) in a child. Children with posterior urethral valve, neurogenic bladder, bladder diverticulum, anorectal malformation, hypothyroidism and Hirschsprung's disease would not be included in the spectrum of BBD. Also children with neurological deficits of brain, spinal cord, muscles or nerves and psychiatric problems will not come under this category. BBD represents approximately 40% of children presenting to the pediatric nephrologist and pediatric urologist.¹

Regular passage of urine and stool is very important for the wellbeing of any child. Toilet training is needed by 1 to 1.5 years, the age by which they could understand parental commands. The age of onset of BBD is mostly after the toilet training years, 1-2 years of age. If toilet training is not ensured at appropriate age, it may lead onto both bladder and bowel disturbances with consequences on the urinary tract like recurrent febrile UTI, vesicoureteric reflux (VUR)^{1,2} and if untreated chronic kidney disease (CKD).

The clinical relevance of the spectrum of symptoms is unrecognized by parents, child and the primary pediatrician. Pediatricians do fail to recognize constipation, more importantly fecal retention, in children with bladder complaints, even after extensive urologic evaluation. Likewise, parents may notice constipation but disregard it as an incidental symptom and do not bring it to the pediatrician's attention. It is the bothersome secondary symptoms of wetting, encopresis or febrile UTI, that prompts further evaluation or referral to a pediatric nephrologist or pediatric urologist. If bowel symptoms predominate, referral may be to pediatric gastroenterologist.

Functional integration of bowel and bladder in health

Both bladder and bowel are derived from the embryologic hindgut, share the same pelvic location and passage through the levator ani, common innervation along with and interaction of the neural network responsible for their normal functioning. Both bladder function and intestinal function are controlled by the same region in the central nervous system: supraspinal region, such as the anterior cingulate gyrus, prefrontal cortex and the insular region of the cerebral cortex.

Conscious control of both bladder and bowel function results in response to transmission of afferent impulses from these organs to the brain.³ Secondly the common efferent pathway for the external sphincters for voluntary control of both bladder and bowel emptying is through the sacral spinal segments 2, 3 and 4. Similarly the pelvic floor muscles need to relax for both bladder and bowel emptying. Hence, for normal voiding and defecation the pelvic floor muscles and external sphincters together should relax appropriately and in unison.

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Evolution of bladder and bowel function

An understanding of the normal bladder and bowel function is important to comprehend the different clinical presentations of its dysfunction. Children have a standard pattern of maturation of both the voluntary and involuntary components in bladder bowel continence. Normally, from first to fifth year of life, in chronological order, the first to appear is night time bowel control, day time bowel control, day time urinary control and finally night time urinary control.⁴ Infants will have frequent urination >20 times a day, as and when the urine drains to bladder during first year of life. Beyond first year of life children learn to hold urine voluntarily by command. As the child grows, the bladder capacity improves with its maturation and hence the frequency starts coming down to 8-10 times a day. Day time urinary control is attained by 2 to 4 years and night time urinary control by 5 years of age. As the level of maturation varies in children, the evaluation of nocturnal enuresis is done beyond the age of 5 years.

The function of the bladder is to behave both as a receptive organ to urine from the upper tracts at low pressure and as an efficient emptying organ by increasing the bladder pressure. This process involves integration of activity from both brain and spinal cord. The child gets a sensation of urgent void when the bladder reaches two thirds of its capacity. The expected bladder capacity (EBC) is calculated in mL: Children >1 year of age = age in years + 2 × 30; children <1 year = 7 × weight in Kg.⁵ The most accurate formula for all ages is 2 x age (years) + 2 = capacity (ounces) for children less than 2 years old, and age (years) divided by 2 + 6 = capacity (ounces) for those 2 years old or older.^{4,6} Once the bladder call for void comes, the detrusor starts to contract involuntarily, but the voluntary component, the external urethral sphincter, needs to relax to empty the bladder coordinating with the detrusor (Fig.1). If the place and time is not socially acceptable for a urinary void, it can be postponed till the bladder reaches the fullest capacity.

Toilet training in children is initiated as early as 1 year to ensure smooth passage of stool at least once a day. Functional constipation is defined as a bowel disorder that causes persistently difficult, infrequent or perceptually incomplete defecation. The process of normal defecation of the bowel is similar to voiding by the bladder. As the rectum fills with feces through peristaltic activity in the sigmoid colon, stretch receptors in the rectal wall signal that the rectum is becoming distended. Rectal distension prompts involuntary contraction of the rectal muscles and striated external anal sphincter, which triggers the urge to

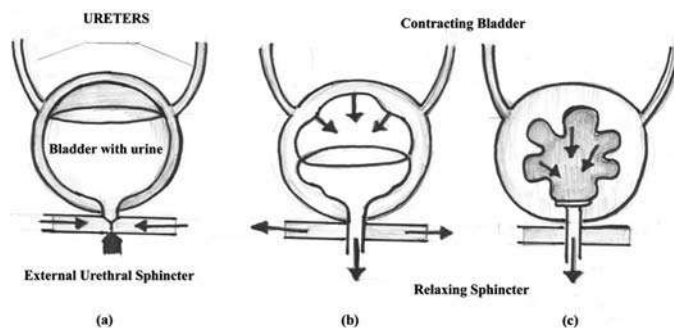


Fig 1: a) Normal bladder storage involves bladder filling, relaxed bladder muscle, adequate low pressure and closed external urethral sphincter b) voiding involves a continuous detrusor contraction with adequate relaxation of the sphincter complex c) bladder emptying, associated with unobstructed urine out flow.

defecate. If the place and time is not socially acceptable for defecation, it can be postponed till the rectum reaches the fullest capacity.

Bladder bowel dysfunction

The spectrum of BBD includes dysfunction of two organ systems, the urinary and gastrointestinal system. The most lower urinary tract symptoms are defined as overactive bladder (OAB). In 2002, the International Children's Continence Society (ICCS) reported a consensus definition for the symptoms associated with OAB which included urinary urgency, with or without urge incontinence, urinary frequency and nocturia, in the absence of pathologic or metabolic factors.⁷ OAB is best characterized by frequent episodes of an urgent need to void, countered by contraction of the pelvic floor muscles and holding maneuvers known as Vincent Curtsy sign. Common holding maneuvers are squatting with the heel pressed into the perineum (Fig.2a), standing on tiptoes, crossing of the legs (Fig.2b), compressing the glans (Fig.2c) to avoid dribbling of urine. These are the symptoms commonly observed by the parents, teachers and the caretakers. This is the commonest presentation to the primary pediatrician as a LUTS. Patients with OAB usually have incontinence secondary to detrusor over activity while simultaneously contracting the urethral sphincter during voiding. This is called detrusor sphincter dyssynergia.^{4,5} This triggers the array of LUTS. The bladder is overstretched when urination is postponed voluntarily or when the external sphincter is closed voluntarily against a working detrusor and can be inferred by the symptoms mentioned above.

Children who voluntarily hold urine for longer periods will gradually present with decreased sensation to void urine or urge to evacuate with regular frequency which are the other important presentation of BBD. This is called lazy bladder or an underactive bladder where the child voids less than 2-4 times a day. These children have a reduced somatic input as they frequently decline the bladder call. Bladder becomes overstretched and an insensitive organ. This is the voiding postponement group who present with straining to micturition, difficulty in initiation, staccato voiding, overflow dribbling, large postvoid residue who later may develop a secondary VUR and upper tract changes.

The common pathway of S2, S3, S4, for voluntary control of both the external sphincters and pelvic floor relaxation contributes for bladder bowel emptying. O'Regan and Yazbeck² postulated that when the external anal sphincter contracts for prolonged periods in the context of large fecal load, this long term contraction results in abnormal pelvic floor contraction and ultimately non-relaxation of the urethral sphincter. This leads to chronic pelvic spasms in BBD. The result is a potential buildup of very high intravesicular pressures that can cause structural damage to the bladder, dilatation of the upper urinary tract that and in very severe cases, can cause renal damage.¹

Bowel dysfunction is defined as constipation which is hard stools with reduced frequency. Habit constipation is a common problem in children worldwide and its prevalence range from 0.7% to 29.6%.⁸ Hard stools may cause painful defecation, blood in the stools, fissure in ano, pelvic spasms, pain abdomen, bloating of abdomen and feed intolerance. If not attended to on time, it leads on to loaded rectum and colon causing stool leak involuntarily, called spurious diarrhea, which is the first bothersome complaint from the school and caretakers. As the child is habituated to constipation, postponement maneuvers are very classical like that of Vincent curtsy in LUTS, (Fig.2a,b,c) running to corners to avoid passing stool, standing posture to defecate, flat sitting posture in the floor and avoiding the closet or potty.

Constipation with consequent retention of fecal matter causes bladder dysfunction by the following mechanism: when the rectum is filled with stools, stretch receptors are stimulated and transmitted to the brain, which induce temporary involuntary relaxation of the external anal sphincter and the puborectalis muscles. If defecation is not possible, the muscles contract voluntarily. As this voluntary process is repeated, the feces accumulate within the rectum and this shortens the bladder contraction period and ultimately bladder activity is stopped. Secondly Choi,

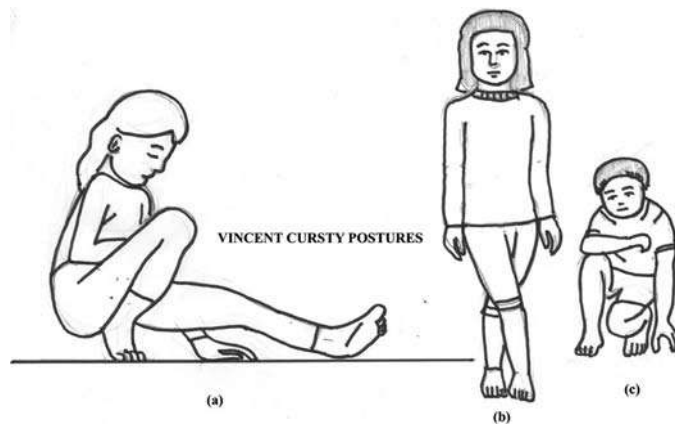


Fig 2 : Vincent curtsy postures (a) pressing the perineum urethra, (b) tightening the urethral sphincter by crossing the legs, (c) compressing the glans between the thighs.

et al,⁹ and Burgers, et al¹⁰ have proposed that a loaded rectum causes OAB by mechanical compression of the bladder lying in front anatomically. The local compression over the bladder reduces the distensibility and in turn reduces the capacity of the bladder leading onto frequency/urgency of urination or incontinence.¹¹ This increased pressure can also result in mechanical compression of the bladder, which eventually leads to trigonal irritation or even obstruction of bladder neck and urethra. If the bladder neck/urethra is compressed, it may lead onto acute retention urine caused by the loaded fecal mass (Fig.3). This creates raised bladder pressure leading onto secondary VUR affecting the upper tracts. Hence, the pathophysiology of BBD spectrum contributed by both bowel and bladder should be identified and treated simultaneously to effectively manage these children.

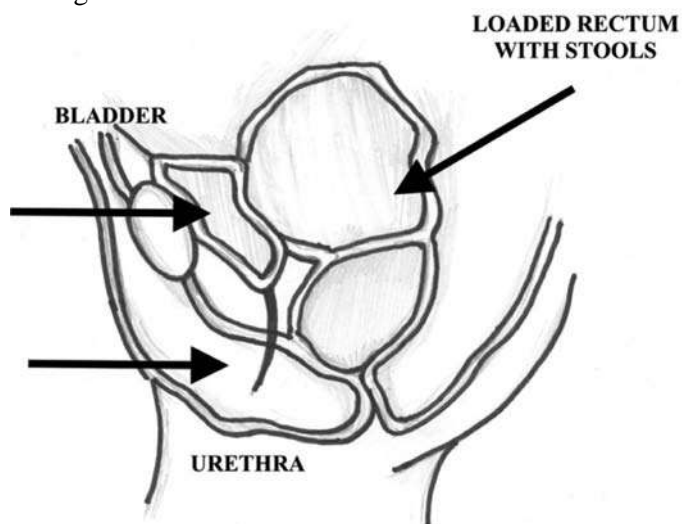


Fig 3 : Loaded rectum mechanically pushes the bladder in front reducing the holding capacity of bladder, increasing the frequency of urination and secondary VUR .

