INDIAN JOURNAL OF PRACTICAL PEDIATRICS

IJPP

- **IJPP is a quarterly subscription journal of the Indian Academy of Pediatrics committed to presenting practical pediatric issues and management updates in a simple and clear manner**
- **Indexed in Excerpta Medica, CABI Publishing.**

Vol.14 No.2	**APR.-JUN. 2012**
Dr. K.Nedunchelian Editor-in-Chief	**Dr. S.Thangavelu** Executive Editor

CONTENTS

TOPIC OF INTEREST : "NEPHROLOGY"

Journal Office and address for communications: Dr. K.Nedunchelian, Editor-in-Chief, Indian Journal of Practical Pediatrics, 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India. Tel.No. : 044-28190032 E.mail : ijpp_iap@rediffmail.com

Published by Dr.K.Nedunchelian, Editor-in-Chief, IJPP, on behalf of Indian Academy of Pediatrics, from 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai - 600 008. Tamil Nadu, India and printed by Mr. D. Ramanathan, at Alamu Printing Works, 9, Iyyah Street, Royapettah, Chennai - 14.

PEDICON 2013

17-20 January 2013
Science City Convention Center, Kolkata
Golden Jubilee Conference of Indian Academy of Pediatrics
"50 Years of Child Care : Mission Achieved and Vision Ahead"

Important dates
16th January 2013 : Preconference Workshops
17th January 2013 : CME and Inauguration from 5.30 pm
18th to 20th January 2013 : Conference

Category	1 Feb - 30 Apr 2012	1 May - 31 Aug 2012	1 Sep - 31 Oct 2012	1 Nov - 31 Dec 2012
IAP Member	7500	8500	11000	12000
IAP Non Member	8500	9500	12000	13000
PG Student*	5500	6500	8000	9000
Senior Citizen (65 - 70 years)*	5500	6500	8000	9000
Accompanying Delegate (Including children above 110 cm)	7500	8500	11000	12000
Foreign Delegate	$750	$800	$900	$1000
Accompanying Delegate (Foreign)	$750	$800	$900	$1000
Trade Delegate	9000	10000	12000	14000
Refund Cancellation#	75%	50%	25%	Nil

* Valid certificate to be produced
\# Refund only after 1 March 2013

Bank Details : Kotak Mahindra Bank Ltd. Salt Lake Branch, Swift : KKBKINBBCPC, IFSC/NEFT Code : KKBK 0000326
A/c No. 6711148802 In favour of PEDICON 2013.
Please Note : Cheque are subject to realisation.
Payment from Indian delegates and foreign delegates will be accepted in INR and USD respectively.
Senior IAP Member above 70 years of age are exempted from Conference Registration till 30 September 2012.
Each member's contribution includes Rs.1000/- for Central Indian Academy of Pediatrics corpus fund.

PEDICON 2013 Pre-Conference Workshops
Date : 16 January 2013

1. Basics of Pediatric Intensive Care (Few seats vacant) (2 Day workshop - 15,16 January 2013).
2. Pediatric Emergencies - In OPD and ER (Few seats vacant)
3. Pediatric Imaging - Man behind the Machine
4. Pediatric Nephrology - Interpreting the Biochemistry
5. Pediatric Cardiology - Problems in Office Practice
6. Pediatric Pulmonology - New Horizons
7. Modules on Developmental Assessment and Autism IAPGDBP Chapter
8. Pediatric Hematology & Oncology
9. Neonatal Ventilation
10. Computer Skill for Doctors
11. Genetics for Clinicians
12. Pediatric Rheumatology
13. G I Endoscopy
14. Medicolegal Issues in Office Practice

Workshop Registration :
INR 1000 for Indian delegates
INR 1500 for SAARC delegates,
USD 100 for International delegates

Workshop No.1 (Basics of Pediatric Intensive Care) Fee :
INR 2000 for Indian delegates
INR 3000 for SAARC delegates,
USD 200 for International delegates

Only 40 delegates per workshop. Conference registration is mandatory.
Dr Monidipa Banerjee,
Convener, Workshop Committee.
Email : monidipa@hotmail.com
workshop@ pedicon2013.org
Please visit the website www.pedicon2013.org

Conference Secretariat :
Dr Jaydeep Choudhury, Organising Secretary
West Bengal Academy of Pediatrics, Oriental Apartments, Flat H1, 15C, Canal Street, Kolkata 700014
Phone : (033) 2265 4072, Email : pedicon2013@gmail.com, Website : www.pedicon2013.org
Helplines : Dr Ritabrata Kundu (9831194865), Dr Jaydeep Choudhury (9831191020) Dr Arup Roy (9434074434), Dr Nupur Ganguly (9830454874), Dr Pallab Chatterjee (9830178987), Dr Sutapa Ganguly (9831369441)

PEDICON 2013

50th Annual National Conference of IAP

Science City Convention Center, Kolkata ● 16-20 January 2013

***Organised by* West Bengal Academy of Pediatrics**

Registration Form

Please fill the form in **Block Capital Letters** only

Receipt No. ....

IAP Membership No. .... , IAP Non-Member ☐, PG Student ☐, Accompanying ☐

SAARC/Foreign Delegate ☐, Trade Delegate ☐, Sr. Member > 70 years ☐

Name ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Corresponding Address ....

.... City ....

State .... Pin .... Country ....

Email .... Mobile ....

Telephone with STD ....

Accompanying Person Details : Number ☐

Name(s) ....

Total amount .... Amount in words ....

Mode of payment : Cash / DD / Cheque / Debit Card / Credit Card ....

Bank Details : Kotak Mahindra Bank Ltd. Salt Lake Branch, Swift : KKBKINBBCPC, IFSC/NEFT Code : KKBK 0000326
A/c No. 6711148802 In favour of **PEDICON 2013.**

Please Note :
Cheque are subject to realisation.
Payment from Indian delegates and foreign delegates will be accepted in INR and USD respectively.
Senior IAP Member above 70 years of age are exempted from Conference Registration till 30 September 2012.
This member's contribution includes Rs.1000/- for Central Indian Academy of Pediatrics corpus fund.

Date .... Signature ....

Conference Secretariat :
Dr Jaydeep Choudhury, *Organising Secretary*
West Bengal Academy of Pediatrics
Oriental Apartments, Flat H1, 15C, canal Street, Kolkata 700014
Phone : (033) 2265 4072, email : pedicon2013@gmail.com, Website : www.pedicon2013.org

INSTRUCTIONS TO AUTHORS

General

Print the manuscript on one side of standard size A4, white bond paper, with margins of at least 2.5 cm (1") in double space typescript on each side. Use American English using Times New Roman font 12 size. Submit four complete sets of the manuscript.

They are considered for publication on the understanding that they are contributed to this journal solely.

All pages are numbered at the top of the right corner, beginning with the title page.

All manuscripts should be sent to: The Editor-in-Chief, Indian Journal of Practical Pediatrics

Manuscript

1st Page –

Title

Name of the author and affiliation

Institution

Address for correspondence (Email, Phone, Fax if any)

Word count

No. of figures (colour / black and white)

No. of references

Authors contribution

2nd Page –

Abstract (unstructured, not exceeding 100 words) with key words (not exceeding 4)

3rd Page -

Acknowledgement

Points to remember (not more than 5 points)

Text

References

Tables

Legends

Figures – should be good quality, 4 copies black & white / colour,*

(4 x 6 inches – Maxi size) Glossy print

* Each colour image will be charged Rs. 1,000./- separately, with effect from January 2006 (Except for invited articles).

Text

Only generic names should be used

Measurements must be in metric units with System International (SI) Equivalents given in parentheses.

References

Recent and relevant references only

Strictly adhere to Vancouver style

Should be identified in the text by Arabic numerals as superscript.

Type double-space on separate sheets and number consecutively as they appear in the text.

Articles without references / defective references will entail rejection of article.

Tables

Numbered with Roman numerals and typed on separate sheets.

Title should be centered above the table and explanatory notes below the table.

Figures and legends

Unmounted and with figure number, first author's name and top location indicated on the back of each figure.

Legends typed double-space on separate sheet. No title on figure.

All manuscripts, which are rejected will not be returned to author. Those submitting articles should therefore ensure that they retain at least one copy and the illustration, if any.

Article Categories

Review article

Article should be informative covering the recent and practical aspects in that field. Main articles can be in 1500 – 2000 words with 12 – 15 recent references and abstract not exceeding 100 words.

Case report (covering practical importance)

250 – 600 words, 8 – 10 recent references

Clinical spotters section

150 – 200 words write up

With 1 or 2 images of clinically recognizable condition

(of which one could be in the form of clinical photograph / specimen photograph / investigation)

Letters to the Editor

200 – 250 words pertaining to the articles published in the journal or practical viewpoints with scientific backing and appropriate references in Vancouver style.

Check List

Covering letter by corresponding author

Declaration (as enclosed) signed by all authors **

Manuscript (4 copies)

Accompanied by a copy in CD / or submit as an email attachment in addition to hard copy.

Failing to comply with the requirement at the time of submission would lead to the rejection of the article.

Author's contribution / Authorship Criteria

All persons designated as authors should qualify for the authorship. Authorship credit should be based on substantial contributions to i) concept and design, or collection of data, or analysis and interpretation of data; ii) drafting the article or revising it critically for important intellectual content; and iii) final approval of the version to be published. All conditions 1, 2 and 3 must be met. Participation solely in the collection of data does not justify authorship and can be mentioned in the acknowledgement if wanted.

Declaration by authors

I/We certify that the manuscript titled '…….' represents valid work and that neither this manuscript nor one with substantially similar content under my/our authorship has been published or is being considered for publication elsewhere. The author(s) undersigned hereby transfer(s), assign(s), or otherwise convey(s) all copyright ownership, including any and all rights incidental thereto, exclusively to the Indian Journal of Practical Pediatrics, in the event that such work is published in Indian Journal of Practical Pediatrics. I / we assume full responsibility for any infringement of copyright or plagiarism.

Authors' name(s) in order of appearance in the manuscript

Signatures (date)

Selection procedures

All articles including invited articles will be peer reviewed by two masked reviewers. The decision of the Editorial Board based on the reviewer's comments is final. All manuscripts, which are rejected will not be returned to author. Those submitting articles should therefore ensure that they retain at least one copy and the illustration, if any.

NEPHROLOGY

NEWER DEVELOPMENTS IN MINIMAL CHANGE NEPHROTIC SYNDROME

**** Uma Ali***

Abstract: *Minimal change nephrotic syndrome (MCNS) is often associated with frequent relapses and complications such as hypovolemia, massive edema, infections and thromboembolism. Initial steroid therapy for 3 months or more is associated with reduction in the risk of relapses at 12 to 24 months. In frequently relapsing nephrotic syndrome (FRNS) Steroid dependent nephrotic syndrome (SDNS) maintenance of remission is achieved with alternate day steroid therapy. Steroid sparing agents currently in use include levamisole, cyclophosphamide, chlorambucil, cyclosporine, tacrolimus and mycophenolate. No drug has been proved superior to another. Cyclophosphamide is inexpensive and may give more sustained remission when compared to other drugs. Rituximab has been used as rescue therapy in some children. Diuretics and albumin infusions need to be used judiciously. Pneumococcal vaccine is recommended for prevention of invasive pneumococcal infections. Some children with SDNS may continue to relapse in adulthood.*

Keywords: *Minimal change nephrotic syndrome, Steroid dependent nephrotic syndrome, Frequently relapsing nephrotic syndrome, Management.*

* Chief of Nephrology Division and PICU, BJ Wadia Hospital for Children, Mumbai.

Several etiologically diverse and pathologically different conditions can give rise to childhood nephrotic syndrome. MCNS is unique among these entities in that despite dramatic clinical features the kidney shows either very minimal or no changes on light and immunofluorescent microscopy.

The International study of kidney diseases in children (ISKDC) study in the seventies revealed that 80% of children with nephrotic syndrome had minimal change as the underlying histopathology. 90% of children with MCNS showed disappearance of proteinuria with 8 weeks course of steroids.[1,2] Because of this predictable response to steroids initial renal biopsies are no longer standard clinical practice. The diagnosis of MCNS today is a presumptive one based on steroid responsiveness. However not all steroid responsive children have MCNS. Other histopathological entities account for 8.2% of all steroid sensitive nephrotic syndrome (SSNS) while 91.8% would have MCNS.[2]

Clinically the child with MCNS usually has the onset of nephrotic syndrome between 2 to 7 years of age, does not have gross hematuria, persistent hypertension or azotemia. Serum C3 levels are normal without any evidence of other systemic diseases. No underlying genetic mutation has been identified. MCNS occasionally runs in families. Recent genetic familial studies have identified a possible locus for SSNS gene at 2p12-p13.2.[3] Table I gives the definitions for nephrotic syndrome, remission, relapse, frequent relapse and steroid dependence.

Treatment of the first episode of nephrotic syndrome

The primary goal of treatment of the initial attack of nephrotic syndrome is to induce remission with prednisolone. The most widely used regime until recently which forms the standard against which all other regimes have been compared is the one recommended by ISKDC. In this regimen children received prednisolone at 60mg/m^2 daily for 4 weeks followed by 40 mg/m^2 for 3 out of 7 days for the next 4 weeks. Alternate day (AD) therapy for the second month is now the preferred therapy. Remission was achieved in 80% of children but greater than 70% relapsed after completion of steroids with 50% having frequent relapses.[1,2] As relapses and their treatment are the major cause of morbidity in children with nephrotic syndrome it became increasingly evident that the goal of initial therapy should be not only the induction of remission but also the reduction of the risk of future relapses.

The APN regime in 1993 clearly showed that 6 weeks of daily steroids followed by 6 weeks of AD therapy resulted in lesser relapses in the subsequent 12-24 months when compared to the 8 week ISKDC regime.[4] This 12 week regime has now become the standard of care in most parts of the world and has been recommended for initial therapy by the Indian Pediatric Nephrology Group.[5]

Several studies since then have tried to address the issue of whether these results could be improved upon by an even longer treatment of the first attack. A metanalysis of 6 RCTs that compared 2 months with 3 -7 months of therapy revealed that there was reduction in the number of frequent relapses and the risk of relapse was reduced by 30% at 12-24 months with longer duration of treatment. Similar findings were found in a meta analysis of 4 RCTs that compared a 6 month course of corticosteroids with a 3 month course.[6]

Two studies compared higher doses of prednisolone with standard doses administered for the same duration .The risk of relapse was reduced by 40% with higher doses of steroids.[7,8]

A recent German study compared an even more aggressive treatment of the first attack with a 12 week course of cyclosporine (CsA) along with prednisolone vs prednisolone monotherapy. Although the initial relape rate in the first 9 months appeared less in the cyclosporine group there was no advantage in the use of a CsA for the initial attack in terms of reduction in relapse rate at 12 -24 months.[9]

Currently prednisolone remains the drug of choice for the initial treatment of nephrotic syndrome. Evidence suggests that to reduce the risk of relapse following the first episode of nephrotic syndrome prednisolone should be given for 3 months are more. However the optimum duration of the initial therapy beyond 3 months that gives the best cost benefit ratio is as yet not clear.

Treatment of relapsing nephrotic syndrome

Although steroid sensitive nephrotic syndrome has a favorable long term outcome, frequently relapsing/ steroid dependent nephrotic syndrome is not a benign condition. Recurrent disease activity as well as potential for drug toxicities place these children at high risk for complications. An early age of onset and male gender are associated with a high risk of frequent relapses and steroid dependence.[10] The tendency for frequent relapses often lasts for several years. However, the therapeutic armamentarium is limited in the number of drugs available as well as in the dose and duration of their usage (Table II). Thus knowledge needs to be tempered

by wisdom while using drugs to prevent relapses in order to minimize toxicity and preserve drugs for future use. The drugs that are available for preventing relapses consist of corticosteroids and non-corticosteroid medications.

Corticosteroids

Treatment of frequent relapsers consists of inducing remission with daily steroids followed by maintenance with alternate day (AD) therapy at the lowest possible dose to maintain urine protein free. This dose may range from 0.2 to 0.5 mg/kg alternate day, which can be continued for a variable period of 6 to 18 months in the absence of steroid toxicity. Single daily dose of prednisolone has been shown to be as effective as divided doses in the time taken to achieve remission as well as in reducing the risk of relapse.[11] The use of long term steroids carries with it the risk of several serious adverse effects such as growth retardation, osteopenia, cataracts and cosmetic changes that need to be anticipated and minimized by timely use of steroid sparing agents.