Table 1. Symptoms in BBD

Bladder Symptoms	Bowel Symptoms
Postponement of urination	Avoiding closet
Urge incontinence	Standing to stool
Day/Night wetting	Hard stools
Frequency	Encopresis
Dysuria / Straining	Irregular timings to stool
Hesitancy	Fissure in ano
Holding maneuvers	Poor/ picky eaters
Insignificant CFU in urine	Discharge of liquid motion

Evaluation

The symptoms of BBD vary in two different age groups (Table I). The younger age group between 2- 5 years present more as bowel dysfunction like constipation, running to corners to avoid passing stool, standing posture to defecate, flat sitting posture in the floor and avoiding the closet or potty. When leading questions on the urinary symptoms are probed, child can be identified to have bladder symptoms overlap in the form of postponement and over active bladder. The older children between 5-10 years present more as bladder dysfunction like holding, frequency or recurrent LUTS. These children always deny the constipation history avoiding the parents from supervising them on regular stool habits. These children will invariably have a loaded colon by clinical examination or as seen in the X ray or USG abdomen. Physical examination involves identifying a palpable bladder, palpable or loaded sigmoid colon, phimosis and vulval synechia.

Laboratory investigations: A complete urine analysis, urine culture for bacterial growth, (ensure mid stream, clean catch technique) and thyroid function tests are the baseline investigations.

Imaging: USG abdomen and pelvis is a key tool in the evaluation of pediatric lower urinary tract (LUT) function. Ultrasonographic bladder scan machines calculates bladder volume and thus are useful in measuring pre- and post void residual volume (PVR) or as a B-mode sonographic probe that provides anatomical details of the LUT and adjacent rectum. Bladder wall thickness and PVR are the prime factors to be noted.

Standard conditions should be applied to measure PVR. The bladder should not be under-distended (<50%)

nor over-distended (>115%) in relation to the EBC. PVR must be obtained immediately after voiding (<5minutes) and >10% of expected bladder capacity for age is considered as significant PVR. Thickened bladder wall alerts the clinician to longstanding problems with urine storage and emptying correlating to LUTS. Bladder wall thickness can be measured in a full and empty bladder: thickness of >3mm in full bladder and >5mm in empty bladder is considered significant, indicating a longstanding detrusor sphincter dyssynergia. There is insufficient evidence that the transverse diameter of the rectum can be used as a predictor of fecal impaction. Rectal diameter of >3cm on pelvic ultrasound can be correlated with a finding of rectal impaction.

Plain X ray abdomen: To identify the extent of loading in the colon, X ray abdomen has shown to be a better choice. Two thirds of the colon being loaded with particulate matter is considered as significant colonic fecal impaction. The same can be used as a documented evidence to convince the parents on the gravity of the bowel dysfunction. Evaluation and management of BBD is given in fig.4 and Box 1.

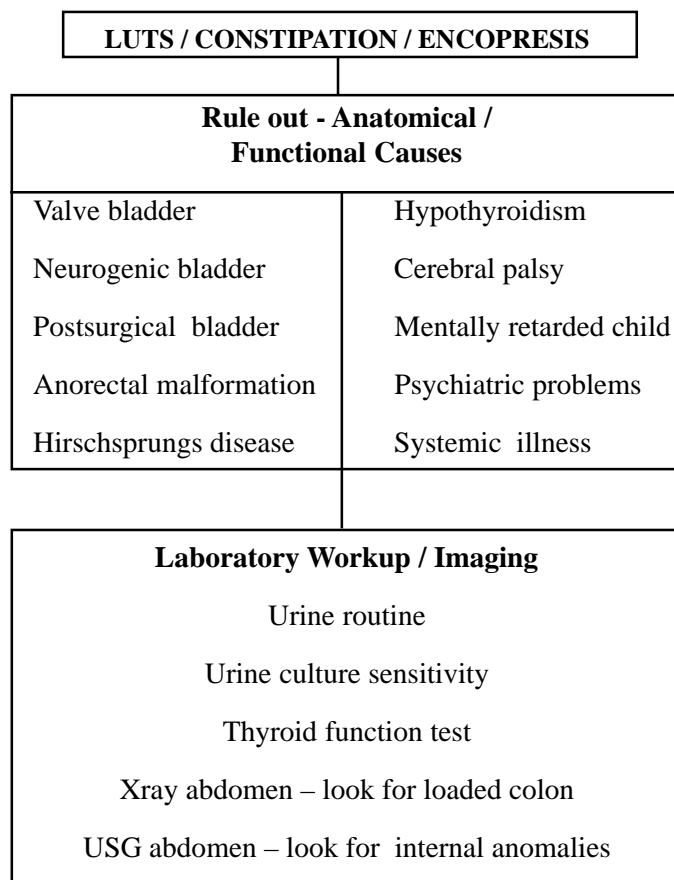


Fig.4. Bladder bowel dysfunction evaluation - Flow chart

Box 2. Management of BBD**Urotherapy + Laxatives (minimum 6 months)**

- Bladder training
- Bowel training
- Dietary modification
- Bladder bowel diary – weekly charts
- Monthly followup – BBD clinic
- Laxatives – Lactitol / polyethylene glycol +/- fibre supplement

Therapy

Urotherapy: It is conservative-based therapy and treatment of LUT dysfunction that rehabilitates the LUT and encompasses a very wide field of healthcare professionals. Urotherapy^{12,13,14} can be divided into standard therapy and specific interventions.

1) Standard urotherapy: a) Parental education - Information and demystification. Explanation about normal LUT function and how the particular child deviates from normal b) Behavioral modification with regular voiding habits, proper voiding posture and regular bowel habits c) Life-style advice - Encompasses balanced fluid intake and diet, diminished caffeine, regular bladder and bowel emptying patterns d) Registration of symptoms and voiding habits, using bladder diaries or frequency - Volume charts and potentially mobile apps e) Support and encouragement via regular follow-up with the caregiver in BBD clinic.

2) Specific interventions of urotherapy: Defined similar

to International Children's Continence Society (ICCS) guidelines¹⁴ that include various forms of pelvic floor muscle retraining (biofeed back), neuromodulation and intermittent catheterization. Additional interventions of urotherapy involve cognitive behavioral therapy and psychotherapy.

Bladder training: This is the first step in the urotherapy by ICCS guidelines. Parents should be educated on the normal bladder functioning as both a storage and emptying organ. The normal voiding pattern is 6-8 times during day time i.e. child must void every 2-3 hours. There should not be any hurry in voiding. Child should take time to relax the pelvic floor to ensure a complete emptying of the bladder. Parents should be individually educated as how their child is deviating from normalcy and to correct them. Special attention to obese girl children, who tend to adduct their thighs and avoid a complete emptying of bladder. They should be encouraged to sit on the western closet facing the wall so that the thighs are set wide apart to ensure proper abduction of thighs and pelvic floor relaxation while voiding urine. Timed voiding, double voiding should be insisted upon by the parents as a routine.

Bowel training: This is the second step in the urotherapy by ICCS guidelines. Parents should be educated on the normal bowel movement daily. Child and the parents should be taught the normal posture for sitting to defecate. Regular timing in the morning has to be adhered to, for mental habituation of the child. Parents need to understand that until the oral intake improves with good fiber diet and adequate hydration, the stool habits cannot be regulated. Depending on the severity of symptoms like encopresis, child may require rectal enemas with or without suppositories. Physician must institute a laxative of choice,

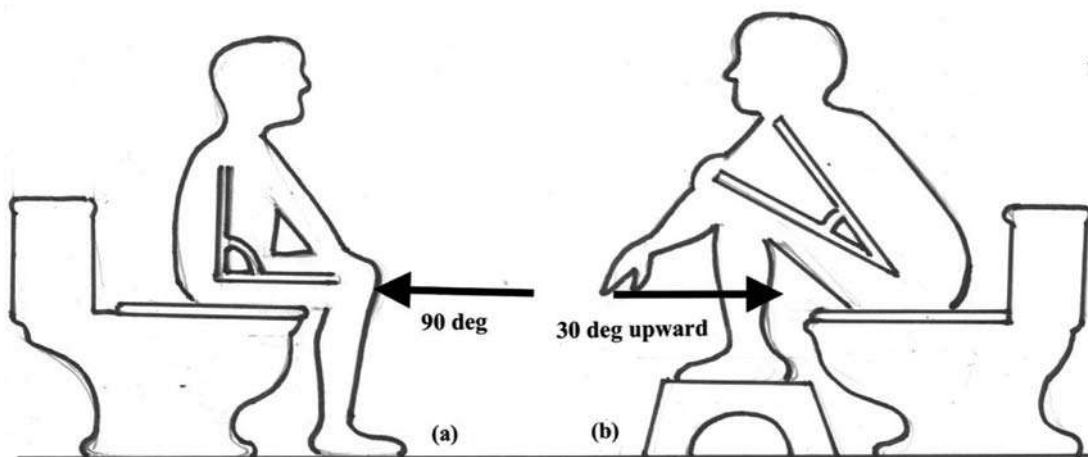


Fig.5:(a) 90 degree posture in the western closet - pelvic floor not relaxed. (b) 30 degree upward posture by a foot support - pelvic floor for relaxed.

a step beyond the one which the child has already been treated with. This should be noted in weekly bowel diary and monitored in monthly follow up to make corrections.

Parents must be educated on the proper positioning to pass stool. During the toilet training years, the mother should train the child to sit in squatting position between her legs. This is basically to gain confidence of the child that mother is always there in new position holding the child. As the child grows, he can be put onto Indian closet or a potty. Potty should be of appropriate height of the child or the regular western closet should have a foot stool to support the child's feet (Fig.5a and 5b). This will remove the child's fear of falling into the closet.

Squatting position is considered the best position for passage of stool as it relaxes the puborectalis sling effect from the rectum and the rectum forms a straight channel for defecation. The same effect of puborectalis relaxation happens with a potty with footrest: this 30 degrees upliftment of the foot in a potty¹⁵ and foot rest eases the child with straight channel rectum (Fig 6a and b).

Hence parents need to be taught on the normal toilet training modalities as well.

Another common mistake in bowel habit is utilization of hand flush. The hand flush used for cleaning the perineum from backwards, drives the abluition water to the front in children especially in girls. This triggers a local erythema, itching inviting the LUTS and vulvovaginitis. The frequency, urgency, perineal itching, white discharge, asymptomatic bacteriuria are most often caused by this hand flush utilization. Parents must be advised to use only cup and water to cleanse the perineum directing the water stream always from front to backwards.

Dietary modification

Understanding the food pattern of the child by detailed history will give an idea on what the child is lacking. Advise them to improve water intake of about 2-3 litres a day and improvise the methods of high fiber introduction in daily staple diet. Pediatric nutritionist can be involved for the same or arbitrarily can be advised to have 50% of diet

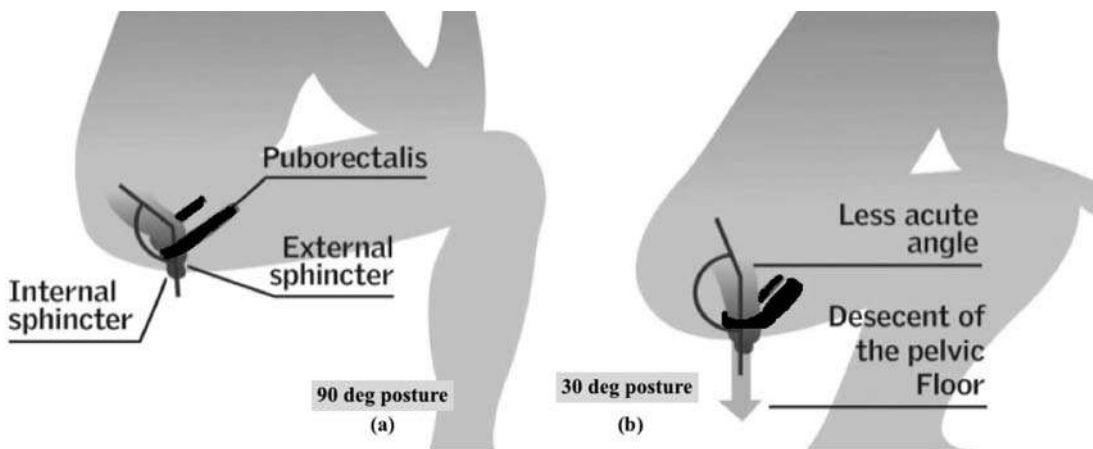


Fig.6a. 90° posture in western closet tighten the puborectalis sling - prevent descent of pelvic floor. (b) 30° posture relaxes puborectalis sling allows easy descent of pelvic floor.

Follow up	Bladder symptoms	Bowel symptoms	Food habits	Suppository used
At initiation				
1 week				
2 week				
3 week				
4week				

Fig.7. Bladder bowel charts

consumption containing fiber i.e. vegetables and fruits with a minimum of 2 servings a day. Sprouts / cereals are to be included in the diet. This diet charting (Fig.7) along with the laxatives will get the child into the regular bowel training.

Regular monthly followup

Final steps in the standard urotherapy is to follow up the bladder bowel diary maintained by the parents and to get them corrected whenever necessary. In general, the child and parents will take a couple of months to get on track with bladder, bowel and diet modifications and once they are regular, the child can be treated for another 3-4 months, the laxatives tapered and can be weaned off the urotherapy by the end of 6 months.

Conclusion

In Indian scenario, there is less awareness about the BBD spectrum. This is basically a time consuming ailment requiring detailed history taking and creating a behavioral modification in the child. Hence, both the pediatricians and the working parents pay less attention to this. According to the ICCS guidelines, "the standard urotherapy is the simplest method to imbibe in our society". If the basic principles of standard urotherapy can be incorporated in our routine treatment protocol for BBD, it will surely improve the quality of life in children.

LUTS and habit constipation is a simple issue to be treated, if caught early before it evolves as a BBD spectrum. If caught late with the changes seen in the form of bladder wall thickening, significant post void residue, loaded colon by plain x ray abdomen, febrile UTI with scars, it warrants a detailed workup, systematic protocol to treat for a longer period of time of minimum 6 months to one year. Any change in the upper tracts in the form of scars, loss in function, secondary VUR, hypertension and proteinuria should be attended by the pediatric nephrologist for the supportive management. This may have grave consequence in the form of chronic kidney disease if not acted on time.

Parents must be educated on the normal bladder and bowel voiding pattern in well baby clinics to create awareness about this condition. Parents should be educated to follow their child's bladder and bowel pattern. It is the duty of the primary care pediatrician to identify these children and treat appropriately. This is rather a preventable condition if everyone is aware of the consequences.

Points to Remember

- **Bladder and bowel dysfunction (BBD) includes coexisting urinary and bowel dysfunction in children between 5-13 years of age.**

- **Overactive bladder (OAB) and constipation share a common pathophysiology.**
- **The initial step is to treat constipation.**
- **Urotherapy in the form of basic education on toilet training, toilet seating, frequency of urination, the normal functioning of bladder and bowel is mandatory.**
- **Non-pharmacological approaches to manage functional constipation include increasing fluids, fiber intake, and physical activity. Secondary measure is osmotic laxatives.**
- **Patience and perseverance is the key to success in treatment.**

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CLIPPINGS

Maternal/neonatal vitamin D deficiency: a new risk factor for necrotizing enterocolitis in preterm infants?

The objective of the study was to investigate the possible association between maternal/ neonatal 25-hydroxy vitamin D (25-OHD) levels and development of necrotizing enterocolitis (NEC). One hundred and forty-five preterm infants less than or equal to 36 weeks of gestation were enrolled. 25-OHD levels were determined in maternal/neonatal blood samples that were obtained at the time of admission to the neonatal intensive care unit

Of the 145 enrolled patients, 26 (18%) developed NEC. Maternal / neonatal 25-OHD levels in the NEC group were significantly lower than those of the no-NEC group (P=0.001 and 0.004, respectively). In univariate logistic regression analysis, both maternal / neonatal vitamin D levels were a significant predictor of NEC (Odds Ratio (OR): 0.92 and 0.89; P<0.001 and P<0.005, respectively). However, multivariate logistic regression analysis revealed that only maternal vitamin D level was a significant predictor of NEC (OR: 0.86, P<0.0009). This is the first study to propose a possible association between maternal / neonatal 25-OHD levels and subsequent development of NEC in preterm infants.

Cetinkaya M, Erener-Ercan T, Kalayci-Oral T, Babayiđit A, Cebeci B, Semerci SY and Buyukkale G Maternal/ neonatal vitamin D deficiency: a new risk factor for necrotizing enterocolitis in preterm infants? J Perinatol 2017; 37(6):673-678.

High-sensitivity cardiac troponin T predicts mortality after hospitalization for community-acquired pneumonia

Mortality after hospitalization with community-acquired pneumonia (CAP) is high compared with age-matched controls. The present study aimed to explore the prognostic value of high-sensitivity cardiac troponin T (cTnT) for mortality in patients hospitalized with CAP. cTnT level on admission was measured in 295 patients hospitalized with CAP who participated in a randomized placebo-controlled double-blind trial on adjunctive dexamethasone treatment. Outcome measures were short (30-day) and long-term (4.1-year) mortalities. Elevated cTnT level on admission is a strong predictor of short- and long-term mortalities in patients hospitalized with CAP.

Stefan MT, Vestjens, Simone MC, Spoorenberg, Ger T, Rijkers, Jan C, Grutters, Jurriën M, Ten Berg, Peter G, Noordzij, et al. High-sensitivity cardiac troponin T predicts mortality after hospitalization for community-acquired pneumonia. Respirology 02/27/2017.

GENERAL ARTICLE

JUVENILE DERMATO MYOSITIS***Suma Balan**

Abstracts: *Juvenile dermatomyositis (JDM) is an inflammatory myositis that is easily diagnosed with the classical cutaneous features, proximal myopathy and raised muscle enzymes. However, less typical and uncommon presentations may require high index of suspicion and investigations to prove the same. With the ability of MRI to detect inflammation in the skin and muscle, the practice of doing electromyography and muscle biopsy has significantly reduced in the present day practice. Early diagnosis and appropriate therapy with dual immunosuppression promises the best outcome. Unlike in adults the association with malignancies in JDM is relatively rare.*

Keywords: *Heliotrope rash, Dermatomyositis, Proximal myopathy*

Juvenile dermatomyositis (JDM) is the most common of the spectrum of the childhood idiopathic inflammatory myopathies.¹ The classic presentation is an insidious onset proximal muscle weakness with the pathognomonic rash comprising heliotrope rashes and Gottron's papules.² Besides the skin and muscle, JDM can also affect joints and internal organs like gastrointestinal system, lungs and cause pulmonary hypertension. Inflammation of the skeletal muscle leads to progressive muscle weakness which has to be differentiated from muscular dystrophies and infectious myositis.¹ Juvenile polymyositis is extremely rare unlike in adults.¹

Epidemiology

The annual incidence of JDM in children is 1.9-4.1 per million per year.¹ There is no racial predilection.² The disease is more common in girls than boys. The National Institute of Arthritis and Musculoskeletal and

Skin diseases (NIAMS) registry found a sex ratio of 2.3:1.¹ The peak age of onset is between 4 and 10 years.² 25% of cases present before 4 years of age.³ A clustering of cases has been known to occur and a seasonal association in the incidence of IIM has been suggested.¹ Epidemiological studies from India are lacking.

Classification⁴

The IIMs in children are classified as shown in Table I.

Etiology

The etiology of JDM is multifactorial.² Environmental factors such as viruses, noxious substances and photosensitivity interact in a genetically predisposed individual leading to immune dysregulation and inflammation of tissues.¹ Though a history of infection (upper respiratory or GI) in the 3 months preceding the onset of disease has been commonly reported, no causative organisms have been identified. Group A streptococcus, coxsackie virus B, toxoplasma, enteroviruses, parvovirus B19 and several other organisms have been postulated as possible pathogens in the etiology of JDM.²

Autoantibodies in IIM are categorised into MSA (myositis specific antibodies) and MAA (myositis associated antibodies). While MSA are specific to myositis patients, MAA can be seen in different myositis subtypes, overlap syndrome and other autoimmune conditions. 70% of patients with JDM have MSA or MAA. Some of these antibodies in JDM such as anti 155/140 [Transcriptional intermediary factor 1-gamma (TIF 1-gamma)] are associated with worse skin disease and lipodystrophy while others like anti-nuclear matrix protein 2 (anti-NXP2) are associated with an increased risk of calcinosis.¹

Pathogenesis

JDM is predominantly a vasculopathy affecting the skeletal muscle, skin gastrointestinal tract and sometimes the lungs, kidney and heart. Both innate and acquired immunity contribute to the pathogenesis. It is believed that children who have a genetic predisposition to JDM (HLA DQA1*501, HLA DRB*301) may have a prolonged exposure to a yet unknown environmental trigger and also

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Table I. Classification of IIMs⁴

Clinicopathologic phenotype	Frequency in IIM
Dermatomyositis	85%
Overlap myositis (Often meet criteria for other autoimmune disease-SLE, scleroderma, etc)	6–12%
Polymyositis (Only muscle weakness with no cutaneous changes)	4–8%
Amyopathic or hypomyopathic DM, Inclusion body myositis (IBM), Cancer-associated myositis, Focal myositis, Orbital myositis, Immune-mediated necrotizing myopathy, Macrophagic myofasciitis, Eosinophilic myositis, Granulomatous myositis, Proliferative myositis, Graft-versus-host myositis	Rare

to maternal chimeric cells which results in an autoimmune inflammatory response. The role of type 1 interferons, secreted often by activated plasmacytoid dendritic cells (antigen presenting cells that activate naïve T cells and initiate immunity) is gaining importance in the pathogenesis of JDM.² JDM is characterised by perivascular infiltrates comprising of B cells, T cells and macrophages. They induce T cell mediated response that causes muscle damage.¹ Type 1 interferon upregulates MHC class 1 protein expression on muscle cells and also leads to maturation of dendritic cells. This results in upregulation of adhesion molecules and subsequent lymphocyte migration and inflammatory infiltration of muscles. Muscle inflammation further increases type 1 interferon response which regenerates the inflammatory cycle.²

Clinical manifestations

JDM can have a variable presentation. Children can present either with a rash or muscle weakness or both. Systemic features like fever, tiredness, irritability and weight loss are quite common.² In 50% of cases, rash is the first symptom to appear and these children could first present to a dermatologist. Concomitant muscle weakness is present only in 25% of the cases.² The rash may be transient and go unnoticed by the parents.¹ There can be extreme photosensitivity to UV light exposure causing generalised erythema in the areas of skin exposed to the sun. Erythema over the chest and neck is known as the “shawl sign”. Erythema can also be present over the knees and elbows. The typical heliotrope rash is a violaceous discolouration of the eyelids quite often associated with periorbital oedema.

Another common feature is facial erythema that crosses the nasolabial folds unlike the malar rash seen in SLE where nasolabial folds are not involved.² Generalised erythema or livedo type rash can also occur. Gottron’s papules (Fig.1) are classically pale or bright



Fig 1. Gottron’s papules



Fig 2. Gottron’s papules over knees

pink, shiny, thickened or atrophic plaques over the proximal interphalangeal and distal interphalangeal joints (PIP and DIP). It can also appear on knees (Fig.2), elbows, small joints of the toes and ankle malleoli. Gottron’s papules can be mistaken for psoriasis.

Small vessel inflammation manifests in nail folds and gums as thickened, tortuous or absent capillary loops.² Nail beds are often swollen and erythematous with abnormal dilatation of the capillaries which can be visualised with a capillaroscope or with a magnifier like an ophthalmoscope or auroscope and KY jelly.^{1,5} Telangiectasia may be visible to the naked eye. Severe vascular inflammation can lead to skin ulceration

over the flexor surfaces, toes, fingers and medial canthus of the upper eyelid.² Edema of the subcutaneous tissues including periorbital region and generalised anasarca can also be a presentation of the cutaneous vasculopathy of JDM. Skin ulceration with typical vasculitic punched out ulcers can also be seen suggestive of severe disease often involving the elbows and ankles.

Skeletal muscle weakness is typically proximal and symmetric affecting neck flexors, shoulder girdle and hip flexors. It can initially be mild and mistaken for fatigue. It is associated often with muscle tenderness. Muscle weakness is progressive and children develop difficulty in lifting objects overhead, combing hair, climbing stairs and getting out of bed. Neck muscle weakness causes children difficulty in lifting the head off the pillow. As weakness progresses, distal muscles also become involved resulting in a weak grip. Involvement of palatal muscles causes dysphagia and dysphonia. Swallowing difficulty manifests as coughing during eating or drinking and has to be enquired in the history. Esophageal and respiratory muscles are also affected and this can lead to aspiration and respiratory failure. Weakness of respiratory muscles is a medical emergency and has to be recognised early. Children do not present with increased work of breathing or hypoxemia but present instead with hypercarbia. Silent aspiration has been recognised in symptomatic children with JDM. Dysfunction in swallowing or aspiration are not restricted only to those who have severe skeletal muscle weakness. Physical examination will reveal head lag in a child after infancy and inability to perform a sit up. Children with JDM compensate for truncal weakness by rolling on to their side instead of sitting straight up from lying. An excellent screening test to assess for lower extremity muscle weakness or pelvic girdle weakness is Gower's sign, which is seen in many other conditions characterised by proximal muscle weakness. Thirty percent of patients can present with polyarticular arthritis.