Deflazocort, is an oxazoline derivative of prednisolone. In a randomized controlled study, 20 children with SDNS who received deflazocort for 12 months had a 60% reduction in the number of relapses when compared to 20 SDNS children who received equivalent doses of prednisolone. Cushingoid effects, weight gain and decrease in bone mineral content were all lesser in the deflazacort group compared to the prednisolone group.[12] Although promising, there is as yet not enough studies to support its routine use in preference to prednisolone.

Non-corticosteroid therapy

Steroid sparing agents may have to be considered in the event of continuing frequent relapses despite AD steroids, need for steroid doses greater than 0.5 mg/kg to maintain remission, decrease in height velocity or other evidence of steroid toxicity.

The drugs include levamisole, alkylating agents, calcineurin inhibitors, mycophenolate and rituximab. There is no evidence at present to support the use of one drug over the other and the choice of the drug is often governed by parents' and/or physician preference.

Levamisole is different from all the other corticosteroid sparing agents in that it is not immunosuppressive in nature. It is an immunomodulator with a moderate steroid sparing effect and an attractively mild side effect profile. It is suitable for those children who do not have high steroid requirements. It can be given on an AD basis for 6 months to 2 years. Leucopenia, abnormal liver function tests, vomiting, skin rashes and neurological symptoms are side effects seen rarely. 60% of children may show a favorable effect in terms of reduction of relapse rate and steroid burden in SDNS. It may have long term beneficial effects even after omission of the drug.[13,14]

Alkylating drugs have been in use for nephrotic syndrome for more than 40 years. Cyclophosphamide (CP), an alkylating agent is effective in reducing the relapses in more than 70% of frequent relapsers.[15, 16, 17] Leucopenia, hemorrhagic cystitis, severe infections and alopecia are important side effects that may mar the therapy. Azoospermia in males may occur as a long term toxicity. This can be minimized by restricting the cumulative dose to not more than 168mg/kg and avoiding second courses of cyclophosphamide. A unique feature not found with other agents is its ability to sustain remission or reduce the relapsing rate even after omission of the drug. Sustained remission is more likely to occur when the cumulative dose of cyclophosphamide was > 5020mg/m2 BSA, older age at institution of and prior steroid dependence

Table.I Definitions

Nephrotic syndrome	Proteinuria > 1g/m^2/day, serum albumin < 2.5g/dL, generalized edema (anasarca)
Remission	Urine protein absent on 3 consecutive days
Relapse	Urine proteins ++ or more on 3 consecutive days
Frequent relapser	2 relapses in 6 months or 3 in a year
Steroid dependent	Relapse while tapering steroids or within 2 weeks of omission on 2 consecutive occassions

Table.II Drug dosages

Drug	Dose	Duration	Monitoring
Levamisole	2.5mg/kg/AD	6-24 months	CBC, LFT 3 monthly
Cyclophosphamide	2 mg/kg/ OD	12 weeks	CBC fortnightly
Chlorambucil	0.2mg/kg/OD	12 weeks	CBC fortnightly
Cyclosporine	4-5 mg/kg/BD	1-2 years	Serum creatinine monthly CsA blood levels as needed
Tacrolimus	0.1 -0.2 mg/kg/BD	1-2 years	Serum creatinine monthly, RBS, Tac levels
Mycophenolate	1200mg/m2/ BD	1-2 years	CBC monthly
Rituximab	375mg/m2/IV weekly	2 to 4 doses	CBC weekly, IgG levels

at dosage <1.4 mg/kg.[18] Chlorambucil has comparable results and adverse effects.[19]

Cyclosporinae (CsA), a calcineurin inhibitor, is an effective steroid sparing agent and helps to control relapses. Relapse free state at 1 and 2 years is 60% and 40% respectively. 40% of children require long term alternate day steroids to sustain remission despite adequate CsA levels.[20] Its most serious adverse effect is its potential for nephrotoxicity. This necessitates regular monitoring of serum creatinine levels. The dose of CsA needs to be individually titrated and may have to be increased in the first few months of therapy with close monitoring of serum creatinine and blood level of CsA in order to achieve the desired results. The usual duration of therapy is for 1 to 2 years. In the event of continuation of therapy for a longer duration, a repeat renal biopsy is needed to look for CsA

nephrotoxicity as interstitial changes may exist despite normal serum creatinine levels. Some of the risk factors for toxicity include age below 5 years at start of therapy, longer than 3 years of therapy, more than 30 days of heavy proteinuria during therapy.[21,22] Gingival hypertrophy, hypertension and hirsutism are other distressing side effects. The relapse free status with CsA is often not sustained when it is withdrawn and children often go from steroid dependence to cyclosporine dependence.

Both cyclophosphamide and cyclosporine help to reduce the risk of relapses when compared to steroid monotherapy. A retrospective analysis of the outcome of SDNS treated with cyclophosphamide vs cyclosporine revealed that the relapse rate was lower and remission following cyclophosphamide was more sustained when compared to that obtained from cyclosporine.[23]

Tacrolimus is a calcineurin inhibitor like cyclosporine and shares several similarities including its potential for nephrotoxicity. It has less cosmetic effects making it more acceptable. Blood sugar needs monitoring as it increases the risk of diabetes mellitus. Its effects in relapsing NS is comparable to that of cyclosporine.[24,25]

Mycophenolate has antiproliferative action against T and B cells.Reduction in relapse rate of 50-75% and reduction of steroid dosage has been documented with mycophenolate treatment for 6 to 12 months.[26,27,28] Omission of the drug generally leads to relapse. Its ability to reduce the relapse rate may be lesser than that of cyclosporine. However, it has no nephrotoxicity but may cause gastrointestinal upset and bone marrow depression. It may be useful to add mycophenolate at the time of omission of cyclosporine to prevent relapses due to cyclosporine withdrawal.

Rituximab, an anti CD20 monoclonal antibody that induces B cell depletion has been used sporadically in difficult nephrotic syndrome. Benefits have been reported in case reports and in small series of pathologically diverse steroid dependent or resistant patients. 2 larger studies, a multicentric one and a single centre one of 22 cases each have looked at the effect of rituximab on severe, prolonged steroid/ cyclosporine dependent nephrotic syndrome. Most of these children had MCNS as the underlying histopathology. Two to four weekly infusions of rituximab induced remission associated with B cell depletion in 75% of the children. Remission was sustained for several months enabling reduction in the dosage of other immuno-suppressive therapy in many and total omission in some. Relapses after a variable period were common and were associated with return of B cells in the circulation. Some patients were able to sustain remission despite return of B cells in the circulation.[29, 30] A single dose of rituximab was shown to have a disease modifying effect in 10 children with MCNS and severe SDNS in the form of reduction in steroid and CsA dosages to maintain remission and in restoration of CsA sensitivity.[31] Rituximab given during remission appeared to be more effective than when given during periods of heavy proteinuria. Side effects noted were reversible neutropenia, cytokine shock syndrome and infections. Hypogammaglobulinemia was noted in half the patients necessitating infusions of intravenous immunoglobulins. Fatal pulmonary toxicity has been reported with the use of rituximab although not seen in any of these studies. At present the use of rituximab in severe nephrotic syndrome can be considered in specialized centres as an off label rescue therapy.

Management of extra renal complications

Children with MCNS are at risk for several extra renal complications such as hypovolemia,

severe edema, infections and thromboembolic complications.

Hypovolemia

Low serum albumin leads to decreased oncotic pressure resulting in seepage of fluid out of the vascular compartment into the interstitial space causing intravascular volume contraction. This may be aggravated by injudicious use of diuretics or by diarrheal losses. Signs of hypovolemia may not be easily detectable in the edematous child. Dry mucous membrane, orthostatic hypotension, raised hematocrit and blood urea may be evidence of intravascular volume depletion. Severe hypovolemia may manifest as tachycardia, poor capillary refill with or without hypotension. Hypovolemia is also a risk factor for thrombotic complications.

In hypovolemic children volume restitution can be achieved with the administration of isotonic fluids. Crystalloid solutions such as normal saline or Ringer's lactate may be given at 10-20ml/kg over an hour. Where hypovolemia coexists with shock or very low serum albumin, 1 g/kg of 5% albumin can be given over 2 to 4 hours to correct the hypovolemia. Not all edematous nephrotics have contracted intravascular volume. Some nephrotics may be edematous and overfilled. Additional volume in such patients may provoke pulmonary edema.

Edema

Remission of proteinuria with steroids is the best diuretic for NS. Edema that is confined to the face and the limbs without severe oliguria needs only salt restriction in the diet. This usually consists of no added salt in the diet, no salty snacks and avoidance of chips, pickles, papads, baked and canned foods. Occasionally a mild diuretic such as thiazide may be used.

Children who may need additional therapy for edema include those with ascites, hydrothorax, genital edema, impending skin breakdown and/or oliguria. The diuretic most commonly used is furosemide 1-2 mg/kg per dose orally. IV furosemide is reserved for those resistant to oral furosemide and should be administered under close medical supervision. The addition of spironolactone may help to prevent hypokalemia.

The child with furosemide resistant edema needs to be assessed for intravascular volume status, serum albumin levels and for the presence of acute kidney injury. In suspected hypovolemia volume restitution may be needed. Normal saline or Ringer's lactate 20ml/kg over 1 hour followed by IV furosemide may help. In children with severe furosemide resistant edema with serum albumin less than 1g/dL intravenous albumin infusion followed by furosemide may be considered. 1 gm/kg of 20% albumin should be infused slowly over 4 hours with close monitoring followed by IV furosemide 1-2mg/kg. The risks of albumin infusions are very real and consist of pulmonary edema and hypertension if the volume status has been wrongly judged or if there is acute kidney injury.[32] In SSNS the need for albumin infusion is exceptional and is usually restricted to those cases with severe infections that may preclude the use of steroids. Occassionally, the addition of metalazone along with furosemide might induce diuresis in refractory edematous states. Fluid restriction may be needed in children who have anasarca with oliguria.

Infections

Infections are common in nephrotic syndrome and are an important cause of death accounting for mortality rates of 4-7%. Hypoalbuminemia, low immunoglobulin levels, T cell dysregulation, loss of complement alternate pathway components factor B and D, immuno-suppressive therapy as well as massive edema contribute to the increased risk of infections. Infections by encapsulated organisms such as

Streptococcus pneumonia and gram negative organisms such as Escherichia coli are particularly common and may lead to infections such as cellulitis, gastroenteritis, respiratory tract and urinary tract infections. Spontaneous bacterial peritonitis (SBP) is common and should be suspected whenever the nephrotic child presents with abdominal pain and/or vomiting and diarrhea. Diagnostic ascitic tap shows more than 100 cells/high power field with predominant neutrophils. Empirical antibiotics should be started against pneumococcus based on local patterns of antibiotic resistance. Crystalline penicillin is the drug of choice when sensitivity prevails. Where penicillin resistance is significant, a third generation cephalosporin can be used. When the peritonitis is acquired in hospital settings or in children who have received recent antibiotic therapy antibiotics should have a broader coverage. The American Academy of Pediatrics (AAP) recommends 2 doses of pneumococcal conjugate vaccine followed by one dose of the 23 polysaccharide vaccine for preventing pneumococcal infections in children with nephrotic syndrome.[33] Children with recurrent infections and very low immunoglobulin levels may benefit with IV immunoglobulin infusions for prevention of infections.[34]

Thrombosis

Thromboembolic complications are seen in 2 to 4% of children with nephrotic syndrome. Venous thrombosis is more common than arterial thrombosis. Renal veins, leg veins and cranial venous sinuses are common sites of thrombosis. The incidence of thromboembolism may actually be higher. Ventilation perfusion scans in nephrotic children with respiratory symptoms have suggested a high probability of pulmonary embolism in many. In a study of 26 nephrotic children, ventilation-perfusion scans revealed abnormal scans suggestive of pulmonary embolism in 7 children.[35] Loss of anticoagulants such as antithrombin III as well as increased synthesis of procoagulants makes nephrotic syndrome a thrombogenic state. Hyperlipidemia increased platelet aggregation and volume contraction as a result of gastrointestinal losses and diuretic therapy may aggravate the thrombotic tendency. Treatment of established thrombosis is with anticoagulation using regular heparin or with low molecular weight heparin. Measures to prevent thrombosis include avoidance of bed rest, prompt treatment of sepsis, prevention of dehydration and avoidance of injudicious use of diuretics. Central venous catheters should be avoided unless essential.

Steroid sensitive MCNS has less than 1% chance of progressing to ESRD. The majority of children will stop relapsing by puberty. However it is becoming increasingly apparent that an average of 25% of frequent relapsers may continue to relapse as adults.[36] Careful use of immunosuppressive drugs and expert management of the extrarenal complications is mandatory to enable a safe transit to adulthood.

Points to Remember

- ***Minimal change nephrotic syndrome constitutes about 80% of children with nephrotic syndrome.***
- ***Prednisolone for 3 months or more remains the drug of choice for the initial treatment of nephritic syndrome. Optimum duration of initial therapy beyond 3 months with best cost effectiveness yet to be found out.***
- ***Drugs under the categories of corticosteroids and non corticosteroids are tried with equivocal effects for the treatment of relapsing nephritic syndrome.***
- ***Extra renal complications like hypovolemia, severe edema, infections and thromboembolism to be looked for picked up in time and managed appropriately to avoid related morbidity and mortality.***

References

1. International Study of Kidney Diseases in Children. Nephrotic Syndrome in Children: prediction of histopathology from clinical and laboratory characteristics at the time of diagnosis. A report of the International Study of Kidney Diseases in Children. Kidney Int 1978; 13: 159-165
2. International Study of Kidney Disease in Children.The primary nephrotic syndrome in children. Identification of children with minimal change nephrotic syndrome from initial response to prednisolone. J Pediatr 1981; 98:561-564.
3. Ruf RG, Lichtenberger A, Karle SM, Lemainique A, Huck K, Wienker T, et al. Identification of the first gene locus (SSNS1) for steroid sensitive nephrotic syndrome on chromosome 2p.J Am Soc Nephrol 2003,14: 1897-190
4. Ehrlich JH, Brodehl J. Long versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. Arbeitsgemeinscaft fur Padiatrische Nephrologie.Eur J Pediatr 1993, 152: 357-361.
5. Indian Pediatric Nephrology Group. Indian Academy of Pediatrics.Management of steroid sensitive nephrotic syndrome; Revised guidelines. Indian Pediatr 2008, 45: 204-214.
6. Hodson EM, Knigh JF, Wills NS, Craig JC. Corticosteroid therapy for Nephrotic syndrome in children.Cochrane Database Systematic Review 2005.1:CD001533.
7. Pecoraro C,Caropresso MR,Malgieri G, Ferretti AVS, Raddi G, Piscetelli A et al.Therapy of first episode of steroid responsive nephrotic syndrome a randomized controlled trial. Pediatr Nephrol 2004:19: C72.
8. Hiraoka M, Tsukahara H, Matsubara K, Tsurusawa M,Takeda N, Haruki S, et al. Older boys benefit from higher initial prednisolone therapy for nephrotic syndrome.The West Japan Cooperative study of kidney disease in children.Kidney Int 2000;58: 1247-1252.
9. Hoyer PF, Brodehl J. Initial treatment of idiopathic nephrotic syndrome in children; prednisone vs prednisone plus cyclosporine A. A prospective randomized trial J Am Soc Nephrol 2006;17:1151-1157.
10. Anderson RF, Thrane N, Noergaard K, Rytter L, Jespersen B, Rittig S. Early age at debut is a predictor of steroid dependent and frequently relapsing nephrotic syndrome. Pediatr Nephrol 2010;25:1299-1304.
11. Ekka BK, Bagga A, Srivastava RN, Single vs divided dose prednisolone therapy for relapses of nephrotic syndrome.Pediatr Nephrol 1997;11: 597-599.
12. Broyer M, Terzi F, Lehnert A, Gagnadoux MF, Guest G, Niaudet P. Acontrolled study of Deflazacort in the treatment of idiopathic nephritic syndrome. Pediatric Nephrol 1997; 11: 418-422.
13. British Association for pediatric nephrology. Levamisole for corticosteroid dependent nephrotic syndrome in childhood. Lancet 1991; 337:1555-1557.
14. Boyer O, Moulder JK, Grandin L, Somers MJG. Short and long term efficacy of levamisole as adjunctive therapy in childhood nephrotic syndrome. Pediatr Nephrol 2008; 23:575-580.
15. Report of the International Study of Kidney Disease in children.Prospective Controlled trial of cyclophosphamide therapy in children with nephritic syndrome. Lancet 1974;ii(7878): 423-427.
16. Durkan AM, Hodson EM, Willis NS, Craig JC. Immunosuppressive agents in childhood nephrotic syndrome. A meta-analysis of randomized controlled trials.Kidney Int 2001;59;1919-1927.
17. Hodson EM, Willis NS, Craig JC. Non corticosteroid treatment for nephrotic syndrome in children. Cochrane database Syst Rev 2008, CD002290
18. Zagury A, de Oliviera AL, de Moraes CA, de Araujo monta lvao JA, Novaes RH, de Sa NM, et al. Long term follow-up after cyclophosphamide therapy in steroid dependent nephrotic syndrome. Pediatr Nephrol 2011; 26:915-920.

19. APN.Effect of cytotoxic drugs in frequently relapsing nephrotic syndrome with and without steroid dependenc.N Engl J Med 1982; 306: 451-454.

20. Hulton SA, Neuhas TJ, Dillon MJ, Barratt TM. Long term Cyclosporine A treatment of minimal change nephrotic syndrome of childhood. Pediatr Nephrol1994; 8: 401-403.

21. Iijima K, Hamahira K, Tanaka R, Kobayashi A, Nozu K, Nakamura H, et al. Risk factors for cyclosporine induced tubulointerstitial lesions in children with minimal change nephrotic syndrome. Kidney Int 2002; 61:1801-1805.

22. Fujinaga S, Kaneko K, Muto T, Ohtomo Y, Murakami H, Yamashiro Y. Independent risk factors for chronic cyclosporine induced nephropathy in children with nephrotic syndrome. Arch Dis Child 2006;91:666-670.

23. Sumegi V, Haszon I, Bereczki C, Papp F, Turi S. Long term follow-up after cyclophosphamide and Cyclosporine A therapy in steroid dependent and resistant nephrotic syndrome Pediatr Nephrol 2008 23:1085-1092.

24. Sinha MD, MacLeod R, RigbyE, Clark AG. Treatment of severs steroid dependent nephrotic syndrome in children with Tacrolimus. Nephrol Dial Transplant 2006;21; 1848-1854.

25. Dotsch J, Dittrich K, Plank C, Rascher W. Is Tacrolimus for childhood nephrotic syndrome etter than cyclosporine A? Nephrol Dial Transplant 2006;21:1761-1763

26. Bagga A, Hari P, Moudgil A, Jordan SC. Mycophenolate Mofetil and prednisolone therapy in children with steroid dependent nephrotic syndrome. Am J Kidney Dis 2003,42:1114-1120.

27. Hogg RJ, Fitzgibbons L, Bruik J, Bunke M, Ault B, Baqi N, et al. Clinical trial of Mycophenolate Mofetil for frequently relapsing nephrotic syndrome in children. Pediatr Nephrol 2004;19;C18.

28. Mendizabal S, Zamora I, Berbel O, Sanahuja MJ, Fuentes J, Simon j. Mycpphenolate insteroid/cyclosporine dependent nephrotic syndrome. Pediatr Nephrol 2005; 20:914-919.

29. Guignois V, Dallochio A, Baudouin V, Dehennault M, Le Camns CF Afanetti M, et al. Rituximab treatment for severs steroid or cyclosporine dependent nephrotic syndrome: amulticentric series of 22 cases.Pediatr Nephrol 2008, 23:1269-1279.

30. Sellier-Leclere AL, Macher MA, Loirat C, Guerin V, Watier H, Peuchmur M, et al. Rituximab efficieny in children with steroid dependent nephrotic syndrome. Pediatr Nephrol 2010 25: 1109-1115.

31. Fujinaga S, Hirano D, Nishikazi N, Kamei K, Ohtomo Y, Shimizu T, et al. Single infusion of rituximab for persistent steroid dependnt minimal change nephrotic syndrome after long term cyclosporine. Pediatr Nephrol 2010;25: 539-544.

32. Reid CJ, Marsh MJ, Murdoch IM, Clark G. Nephrotic syndrome in childhood complicated by life-threatening pulmonary edema. Br Med J 1996; 312: 36-38.

33. American Academy Pediatrics Committee on infectious diseases. Policy Statement. Recommendations for the prevention of pneumococcal infections including the use of conjugatevaccine, pneumococcal polysaccharide vaccine and antibiotic prophylaxis. Pediatrics 2000; 106:362-366.

34. Wu HM, Tang H, Sha ZH, CaoI, Li YP. Interventions for preventing infections in nephrotic syndrome(Cochrane review), The Renal Health Library, Update software Ltd, Oxford, 2005.

35. Hoyer PF, Gonda S, Barthels M, Krohn HP, Brodehl J.Thromboembolic complications in children with nephrotic syndrome .Risk and Incidence. Acta Pediatr Scand 1986;75: 804-810.

36. Webb NJ. Epidemiology and general management of childhood idiopathic nephritic syndrome. In: Evidence based nephrology. Eds, Molony DA, Craig JC. DOI: 10.1002/978144430339.ch66.

NEPHROLOGY

PRACTICAL APPROACH TO NOCTURNAL ENURESIS AND VOIDING DYSFUNCTION

**** Col Madhuri Kanitkar***

Abstract:*The main functions of the urinary bladder are storage and evacuation at a socially acceptable time and place. Disorders of these functions can result in a wet child. The cause for continuous incontinence is generally an anatomical or neurologic anomaly of the lower urinary tract but intermittent incontinence is most often a functional voiding disorder (FVD), commonest being enuresis. Bladder disorders may result in deterioration of renal function and are often associated with constipation. The common FVD's are an overactive bladder, dysfunctional voiding or an underactive bladder.*

Evaluation needs to be structured and begins with the ruling out of an anatomical or neurological anomaly. Non invasive urodynamics can predict the type of voiding disorder, reducing the need for the more invasive cystometric studies.

Enuresis is best treated with behavioral modification, dry bed training and use of the alarm device. Pharmacotherapy is rarely required. Treatment of bladder dysfunction involves the treatment of constipation, bladder retraining and pelvic floor relaxation with the judicious use of anticholinergic medication. Clean intermittent catheterization is required to protect the upper tract in children with large post void residual urine and high bladder pressures.

Keywords: *Overactive bladder, Dysfunctional voiding, Underactive bladder, Incontinence, Noninvasive urodynamics.*

The urinary bladder is an important organ that ensures continence. It functions as a storage organ that can empty to completion at an appropriate time and place. An aberration of this function, once bladder control is achieved results in a wet child, or a child who cannot void to completion. This is bladder dysfunction, broadly classified as a primary functional voiding disorder which occur in the presence of an intact neuronal pathway and no congenital or anatomical abnormality of the urinary tract; or secondary to an anatomic anomaly or neurological deficit where the child has incontinence or continuous dribbling.[1] Knowledge of these situations is important, for pediatricians to be more attentive to wetting in children and initiate discussion about urinary or fecal problems with parents. It is not enough to tell parents seeking attention, that the child will grow out of the problem.

The importance of diagnosing voiding disorders cannot be underestimated from the current day knowledge of their being associated with recurrent urinary tract infections with or without a vesicoureteric reflux[2] and incontinence or enuresis with daytime symptoms like dribbling.[3] They may cause significant distress to the child and parents. The persistence of

* Professor, HOD Pediatrics,
Base Hospital, Delhi Cantt and
Army College of Medical Sciences,
New Delhi.

voiding problems following fulguration of posterior urethral valves has long-term consequences that need attention.[4]

Nomenclature

The urinary bladder is a storage organ that ensures continence due to an adequate capacity and a functional sphincter. Disorders affecting it are as a result of either a problem with storage or with evacuation. The spectrum of disorders is wide. The International Children's Continence Society has standardized the nomenclature for urinary bladder symptoms.[5] The classification is depicted in Fig.1-Step I Whereas continuous incontinence is almost always due to an underlying anatomical or neurological anomaly, intermittent incontinence is mostly functional. This may be accompanied by a bowel disorder in a significant number of children when it is termed as Bowel Bladder Dysfunction (BBD).

Based on clinical symptoms and urodynamic studies the voiding disorders are classified as either an overactive bladder with or without incontinence when it is a filling phase disorder or a dysfunctional voiding (DV) when it is an evacuation phase disorder.[5] Dysfunctional voiding may be a staccato or fractional voiding if there is bladder-sphincter incoordination referred to as dysynergia. Over a period of time a dysynergic bladder may result in a low pressure hypotonic underactive bladder leading to overflow incontinence. A severe bladder sphincter dysynergia is noted in the Hinman syndrome where the urinary bladder is trabeculated, develops a high pressure state with bilateral vesicouretric reflux and a large post void residue akin to a neurogenic bladder without an obvious underlying neurological abnormality.

The common factor underlying the functional voiding disorders is the pelvic floor contractions. A child may have features of an overactive bladder with urgency, frequency with small voided volumes many times a day. This is often neglected, thinking it is a behavioral problem or simply saying that "he will grow out it". The child uses holding maneuvers like squatting, crossing legs etc to prevent leakage by contracting the pelvic floor muscles which form the external sphincter. Over time this may progress to DV as the bladder has to empty against a closed external sphincter with increased post void residual urine. A major aggravating factor for bladder dysfunction is constipation noted in a significant number of the children with a FVD.[6] Children may reduce fluid intake to minimize wetting and the powerful pelvic floor muscle contractions lead to postponement of defecation. Net result of the two is constipation. This further worsens bladder functioning.

Enuresis

Bladder control is usually attained between the ages of one and five years. More than 85% children will have complete diurnal and nocturnal control by five years of age.[7] A child having nearly complete evacuation of the bladder at least twice a month after the fifth year of life has enuresis and definitely warrants attention. As a rule the bed will be soaking wet as against incontinence, which is loss of urine without normal emptying of the bladder. It is termed primary when the child has never been dry and secondary when bedwetting starts after a minimum period of six months of dryness at night. It is termed monosymptomatic if it is not accompanied by any lower urinary tract symptoms. Uncomplicated enuresis is possibly the most commonly encountered functional bladder problem in everyday practice. This is to be differentiated from enuresis with daytime urge symptoms, recurrent urinary tract infections or daytime wetting in which case the child is likely to have a FVD which may originate from behavioural factors that affect toilet training and inhibit the maturation of normal urinary control.

Etiology

There is no single definite underlying cause for enuresis; the condition may be multifactoral. Attempts to identify the possible cause in a given child can help translate that information into therapeutic options. Some of the factors responsible for a child to have enuresis are maturational delay, deep sleep and a loss of circadian rhythm of the antidiuretic hormone secretion. Knowledge of a genetic basis helps in counseling. If both the parents, or the father alone had enuresis, the chances of the child having the problem are more than if the mother alone had enuresis.

Investigations

Less than 5 percent of children with nocturnal enuresis have an organic basis. Based on history and an initial examination, children with uncomplicated enuresis require no further evaluation. A urinalysis to rule out infection and glycosuria is warranted in all children. Clinical and neurological examination helps exclude an anatomical or neurological cause for incontinence. A voiding diary with frequency and volume charting of urine output and oral fluid intake for two to three days with a record of daytime accidents or wetting is useful to diagnose polyuria or a possible voiding disorder, in case the history is not forthcoming.

Treatment

Supportive measures

Timely treatment of nocturnal enuresis prevents psychological damage to the child and provides relief to the family and should be offered to any child who is motivated to sleep dry. No single therapeutic plan is ideal for all patients. Various modalities of treatment are available for the treatment of enuresis and the final choice is best left to the child and parent. Dry bed training includes measures such as emptying the bladder before retiring to bed, encouraging bedtime resolution and keeping a chart of wet and dry nights. The child should be rewarded for active co-operation for therapy and not just for dry nights. Behavioural changes significantly improve the outcome and advice is given to drink more water during the daytime, avoid extra fluids after dinner, prevent constipation with a proper diet and an increase physical activity. The child is encouraged for timely voiding. Randomized trials have shown that neither bladder holding nor "stretching" exercises are efficacious.[8] The alarm device is used to elicit a conditioned response of awakening to the sensation of a full bladder. The alarm is best used after seven years of age and its use is continued for six months for better long term success.

Pharmacotherapy

A number of medications are used in the treatment of nocturnal enuresis.[7] Therapy once initiated, is continued for 2 weeks before assessing efficacy and adjusting the dose. Once the child is dry the dose is maintained for three to six months and then gradually weaned over three to four weeks. Relapse rates are high after stopping therapy especially if the drug is withdrawn abruptly. Anticholinergic drugs like oxybutinin 2.5-5mg reduce uninhibited bladder contractions and are useful in children who manifest urge incontinence during the daytime. It maybe used as an adjunct to treatment with the alarm or desmopressin, when either of them fail as single therapy. Desmopressin (DDAVP) acts by reducing the urine output to a volume less than the functional bladder capacity. Administration of DDAVP 10-20μg at bedtime is particularly useful in patients showing high nocturnal urine production or a less concentrated urine prior to therapy. The spray should be administered under the supervision of parents to prevent children from accidental overdose, or an

intentional overdose taken in the enthusiasm of achieving dry nights. Oral desmopressin may be used as an alternative to the nasal spray. The preparation is given an hour before bedtime at a dose of 0.2 mg increasing to 0.6 mg daily to achieve dry nights and continued for at least eight weeks. Tricyclic antidepressants are used only as third-line therapy, when all other therapeutic options have failed.

Current recommendations for the modality of choice in a given child suggest that the alarm be offered as the initial treatment, if the child is not responding to dry bed training unless the parents are averse to it or the pediatrician considers the child unsuitable. If the child is unresponsive to the alarm, desmopressin (DDAVP) may be added as an adjunct. DDAVP may be used as the initial option if short term immediate gain is a priority.[8]

Functional voiding disorders

A FVD presents with daytime wetting or recurrent urinary tract infections. Children with enuresis refractive to therapy or a persistent vesicoureteric reflux, may also have a VD.

Evaluation

A wet child requires a systematic evaluation in a step wise manner as depicted (Fig.1)

Prior to evaluation for FVD, a neurological basis for the problem needs exclusion. A history of continuous small quantity dribbling with constant wetness of the underpants often accompanied by perineal excoriation is noted in such situations. Clinical examination should include the lower back to look for clues suggesting spinal and sacral anomalies and the abdomen for palpable bladder/kidneys. Well-developed lower abdominal muscles may occasionally be noted, especially in girls who use them to aid voiding. The lower limbs are assessed for tone power and sensations, and the perineum for ectopic ureters, epi-spadias or vaginal pooling and labial adhesions in girls. A history of frequency and holding maneuvers like squatting with or without dampness of the underpants suggests an overactive bladder. A child may also demonstrate the Vincents' curtsy (a typical position wherein the child bends forward or sits on the floor with the heel of a folded leg tucked into the perineum), to increase the external sphincter tone during bladder contractions. There may be some wetting of the undergarment following this episode. DV usually presents with incontinence, urinary tract infections and constipation. The overactive pelvic floor muscles may not relax during voiding and simulate a true detrusor sphincter dysynergia secondary to a neurological problem.

The underactive bladder presents with infrequent voiding, urinary tract infections and overflow incontinence. Abdominal pressure is the driving force for voiding. This situation may result from long standing over-activity of the pelvic floor but no data is available to support this view.

A detailed history should include a frequency volume charting of urine in the voiding diary with a record of accidents/wetting. The voided volume of urine each time is then compared to the expected capacity of the bladder.