Longstanding or poorly controlled disease is associated with calcinosis and lipodystrophy. Calcinosis has been found to be present in 40% of children with JDM.



Fig.3. Calcium deposits in limbs

Calcium gets deposited as subcutaneous nodules and plaques (Fig.3). These can extrude from the skin as crystals or calcific liquid causing painful ulcers. Increasing understanding suggests that inadequate control of initial muscle inflammation or nonaggressive initial treatment of the disease is the single most important risk factor for the development of calcinosis. Calcinosis is associated far more with juvenile dermatomyositis than adult disease.

Lipodystrophy is characterised by progressive loss of subcutaneous and visceral fat over the face and upper body and can be associated with insulin resistance. Children with severe JDM can develop vasculitis of the GI tract characterised by crampy abdominal pain, pancreatitis and GI bleeding. It can also lead to intestinal perforation. Interstitial lung disease, pericarditis, myocarditis and conduction defects are the rare complications of severe disease.^{1,2} Children presenting with the classic rash but no apparent muscle weakness or inflammation are said to have amyopathic JDM.²

Diagnosis

Definite diagnosis of dermatomyositis requires the presence of the characteristic rash (heliotrope rash over the eyelids with periorbital oedema, Gottron's papules) and at least 3 signs of muscle inflammation and weakness (Table II).

JDM/JPM are defined with age of onset being before 16 years in Europe and before 18 in America.¹ The Bohan and Peter criteria were developed before the advent of MRI.² Typical cases of JDM can be diagnosed clinically by the presence of symmetrical proximal muscle weakness and the characteristic rash. The clinical diagnosis is then confirmed by supportive investigations like muscle enzymes, EMG, MRI or muscle biopsy. With the new criteria (Table III) the requirement for electromyography and muscle biopsy has significantly reduced in the diagnosis of JDM. Currently in the presence of typical cutaneous features, a proximal muscle weakness and elevated muscle enzymes, an MRI of the thigh looking at the typical changes in the proximal muscles can provide enough evidence for diagnosis and further investigations are not required. At diagnosis all muscle enzymes need to be tested as CPK is not necessarily elevated in all patients with JDM.

Differential diagnosis

Other causes of weakness including neuromuscular problems have to be thought off when the typical rash is absent.¹ Muscular dystrophies, myasthenia gravis and neuropathies must be considered in the differential

Table II. Bohan and Peter diagnostic criteria¹

Feature	Details
Symmetrical weakness	Of limb-girdle muscles and usually progressive
Muscle biopsy evidence of myositis	Necrosis of type I and type II muscle fibres. Phagocytosis, degeneration and regeneration of myofibres with variation in myofibre size with perifascicular atrophy. Endomysial, perimysial, perivascular or interstitial mononuclear inflammatory cells
Elevation of serum levels of muscle-associated enzymes	CK, LDH, aldolase, transaminases (ALT/SGPT and AST/SGOT)
Electromyographic (EMG) triad of myopathy	Short, small, low-amplitude polyphasic motor unit potentials, fibrillation potentials, even at rest, bizarre high-frequency repetitive discharges
<p><i>Definite JDM/JPM – presence of 3 out of 4 features plus rash for JDM</i></p> <p><i>Probable JDM/JPM – presence of 2 out of 4 features plus rash for JDM</i></p> <p><i>Possible JDM/JPM – presence of 1 feature plus rash for JDM</i></p> <p><i>JPM: Juvenile polymyositis</i></p>	

An international consensus survey for diagnostic criteria for JDM is given in Table III.

Table III. International consensus survey for diagnostic criteria for JDM

Standard criteria	Additional criteria
Skin rash	Biopsy
Proximal muscle weakness	EMG
Elevated muscle enzymes	Muscle MRI
	Nail fold capillaroscopy
	Calcinosis
	Dysphonia

diagnosis. The detection of myotonia, paramyotonia or hypertrophy of muscles should suggest neuromuscular causes. Nerve pathology leads to distal weakness and sensory loss. Neuromuscular junction disorders cause patchy or diffuse weakness. Cranial nerve weakness has an early onset. In contrast, muscle involvement leads to symmetrical proximal and persistent weakness. There is minimal wasting, no sensory loss and reflexes are usually intact.¹

Besides neurologic causes like muscular dystrophies (Duchenne and Becker’s), myasthenia gravis, Guillain Barre (GB) syndrome and other systemic myopathies

Box 1. Systemic myopathies

- 1) Infection related myositis
- 2) Endocrine-hypothyroidism, hyperthyroidism, hypoparathyroidism, hyperparathyroidism, Cushing’s syndrome, adrenal insufficiency, acromegaly.
- 3) Metabolic myopathies - hypokalemia, hyperkalemia, hypernatremia, hypercalcemia, hypocalcemia, hypophosphatemia, CRF, hypomagnesemia, organ failure (cardiac, respiratory, hepatic failure)
- 4) Drug or toxin induced myopathies- glucocorticoids, other drugs like D-penicillamine, procainamide, L-tryptophan, amiodarone, chloroquine.
- 5) Paraneoplastic myopathy- very rare in children. Presence of significant lymphadenopathy, splenomegaly, etc may be the clues.
- 6) Critical illness myopathy¹

should be considered in the differential diagnosis and excluded before diagnosing an inflammatory myopathy.¹ Systemic myopathies are in Box 1.

Besides JDM, inflammation of muscles can also be seen in children with juvenile idiopathic arthritis (JIA) systemic lupus erythematosus (SLE), mixed connective tissue disorders (MCTD), inflammatory bowel disease (IBD) and ANCA positive vasculitides.²

Investigations

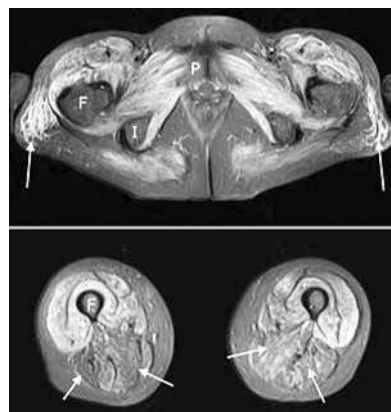
The aims of investigations are to 1) confirm the diagnosis, 2) exclude systemic causes of myopathy and 3) establish the extent of organ involvement.

Blood tests should include inflammatory markers (C reactive protein and ESR), renal function tests, liver function tests, muscle enzymes, auto antibodies, thyroid function (other endocrine tests if needed), virology/infection screen and a bone profile (calcium, parathyroid hormone, vitamin D). A toxicology screen should also be considered¹ Inflammatory markers can be normal in active muscle inflammation.²

Raised levels of muscle enzymes (creatine kinase, aldolase, aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase) in the serum indicate muscle inflammation. Alanine aminotransferase is elevated on initial presentation whereas CK may be normal in 20% of patients. Despite ongoing active disease or disease flare, muscle enzymes may be normal.^{1,2} Anemia of chronic disease may be present. Eighty percent of children with JDM have ANA positivity. Myositis specific antibodies (MSA) are newer specialised tests which are considerably expensive and less frequently seen in children unlike adults.² The anti Jo1 antibody is associated significantly with the development of interstitial lung disease. Anti-NXP2 (anti p 140/MJ) in JDM cases is associated with increased risk of calcinosis and increased muscle weakness. Anti-TIF1-gamma (anti p155/140), has been found to be associated with severe skin disease, risk of skin ulceration, lipodystrophy, and contractures.¹ While there is increasing understanding of the role of muscle specific antibodies in JDM, the high cost precludes the routine use of the same at present.

EMG is part of the traditional diagnostic criteria of JDM/JPM and shows signs of denervation and myopathy as well as muscle fibre necrosis but is rarely required for diagnosis currently. Nerve conduction studies are typically normal in juvenile dermatomyositis.²

MRI has been validated as an indicator of disease activity and is being increasingly used in the diagnosis of JDM.¹ MRI studies using T2 weighted images and Short-Tau Inversion-Recovery (STIR) fat suppressed sequences detect sites of active muscle inflammation (Fig.4) and edema of skin, subcutaneous tissue and myofascia. Use of MRI reduces sampling error and increases the sensitivity of muscle biopsy and EMG.² Additionally quantitative parameters (fc-T2 mapping or fat-corrected T2 mapping) on MRI can also be used to further enhance its utility in diagnosis as well as in assessing chronicity.⁶



F-Femur, P-Pelvis, I-Ischium

Fig.4. MRI of thigh showing the increased signals in T2 images suggestive of myositis

Musculoskeletal USG is a safe, inexpensive and noninvasive imaging modality that does not need sedation. It can be used to support the clinical diagnosis of JDM and to monitor the progression of the disease. But USG needs a significant level of expertise and worldwide there are only very few areas of significant expertise in the same.¹

Muscle biopsy is considered the gold standard for confirming the diagnosis of JDM/JPM. However muscle inflammation can be patchy in both muscle groups as well as in individual muscles. Muscle biopsies are scored under the four domains of : a) inflammatory changes, b) vascular endothelial changes, c) muscle fibre abnormalities and d) connective tissue changes.

When clinical presentation and course is atypical, it is advisable to perform a muscle biopsy to exclude muscular dystrophies and mitochondrial cytopathies.^{1,5}

The invasiveness of a muscle biopsy, as well as the time taken for healing have made it a less common procedure today. For the child with classic cutaneous features, proximal muscle weakness and typical MRI changes, a muscle biopsy is no longer required for diagnosis. Recently however Gitiaux, et al., have proposed a better understanding of severe JDM at onset using the combination of initial childhood myositis assessment scale childhood myositis assessment scale (CMAS) (<or=34), initial GI involvement (present/absent) and endomysial fibrosis diagnostic biopsy (present/absent) as predictive of first-line therapeutic response.⁷

Lung involvement is investigated by chest radiographs, HRCT chest and lung function tests. Cardiac involvement is assessed by ECG and ECHO and abdominal involvement by ultrasound. If there are symptoms of dysphagia, dysphonia or aspiration, then a speech and

language assessment with video fluoroscopy can be done. Nail fold capillaroscopy can be used to distinguish JDM from other myopathies and muscular dystrophies.¹

Follow up

The monitoring of disease activity in JDM involves both global assessment and organ specific assessment. The latter includes muscle disease activity, skin disease activity and assessment of other organ involvement.

Global assessment

JDM disease activity score is used to assess the extent and distribution of muscle weakness, skin involvement, vasculopathic manifestation and functional status. It can be assessed by: Parent / patient global assessment of disease activity on a visual analog scale and functional ability by the childhood health assessment questionnaire.³

Assessment of muscle disease: Muscle strength has to be assessed at diagnosis and then regularly during follow up. The two tools useful in clinical practice and also recommended as an outcome measure in clinical trials are the CMAS and Kendall manual muscle testing 8 (MMT 8).¹

CMAS is a 14 item observational assessment and monitoring tool used clinically as well as in research to assess muscle strength and function and muscle stamina in children with inflammatory myositis. A complex description is available on the ACR website (www.rheumatology.org). Kendall MMT8 assesses eight specific muscle groups (neck flexion, shoulder abduction, elbow flexion, wrist extension, hip extension, hip abduction, knee extension, ankle dorsiflexion) on a 0-10 point scale and gives an overall score that can be followed over time.^{1,3}

Assessment of damage: The myositis damage index assesses the damage in different organ systems. The extent of damage is quantified by a visual analogue scale (VAS).³

Management

JDM should be treated aggressively and early to induce remission.¹

Corticosteroids: It is the first line treatment for JDM. The current recommendation is to use high dose intravenous methylprednisolone in children with moderate to severe disease for 3-5 doses and then convert to oral dose of 2 mg/kg /day upto a maximum of 60mg/day. In mild cases oral steroids can be commenced upfront. The IV route has the advantage of faster control of

symptoms. It also bypasses the problems associated with absorption secondary to gut inflammation. In children with significant edema and anasarca, it is advised to give the oral dose equivalent as intravenous for 2 weeks as gut edema is hypothesized to cause a significant impairment in the response.^{1,8,9} In children with severe weakness including bulbar muscle involvement, IV immunoglobulin is considered an early addition to the treatment.

Methotrexate: It is used by many centres as the disease modifying anti rheumatic drug of choice and steroid sparing agent irrespective of the severity of JDM. It is commenced at the onset of treatment. Evidence has shown decreased incidence of calcinosis when these drugs are introduced early after the onset of disease.¹ The cumulative dose of steroids needed for disease control is reduced by half by the concomitant use of methotrexate. Oral, subcutaneous or IV methotrexate is used weekly in the dose of 0.5-1 mg/kg or 15-20mg/m² (max 25 mg). It is well tolerated in most of the pediatric patients. Subcutaneous route is again preferred while starting treatment as the likely association with gut inflammation can affect absorption.^{8,9} Folic acid is administered at a dose of 1mg daily to counter the side effects of folate inhibition.² The presence of raised SGOT and SGPT should not deter the commencement of methotrexate as in this context they often reflect the muscle component of the enzyme.

Intravenous immunoglobulin (IVIg): It is also widely used particularly for the treatment of significant skin disease and severe or refractory JDM.^{1,8} It should be part of severe disease management at onset of treatment and considered on a monthly basis if there is recurrence of disease on tapering steroids or refractory disease.⁸

Mycofenolate mofetil: It is being increasingly considered in refractory diseases often as additive to methotrexate.¹⁰ Tacrolimus is also reported in small series to be effective.¹¹

Other DMARDs: Azathioprine currently has little role in childhood JDM. Hydroxychloroquine is often helpful in recalcitrant skin disease. These drugs may be used in combination with methotrexate which further increases the toxicity of treatment and mandates strict follow up.

Pulsed IV cyclophosphamide: It is used to treat severe disease such as ILD, GI perforation and skin ulceration.^{1,12}

Anti TNF monoclonal antibodies: Like etanercept and infliximab have been shown to be effective in the treatment of inflammatory myositis especially for children with calcinosis in very small case series. Infliximab has been shown to lead to improvement in two case series of JDM.¹³ Rituximab has also been shown to have promising results

Table IV. Treatment plan – Moderately severe JDM¹⁴

Treatment A	Treatment B	Treatment C
IV methylprednisolone:30 mg/kg/dayIV (max 1 g) once a day for 3 days. May continue 1x per week (optional) Methotrexate: (subcutaneous unless only oral possible): Lesser of 15 mg/m ² or 1 mg/kg (max 40 mg) once weekly Prednisolone: 2 mg/kg/day (max 60 mg) once daily × 4 weeks*	methylprednisolone: 30 mg/kg/day (max 1 g) once a day for 3 days. May continue 1x per week (optional) Methotrexate (subcutaneous unless only oral possible): Lesser of 15 mg/m ² or 1 mg/kg (max 40 mg) once weekly Prednisolone 2 mg/kg/day (max 60 mg) once daily × 4 weeks* IVIg 2 g/kg (max 70 g), q2 weeks × 3, then monthly (Optional) IV methylprednisolone × 1 with each dose)	Methotrexate (subcutaneous unless only oral possible): Lesser of 15 mg/m ² or 1 mg/kg (max 40 mg) once weekly Prednisolone 2 mg/kg/day (max 60 mg) once daily × 4 weeks*

**Then taper prednisolone dose by 20% (as dictated by the treating physician)*

in refractory patients.¹ However, the data available today for biologics are from very small case series and evidence is not strong enough to give a clear recommendation as to when to use.

Treatment of calcinosis with diltiazem, infliximab and bisphosphonates has been anecdotally reported. Early use of DMARDs not only controls disease but also helps to prevent calcinosis. Calcinosis can present as isolated lesion or as sheets of calcium deposits. Delay in definitive treatment and failure to aggressively control disease early is the main reason for the occurrence of calcinosis. Increasing calcinosis in JDM should be treated with more intensive DMARD use. NSAIDs can be used to reduce inflammation around calcinotic deposits while flucloxacillin is used to treat secondary infection.¹

Children’s Arthritis and Rheumatology Research Alliance (CARRA) has surveyed treatment practices in JDM and after a consensus conference has come up with three consensus treatment plans for moderately severe cases of JDM for the initial four weeks (Table IV).¹⁴ Physicians can then decide on the treatment plan most suitable for their patient and most akin to their practice.¹

Supportive care

Children with JDM who develop pharyngeal weakness will need feeding via nasogastric tube or gastrostomy. Those with GI vasculitis need full bowel rest. Rarely, children who develop significant respiratory weakness need

ventilator support and even tracheostomy till the respiratory weakness improves.² The treatment of JDM has to incorporate physiotherapy and occupational therapy for passive stretching of the muscles early on and then for active reconditioning of muscles once active inflammation has subsided.² Children with JDM should be advised to avoid exposure to the sun and apply a high sun protection factor (SPF) sunscreen on a daily basis, even on cloudy days and in winter. All children on long term corticosteroid therapy must take calcium and vitamin D supplements to reduce the risk of osteopenia and osteoporosis.² Liaising with schools is helpful as the children may be able to return on a part time basis initially and then to full time school as their stamina returns. A supportive team of experienced nursing staff, play specialists, social workers and psychologists can be invaluable in helping children and families cope with the impact of JDM on their daily lives.¹

Prognosis

After the advent of corticosteroids, the mortality rate of JDM has dropped from around 33% to about 1%. More aggressive immunosuppressant therapy has reduced the period of active symptoms from 3.5 to less than 1.5 years. The skin, muscle and vascular symptoms respond well to treatment. 75% of patients at seven years of follow up are asymptomatic in terms of muscle weakness but 25% continue to experience chronic weakness and 40% suffer from chronic rash. Upto one third of affected children will need long term immunosuppressive therapy to control the disease.²

Points to Remember

- *Juvenile dermatomyositis is the most common of the childhood idiopathic inflammatory myopathies with peak age of onset between 4 and 10 years.*
- *Classical presentation of JDM are heliotrope rash and Gottron's papules along with proximal symmetric muscle weakness (affecting neck flexors, shoulder girdle and hip flexors) but presentation can be variable.*
- *Creatine kinase and inflammatory markers (ESR, CRP) can be normal even during active muscle inflammation initially in some children.*
- *MRI is useful as it detects sites of active muscle inflammation, reduces sampling error and increases the sensitivity of muscle biopsy and EMG*
- *CMAS and Kendal MMT-8 are used to assess muscle strength at diagnosis and follow up.*
- *The disease should be treated aggressively and early to induce remission.*
- *Corticosteroids are the first line treatment for JDM. Methotrexate is the steroid sparing DMARD of choice which is commenced upfront along with steroids. Early use of DMARDs helps to control disease and prevent calcinosis.*
- *Physiotherapists, occupational therapists, play specialists, social workers and psychologists play an important role in the holistic management of children with JDM.*

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DRUG PROFILE

DIURETICS IN PEDIATRICS

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Abstract: *Diuretics are a class of drugs having extensive use in various age groups which include renal as well as non-renal conditions. Their classification, clinical uses, dosage and adverse effects are discussed in this review.*

Keywords: *Diuretics, Edema, Hypertension, Loop diuretics, Thiazides*

Diuretics are used in a variety of clinical conditions in children as well as adults. Common indications in children include situations of fluid overload conditions, congestive cardiac failure, hypertension, chronic lung disease, etc. Their predominant action is by inhibition of sodium and water reabsorption.

According to their efficacy they are classified as high ceiling (loop and osmotic diuretics), medium ceiling (thiazides) and low ceiling (carbonic anhydrase inhibitors and potassium sparing) diuretics.¹ The clinical use of diuretics is extensive as they are important in treating various disease conditions in different age groups which is summarized in Box 1.² They are further classified based on their site of action (Table I).³

Drugs acting on the proximal tubules

These include the carbonic anhydrase inhibitors. They inhibit the reabsorption of sodium in the proximal tubular portion of the nephron. Role of carbonic anhydrase is in the generation of carbonic acid which subsequently breakdown and results in absorption of sodium and bicarbonate. Acetazolamide, dichlorphenamide and methazolamide inhibits the enzyme and result in excretion of sodium and bicarbonate in the urine.

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Acetazolamide

Pharmacokinetics: Absorption is complete after oral administration. Plasma half-life is 4-8 hours. Excreted unchanged in the urine. Plasma protein binding 70-90%.⁴

Dosage: Epilepsy: It is often used as an adjunct. Starting dose - upto 12 years 2.5 mg/kg and 12-18 years 250 mg 2-3 times daily and increase every 4-5 days to maintenance dose of 5-7mg/kg/ dose 2-3 times daily upto 750mg/day in <12 year old and 1g/day in 12-18 year old. The IV bolus dose is 6-7mg/kg 2-3 times daily in < 12 year and 250mg 2-4 times in 12-18 year. **Edema:** Oral or IV starting dose - upto 12 years 2.5 mg/kg and 12-18 years 250 mg 2-3 times daily. **Raised intracranial pressure:** oral/IV 8mg/kg thrice daily and gradually increased. **Hydrocephalus:** due to communicating intraventricular hemorrhage (IVH) - Neonates 25mg/kg/24 hour **Glaucoma:** oral/IV 5mg/kg in < 12 year and 250mg in 12-18 year 2-4 times daily to a maximum of 750mg/day in < 12 years and 1g/day in 12-18 year. If creatinine clearance is 10-20ml/min/1.73 M², reduce to twice daily and if <10 avoid.^{4,5}

Administration: Oral: injection solution is alkaline but can be given orally. IV: reconstitute each vial with 5 ml water for injections, and administer as a bolus.

Contra-indications: Not used if sodium and/or potassium plasma levels are decreased, marked liver and kidney disease or dysfunction, adrenal failure, hyperchloremic acidosis and sulphonamide hypersensitivity. Long-term use contraindicated in chronic non-congestive closed-angle glaucoma. Increasing the dose does not increase the diuresis and may cause increased incidence of paraesthesia and/or drowsiness.

Clinical uses of acetazolamide in addition to the above mentioned uses include epilepsy especially in cases of absence seizure by raising the seizure threshold,⁶ glaucoma by reducing the aqueous humor formation⁷ in conditions of raised intracranial tension,⁸ acute mountain sickness⁹ and to alkalinize urine for the excretion of acidic drugs.¹⁰

Dorzolamide and brinzolamide are some topically acting carbonic anhydrase inhibitors which can be used as eye drops for treatment of glaucoma but their use is limited

Box 1. Diuretics - Clinical use**1. To decrease the expanded extracellular volume (edema)****a. Systemic edema (thiazides, loop diuretics):**

- Cardiac edema: Congestive heart failure
- Renal edema: Chronic renal disease, nephrosis
- Hepatic edema: Liver cirrhosis (+ aldosterone antagonists)

b. Localized edemas (all are acute, dangerous conditions): -

- Brain oedema (mannitol infusion)
- Pulmonary edema (furosemide iv.)
- Glaucoma
(acute: mannitol or urea infusion, or isosorbide (oral)
chronic: acetazolamide(oral)/IV.; dorzolamide or brinzolamide topically)

2. To decrease the blood pressure in hypertensive patients

- Chronic hypertension: Thiazides, hydrochlorothiazide + amiloride, aldosterone antagonists (eplerenone)
- Acute hypertensive crisis: Furosemide IV

3. To increase urinary excretion of inorganic ions, such as

- in acute hypercalcemia: furosemide
- in acute hyperkalemia: furosemide
- in lithium intoxication: amiloride
- in bromide intoxication: thiazides

4. To prevent anuria in acute renal failure

- Furosemide
- Mannitol infusion (only if it produces diuresis)

5. Other indications: -

Dialysis disequilibrium syndrome (mannitol infusion to correct hyposmolality of blood)

- Calcium nephrolithiasis (thiazides to decrease calcium excretion into urine)
- Osteoporosis (thiazides to decrease calcium excretion into urine)
- Nephrogenic diabetes insipidus, i.e. ADH refractoriness (thiazides)*
- Epilepsy (carbonic anhydrase inhibitors to increase CO₂ concentration in brain)
- Metabolic alkalosis (carbonic anhydrase inhibitors to increase NaHCO₃ excretion)
- Altitude sickness (carbonic anhydrase inhibitors)
- Cystic fibrosis (inhalation of Na⁺ channel inhibitor solution or of mannitol powder to dilute the bronchial secretion and thus promote the mucociliary clearance)
- Cardiovascular diseases, e.g. congestive heart failure, cardiac infarct and hypertension (aldosterone antagonists: spironolactone, eplerenone)

* *Indomethacin (a NSAID) may also be useful in nephrogenic diabetes insipidus.*

Table I. Classification of drugs and their site of action

Class	Drugs	Site of action
Carbonic anhydrase inhibitors	Acetazolamide, Dorzolamide, brinzolamide	Proximal convoluted tubules
Loop diuretics	Furosemide, torsemide, Bumetanide, ethacrynic acid	Loop of Henle
Osmotic diuretics	Mannitol, glycerol	Loop of Henle
Thiazides	Chlorothiazide, hydrochlorothiazide, benzthiazide, chlorthalidone, metolazone	Distal convoluted tubules
Potassium sparing diuretics	Amiloride, triamterene, spironolactone	Collecting ducts

in children. Side effects include bone marrow suppression and hypersensitivity reaction as acetazolamide is a sulphonamide group of drug. Its use is contraindicated in case of liver disease as it can precipitate hepatic encephalopathy.¹¹

Drugs acting on the loop of Henle

There are 2 classes of drugs which act at the level of loop of Henle which include Na⁺-K⁺ ATPase inhibitors or loop diuretics and osmotic diuretics.