Investigations

In most children with a voiding disorder a detailed clinical assessment with a voiding diary and an ultrasonography of the abdomen is all that is required. Plain X-ray of the abdomen and spine may be useful to look for calculi, evidence of constipation and bony malformations. Where necessary an MRI scan of the spine is helpful to detect an occult problem of the spinal cord resulting in a neurogenic bladder. Urinalysis for evidence of UTI and a baseline specific gravity/osmolality for a possible concentration

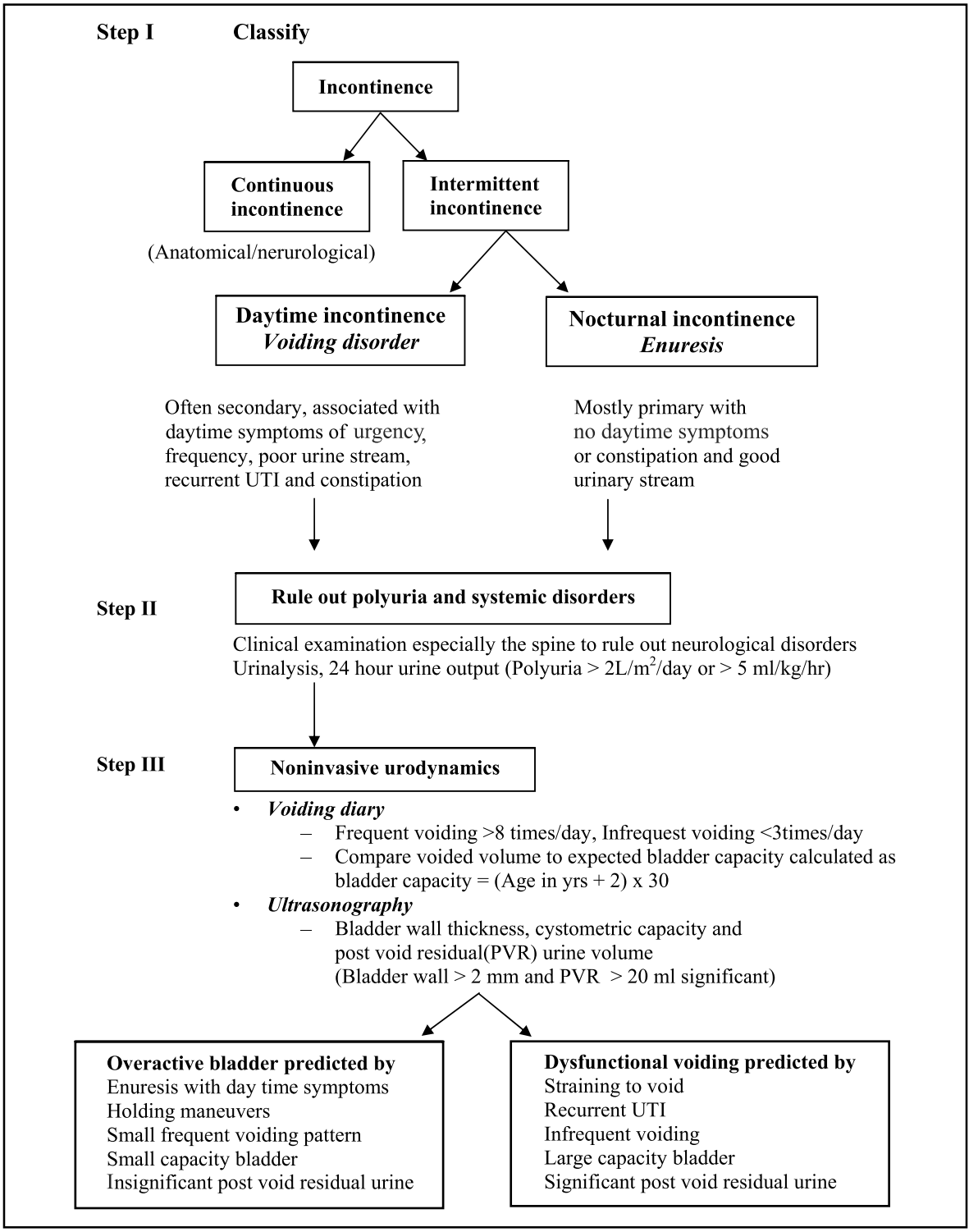


Fig.1. Evaluation of a wet child

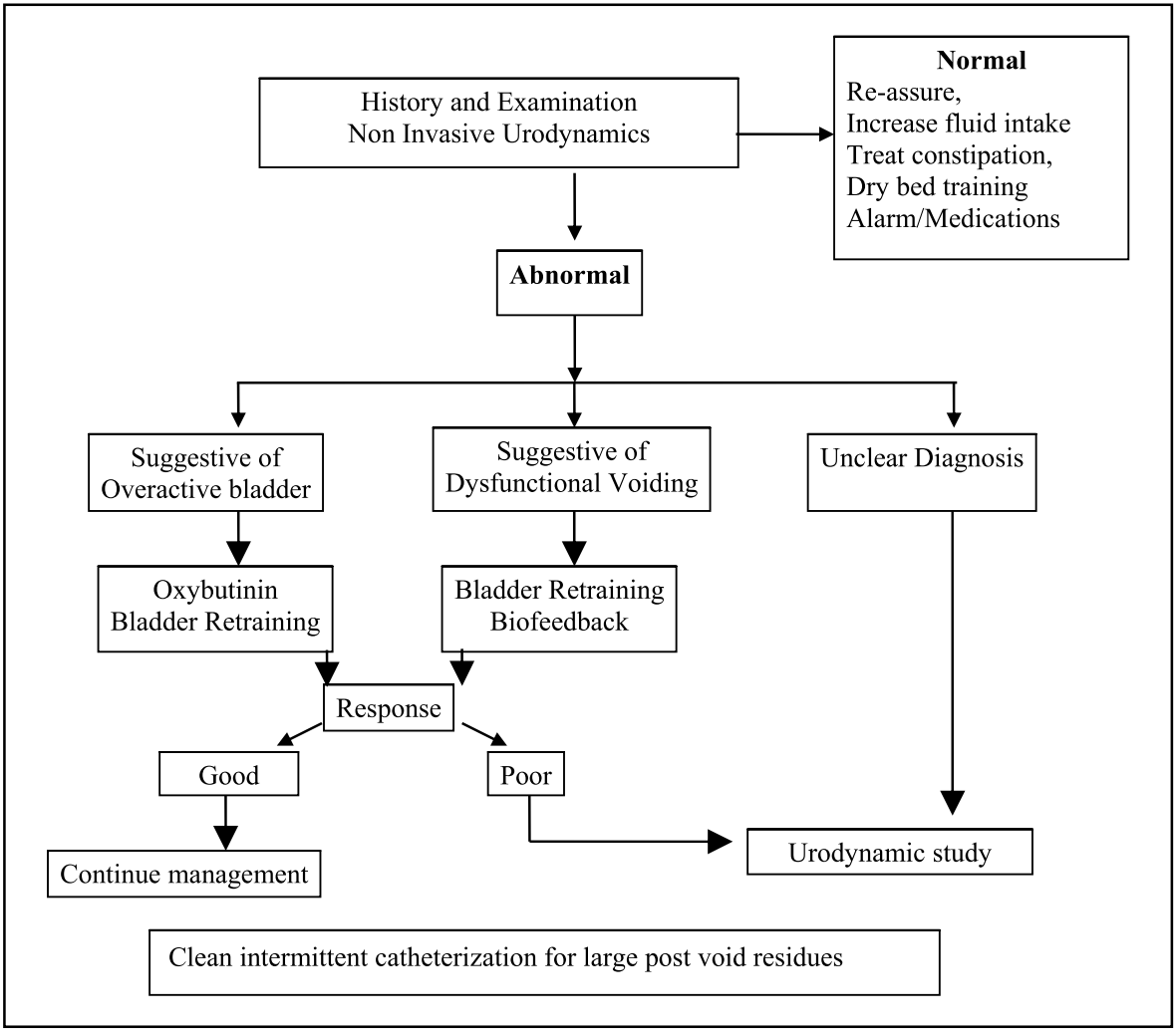


Fig.2. Management of a child with a bladder dysfunction

defect are recommended. Dilatation of the upper tract, bladder volume, wall thickness and the presence of post void residual urine is noted on ultrasonography.

A micturating cystourethrogram (MCU) helps determine the presence of and severity of a reflux and delineates the posterior urethra if the child presents with an infection of the urinary tract. Presence of bladder wall irregularity, elongation of the bladder shape and filling of the posterior urethra[9] as well as the spinning top configuration of the bladder during the cystogram suggest a VD.

The urodynamic study is an invasive procedure and carried out if the child does not respond to therapy for a predicted VD based on noninvasive urodynamics.[10] The presence of nocturnal enuresis with day time symptoms,

holding maneuvers, small frequent voiding pattern and small capacity bladder with insignificant post void residual (PVR) urine predicts an overactive bladder. The presence of enuresis with straining, recurrent UTI, infrequent voiding pattern, large capacity bladder with significant PVR in the absence of a VUR predicts a DV. A uroflow study combined with EMG for pelvic floor muscles is less invasive and can delineate most children requiring further evaluation.

Treatment

The basis of treatment lies in the exclusion of neurological causes, treatment of intercurrent infections and (re)-institution of structured voiding patterns with good hydration, hygiene and timed voiding. It is essential that coexistent constipation be corrected. Double voiding for children with a vesicoureteric reflux is recommended.

In children with the urge syndrome due to an overactive bladder an anti-cholinergic medication like oxybutinin or tolterodine is effective.[11]

Biofeedback therapy can aid retraining children to develop relaxed voiding.[12] The five main components of behavioural intervention or bladder re-education initiative are patient education, scheduled voiding regimen with gradual increasing intervals, urgency control strategies, self-monitoring and positive reinforcement by the pediatrician. Computer games have been used successfully to help children relax the pelvic floor muscles.[13]

In children with established dysfunctional voiding with large post void residues it is imperative to lower intravesical pressures in order to protect the upper tract. Clean intermittent catheterization (CIC) can be instituted with training. The management of a child with bladder dysfunction is depicted in Fig. 2.

Points to Remember

- ***Wetting in a child who has attained bladder control needs evaluation***
- ***The cause for continuous incontinence is generally an anatomical or neurologic anomaly of the lower urinary tract***
- ***Commonest bladder disorder resulting in nocturnal intermittent incontinence is enuresis***
- ***A functional voiding disorder may present with daytime intermittent incontinence, recurrent urinary tract infections, enuresis with daytime symptoms which may be refractive to therapy.***
- ***Noninvasive urodynamics can predict the type of voiding disorder. Invasive urodynamics is carried out in a select few.***

References

1. Kanitkar M. Disorders of micturition. In: Pediatric Nephrology, Srivastava RN, Bagga A, Eds 5th Edn, New Delhi, Jaypee Brothers, 2011; pp 464-490.
2. Ramamurthy HR, Kanitkar M. Recurrent urinary tract infection and functional voiding disorders. Indian Pediatr 2008; 45: 689-691.
3. Toktamis A, Demirel Y, Ozkan KU, Garipardiç M, Gözüküçük A, Nur N. Prevalence and associated factors of day wetting and combined day and night wetting. Urol Int 2008;81: 54-59.
4. Ghanem MA, Wolffenbuttel KP, De Vylder A, Nijman RJ. Long-term bladder dysfunction and renal function in boys with posterior urethral valves based on urodynamic findings. J Urol 2004;171:2409-2412.
5. Nevéus T, von Gontard A, Hoebeke P, Hjälmås K, Bauer S, Bower W, et al. The standardization of terminology of lowerurinary tract function in children and adolescents: report from thestandardisation

committee of the International Children's Continence Society (ICCS). J Urol 2006; 176:314–324.

6. Averbeck MA, Madersbacher H. Constipation and LUTS - How do they affect each other? Int Braz J Urol 2011; 37:16-28.
7. Kanitkar M, Dua T. Nocturnal enuresis. Indian J Pediatr 2003;70:251-255.
8. Nunes VD, O'Flynn N, Evans J, Sawyer L. Management of bedwetting in children and young people: summary of NICE guidance. Br Med J 2010; 341:936-938.
9. Bachelard M, Verkauskas G, Bertilsson M, Sillen UJ, Jacobsson B. Recognition of bladder instability on voiding cystourethrography in infants with urinary tract infection. J Urol 2001;166:1899-1903.
10. Ramamurthy HR, Kanitkar M. Non Invasive Urodynamic Assessment in Children-Are they reliable? Validation of Non-Invasive Urodynamics in Children with Functional Voiding Disorders. Indian J Pediatr 2010; 77:1400-1404.
11. McDonagh MS, Selover D, Santa J, Thakurta S. Drug Class Review: Agents for Overactive Bladder. Final Report Update 4. Portland (OR): Oregon Health & Science University; 2009. Downloaded http://www.ncbi.nlm.nih.gov/books/NBK47183/pdf/TOC.pdf on 16 Mar 2011
12. Khen-Dunlop N, Van Egroo A, Bouteiller C, Biserte J, Besson R. Biofeedback therapy in the treatment of bladder overactivity, vesico-ureteral, reflux and urinary tract infection. J Pediatr Urol 2006;2(5):424-429.
13. Herndon CD, Decambre M, McKenna PH. Interactive computer games for treatment of pe lvic floor dysfunction. J Urol 2001;166: 1893-1898.

NEWS AND NOTES

Publications of IAP, released at Pedicon 2012, now available for sale

1) **"Childhood Disability – A Pediatrician's Perspective" (1st Edition)**

Editors: Dr. Anju Aggarwal / Dr. S. S.Kamath / Dr. T.U. Sukumaran, Price Rs.250/- + mailing charges Rs.50/- (Total amount payable Rs.300/-) to be paid by a crossed bank draft drawn in favour of **"**IAP National Publication House Gwalior **"** payable at Gwalior.

2) **IAP Specialty Series on "Pediatric Nephrology" (2nd Edition - 2012)**

Editor-in-Chief: Dr. A S Vasudev, price Rs.400/- + mailing charges Rs.50/- (Total amount payable Rs.450/-) to be paid by a crossed bank draft drawn in favour of **"**IAP National Publication House Gwalior **"** payable at Gwalior . Please write to, and post DD to Dr. A. K. Banga, 9, Munshipuri, Residency Surya Mandir Marg, Gwalior 474005. Email: ashokbanga@gmail.com, iap.publication @gmail.com

NEPHROLOGY

ACUTE KIDNEY INJURY: THE NEW CLASSIFICATION, PREVENTION AND MEDICAL MANAGEMENT

*** *Sushmita Banerjee***

Abstract: *The new terminology of "Acute Kidney Injury" (AKI) has been adopted to replace "Acute Renal Failure" with the aim to define renal damage early and allow interventions to limit damage. The criteria defined by RIFLE and Acute Kidney Injury Network (AKIN) staging allow objective grading of AKI and have been validated to have a bearing on clinical outcome. Since AKI may be associated with increased mortality and long-term renal damage, identification and close monitoring of high-risk groups in an attempt to prevent renal damage is the optimum goal. New biomarkers of renal injury may in the near future provide sequential screens for rapid detection of AKI, even before the rise of serum creatinine and thus allow early interventions aimed at reversal.*

Keywords: *Acute renal failure, RIFLE score, Acute kidney injury network staging, Hypovolemia.*

The kidneys are vital body organs that are responsible for excretion of solutes, fluid-electrolyte and acid-base balance and also for various synthetic and enzymatic functions. Damage to this organ can cause disruption to some or all of these activities. Injury to the kidneys may occur in primary renal disease or in patients who are critically ill with multi-system involvement. Despite major advancements in intensive care and in renal replacement therapies, the prevalence of renal failure continues to rise. The mortality of patients with multi-system involvement increases if renal failure is associated.[1] Although the outcome is somewhat better in patients suffering from isolated renal injury, long-term chronic impairment is more common in this group. Therefore, the aim of management in all patients should be to recognize those at high risk, monitor closely and intervene early in an attempt to prevent renal injury and to treat rapidly so as to limit damage. New definitions and grading of acute renal injury have been recently developed that enable early recognition and thereby prompt management, particularly in the hospital setting.

Nomenclature, definitions and staging

For decades we have used the term "Acute Renal Failure (ARF)" to denote a sudden and potentially reversible inability of the kidneys to perform their normal homeostatic functions. However this description is largely subjective and does not mention any definite cut-off parameters of renal function or markers of renal damage, beyond which ARF is defined. Additionally it refers to a damage that has already occurred and does not leave any capacity for early detection of "injury" or intervention, to prevent "failure".

To address these concerns and to provide objective values that may define kidney injury

* Consultant, Department of Pediatrics, Calcutta Medical Research Institute, Kolkata.

of different severities in an universal manner the term "Acute Kidney Injury (AKI)" was adopted and criteria to define early renal injury and stage different levels of renal injury categorically were sought.

AKI may now be defined objectively by the criteria proposed by the AKI Network (AKIN)[2] as an abrupt (within 48 hours) reduction in kidney function, involving:

- an absolute increase in serum creatinine > 0.3 mg/dL from baseline OR
- an increase in serum creatinine > 50% (1.5-fold from baseline) OR
- a reduction in urine output < 0.5 mL/kg/hr for more than 6 hours).

The RIFLE criteria for Acute Kidney Injury (AKI) were proposed by the Acute Dialysis Quality Initiative (ADQI) Group[3] in 2004 and modified for pediatric use (pRIFLE)[4] in 2007. Further modifications resulted in the AKIN (Acute Kidney Injury Network) criteria in 2007.[2] The values set out in these schemes now enable us to attempt to pick up kidney injury early and use terminologies to qualify AKI that are standardized all over the world (Table I). The aim thereby is to intervene in the early stages so as to prevent progression and to have categories by which data from different interventions can be compared. These definitions and scores have been validated subsequently although in mainly adult studies, with definitive proof that clinical outcome gets worse with rising RIFLE and AKI scores.[1]

The major limitations of these scores however, are that they depend on a rise in serum creatinine from baseline and on urine output. Serum creatinine is recognized to rise only late in the evolution of renal damage and additionally at presentation, the baseline (well-state) serum creatinine is often not known. Urine output guidelines are erroneous in detection of AKI in non-oliguric renal failure which is more common in children, particularly neonates. However, until better biomarkers of early renal damage become available, these are the best objective criteria available and importantly, known to have effect on clinical outcome.

Etio-pathogenesis

The causes of AKI are conventionally classified as (i) Pre-renal (ii) Renal and (iii) Post-renal.

Pre-renal are those factors that cause reduction of effective renal perfusion. In the early stages, the renal autoregulatory system protects the kidneys.[5] Prostaglandin release causes renal vasodilation with increased blood flow to the parenchyma. Activation of the renin - angiotensin - aldosterone axis, results in constriction of efferent glomerular arterioles and an improvement in intraglomerular hydrostatic pressure. Avid sodium and water retention occurs in the tubules in an attempt to maintain blood volume. As a response to these appropriate mechanisms, clinically there is oliguria with concentrated urine which contains very little sodium. However if the insult continues, it eventually surpasses the capacity of this corrective system and results in intrinsic renal injury i.e. acute tubular necrosis (ATN). Common pre-renal causes of ARF are[5,6]:

(a) Conditions causing fluid loss and true hypovolemia - acute gastroenteritis, severe hemorrhage, burns, salt wasting renal or adrenal disease and diabetes insipidus.

(b) Conditions in which there is a maldistribution of intravascular fluid due to edema, capillary leak or vasodilation - nephrotic syndrome, sepsis, dengue and systemic inflammatory response syndrome (SIRS).

(c) Conditions in which the cardiac output is compromised-cardiomyopathy, left ventricular failure, severe aortic co-arctation.

Table.I. AKIN and pRIFLE staging of AKI[2,3]

AKIN Stage	Serum creatinine	Urine output	Equivalent RIFLE grade
I	Increase in serum creatinine of more than or equal to 0.3 mg/dl or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	<0.5 ml/kg/hr for more than 6 hours	Risk
II	Increase in serum creatinine to more than 200% to 300% (> 2- to 3-fold) from baseline	<0.5 ml/kg/hr for more than 12 hours	Injury
II	Increase in serum creatinine to more than 300% (> 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl with an acute increase of at least 0.5 mg/dL	< 0.3 ml/kg/hr for 24 hours or Anuric for 12 hours	Failure
	Persistent loss of kidney function for more than 4 weeks		Loss
	End Stage Renal Damage (more than 3 months)		End stage

NB:this category fulfills AKI criteria only if the lesions are bilateral or they occur in a solitary kidney.

(d) Factors that cause a failure of the renal autoregulatory mechanism that maintains renal perfusion within a wide range - NSAIDs inhibit prostaglandin induced renal arteriolar dilatation. ACE inhibitors and Angiotensin receptor blockers (ARBs) can inhibit the constriction of glomerular efferent arterioles thus causing a drop in intraglomerular perfusion pressures.

(e) Renal arterial or venous obstruction - occurs more commonly in neonates after hypoxic injury or umbilical arterial catheterisation, or in older children with dehydration or hypercoagulable states like nephrotic syndrome.

Intrinsic renal Injury occurs either de-novo when there is direct renal cell injury, or as an evolution of uncorrected pre-renal factors. Such direct renal parenchymal damage can occur in the following settings:

(a) Acute glomerular damage - acute glomerulonephritis, hemolytic uremic syndrome, vasculitides like SLE. The urine contains an

"active' sediment with presence of erythrocytes, leukocytes and casts, due to glomerular inflammation and damage.

(a) Acute Tubular damage - ATN occurs if there is prolonged hypoxic ischemic injury with resultant vasoconstriction. It is the final common pathway of many types of renal injury. A large number of inflammatory mediators are released both initially after the original insult and subsequently when the perfusion returns, causing a re-perfusion injury which may be of even greater significance and responsible for perpetuating the inflammatory cascade. ATN can also occur secondary to directly acting toxins like snake venom, drugs like amino-glycosides, cisplatin, amphotericin B and intravascular contrast media and poisons like ethylene glycol and methanol. Direct tubular damage and obstruction also occurs in tumour lysis syndrome, intravascular hemolysis with hemoglobinuria and myoglobinuria. When urine is produced, it is dilute and high in sodium as the concentrating and resorbtive capacities of the renal tubules are lost.

(b) Acute interstitial nephritis (AIN) –It may be precipitated by infections, SLE and drugs such as penicillins, sulfonamides, rifampicin and NSAIDs. Eosinophilia in the blood and urine is characteristic.

(c) Acute papillary necrosis – sickle cell anemia, diabetes mellitus.

Post-renal causes of AKI include obstructive uropathies, stones and tumours. To cause a rise in creatinine, the obstruction has to be bilateral, involve bladder or urethra or occur in a solitary kidney. Common diseases are posterior urethral valves, large or bilateral ureterocoeles or bilateral ureteric blockage due to tumour or stone. Early reversal of the obstruction or proximal drainage can result in rapid improvement, however if persistent, chronic damage will ensue.

Clinical effects

The clinical features of AKI initially depend on the cause. It is a common event in patients who are critically ill and under multiple interventions in the PICU. Features of sepsis, hypotension, edema and poor peripheral perfusion may be present in such patients. Signs of dehydration may be present in patients who have a history of vomiting or diarrhoea. Children with nephrotic syndrome are prone to hypovolemic episodes during untreated relapses, and if there is concurrent vomiting or diarrhea. Abdominal pain, vomiting, tachycardia and cool peripheries may be the alerting symptoms. If the intravascular volume can be restored and blood pressure corrected, then many of these patients will improve.

Children with HUS too may have preceding dysentery. Patients with AGN present with oliguria, hematuria and hypertension. Bright red urine with the presence of blood but not RBCs is indicative of hemoglobinuria as in G6PD deficiency. AIN may be associated with systemic symptoms like fever, arthritis, rash and uveitis. Obstructive uropathy may present with a poor urinary stream, bladder or kidney mass, or with renal colic. A history of drug intake should be taken in all patients.

Although oliguria is the most common presenting feature, non-oliguric renal failure can occur particularly in nephrotoxic AKI and acute interstitial nephritis.

Once intrinsic renal failure occurs, fluid intake should be restricted to match output and insensible losses. If this balance is not maintained, fluid overload ensues and the child may develop a raised blood pressure and JVP, and peripheral oedema. More serious complications include left ventricular failure with pulmonary edema and hypertensive encephalopathy.

Rapidly increasing levels of urea can cause confusion, anorexia and vomiting. Severe hyperkalemia can cause cardiac arrhythmias and cardiac arrest. Acidosis can cause hyperventilation.

In the recovery stages, a period of excessive diuresis may occur.

Prevention

Since the occurrence of renal failure is associated with increase in mortality and morbidity, it is important to recognize certain high risk groups who are more prone to AKI and monitor them closely so that rapid interventions can be taken. Such groups are:

i. Sick children in PICU with sepsis, SIRS and multi-organ dysfunction (MODS), dengue, cardiac anomalies, etc.

ii. Children with dehydration or hypovolemia due to any cause.

iii. Children with large tumor mass undergoing chemotherapy.

iv. Patients with known G6PD deficiency who have a hemolytic episode.

v. After major trauma.

vi. Patients treated with nephrotoxic dugs, and IV contrast media.

The commonest causes of AKI in the community are dehydration due to diarrhea and vomiting, poor fluid intake in an ill child, burns and trauma, and more rarely the intake of nephrotoxic drugs or snake bites. In many instances AKI can be prevented by prompt fluid resuscitation with isotonic fluids.

In all critically ill patients it important to maintain adequate oxygenation by rapid resuscitation and early airway and ventilation support. Restoration of intravascular fluid volume and blood pressure is essential with adequate fluid replacement and inotropes as the situation demands. In all high risk patients nephrotoxic drugs and intravenous contrast media must be avoided.

"Renal" doses of dopamine were earlier used in an attempt to increase renal perfusion in patients at risk of AKI. However current opinion is that such action of dopamine is short-lived and metanalyses have failed to show any advantage over other ionotropes.[7] The primary goal appears to be the maintenance of BP by using dobutamine, adrenaline or nor-adrenaline as per clinical situation. Vasopressin has been shown to be specially useful in maintaining renal perfusion in catecholamine resistant septic shock.[8]

Hydration regimes should be followed prior to starting chemotherapy or administering IV contrast agents. Drugs like sodium bicarbonate, statins and N-acetylcysteine have been used as reno-protective agents in the latter situation.[9] Allopurinol reduces the formation of uric acid and therefore is used prophylactically where there is a risk of tumor lysis. However it causes accumulation of uric acid precursors: hypoxanthine and xanthine which can also cause tubular obstruction. Rasburicase, a recombinant form of urate oxidase catalyses uric acid to the much more soluble allantoin and has been shown to be effective in preventing AKI in tumor lysis syndrome.[10]

Good fluid resuscitation and use of diuretics to maintain a good urine flow may prevent renal tubular deposition of pigment in myoglobinuria after trauma or hemoglobinuria in G6PD deficiency.

Management

Supportive treatment

Decisions about fluid therapy

The essential supportive therapy of AKI consists of maintaining fluid, electrolyte and acid

base homeostasis until there is recovery of renal function.

Assessment of intravascular volume status is performed by looking for signs of edema, dehydration, JVP, blood pressure, pulse rate and volume, peripheral temperature, capillary return and chest X-Ray. This may require CVP monitoring in the very sick individual who has edema, capillary leak syndrome or cardiac disease. If hypovolemia is present, restoration to normal is performed with normal saline boluses or other appropriate fluid therapy (e.g.: albumin in nephrotic syndrome or blood in trauma). If the patient is hypotensive despite adequate volume replacement, or if there is poor cardiac function, vasopressors or inotropes are used. Accurate measurement of urine output is important and may require catheterization in very sick children.

Once intravascular fluid deficits are corrected, fluid balance may be maintained by administering the volume of urine output plus insensible losses (400 ml/m^2/day). Fluid should be given enterally in the form of nutrition as much as possible. If IV fluids are required, they are generally given in the form of 5 or 10% dextrose which may be changed according to electrolytes and serum glucose measurements.

If there are signs of fluid overload, fluid intake should be restricted further and diuretic therapy started. Fluid overload had been shown to be a predictor of poor outcome in critically ill patients and efforts should be made to restrict fluid overload to less than 10% of body weight.

The controversy about frusemide

The use of frusemide to improve urine output once the intravascular volume is restored, is controversial. Reports have suggested that it may be effective in converting oliguric to non-oliguric renal failure and thereby obviating the requirement of dialysis in some patients, but not shortening the duration of renal failure. The improvement in mortality that occurs is thought to be due to improvement in fluid overload that may occur with its use.[11]

Diet

Diet should be of good caloric content, with salt, potassium and phosphate restriction. Since most patients are catabolic and have poor intakes, protein restriction is not normally required.

Monitoring

The blood urea, creatinine, electrolytes, calcium and phosphate should be monitored regularly. The differentiation between pre-renal and intrinsic renal failure may be assisted by urinary and serum measurements of sodium, urea, creatinine and osmolarity (Table II). Although in most circumstances the clinical situation and response to fluid bolus obviates the requirement for these tests, they may be helpful in some situations e.g. a very oedematous child with nephrotic syndrome in whom assessment of early intravascular fluid deficit is difficult. However, diuretic therapy confounds these criteria.[12]

Treatment of hyperkalemia

Acute hyperkalemia may be treated initially with (i) stabilisation of cardiac myocytes with IV Calcium and methods that cause shift of potassium from extra cellular to intracellular space which reduces risk of cardiac toxicity temporarily: (ii) nebulised salbutamol, glucose-insulin infusion and sodium bicarbonate infusion. (iii) Removal of potassium from the body by diuretics, potassium exchange resins and dialysis (Table III).

Indications of dialysis

Dialysis is indicated when conservative means of maintaining fluid and electrolyte

Table.II Biochemical differentiation between pre-renal and intrinsic renal AKI

Biochemical parameter	Pre-renal AKI	Intrinsic renal AKI
Urinary sodium (mmol/l)	< 5	> 20
Fractional excretion of sodium = UNa/UCr x SCr/SNa	< 1%	> 2%
Urine osmolarity : Serum osmolarity	> 1	< 1
Blood urea nitrogen : Serum creatinine	> 20	< 15

UNa: urinary sodium, UCr: urinary creatinine, SCr: serum creatinine, SNa: serum sodium

Table.III Treatment of acute hyperkalemia

1	Restrict K intake
2	Transient reversal of cardiotoxicity with • Calcium Gluconate (10%) 1ml/kg in distilled water, slow IV infusion
3	Temporary reduction of potassium in extracellular fluid with: • Nebulised Salbutamol • Sodium Bicarbonate : 1-2 mmol/kg • Glucose (0.5g/kg) + Insulin (0.1U/kg) infusion
4	Removal of potassium from the body by: • Frusemide (1-2 mg/kg) • Potassium exchange resins (1 g/kg/day) • Dialysis

homeostasis fail and there is increasing hyperkalemia, uremia, acidosis and fluid overload. Early dialysis other than treating the effects of ARF, often helps in therapy by providing space for instillation of drugs, nutrition and blood products.

The diuretic phase

During the recovery stages, excessive diuresis can occur, and since the resorbtive capacity of the tubules may not be optimum, electrolyte and bicarbonate losses may occur. Continued monitoring of fluid and electrolytes and their replenishment is required to prevent recurrent injury.

Specific management

Investigations to find the specific cause of AKI have to be planned according to the clinical

Table.IV. Current status of promising acute kidney injury (AKI) biomarkers in various clinical situations[13]

Biomarker name	Sample source	Cardiac surgery	Contrast nephropathy	Sepsis or ICU	Kidney transplant
NGAL	Plasma	Early	Early	Early	Early
Cystatin C	Plasma	Intermediate	Intermediate	Intermediate	Intermediate
NGAL	Urine	Early	Early	Early	Early
IL-18	Urine	Intermediate	Absent	Intermediate	Intermediate
KIM-1	Urine	Intermediate	Not tested	Not tested	Not Tested

NGAL neutrophil gelatinase-associated lipocalin, IL-18 interleukin 18, KIM-1 kidney injury molecule 1

scenario. Patients with a "nephritic" presentation require serum ASO titres, throat swab, C3 and in severe cases ANA and ANCA levels to be checked. A complete blood count, reticulocyte count, LDH and peripheral blood smear is required to confirm suspected HUS. Urine examination is helpful in pyelonephritis, ATN and AIN. An ultrasound primarily to exclude an obstructive uropathy or any chronic kidney disease should be performed early. A renal biopsy is performed if there is suspected rapidly progressive glomerulonephritis (RPGN), or if there is prolonged renal failure where the cause is uncertain.

Specific treatment of the causative factor has also to be continued simultaneously with supportive regimes. Antibiotics and other supportive measures are continued in sepsis and UTI. Nephrotoxic drugs should be stopped and drugs having renal clearance should have their dosages adjusted according to estimated GFR. Patients with atypical HUS require plasma infusions or plasma exchange. Patients with RPGN or vasculitis require immuno- suppressive therapy. Obstructive uropathies require urgent drainage. Patients with tumor lysis syndrome may be treated with rasburicase. Cardiac anomalies require treatment with ionotropes and other definitive measures as per specific anomaly.