Loop diuretics

It inhibit Na⁺ K⁺ 2Cl⁻ symporter present at the luminal membrane of the ascending limb of loop of Henle. These agents have the maximal natriuretic effects and the commonly used ones are furosemide, torsemide, bumetanide and ethacrynic acid. Furosemide and Bumetanide are almost similar in their action. After oral administration, the action starts in an hour and the effect usually lasts for 6 hours, hence usually given as twice daily.¹

Furosemide

Pharmacokinetics: Oral bioavailability range is 27-80% and is extensively plasma protein bound (96-89%). It is mainly excreted unchanged in urine and some elimination by metabolism and fecal excretion which contribute almost equally to the total plasma clearance. Half-life in adults is 30-120 minutes. Half-life in healthy children on an average is 28 minutes. Half-life is very variable in the neonatal period, and may be as much as 24 hours in the young preterm infant, but is closer to 8 hours in full term infants >1 week old.¹²

Pharmacodynamics: The onset of action starts in 10-20 minutes after an IV dose and 20-30 after oral administration. The duration of action is six hours.

Uses: Congestive cardiac failure, renal failure, fluid overload, hypertension.

Dosage: Oral: Newborn 1-2mg/kg/day in 2 divided doses; 1 month-12 year 1-2mg/kg/dose and 12-18 year 20-40mg/dose 2-3 times daily. IV bolus: Birth -12 year 0.5-1mg/kg and 12-18 year 20-40 mg as single dose (max 4mg/kg). The dose could be repeated every 8 hours. Continuous infusion at 0.1-2mg/kg/hour may be better and safer in acute heart failure and in postoperative setting. The dose does not need to be adjusted in renal or hepatic impairment.¹³

Administration: IM: This route is rarely used. IV: Bolus doses must be administered slowly over at least 2 minutes. Some centres give bolus doses at slower rates (5-10 minutes) because of risk of ototoxicity, especially if the child is also on aminoglycosides. The manufacturer recommends that if larger doses need to be infused, infusion rates should not exceed those outlined. Compatibility with infusion solutions: Furosemide may be mixed with NaCl 0.9%. It is incompatible with glucose solutions. It activates the renin angiotensin aldosterone system (RAAS), producing vasoconstriction, which is detrimental in heart failure. Concomitant use of angiotensin converting enzyme inhibitors (ACEi) a vasodilator, is recommended whenever possible (watch for marked fall in BP).¹²

Contra-indications: Established anuria, electrolyte deficiency especially hypokalemia, precomatose states associated with liver cirrhosis, hypersensitivity to furosemide or sulphonamides. It is always necessary to correct hypotension or hypovolemia before commencing therapy. Latent diabetes may become manifest or the insulin requirements of diabetic patients may increase when furosemide is used. It may have to be stopped if child develops diarrhoea or vomiting and used with caution when using digoxin (avoid hypokalemia) and aminoglycosides (higher risk of ototoxicity).

Side-effects: Hypokalemia (best managed by combining furosemide with ACE inhibitors or spironolactone. Alternatively, potassium supplements may be prescribed), hypomagnesemia, hyponatremia (common, especially with

high doses and it results in further drug resistance - managed with fluid restriction), chloride depletion, leading to metabolic alkalosis (supplementation with potassium chloride helps), hyperuricemia, hyperglycemia due to impaired glucose tolerance, hypocalcemia, nephrocalcinosis in premature infants, transient increase in blood urea and serum creatinine, increase in serum triglyceride and LDL cholesterol levels, gastrointestinal disturbances, skin rashes, headache, hypotension or muscle cramps due to electrolyte and water disturbance, ototoxicity (usually reversible and rare in children), acute pancreatitis (isolated cases) and bone marrow depression (rare).

Drug-interactions: NSAIDs may reduce the antihypertensive and diuretic effect. Loop diuretics may attenuate the effects of antidiabetics. There is increased risk of hypokalemia with other loop diuretics, thiazides and corticosteroids. Diuretic-induced hypokalemia may increase the risk of arrhythmias with cardiac glycosides. A marked fall in blood pressure may be seen when ACE inhibitors are added to diuretic therapy. There is increased risk of ototoxicity with aminoglycosides (avoid prescribing at the same time of day).

Clinical uses include removal of edema fluid in renal, hepatic or cardiac diseases. They are the diuretics of choice in mild to moderate renal failure as it does not affect the GFR.¹⁴ Furosemide has additional vasodilatory action which makes it the drug of choice in acute left ventricular failure and pulmonary oedema.¹⁵ These drugs can also be used for the treatment of hypercalcemia as it causes excretion of calcium ions.¹⁶

Bumetanide

Dosage: Oral 1 month-12 year - 0.015-0.05mg/kg/dose (max 2 mg); 12-18 year 1-2 mg 1-4 times daily. IV bolus - 12-18 year - 1-2 mg repeated after 20min, if required. IV infusion over 30- 60 min – 1 month-12 year - 0.025 - 0.050 mg/kg; 12-18 year 1-5 mg. For IV administration it has to be diluted with 5% dextrose or normal saline to a conc. of 24 microgm/ml.¹⁷

Contra-indications: It has to be used with caution in hepatic impairment as the hypokalemia it may precipitate hepatic coma in severe cases. If used in hepatic impairment, it must be in conjunction with a potassium sparing diuretic.

Torsemide

Pharmacokinetics: Following oral administration torsemide is rapidly absorbed with about 80% bioavailability. First-pass metabolism is insignificant. Peak plasma concentration is achieved in about one hour after oral

administration and is proportional to the dose. Onset of diuresis occurs within the hour and a peak diuretic effect occurs within 1-2 hours. Following IV administration, diuresis begins within 10 minutes and is maximal within one hour. The duration of diuresis is independent of the route of administration and lasts 6-8 hours. The volume of distribution is approximately doubled in patients with hepatic cirrhosis, compared to healthy patients and in those with mild to moderate renal failure or congestive heart failure. Plasma protein binding is 97-99%. Torsemide is metabolized by the hepatic cytochrome P450 enzyme system. Three metabolites, one of which is active, are produced. The active metabolite does not contribute significantly to the clinical activity of torsemide. In normal adults, about 80% of torsemide is cleared through hepatic metabolism and 20% is cleared in the urine as unchanged drug. In healthy adults, torsemide elimination half-life is about 3.5 hours.

Uses: Cardiac failure, pulmonary/oedema, hypertension, renal failure, and fluid overload due to other causes.

Dosage: On a weight to weight basis torsemide is twice as potent as furosemide and provides a longer duration of action at lower urinary concentrations - allows for a 24-hour dosage interval and avoids the paradoxical antidiuresis seen with furosemide. Edema associated with congestive heart failure or CRF: Oral or intravenous dosage: Adolescent: Initially, 10-20 mg PO or IV once daily. If needed, titrate by doubling the dose up to 200 mg PO or IV to achieve a satisfactory diuretic response. The safe use of a single dose \geq 200 mg has not been evaluated. Adjunctive treatment of ascites (e.g., due to hepatic cirrhosis) either alone or in combination with spironolactone or amiloride: Oral or intravenous dosage: Adolescent: Initially, 5-10 mg PO or IV once daily. If needed, titrate upwards by doubling the dose up to 40 mg PO or IV to achieve a satisfactory diuretic response. Doses \geq 40 mg have not been evaluated in patients with hepatic cirrhosis. Chronic use in hepatic disease has not been evaluated. Hypertension: Oral dosage: Adolescent: Initially, 5 mg PO once daily and can be increased to 10 mg PO once daily if the desired reduction in blood pressure is not achieved in 4-6 weeks, If this dose is insufficient an additional antihypertensive agent should be added to the regimen. Patients with hepatic impairment: No dosage adjustment is needed; (see the dosage for the treatment of ascites). Diuretics should be used with caution in patients with hepatic disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Patients with renal impairment: No dosage adjustment is needed; however, high doses may be effective in patients

with end-stage renal disease. Intermittent hemodialysis: Torsemide is not removed by hemodialysis; no dosage adjustment is needed. Torsemide can be safely used, and appears to be effective for treatment of heart failure in children.¹⁸ Future clinical trials are warranted to verify the results of this study.

Administration: Oral - May be administered without regard to meals. The oral bioavailability of torsemide is sufficiently high to allow for 1:1 equivalency between the oral and intravenous dosage forms. IV- Preparation for IV use only should be administered either slowly as an IV bolus or as a continuous IV infusion. Based on clinical data of diuretic potency, 10-20 mg IV of torsemide is approximately equivalent to 40 mg IV of furosemide. Ampoules are single use containers. Discard any unused portion after opening. Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit. IV bolus -No dilution is necessary if given as a slow IV injection over 2 minutes. If administered through an IV line, flush the line with 0.9% NaCl before and after administration. The torsemide injection is formulated above pH 8.3. Flushing the line is recommended to avoid the potential for incompatibilities caused by differences in pH which could be indicated by colour change, haziness or the formation of a precipitate in the solution. Continuous IV Infusion: Same precautions as above. As a continuous infusion, stability has been demonstrated through 24 hours at room temperature of 15-30°C (59-86°F), in plastic containers, for the following fluids and concentrations: - 200 mg torsemide (10 mg/ml) added to: 250 ml D5W (0.8 mg/ml), 250 ml 0.9% NaCl (0.8 mg/ml), or 500 ml 0.45% NaCl (0.4 mg/ml). -50 mg Torsemide (10 mg/ml) added to: 500 mL D5W (0.1 mg/ml), 500 ml 0.9% NaCl (0.1 mg/ml), or 500 ml 0.45% NaCl (0.1 mg/ml).

Contra-indications: Known hypersensitivity to this drug, severe sodium and volume depletion, anuria with caution in renal or hepatic impairment, juvenile diabetes and advanced CCF. Serum electrolytes should be monitored.

Osmotic diuretics

Osmotic diuretics like mannitol and glycerol exerts its effect by increasing the osmotic pressure inside the blood vessels and consequent removal of excess fluids from the cells resulting in expansion of extracellular fluids volume.

Mannitol

Pharmacokinetics: Oral absorption is negligible. Plasma half-life is 2.17 hours (range 2-36 hours). Volume of distribution is 0.16-0.27L/kg. After IV administration, 80%

of mannitol is excreted in the urine unchanged. Very little metabolism of mannitol occurs, with unchanged mannitol also being excreted in bile, particularly in renal failure.

Uses: Edema, ascites, and increased intracranial pressure.

Dosage: A test dose may be given to assess renal function - 200mg/kg (max 12.5gm) over 3-5 min to produce urine output of 1ml/kg/hour for 1-3 hour. Cerebral and ocular edema - 0.5-1g/kg IV over 30 min initially followed by maintenance of 0.25-0.5gm/kg every 4-6 hour as required. Peripheral edema and ascites 1-2g/kg IV infusion over 2-6 hour.

Administration: Do not mix with any other drugs. The 20% solution is supersaturated and an administration set with a filter should be used for infusions containing 20% or more of mannitol.

Contra-indications: Known hypersensitivity to mannitol; pulmonary edema or congestive heart failure; inadequate urine flow; dehydration and/or acidosis; intracranial bleeding.

Side-effects: Administration of hypertonic mannitol solutions in therapeutic amounts may produce severe fluid and electrolyte imbalance. Pulmonary oedema, water intoxication, convulsions and hypertension or hypotension may result. Irreversible crenation of red blood cells may occur if mannitol is administered too quickly. Long-term use of mannitol results in hypernatremia and dehydration. Hyperkalemia and acidosis may occur and depend on the dose, rate of administration and insulin response. Hypokalemia may occur due to increased urine flow and hyperaldosteronism associated with extracellular fluid expansion. Hypersensitivity reactions, including urticaria. Extravasation may cause edema, inflammation, skin necrosis and thrombophlebitis. Thirst, headache, dizziness, chills, fever, tachycardia, chest pain, nausea and vomiting, urinary retention and blurred vision have all been reported.

Drug-interactions: Aminoglycosides: Mannitol potentiates ototoxic effects. Lithium: Renal excretion of lithium may be increased. Neuromuscular- blocking drugs: Effect of tubocurarine and other competitive or depolarizing neuromuscular blockers may be enhanced. Oral anticoagulants: Mannitol may reduce the effect of anticoagulant drugs by concentrating circulating clotting factors secondary to dehydration. Digoxin: Increased risk of digoxin toxicity if mannitol administration produces hypokalemia. Cisplatin: Mannitol reduces the renal toxicity of cisplatin. Potassium chloride, sodium chloride, other electrolytes, or drugs should not be added to mannitol solutions due to risk of precipitation.