Promising research

New biomarkers of renal injury

The only biomarker of AKI that has been available for clinical use till date is the serum creatinine. However the rise of serum creatinine after renal injury occurs late, after almost 50% loss of renal function. Additionally the serum creatinine is affected by other factors like age, sex, muscle mass and state of hydration. Therefore a better biomarker, which would rise promptly after renal injury and allow rapid intervention has been sought. Several serum and urinary biomarkers produced in the damaged renal tissues are under study and have shown promise in enabling a "AKI diagnostic panel" with sequential elevation of different proteins after renal injury, much like the cardiac enzyme panel that is performed after suspected myocardial ischemia.

The earliest amongst these to rise exponentially after AKI is plasma and urinary NGAL (neutrophil gelatinase associated lipocalin) which are detected in very high levels in post cardiac surgery AKI, within 2-6 hours, where the serum creatinine level rises after 1-3 days. Plasma and urinary NGAL are also markedly raised after AKI due to sepsis, ischemia or nephrotoxins.[1,13]

Other proteins that rise in AKI after NGAL but before serum creatinine are: plasma Cystatin C, urinary IL-18 (interleukin 18) and KIM-1 (kidney injury molecule 1). IL-18 is not raised in AKI due to nephrotoxins.

It is likely that with ongoing research such sequential AKI panels will soon be commercially available that will not only enable an earlier diagnosis of AKI but also differentiate between pre-renal and renal failure, different etiologies of renal injury and prognosticate regarding duration of AKI (Table IV).

Pharmacological interventions to limit AKI

A large number of vasoactive and inflammatory proteins (such as adenosine, endothelin, reactive oxygen radicals, adhesion molecules, etc.) have been identified, that promote renal injury and persist even after the original insult has ceased. A number of studies looking at experimentally produced AKI in animals have shown positive results by using inhibitors of such substances, with rapid improvement of renal parameters. Unfortunately none of these agents have been proven to be effective in humans, probably since we can only identify renal injury late in humans by means of serum creatinine. Thus in interventional studies also the early renal injury biomarkers are expected to have a big role.[12]

Fenoldapam, a selective dopamine A1 antagonist and Natriuretic peptides have been shown in trials to be useful in increasing urine output in AKI after cardiac surgery.[14] However randomized trials in children have not been performed yet.

Conclusions

Critically ill patients with multi-system disease have a poorer prognosis if AKI is associated. Isolated AKI also may cause long-term renal damage. For both these reasons, identifying high-risk groups and intervening early to prevent or limit AKI should be the goal. Close monitoring and maintenance of fluid, electrolyte and acid-base balance is required in established AKI. Sequential early markers of renal injury may soon be available for clinical use that will allow rapid detection before the rise of serum creatinine and therefore further aid preventive and therapeutic interventions.

Points to Remember

- ***The association of acute kidney injury worsens the outcome of critically ill children with sepsis, SIRS or MODS.***
- ***Acute kidney injury may result in long-term renal damage.***
- ***Pre-renal etiologies form the most common causes of acute renal injury and are therefore amenable to early intervention.***
- ***Certain high-risk groups are more prone to develop acute kidney injury and should be identified, monitored and specific preventive steps taken early.***
- ***In established acute renal failure maintenance of careful fluid, electrolyte and acid-base homeostasis remains the goals of management.***

References

1. Murugan R, Kellum JA. Acute kidney injury: what's the prognosis? Nat Rev Nephrol 2011;7:209-217.
2. Mehta RL, Kellum JL, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A and the Acute kidney injury network. Acute kidney injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11: R31.
3. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-R212.
4. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int 2007; 71:1028-1035.
5. Andreoli SP. Acute kidney injury in children. Pediatr Nephrol 2009;24: 253–263.
6. Andreoli SP. Clinical Evaluation of acute kidney injury in children. In: Pediatric Nephrology 6th Edn, Eds: Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Springer-Verlag, Berlin. 2009;pp:1603-1618.
7. Jones D, Bellomo R. J Renal-dose dopamine: from hypothesis to paradigm to dogma to myth and, finally, superstition? Intensive Care Med 2005;20:199-211.
8. Gordon AC, Russell JA, Walley KR, Singer J, Ayers D, Storms MM, et al. The effects of vasopressin on acute kidney injury in septic shock. Intensive Care Med. 2010;36:83-91.
9. Weisbord SD, Palevsky PM. Strategies for the prevention of contrast-induced acute kidney injury. Curr Opin Nephrol Hypertens 2010;19:539-549.
10. Goldman SC, Holcenberg JS, Finklestein JZ, Hutchinson R, Kreissman S, Johnson FL, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood 2001;97:2998-3003.
11. Grams ME, Estrella MM, Coresh J, Brower RG, Liu KD; for the National Heart, Lung, Blood Institute Acute Respiratory Distress Syndrome Network. Fluid Balance, Diuretic Use, and Mortality in Acute Kidney Injury. Clin J Am Soc Nephrol. 2011 [Epub ahead of print] PubMed PMID: 21393482.
12. Zappitelli M, Goldstein SL. Management of acute kidney failure. Pediatric Nephrology 6th Edn, Eds: Avner ED, Harmon WE, Niaudet P, Yoshikawa N 2009;2(66)1619-1628.
13. Nguyen MT, Devarajan P. Biomarkers for the early detection of acute kidney injury. Pediatr Nephrol 2008;23:2151-2157.
14. Patel NN, Rogers CA, Angelini GD, Murphy GJ. Pharmacological therapies for the prevention of acute kidney injury following cardiac surgery: a systematic review. Heart Fail Rev. 2011 [Epub ahead of print] PubMed PMID: 21400231.

NEWS AND NOTES

Pediatric Emergency Medicine Course (PEMC)

Date: 20th and 21st April, 2012

Venue: Kanchi Kamakoti CHILDS Trust Hospital, Nungambakkam, Chennai

Contact for details: Dr. Janani Shankar (9841078101), Dr. Jayanthi Ramesh (9444085033)

Dr. Shanti Sangareddi (9444676615)

NEPHROLOGY

TROPICAL ACUTE KIDNEY INJURY – RECOGNITION AND MANAGEMENT

**** Amitava Pahari***

Abstract: *Tropical acute kidney injury (AKI) refers to acute kidney injury in association with diseases particularly prevalent in tropical countries. Tropical AKI remains the major cause of renal dysfunction in our country. It is important that recognition and management of these mostly infectious and toxin mediated diseases are done early to prevent progression of AKI. This has got immediate survival benefit and also prevents long term damage and future development of chronic kidney disease. In this article, common tropical AKI prevalent in India are discussed with emphasis on early recognition and management of the disease process. General management principles of AKI continue to be equally important while managing these children along with disease specific treatment*

Keywords: *Tropical, Acute kidney injury, Acute renal failure.*

Tropical diseases are usually infectious diseases that either occur uniquely in tropical and subtropical regions or more commonly, are either more widespread in the tropics or more difficult to prevent or control. The clinical spectrum of renal involvement extends from asymptomatic proteinuria or urinary sediment abnormalities to fatal acute renal failure. The respective renal pathologies include glomerular, microvascular and tubulointerstitial lesions. Tropical nephrology is no longer a regional issue. With enormous expansion of travel and immigration, the world has become a global village. Therefore health problems in a particular region have worldwide repercussions. There is also a change in environment in view of global warming with increased incidence of diseases of tropical countries in the western world. Significant numbers of these patients belong to poor socioeconomic conditions without proper access to healthcare facilities which might be an important cause for adverse outcome of tropical acute kidney injury (AKI).

Tropical diseases and AKI: Etiology

Tropical nephropathies causing AKI are broadly classified as infective or toxic. The infective nephropathies are associated with endemic microbial infections: bacterial, viral, fungal and parasitic. Toxic nephropathies include exposure to poisons of animal or plant origin. The common tropical etiological agents responsible for AKI in Indian subcontinent are outlined in Table I and will be discussed further. A tantalizing clue to the pathogenesis of glomerular disease is the marked difference in the incidence of nephrosis and nephritis in western and tropical areas of the world. In several tropical countries, glomerulonephritis (GN) accounts for up to 4% of pediatric hospital admissions; the incidence in temperate climates is 10- to 100-fold less.[1] This difference might be explained by a complex interaction of several

* Senior Consultant Pediatrician, Nephrology and Infectious Diseases, Apollo Gleneagles Hospital, Kolkata.

different factors, including nutrition, racial and genetically determined differences in immune responses and exposure to infectious diseases. A growing body of evidence, however, suggests that long-term exposure to infectious agents is a major factor in the increased prevalence of glomerular diseases in tropical countries.[1] It is also worth mentioning about the increased incidence of impetigo-associated post-streptococcal glomerulonephritis due to increased prevalence of scabies in children living in tropical countries as well as increased incidence of hemolytic uremic syndrome due to increased prevalence of Shiga-toxin producing Shigellosis.

Tropical diseases and AKI: Pathogenesis

Aetiologically there may be direct tissue invasion by the causative organism, remote cellular and humoral effects of bacterial antigens and endotoxins and consequently renal injury due to acute systemic effects of the infection. The pathology of ARF caused by tropical nephropathies include glomerular, microvascular and tubulointerstitial lesions. The tubulo-interstitial lesions include interstitial nephritis and toxic/ischemic acute tubular necrosis (ATN). The pathogenesis of AKI is summarized as follows:

1. Decreased blood supply to the glomerulus: A number of cytokines contribute to this including tumour necrosis factor (TNF), interleukin-1 (IL-1), platelet activating factor (PAF) and angiotensin II. The imbalance between the vasoconstricting effect of endothelin (ET), and the vasodilator effect of nitric oxide (NO) are also contributory.[2]

2. Decreased GFR: This is produced by decrease in blood supply, decrease in glomerular permeability due to endothelial cell swelling, aggregation of neutrophils in glomerular capillaries and high tubular luminal pressure.

3. Tubular damage: This occurs due to injury of the tubules by a complex cascade of interactive injury pathyways which ultimately lead to cell death.[3] Among the factors leading to this is injury by free radicals due to excessive production of NO due to over production of the enzyme inducible nitric oxide synthase (I-NOS) triggered by sepsis. Some injured but viable tubular cells get detached from their basement membrane and are shed in the tubular lumen together with the necrotic cells.

4. Luminal Obstruction: This is caused by the shed tubules, the debris released by the injured cells and intraluminal protein casts.[3]

5. Backleak. Toxic tubular lumen contents leak back into the interstitium due to high luminal pressure and dysfunction of the damaged tubular cells. This further augments tubular damage.

Enteric infections and diarrheal diseases

Diarrheal diseases caused by E. coli, salmonella, shigella, campylobacter, vibrios and yersinia remain important and common bacterial infections in the tropics. Renal involvement in the enteric infections may result from any of the four possible mechanisms.[1]

1. Diarrhea and severe dehydration: Regardless of the causative organism from coliforms to vibrios, diarrhea results in hypovolemia, abnormalities of plasma electrolyte composition and renal underperfusion. If severe dehydration occurs and is persistent, oliguria from prerenal failure is followed by vasomotor nephropathy and established renal failure.

2. Systemic sepsis and endotoxemia: E. coli, shigella and salmonella (particularly S. typhi) may invade the bloodstream and induce septicemia or septic shock. Acute renal failure is commonly seen in infants with E. coli sepsis but

is also reported with Klebsiella, Salmonella and Shigella infections, etc.[1]

3. Enteric pathogen-associated nephritis: Enteric infections with E. coli, yersinia, campylobacter and salmonella have been associated with several different forms of GN, including membranoproliferative glomerulonephritis (MPGN), interstitial nephritis, diffuse proliferative GN and IgA nephropathy.[4,5]

4. Enteric pathogen induced hemolytic-uremic syndrome: HUS is characterized by three distinct clinical signs: acute renal failure, thrombocytopenia and microangiopathic hemolytic anemia. Studies in tropical countries documented that HUS occurs in 3% of all cases of shigella dysenteriae, with nearly 10% of patients having some features of HUS such as hemolysis, thrombocytopenia or impaired renal function.[6]

Enteric fever

Abnormal renal function is reported in about 16% of patients with salmonellosis.[7] The main renal lesions are pyelonephritis, acute tubular necrosis and glomerulonephritis which is exudative. During the febrile phase hematuria and proteinuria, usually less than one gram are common. The renal involvement is usually mild with full recovery within two weeks of typhoid treatment. A more severe illness mimicking post infectious glomerulonephritis was reported from South Africa with generalized edema and hypertension. Renal biopsy showed mild to moderate mesangioproliferative glomerulonephritis with IgG and IgM deposits.

Leptospirosis

Although leptospires do not contain classic endotoxins, the pathophysiology of the disorder has many similarities to that of endotoxemia. In severe cases, jaundice occurs because of hepatocellular dysfunction and cholestasis. Renal functional abnormalities may be profound and out of proportion to the histologic changes in the kidney.[8] Renal involvement is predominantly a result of tubular damage, and spirochetes are commonly seen in the tubular lesions. The inflammatory changes in the kidney may result from either a direct toxic effect of the organism or immune-complex nephritis. However, hypovolemia, hypotension, and reduced cardiac output caused by myocarditis may contribute to the development of renal failure. In severe cases, a hemorrhagic disorder caused by widespread vasculitis and capillary injury also occurs.

The clinical manifestations of leptospirosis are variable. Of affected patients, 90% have the milder anicteric form of the disorder and only 5 to 10% have severe leptospirosis with jaundice.[8] The severe form of the disease (Weil's disease) presents with fever, impaired renal and hepatic function, hemorrhage, vascular collapse and altered consciousness. Urinalysis is abnormal during the leptospiremic phase with proteinuria, hematuria and casts. Uremia usually appears in the second week and acute renal failure may develop once cardiovascular collapse and DIC are present.

The diagnosis of leptospirosis should be considered in febrile patients with evidence of renal, hepatic and mucous membrane changes and rash. Serologic tests to detect leptospirosis are now sensitive. IgM antibody may be detected as early as 6 to 10 days into the illness and antibody titers rise progressively over the next 2 to 4 weeks. Leptospirosis is treated with intravenous penicillin or other β lactam antibiotics. The severity of leptospirosis is reduced by antibiotic treatment, even if started late in the course of the illness. Supportive treatment with volume replacement to correct hypovolemia, inotropes and correction of

Table.I Common causes of tropical AKI in India

Infections	Toxins
Waterborne infections	Snake bite
Diarrheal disorders	Scorpion sting
Enteric fever, Hepatitis (A &E)	
Leptospirosis	
Vector borne diseases	
Malaria	
Dengue	
Chikungunya	
Kala azar	
Filariasis	
Blood borne infections	
Tetanus, hepatitis (B & C)	

coagulopathy is essential. Dialysis may be required in severe cases and may be needed for prolonged periods until recovery occurs.

Hepatitis

Hepatitis B and Hepatitis C nephropathy are mostly chronic with hepatitis B virus-associated polyarteritis nodosa, more common in adults. Hepatitis B virus-associated membranous glomerulonephritis presents mostly with proteinuria rather than AKI. Glomerulonephritis has been described as an important complication of chronic infection with HCV in adults with some reports in children as well but it rarely gives rise to significant AKI unless there is a co-morbid factor.[1] However, infective hepatitis associated hepatorenal syndrome is not uncommon. Hepatorenal syndrome (HRS) is defined as development of renal failure with severe liver disease and absence of other causes of AKI with set diagnostic criteria. The pathophysiology continues to remain unclear. Reduced splanchnic blood supply in association with fulminant hepatic failure gives rise to grossly reduced renal blood flow, caused by severe renal arterial and arteriolar vasoconstriction playing a major role. Recovery of AKI parallels recovery of hepatic function. A small minority of patients (1-7%) with HRS develop end-stage renal disease (ESRD) and require renal replacement therapy (RRT) despite recovery of hepatic function. Treatment is mostly supportive aiming at both hepatic and renal dysfunction. Splanchnic vasoconstrictors, such as the vasopressin analogs may have some benefit while awaiting hepatic recovery.

Malaria

AKI complicates malaria in 1 - 5% of the natives in endemic areas but in non-immune visitors the figure goes up to 30%.[9] It is mostly due to P. falciparum with P. vivax being the causative species in a minority of cases. The main features are oliguria and hypercatabolism in addition to the systemic effects of malaria. Mild proteinuria less than 1gm/day may occur but almost resolves completely after treatment. The urine sediment is usually negative. Hyperkalemia is usually striking due to hemolysis, rhabdomyolysis and acidosis.

The pathogenesis of falciparum malarial renal complications involves two initially independent pathways - red cell parasitization and monocyte activation. These subsequently interact, as the infected red cells express abnormal proteins that induce an immune reaction by their own right, in addition to providing sticky points (knobs) for clumping and adherence to platelets and capillary endothelium. TNF-α released from the activated monocytes shares in the endothelial activation. As both pathways proceed and interact, a variety of renal

complications develop, including acute tubular necrosis, acute interstitial nephritis and acute glomerulonephritis.

Histologically there is a mixture of ATN, interstitial nephritis and glomerulonephritis.[9] ATN is the most consistent finding. The glomerular lesions show prominent mesangial proliferation with modest mesangial matrix expansion. Segmental necrosis may occur due to occlusion of the capillaries by erythrocyte rosettes. Immunofluorescence show finely granular IgM and C3 deposits along the capillary walls and in the mesangium.[3] Mortality depends on the urgency and facilities of treatment ranging from nil in well-equipped centers to as high as 45% when facilities are meagre.[9]

Malaria: Black water fever

The term black water fever refers to the combination of severe hemolysis, hemoglobinuria and renal failure. It was more common in nonimmune individuals receiving intermittent quinine therapy for P. falciparum malaria. Renal failure generally occurred in the context of severe hemolytic anemia, hemoglobinuria and jaundice.[1] The patho- physiology of the disorder is unclear; however it appears that the concomitance of a double sensitization of the red blood cells to the P. falciparum and to the amino-alcohols is necessary to provoke the hemolysis. The mortality rate in early studies were high and survivors were likely to experience further hemolytic episodes with subsequent malaria infections. However recent studies indicate a better outcome with earlier institution of intensive care and dialysis with necessary changes of antimalarial medications.

Dengue

AKI occurs in 5% of patients with dengue hemorrhagic fever.[10] In severe cases, hypotension and shock supervene, largely as a result of hypovolemia. Renal manifestations include oliguria, proteinuria, hematuria and rising urea and creatinine. Acute renal failure occurs in patients with severe shock, largely as a result of renal underperfusion giving rise to ATN which is associated with interstitial oedema and mononuclear cell infiltration.[1] However, glomerular inflammatory changes may also occur and mesangioproliferative glomerulonephritis may be seen with IgG, IgM and C3 deposits.[1] Usually, it is associated with mild proteinuria and abnormal urinary sediment as well as dyselectrolytemia, particularly hyponatremia. Management of patients with severe dengue depends on aggressive circulatory support and volume replacement with careful monitoring of circulatory status including urine output. With correction of hypovolemia, renal impairment is usually reversible, but RRT may be required in patients with established acute renal failure.

Kala-azar

Proteinuria and/or microscopic hematuria or pyuria has been reported in 50% of patients with visceral leishmaniasis.[1] AKI in association with interstitial nephritis has also been reported. Renal histology in patients with visceral leishmaniasis reveals glomerular changes, with features of a mesangial proliferative GN or a focal proliferative GN, or a generalized interstitial nephritis with interstitial edema, mononuclear cell infiltration and focal tubular degeneration. Renal disease in leishmaniasis is usually mild and may resolve after treatment of the infection. Renal dysfunction has been reported to be associated with treatment for visceral leishmaniasis with antimony-compounds as well as amphotericin B.

Filariasis

Proteinuria is more common in filarial hyperendemic regions. Renal histology has

shown a variety of different histopathological appearances with the most common being diffuse mesangial proliferative glomerulonephritis with C3 deposition in the glomeruli.[1] AKI is not a usual manifestation but has been reported in association with nephritis.

Tetanus

A number of mechanisms may lead to development of the AKI associated with tetanus, with rhabdomyolysis and autonomic nervous system over activity being the most prominent. ARF due to tetanus is reported to be high in certain countries like Brazil, where AKI is seen in 34% of cases.[11] It is usually mild and non-oliguric.

Snake bites and scorpion sting

AKI is mainly observed following bites by the Viperidae group, Sea snakes and the Colubridae group, but mostly result from viper bites. Incidence of AKI after poisonous snakes bites are reported between 13 - 22% of victims.[3] AKI is more frequent and more severe in children due to relatively high dosage of snake venom inflicted by the bite in children with smaller body size. There is no direct nephrotoxin present in the venom. The immediate effect of exposure is attributed to direct hematologic toxicity involving the coagulation system and red cell membranes. The massive release of cytokines and rhabdomyolysis also contribute. The resultant effects give rise to hemorrhage, hypotension, shock, intravascular coagulation with or without microangiopathy and contribute to tubular necrosis and cortical necrosis manifesting as AKI. Late effects may be encountered as a consequence of the immune response to the injected antigens. Management of AKI in association with snake venom need early and judicious management of the bite with anti toxin therapy along with careful fluid and electrolyte balance.[12] A number of children need RRT while awaiting recovery from the effects of the venom.

Scorpion sting is an acute life-threatening medical emergency. Case fatality rates of 3-22% were reported among children hospitalized for scorpion stings in India.[13] Scorpion venom is a potent sympathetic stimulator. Scorpion venom is composed of neurotoxin, cardiotoxin, nephrotoxin, hemolytic toxin etc. Cardiac manifestations are common in Indian red scorpion envenomation. Alpha receptors stimulation plays a major role in evolution of myocardial dysfunction and acute pulmonary edema in victims of scorpion sting. Prazosin–an alpha adrenoreceptor antagonist is antidote to venom action. Early administration of prazosin decreases the severity of symptoms of scorpion sting. Recovery from scorpion sting is hastened by simultaneous administration of scorpion antivenom plus prazosin.[14] Some patients have decreased renal plasma flow and toxin-induced ATN and AKI may occur. Rhabdomyolysis and AKI may result from venom-induced excessive motor activity.

Tropical AKI: Management principles

The general management principles of AKI comprising of early recognition of the different stages of AKI and maintaining fluid, electrolyte and acid-base homeostasis until there is recovery of renal function is the basis of managing tropical AKI as well.[15] However the diagnosis of primary disease early in the course and instituting proper anti-infective and anti-toxic therapy may be life saving and prevents the development of AKI as well as long term renal morbidity. Often there is a need for multidisciplinary approach with help from infectious diseases specialist, micro-biologist and intensivist. Necessary renal replacement therapy (RRT) in the form of dialysis or hemofiltration might be indicated awaiting renal recovery.

Summary

In our perspective of disease prevalence in the Indian subcontinent tropical diseases are common causes of AKI. Majority of these problems are preventable either by primary prevention by health promotion like providing a safe environment with supply of clean drinking water and proper waste disposal and also by specific protection by vaccination when available. Secondary prevention by early recognition of the illness and early institution of specific as we well as supportive treatment goes a long way in the management of tropical AKI. The prognosis of tropical AKI in children varies depending on the quality of medical facilities available. Long term outcome is good provided early institution of specific and supportive therapy including RRT is possible.

Points to Remember

- ***Tropical nephropathies causing AKI are broadly classified as infective or toxic. The infective nephropathies are associated with endemic microbial infections. Toxic nephropathies include exposure to poisons of animal or plant origin.***
- ***Early diagnosis of tropical infections and toxins with implementation of specific treatment often prevents renal involvement and sequelae.***
- ***General management principles of AKI with careful fluid and electrolyte balance along with antiinfective therapy remains the cornerstone of management of tropical AKI in children.***
- ***Progressions of AKI and longterm renal damage are often preventable with early intervention along with judicious use of renal replacement therapy.***

References

1. Herberg J, Pahari A, Walters S, Levin M. Infectious Diseases and the Kidney. In: Pediatric Nephrology, Avner ED, et al. Eds, 6th Edn, Berlin: Springer Verlag 2009; pp1235-1274.
2. Thijs A, Thijs LG. Pathogenesis of renal failure in sepsis. Kidney Int 1998;53 Suppl 66: S34-37.
3. Barsoum R, Sitprija V. Tropical Nephrology. In: Diseases of the Kidney, Schrier RW, Gottaschalk CW, Eds, 6th Edn, Boston, Little, Brown & Co. 1997; pp 2221-2268.
4. Srivastava RN. Acute glomerulonephritis in Salmonella typhi infection. Indian Pediatr 1993;30:278-279.
5. Pancharoen C, Wongsawat J, Phancharoen S, Thisyakorn U. Typhoid glomerulonephritis in a child: a rare complication of typhoid fever. Southeast Asian J Trop Med Public Health 2001;32:869-871.
6. Kaplan BS, Cleary TG, Obrig TG. Recent advances in understanding the pathogenesis of the hemolytic uremic syndromes. Pediatr Nephrol 1990;4:276-283.
7. Khosla SN, Lochan R. Renal dysfunction in enteric fever. J Assoc Phys India 1991; 39: 382-384.
8. Lai KN, Aarnos I, Woodroffe AJ, Clarkson AR. Renal lesions in Leptospirosis. Aust N Z M Med 1982; 12:276.
9. Barsoum RS. Malarial acute renal failure. J Am Soc Nephrol 2000; 11 : 2147-2154.
10. Abboud O. Tropical renal failure. J Tro Nephro-Urol 2007;5:11 -13.
11. Martinelli R, Matos CM, Roche H. Tetanus as a cause of acute renal failure: possible role of rhabdomyolysis. Rev Soc Bras Med Trop 1993; 26: 1-4.
12. WHO/SEARO Guidelines for the clinical management of snake bites in the Southeast Asian region. Southeast Asian J Trop Med Public Health. 1999;30 Suppl 1:1-85.

13. Mahadevan S. Scorpion sting. Indian Pediatr 2000; 27: 504-514.

14. Bawaskar HS, Bawaskar PH. Efficacy and safety of scorpion antivenom plus prazosin compared with prazosin alone for venomous scorpion (Mesobuthus tamulus) sting: randomised open label clinical trial. Br Med J 2011;342:c7136.

15. Banerjee S. Tropical acute kidney injury - Recognitions and management. Indian J Pract Pediatr 2012;14:133-142.

6th National Summer CME of Indian Academy of Pediatrics
Infectious Diseases Chapter

Date : 20th May 2012

Time : 8.00 am – 5.30 pm

Venue : Sri Ramachandra University, Porur, Chennai – 600 116.

Organized by : Department of Pediatrics
Sri Ramachandra University &
Indian Academy of Pediatrics – Infectious Diseases Chapter,
Tamil Nadu Branch.

Registration Fee: Rs.1000/- for Delegates
Rs. 800/- for Postgraduates
Till 30th April 2012

Rs. 1500/- after 30th April 2012.

Cheque in favour of **"Pediatric CME"**

Dr. V. Vilvanathan – 09443967167, Dr. Saji James - 09841223038

Organizing Secretaries

Department of Pediatrics, Sri Ramachandra Medical College and University,
Porur, Chennai - 600 116.

NEWS AND NOTES

4th World Congress of Pediatric Gastroenterology,
Hepatology and Nutrition (WCPGHAN 2012) Taipei, Taiwan
Date: November 14-18, 2012

Contact:

Yen-Hsuan Ni, M.D., Ph.D., Congress President

The 4th World Congress of Pediatric Gastroenterology, Hepatology and Nutrition

WCPGHAN 2012 Congress Secretariat

Ms. Celine Kao, c/o Galaxy Scientific Integrated Communication Ltd.

M: +886 938 014 267; F: +886 2 729 7996, Email: secretariat@wcpghan2012.com,
Website:http://www.wcpghan2012.com/Guideline.php

NEPHROLOGY

COMMON UROLOGICAL PROCEDURES THAT PEDIATRICIAN SHOULD KNOW

**** Nandhini G***

Abstract: *Antenatal detection of congenital anomalies in the renal tract has put us in the need for early surgical intervention for correctable problems. With the advent of increasing surgical intervention, it is mandatory for the pediatricians to abreast their knowledge on the surgical procedures, the complications, their maintanence in their office practice . Aim of the article is to improvise our knowledge in the basic bedside procedures in Pediatric Urology with latest updates.we have detailed on the common queries that brew on simpler ones like urine sampling, catheterisation, to the complicated ones like tube diversions – nephrostomy, suprapubic catheterisation, tubeless diversions- ureterostomy, vesicostomy and mitrofanoff with augmentation bladder.*

Keywords: *Catheter, Urine, Diversion, Clean intermittent self catheterization.*

Pediatric urology as a subspeciality of pediatric surgery has undergone phenomenal changes in recent few years in improving the quality of life in children with urological problems. With the increase in parental awareness and quality care in pediatric nephrology, we are able to sort out renal problems early in life. Pediatric population always need special attention to every minute detail in day to day care. Urinary tract in children involves plenty of minor procedures which are to be handled in pediatric clinics itself. Many urological procedures can be done in outpatient clinics. Aim of the article is to improvise our knowledge in the basic bedside procedures in pediatric urology with latest updates.

In regular office practice, wherein a pediatrician would be approached are for the advice on following :

1. Urine sampling : Clean catch/catheter/ suprapubic urine sample
2. Catheterisation and its care
3. Clean intermittent self catheterisation(CIC)
4. Urinary diversions :

   A. Tube diversions - Nephrostomy / suprapubic catheters

   B. Tubeless diversions - Ureterostomy / vesicostomy

   C. Continent diversion - Mitrofanoff

Urine sampling

Urine Specimen - Clean catch / Mid stream/ Catheter sample.

Urine collection[1] in children is difficult for investigation. Urine samples differ depending on the nature of investigations like-urine routine, urine for culture and sensitivity, urine spot protein/ calcium, 24 hours urine collection. Hence accordingly, the mode of urine collection should be detailed to the parents.

* Consultant Pediatric Surgeon, Mehta Children's Hospital, Chennai.

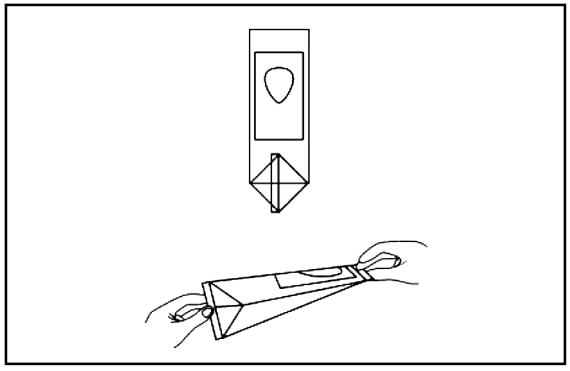


Fig.1. Urine collection bag with adhesive

Urine routine is the simplest of all samples as it can be collected easily interrupting a good urine stream. Sometimes in infants who take a long time to void or dribble few drops of urine, sampling is difficult. Hence a urine collection bag (Fig.1) which is available in soft polyethylene material can be adhered to the genital until child voids. Parents should be taught to cleanse the genital and perianal region. After drying the genitals, adhesive portion of the urine collection bag should be adhered to skin surrounding the vagina in females and with phallus inside the bag in males with excess of bag toward feet. We can reapply diaper, if required, directly over the bag. Once urine is collected, bag is removed carefully and urine sample is sent. This is a simple non invasive method of urine collection with reduced contamination rates and is safe even if left for long time.

Clean catch urine specimen

This method is used in urine samples for culture sensitivity which is easy in collection with toilet trained children above 3 years of age. To obtain a clean-catch sample, boys should cleanse the glans penis with soap and water, after which three wipes are used to disinfect the glans (Fig.2). Two betadine wipes and third with clean saline to clear the color of the betadine in the urine sample. As the child starts to void, 5-10 ml of urine is collected in the appropriate container for culture and sensitivity after allowing the initial stream to fall into the toilet bowl.

Girls should be made to sit on the toilet seat with legs wide open and rest of the procedure is same for collection. Sample should be sent to the lab at the earliest without any delay.

Catheterisation

A urinary catheter is any tube system placed in the body to drain and collect urine from the bladder. It can be single insertion for sampling, intermittent catheterisation or an indwelling catheter for few weeks. It is an invasive procedure, hence informed consent from the parents is a must. It should be done by pediatrician or pediatric surgeon.