Drugs acting at the distal tubules and the collecting ducts

Thiazides and potassium sparing diuretics belong to this group of agents. Thiazides include chlorothiazide, hydrochlorothiazide, benzthiazide, chlorthalidone, metolazone, etc. Several new agents are also identified but the safety profile is not well established in children. They act by inhibiting Na⁺ Cl⁻ symporter at the luminal membrane of the early distal tubules. They act within 1-2 hours of oral administration and effect lasts for 12-24 hours. Ideal time to administer is early in the day so that it does not interfere with the sleep. It is used in the management of hypertension when given at a low dose, in treatment of edema, nephrogenic diabetes insipidus, bronchopulmonary dysplasia, hypercalcuria and in prevention of recurrent calcium stones in the kidneys.

Hydrochlorothiazide

Dosage: Neonates and infants - Oral 2 - 4 mg/kg/24 hour in 2 divided doses.; >6 months - 12 year 2 mg/kg/24 hour in 2 divided doses; 12-18 year 12.5 - 100 mg/24 hour. Nephrogenic diabetes insipidus - Oral < 12 year 3 mg/kg and > 12 year 37.5-75 mg/ day in 3 divided doses.

Contra-indications: Patients with renal failure are usually refractory to hydrochlorothiazide. Doses should be given after dialysis in hemodialysis patients. It displaces bilirubin from albumin.

Chlorothiazide

Pharmacokinetics: The bioavailability of oral doses of chlorothiazide is low. Plasma protein binding is approximately 70%. Chlorothiazide is not metabolized and is excreted almost completely as unchanged drug in the urine. Plasma half-life in adults is 45-120 minutes though clinical effects of the oral preparation last approximately 12 hours.

Uses: Congestive cardiac failure, hypertension, hyperinsulinemia, bronchopulmonary dysplasia, nephrogenic diabetes insipidus.

Dosage: 20-40 mg/kg/day in two divided doses oral; 2-8mg/ kg twice a day IV Contra-indications: Anuria, hypersensitivity to chlorothiazide or other sulphonamide-derived drugs, severe renal or hepatic failure, Addison disease, hypercalcemia.

Warnings: Fluid and electrolyte imbalance can occur. Hypokalemia may develop which can sensitise the myocardium to digitalis compounds. Sensitivity reactions

may occur in patients with or without history of allergy or bronchial asthma. Thiazides may decrease urinary calcium excretion. Thiazides may impair glucose tolerance, latent diabetes may become manifest during thiazide therapy and in renal disease, may precipitate uremia. When creatinine clearance falls below 30ml/minute, thiazide diuretics become ineffective. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Side-effects: GI: Anorexia, gastric irritation, nausea, vomiting, diarrhea, constipation, jaundice and pancreatitis. CNS: dizziness, vertigo, paresthesia, headache and yellow vision. Hematological: Leucopenia, agranulocytosis, thrombocytopenia, aplastic anaemia and haemolytic anemia. Cardiovascular: Hypotension. Hypersensitivity: Purpura, photosensitivity, rash, urticaria and anaphylactic reactions. Metabolic: Hyperglycemia, glycosuria, hyperuricemia, electrolyte imbalance including hyponatremia and hypokalemia. Renal: Renal dysfunction, interstitial nephritis and renal failure. Others: Muscle spasm, weakness, restlessness and blurred vision.

Drug-interactions: Increased risk of hypotension with tricyclic antidepressant and antihypertensive drugs. Antagonism of antidiabetic agents, which may therefore need adjustment of dose with concurrent use. Other antihypertensive drugs may have an additive effect. Corticosteroids or corticotrophin (corticotrophin, ACTH) may intensify any electrolyte depletion. Hypokalemia with corticosteroids and other diuretics. NSAIDs may attenuate the diuretic effects of chlorothiazide and increase risk of nephrotoxicity. Increased toxicity of amiodarone, disopyramide, flecainide, quinidine, pimozide, sotalol, digoxin and lithium in hypokalemia. Antagonism of lidocaine (lignocaine) and mexilitine in hypokalemia. Reduced absorption with cholestyramine. Adverse effects are similar to that of loop diuretics except in the case of calcium excretion. They may also interact with loop diuretics and enhance digitalis toxicity.

Potassium sparing diuretics

These are epithelial Na⁺ channel inhibitors like amiloride and triamterene and aldosterone antagonists like spironolactone. They act in the late distal tubules and collecting ducts to preserve potassium. These are often weak diuretics and used in combination with loop diuretics or thiazides to counteract loss of potassium ions. Potassium supplements should not be given with potassium sparing diuretics and if given to patients who are already on ACE

inhibitors or angiotensin receptors blockers, it can precipitate severe hyperkalemia. Spironolactone can also be used in the treatment of hirsutism due to its antiandrogenic action.¹⁹

Spironolactone

Pharmacokinetics: Oral absorption of spironolactone is variable depending on its formulation. Current formulations are reported to provide a bioavailability of about 90%. There is improved absorption if the drug is taken after food. Protein binding >90%. The major site of biotransformation of spironolactone is thought to be the liver, and excretion is mainly in the urine. Plasma half-life in adults ranges from 1.3-2 hours (active metabolite up to 11 hours).

Uses: 1. Congestive heart failure 2. Diuretic or amphotericin induced hypokalemia - prophylaxis 3. Edema 4. Ascites 5. Nephrotic syndrome 6. Primary hyperaldosteronism. 7. Hirsutism.

Dosage: Oral 1-3 mg/kg/day in 2 divided doses. In resistant ascites, up to 9 mg/kg/day have been given with careful serum potassium monitoring. Hirsutism: Start with 50 mg in 2 divided doses, gradually increasing to 100 mg; max up to 200 mg daily can be given.

Administration: Oral: Tablets may be crushed and taken with food or drink. To convert to IV potassium canrenoate dose multiply spironolactone dose by 1.43.

Contra-indications: Hyperkalemia, hyponatremia, severe renal impairment, acute renal failure, anuria, Addison's disease, hypersensitivity to spironolactone. **Precautions:** Fluid and electrolyte balance should be regularly monitored especially if there is significant renal or hepatic impairment. Hyperkalemia may occur if there is impaired renal function or excessive potassium intake which may cause fatal cardiac irregularities. Should hyperkalemia develop, spironolactone should be discontinued and if necessary active measures taken to reduce serum potassium to normal. Hyponatremia may be induced, especially if administered in combination with other diuretics. Reversible increases in blood urea have been reported particularly if renal function is impaired.

Side-effects: Hyperkalemia, hyponatremia, deterioration in renal function, gynecomastia, menstrual irregularities, gastrointestinal disturbances, drowsiness, headache, lethargy, mental confusion, skin rashes. A reversible increase in plasma urea and creatinine may occur and mild acidosis has been reported. In doses given for hirsutism, it causes menstrual irregularities; estrogen-progestin combination to be given along with.

Drug-interactions: High risk of hyperkalemia with ACE inhibitors, NSAIDs, cyclosporin, potassium salts and other potassium-sparing diuretics. Increased risk of nephrotoxicity and reduced diuretic effect with NSAIDs. Potentiation of the effects of antihypertensive drugs and other diuretics may occur. Spironolactone has been reported to increase serum digoxin concentration and to interfere with certain digoxin assays. Therefore when used concurrently, the digoxin levels should be interpreted in conjunction with clinical presentation. Adverse effects include risk of hyperkalemia, abdominal pain and gastritis. Spironolactone can also cause gynecomastia in children.²⁰

Amiloride

Pharmacokinetics: Plasma half-life is approximately 6 hours but prolonged in renal failure, hepatitis and cystic fibrosis patients.

Uses: Hypokalemia due to loop/thiazide diuretic or amphotericin, nephrogenic diabetes insipidus.

Dosage: Oral-Prophylaxis of drug induced hypokalemia <12 years 100-200 microgram/kg and >12 years 5-10mg twice daily. Nephrogenic diabetes insipidus along with hydrochlorothiazide 100 microgram/kg 3 times daily.

Contra-indications: Risk of hyperkalemia in renal impairment. Do not use for nephrogenic diabetes insipidus in infants or young children (indomethacin is generally used instead).

Side-effects: Gastrointestinal disturbances, dry mouth, rashes, hyperkalemia, hyponatremia.

Drug-interactions: Risk of hyperkalemia increased with ACE inhibitors. Increased risk of nephrotoxicity with NSAIDs.

Conclusion

Diuretics are a group of drugs which are being used in various clinical conditions which involve multiple systems of the body like heart, lungs, renal and central nervous system. Careful selection of appropriate diuretic, titration of doses and monitoring of side effects is necessary for long term use in children.

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CLIPPINGS

Accuracy of Lung Ultrasonography in the Diagnosis of Pneumonia in Adults: Systematic Review and Meta-Analysis

Some studies suggest that lung ultrasonography could be useful for diagnosing pneumonia; moreover, it has a more favorable safety profile and lower cost than chest radiography and CT. The present study aimed to assess the accuracy of bedside lung ultrasonography for diagnosing pneumonia in adults through a systematic review and meta-analysis.

The authors searched MEDLINE, Scopus, The Cochrane Library, Web of Science, DARE, HTA Database, Google Scholar, LILACS, ClinicalTrials.gov, TESEO, and Open Grey. In addition, they reviewed the bibliographies of relevant studies. Two researchers independently selected studies that met the inclusion criteria. Quality of the studies was assessed in accordance with the Quality Assessment of Diagnostic Accuracy Studies tool. The summary receiver operating characteristic (SROC) curve and a pooled estimation of the diagnostic odds ratio (DOR) was estimated using a bivariate random-effects analysis. The sources of heterogeneity were explored using predefined subgroup analyses and bivariate meta-regression.

The study concluded that Lung Ultrasonography can help accurately diagnose pneumonia, and it may be promising as an adjuvant resource to traditional approaches.

Ana M Llamas-Álvarez, Eva M. Tenza-Lozano, Jaime Latour-Pérez. Accuracy of Lung Ultrasonography in the Diagnosis of Pneumonia in Adults: Systematic Review and Meta-Analysis. Chest 2016; 151 (2), 374-382.

RADIOLOGY

OSTEOMYELITIS 4

***Vijayalakshmi G**
****Natarajan B**
****Karthik C**
****Dheebha V**

In this concluding part on osteomyelitis we will see more about tuberculous osteomyelitis. Next to spine, the hip joint is commonly involved in children. Clinically, the child has a painful limp. At that time there may only be an effusion that is seen in the x-ray as a soft tissue swelling centred over the joint. Ultrasound is useful in this stage to demonstrate fluid. Fig.1 is a sagittal section along the length of the femur showing anechoic fluid in the anterior recess of the hip joint under the iliopsoas muscle. The differential diagnosis for the presence of synovial fluid also includes transient synovitis which is a common problem in children. Therefore, if the duration of symptoms is only a few days, with mild fever but no inflammatory markers, transient synovitis is the most likely diagnosis and anti-inflammatory agents can be used to shorten the clinical course.



Fig.1. Transient synovitis of the hip joint with joint fluid (arrow)



Fig.2. Erosion of cartilage (arrow)



Fig.3. Tuberculous osteomyelitis. Lysis in acetabulum(arrow)



Fig.4. Tuberculous osteomyelitis- talus (right)

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Persistence of joint fluid requires aspiration and analysis mainly to rule out tuberculous synovitis. Septic arthritis, we all know, is clinically evident with high temperature and local signs and aspiration is indicated for diagnostic and therapeutic purposes. A plain x-ray is part of the initial work up of any joint swelling though there are no osseous signs in the beginning. Synovial thickening and joint fluid in tuberculous arthritis is followed by destruction of cartilage as can be seen in Fig.2 with a scooped out defect in the anterior articular surface of the lower femur. MRI is very good in this stage as cartilage involvement is delineated very clearly only with this modality. Synovial fluid can be seen as the white area in the joint space. Later, there is erosion of the subarticular epiphysis. At this time pathology is visible in the x-ray as bone destruction. Fig.3 shows lytic destruction at characteristic sites-the superior rim of the acetabulum which is drained by the Batson's prevertebral venous plexus and the neck of the femur. A peculiar feature of tuberculous infection is the lack of sclerosis inspite of significant lysis of bone. This is attributed to the indolent nature of the



Fig.7. Dactylitis



Fig.8. Tuberculous dactylitis



Fig.5. Tuberculous osteomyelitis-talus. Penumbra sign



Fig.6. Disseminated tuberculosis

infection which does not provoke reparative sclerosis. The lack of sclerosis can make the lesion inconspicuous in certain sites. Fig.4 is the lateral view of both ankle joints. The lysis in the left talus is almost imperceptible. Yet, the extent of destruction in the MRI picture is significant. Fig.5 shows a characteristic appearance of tuberculous osteomyelitis. There is an inner nodular, mildly hyperintense focus which represents caseous necrosis surrounded by a grey ring which is the granulation tissue. The diffuse white area in the rest of the talus is inflammatory marrow edema. This is a modified penumbra sign. The classic penumbra sign described in subacute osteomyelitis shows an additional black ring outer to the granulation tissue corresponding to sclerosis which is absent in tuberculous osteomyelitis. The penumbra sign is especially useful in disseminated tuberculosis which presents as expansile lesions in the long bones (Fig.6).



Fig.9. Congenital syphilis

In the issue titled osteomyelitis 1, we saw dactylitis of the first metatarsal which had a white sclerotic appearance (Fig.7). Contrast this with the tuberculous dactylitis in Fig.8. The bone is expanded and trabeculae are partially destroyed so that the bone looks like it is distended with air which is why the condition is called spina ventosa (spina - short bone, ventosa-expanded with air) Multiple and contiguous small bones are likely to be involved.

Fig.9 is that of an infant with fever, irritability and crying on handling. An x-ray of the long bones reveals periosteal reaction in all the bones of both lower limbs. The lower metaphysis of the left tibia shows a punched out area of destruction. Metaphysitis and periosteitis involving almost all the bones is a feature of congenital syphilis.



Fig.10. Caffey disease

In conclusion, we will see a rare condition that mimics osteomyelitis and is usually treated with antibiotics for long periods without success. Fig.10 is a picture of Caffey disease from our museum. Both the tibiae and the fibulae are thickened with exuberant periosteal reaction. The bones usually involved are mandible, clavicles, ribs, scapula, skull, ilium and ulna, but rarely involvement of many bones can be present. In the beginning the child may have fever, pain and swelling near the involved bone. There is periosteal reaction that increases with formation of layers of lamellar bone. This is why it is also called infantile cortical hyperostosis. In the healing phase the new bone that was formed under the periosteum is resorbed and cortical remodelling occurs. Healing might take upto almost two years.

CLIPPINGS

Management of recurrent tonsillitis in children

The study compared azithromycin (AZT) and benzathine penicillin (BP) in the treatment of recurrent tonsillitis in children.

The study comprised of 350 children with recurrent streptococcal tonsillitis, 284 of whom completed the study and 162 children received conventional surgical treatment. The rest of the children, 122, were divided randomly into two equal main groups. Group A children received a single intramuscular benzyl penicillin (BP) (600,000IU for children ≤ 27 kg and 1,200,000IU for ≥ 27 kg) every two weeks for six months. Group B children received single oral AZT (250mg for children ≤ 25 kg and 500mg for ≥ 25 kg) once weekly for six months.

Both groups showed marked significant reduction in recurrent tonsillitis that is comparable to results of tonsillectomy. There were no statistical differences between group A and B regarding the recurrence of infections and drug safety after six-month follow-up. Group B showed better compliance. The study concluded that AZT proved to be good alternative to BP in the management of recurrent tonsillitis with results similar to those obtained after tonsillectomy.

EI Hennawi DE, Geneid A, Zaher S, Ahmed MR. Management of recurrent tonsillitis in children. Am J Otolaryngol 2017 Mar 3. pii: S0196-0709(17)30034-0. doi: 10.1016/j.amjoto.2017.03.001. [Epub ahead of print].

CASE REPORT

A CASE OF HYPEREOSINOPHILIC SYNDROME PRESENTING AS PERSISTENT PLEURAL EFFUSION

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****Nutan Singh**

*****Uthaya Kumaran**

Abstract: *Hyper eosinophilic syndrome is a rare condition characterized by persistent eosinophilia with organ system dysfunction and substantial clinical heterogeneity. Pulmonary involvement usually occurs in 49% of this condition presenting as dry cough, bronchial hyperreactivity without radiological involvement, eosinophilic pneumonia and pulmonary fibrosis. In our case hyper eosinophilic syndrome presented as persistent pleural effusion.*

Keywords: *Eosinophilia, Hyper eosinophilic syndrome, Persistent pleural effusion.*

A 14 year old female child presented with on intermittent fever for 6 months, pain over right side of chest and abdomen for 3 months and difficulty in breathing along with weight loss for 15 days. Child had history of recurrent hospital admissions and received antibiotics with intermittent relief of symptoms. There were no history of rashes, joint pain, yellowish discolouration of eyes, swelling of the limbs, decreased urine output, ulcer in oral cavity and contact with tuberculosis. On examination, child was tachypneic with right sided pleural effusion and not tender hepatomegaly without ascites. Investigations revealed Hb -10.5 g%, ESR- 24 mm/hr, total leucocyte count (TLC) of 15900 cells/mm³, Platelet - 2.52 L/mm³; differential leucocyte count (DLC) - P 36%, L 29%, E 35%. Absolute eosinophil count (AEC) was 5565 mm³. Mantoux test and sputum for AFB were negative. X ray chest (Fig.1)

and USG thorax showed right sided pleural effusion. USG abdomen revealed hepatomegaly with two ill defined hypoechoic lesions in segment 2 and 4 of liver. The pleural fluid was exudative in nature and AFB, Grain stain, culture were negative with normal adenosine deaminase level. GeneXpert TB could not be done. Thyroid function test and echocardiography were normal. Child was treated with IV antibiotics, diethylcarbamazine for 3 weeks along with intercostal drainage (ICD) tube drainage of pleural effusion. However, the pleural effusion reappeared in 2 days after removal of ICD and was bilateral (Fig.2). The differential diagnoses considered were inadequately treated parapneumonic effusion, tubercular effusion, autoimmune disorder, parasitic infestation and immunodeficiency disease. A trial of 5 days albendazole therapy was given suspecting parasitic (toxocariasis) infection but there was no improvement. Repeat complete blood count showed persistent eosinophilia with AEC of 5244/mm³. Repeat USG abdomen showed normal echo texture of liver. Antinuclear antibody (ANA), anti-double stranded DNA (anti ds DNA) and Anti-neutrophil cytoplasmic antibodies



Fig.1. Pleural effusion

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Fig.2. Bilateral pleural effusion

(ANCA), serology for HIV and stool examination for parasites were negative. Contrast-enhanced computed tomography (CECT) thorax did not reveal any pulmonary nodules or mediastinal mass. Bone marrow examination showed mild myeloid hyperplasia with prominent eosinophilia and mild increase in eosinophilic precursors (Fig.3). Immunohistochemistry could not be done. Bronchoscopy was normal and broncho alveolar lavage showed > 60% eosinophils. Most of the diseases causing hypereosinophilia were excluded by relevant investigations and a final diagnosis of hypereosinophilic syndrome (HES) was made on the basis of blood eosinophilia exceeding $1500/\text{mm}^3$ for more than 6 consecutive months. Genetic studies although indicated, could not be done due to non availability. Oral prednisolone (2mg/kg/day) was given once a day for 6 weeks following which the pleural effusion resolved and eosinophil counts showed a decreasing trend and the child is on regular follow up.

Discussion

Hypereosinophilic syndrome (HES) is the term used to describe a wide variety of eosinophilic disorders without a known etiology.¹ Criteria for idiopathic HES include: (1) blood eosinophilia exceeding $1500/\text{mm}^3$ for more than 6 consecutive months, (2) absence of an underlying cause of hypereosinophilia (3) organ damage or dysfunction.^{2,3}

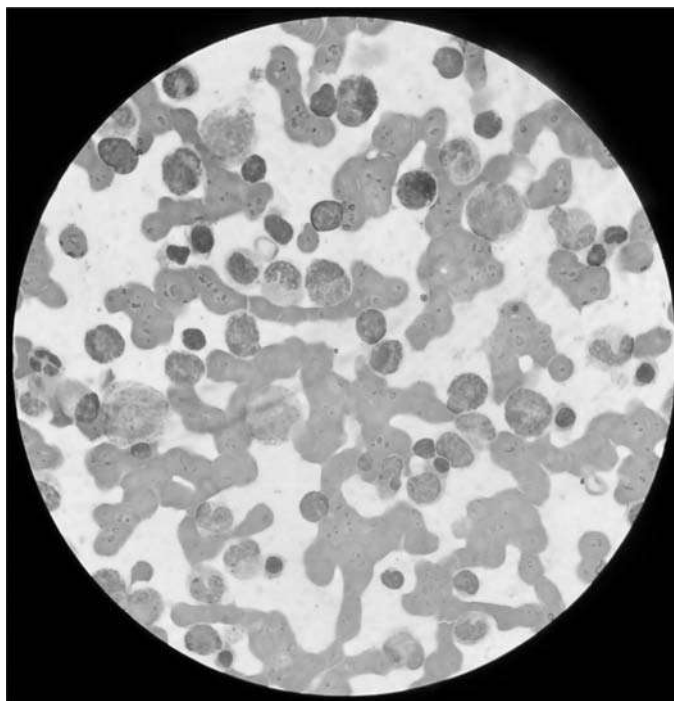


Fig.3. Bone marrow - numerous eosinophilic precursors

Contemporary diagnostic modifications suggest that "persistent" hypereosinophilia is no longer defined by a 6 month duration, but can be shorter period, provided other causes of hypereosinophilia have been excluded. The pathophysiology of this disease is centered on eosinophil mediated tissue damage leading to organ dysfunction. Organs most commonly involved in hypereosinophilic syndrome are: hematologic (100%), cardiovascular (58%), cutaneous (56%), neurologic (54%), pulmonary (49%), splenic (43%), hepatic (30%), ocular (23%) and gastrointestinal (23%).⁴ The commonest respiratory symptom in patients with HES is a chronic, persistent, generally nonproductive cough due to sequestration of eosinophils in pulmonary tissues.⁵ In a study of 49 patients of HES, in 12 patients (24%) pulmonary manifestations were attributable to parenchymal lung involvement and 13 patients (27%) had asthma.⁶ In HES transudative pleural effusion has been reported as a common finding associated with congestive heart failure.⁶ Rarely an eosinophil-containing exudative pleural effusion may occur.⁷ Alfaham, Ferguson, Sihra, and Davies report a 14 year girl child diagnosed with HES presenting with major cardiac manifestations like congestive cardiac failure, pericardial effusion, mitral regurgitation and right sided pleural effusion.⁸ Similarly a study by Libanoff reports pleural effusion and cardiac manifestations in a 9 year old boy

with HES.⁹ Two cases with HES reported by Engfeldt also showed pleural effusion along with cardiac failure.¹⁰ HES presenting as pleural effusion without other manifestation is an uncommon presentation even in adults.¹¹ Treatment of HES includes corticosteroids, cytotoxic agents and interferon alpha. Newer agents imatinib and mepolizumab have the potential to improve clinical outcome. Children with cardiac or neurological manifestations are usually refractory to corticosteroids.

This child presented with persistent pleural effusion and without any other system involvement. However, other manifestations of respiratory involvement e.g., pneumonia, parenchymal diseases, asthma, allergic disorders have been found to be a common presentation. The most significant aspect in the present case of hypereosinophilic syndrome is the rarity of presentation as an isolated persistent pleural effusion and the good response to steroids. The persistence of high AEC beyond six months with suggestive bone marrow examination and absence of any other etiological factor confirmed the diagnosis of HES.

Conclusion

Hypereosinophilic syndrome is a heterogeneous disease syndrome and should be suspected when AEC above 1500 cells/mm³ for more than 6 months. Idiopathic HES is a diagnosis of exclusion. The presentation of hypereosinophilic syndrome as isolated persistent pleural effusion is a rarity in children.

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CLIPPINGS

High-flow nasal cannula therapy beyond the perinatal period.

This article is a review of High-flow nasal cannula (HFNC) as a means of oxygen delivery and respiratory support for a range of conditions outside the perinatal period. The mechanisms of action and advantages of HFNC and clinical benefit in specific pediatric disease processes and in patients with significant respiratory distress has been reviewed. This is a safe and efficacious mode of respiratory support in children. This leads to improvement in oxygenation and reduces the need for invasive procedures like endotracheal intubation in select group of children. It is now emerging as a new intervention prior to endotracheal intubation and ventilation in selected pediatric conditions. Available evidence is more promising towards a better outcome as it is well tolerated by children.

Lee, Michael, Nagler Joshua. High-flow nasal cannula therapy beyond the perinatal period. Curr Opin Pediatr 2017; 29(3):291-296.

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