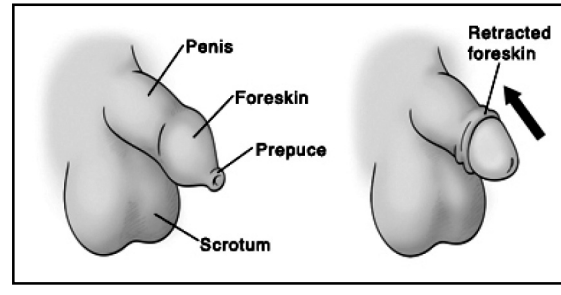


Fig.2. Normal anatomy-Male genitalia

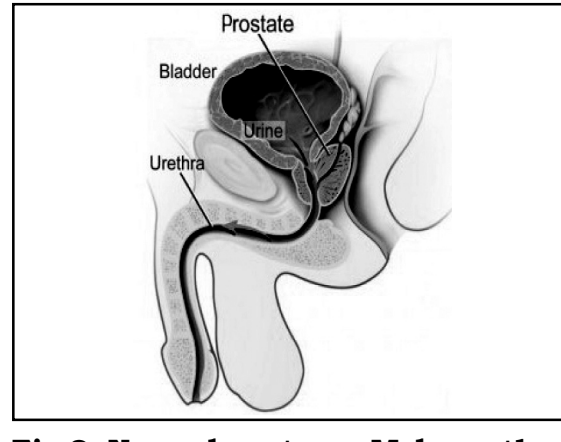


Fig.3. Normal anatomy-Male urethra

Catheter sampling

Urine collection by catheterisation or suprapubic aspiration is required in children with recurrent bacterial colonisation of urine even with clean midstream catch sample. Both are superior samples as it avoids the urethral contamination and fetches direct sample from bladder. Commonly feeding tubes are used for catheter sampling. Feeding tubes are firm enough to glide through urethra without bending but still creates false passage if forced through. Appropriate size has to be chosen - 5, 6, 8, 10Fr depending on the size of the urethra and age of child.

Male urethra has a longer course with angulation at the junction of anterior and posterior urethra (Fig.3). Catheterisation should be done under strict aseptic precaution. After washing hands, betadine is used to sterilise the glans and to clean the urethral meatus. With the sterile gloves on, the appropriate size feeding tube is lubricated with 2% xylocaine jelly. Retract the prepuce and stabilise the phallus by holding the phallus on the sides, perpendicular to the body. Lift the phallus away from the body at 90 degree from the body, which aligns the anterior urethra with posterior urethra in the shape of a boomerang. This helps in easy glide of the feeding tube into the urethra. Begin to gently insert and advance the catheter. Once the urine flow starts, advance the catheter only for 1-2cm. Do not advance more than 2cm since longer tube has a chance to knot inside the bladder and removal becomes difficult.

Suprapubic aspiration

Suprapubic aspiration is a procedure to obtain uncontaminated bladder urine directly. It is easy to perform in the emergency department and is associated with minimal complications. It is superior to clean-catch or transurethral (via catheterization) collection of bladder urine for bacteriologic study. The sensitivity of the aspirated urine for bacteriuria on urinalysis approaches 100% and is rarely associated with contamination.

The common indications for supra pubic aspiration are collection of clean bladder urine sample for culture sensitivity and acute urinary retention. The procedure is deferred in cases of local skin infections in suprapubic region, lower abdominal scar, ascites, known bladder tumors, etc. Full bladders are easy to tap clinically. Partially filled bladders require ultrasound guidance to locate the bladder so as to avoid the presence of bowel loops intervening the bladder and anterior abdominal wall. 1% lignocaine - local anesthesia is placed at the insertion site to reduce discomfort. Sterile syringe of 10 or 20ml is preferable to get the vaccum suction required to aspirate urine. Similarly the needle size required is 22 gauge of length 1.5 inch for pediatric patients. The lower abdominal fat deposition in children increases the needle depth that is required to reach the bladder. Regular landmark for suprapubic aspiration is the site 2 cm or one finger breadth above the symphysis pubis in midline. Insert the needle while aspirating until urine appears within the

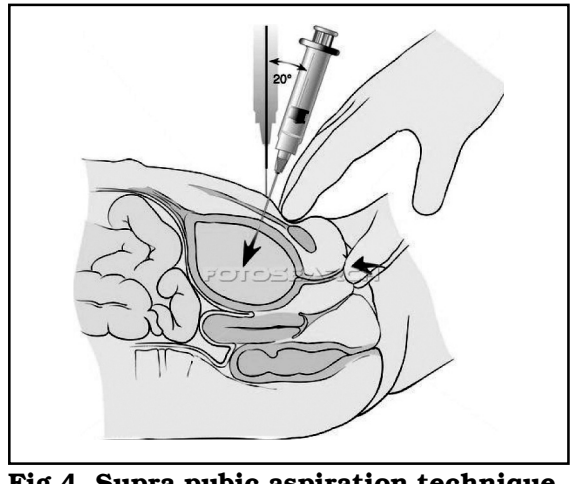


Fig.4. Supra pubic aspiration technique in children

syringe. The insertion approach is slightly different in children and adults.

- **Pediatric:** Insert the needle slightly cephalad (Fig.4), 10-20° off perpendicular, and advance. In a young child, the bladder is still an abdominal organ.
- If the insertion is unsuccessful, do not withdraw the needle fully. Instead, pull back until the needle tip rests in the subcutaneous tissue and then redirect 10° in either direction. Do not attempt more than 3 times.
- Once urine is obtained, remove the needle and apply gentle pressure at the insertion site with sterile gauze. Place a sterile dressing at the site of insertion.

The complications include peritoneal perforation with or without bowel perforation. Infection (eg: intra-abdominal, bladder, skin, soft tissues) more likely to occur with indwelling catheter than with simple suprapubic aspiration. Hematuria -usually transient and microscopic, gross hematuria is uncommon.

Indwelling catheters and care

Catheterization is required for a longer period in circumstances like urosepsis, monitoring urine output in sick children, 24 hours urine collection, postoperative or trauma patients, decompression of dilated urinary tracts, urinary retention, etc. Continuous bladder drainage requires a self retaining indwelling catheter. The various sizes and types are mentioned below:

Types and sizes of catheters

- 6Fr, 8Fr 10Fr, 12Fr, 14Fr, 16Fr, 18Fr, 20Fr, 22Fr, 24Fr, 26Fr.
- The higher the number, the larger the diameter of the catheter.
- 1Fr. = 0.33mm (i.e. a 8Fr. catheter is 2.7mm in diameter)

Table I. Age and catheter size

Age	Catheter size
newborn	5 Fr
3months	6Fr
1yr	6-8 Fr
3yr	8Fr
6yr	8-10Fr
8yr	10Fr
10yr	10-12Fr
12yr	12-14Fr
Adolescent	16Fr

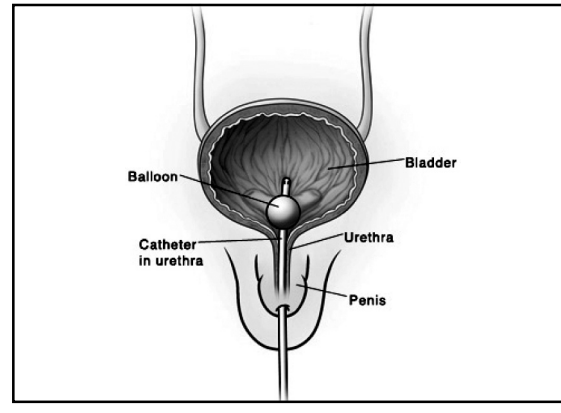


Fig.5. Self retaining Foley catheter

- Catheter sizes are assessed clinically by the weight and build of the child. Smaller size is always enough to drain urine. Table.I. shows an arbitrary size range according to age of the child, but always requirement is individualised.
- Self retaining Foley catheter (Fig.5) has side holes to drain the urine and the tip is smooth to ease the catheterisation. The inflatable balloon seats at the internal urethal meatus

and prevents it from slipping out. Balloon should always be inflated with distilled water as saline might encrust or crystallise in long standing catheters and create difficulty in catheter removal.

- Foley catheter should be inflated only after ensuring complete insertion. If it is inflated halfway, urethral trauma happens with torrential bleed. The inner stylet of the catheter should be removed only after inflating the balloon.
- Foley catheters can be 2 lumen or 3 lumen catheters. One lumen drains the urine through the catheter into a collection bag. The second lumen holds the sterile water when the catheter is inflated and deflates the balloon when water is removed. The third lumen maybe used to instill medications into the bladder or provide a route for continuous bladder irrigation.
- Foley catheter can be latex (commonly used yellow ones) or silicon Foley- transparent white ones. Latex Foley (Fig.6) is the commonly used economical one. This can be used for drainage upto 1 week duration. Longer period of usage causes inflammation, urethritis leading onto stricture urethra later. Children with latex allergy, previous urethral surgeries are safely managed with silicon Foleys.
- Silicone Foley (Fig.7) are transparent white ones with the same principle of drainage. Advantage of this catheter is that it is made of 100% silicone which is completely inert to eliminate tissue irritation or inflammation during long periods of indwelling use. Transparent tube with radio-opaque line, allows it for easy visual inspection and xray confirmation of the position. These catheters can be used for 6-8 weeks safely.

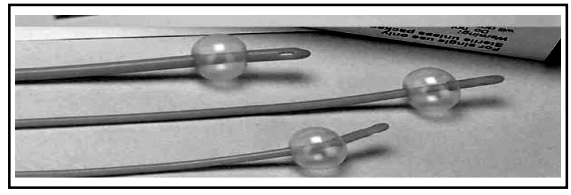


Fig. 6. Latex Foley catheter

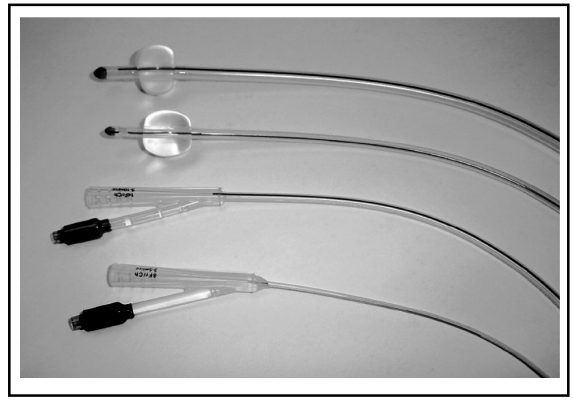


Fig.7. Silicon Foley catheter

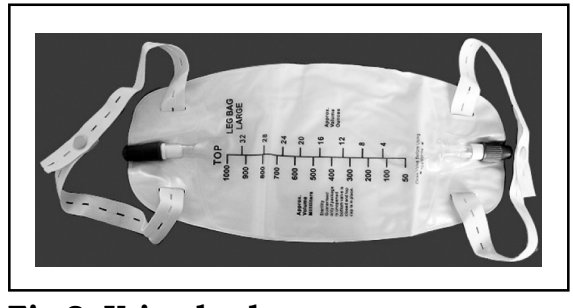


Fig.8. Urine leg bag

- Children can be given bath with the Foley catheters in situ with extra care not to pull the tube inadvertently. After bath, the catheter can be retaped to thigh with a self adhesive tape. If children are too sick to bathe, daily local hygiene is important. The tip of glans or vulva is given betadine wipes once daily to prevent ascending infection from the indwelling catheter.
- If the child is ambulant and attending schools, he can be given leg bags (Fig.8).

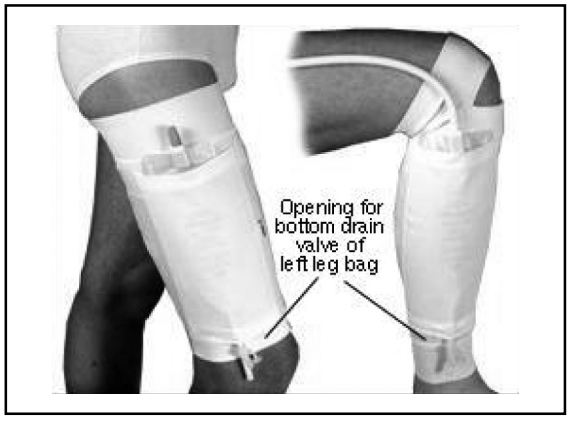


Fig.9. Fabric urine leg bag holder

This is a flexible bag with an inlet for catheter insertion and an outlet for easy letout of urine in school toilet without undressing the straps. The two elastic straps at the top and bottom can be used to tape around the thigh or calf muscle according to the child's comfort and size requirement. This enables them to wear normal school uniforms without being demoralised among the peers.

- If child has to attend any sport activities, the leg bag can be firmly secured using a fabric leg bag holder (Fig.9).
- It is always mandatory that child should be instructed to empty the urine bags once they are one third full which means draining it once in 2-3 hours of time. This will prevent weight of the urine in the urobag from pulling the catheter.

Clean intermittent catheterisation

Clean intermittent self catheterisation (CISC)[2] has been the saviour of renal function in many conditions like neurogenic bladder in meningomyelocele, spina bifida, valve bladder, hinman bladder, detrusor hyperactivity, severe voiding dysfunction or detrusor sphincter dyssynergia. The main principle of the procedure is to reduce the high bladder pressures and its deleterious back pressure effects on kidney - vesicoureteric reflux and renal scarring. This catherisation can be done per via naturalis - sensate urethra or through a continent insensate stoma-Mitrofanoff principle. This warrants high level of patient / parent's compliance in sustaining the CIC in the child's daily routine in order to stabilise the renal function.

The aseptic technique of catheterisation holds good for the patient except that gloves are not used, instead hands are disinfected with only soap and water before the procedure. A clean urine collecting basin is used to collect the urine draining from the catheter. Bladder should be emptied completely, until the flow stops spontaneously. Do not compress the bladder and try to drain urine.

CIC is required 4-6 times a day depending on the nature of the child's condition. If the expenditure of the consumables is a burden to the parents, it is managed by reusing the feeding tubes and urine bags. The used feeding tubes are first cleansed off the urine in running tap water. The intraluminal portion of tube is flushed with syringe of clean tap water or 1:1 diluted betadine solution labelled and kept for the same purpose. Then the tubes are sterilised in two ways, either with hot water or vinegar.

Sterilisation with hot water requires separate vessel for it. As the water comes to boil , heat is turned off and catheter is left in the warm water for 10 minutes. Once cooled, the catheter is removed and left on a clean dry surface to air dry. Similarly white vinegar is utilised in the concentration of 1: 3 along with clean water to sterilise. The catheters are required to soak in the mixture for 30 minutes. Then again the tubes are to be air dried/ sun dried and stored in ziplock pouches or plastic covers. If moisture persists in

Fig.10. Night bottle drain

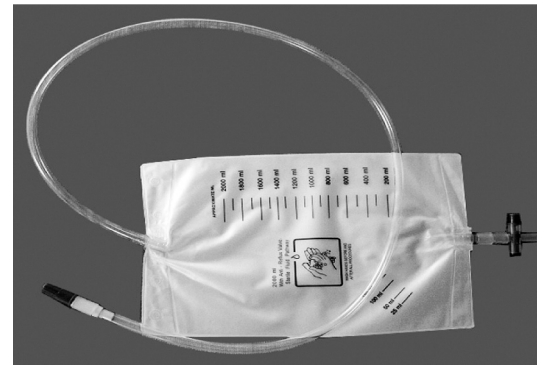


Fig.11. Urobag for continuous night drain

the intraluminal portion of catheter, it promotes fungal colonisation and triggers urosepsis in children using it. These catheters will turn stiff after 4-5 sterilisations and hence a new one is used after that. The urine collection basin also needs similar sterilisation.

CIC is always supplemented by a continuous night time drainage with indwelling catheter which prevents sleep deprivation to do CIC in the night timings. Patients also are more in favour of continuous drain at bedtime without disturbing their daily routine. This involves the same catheterisation which needs a continous drainage into a urobag or night drain bottle (Fig.10). As the feeding tubes are not self retaining ones, they need to be taped to the thigh to avoid slipping out while child is changing position in sleep. Tubes can be anchored to their clothes or bedspread with a napkin pin (pin should go around the catheter and not piercing the catheter). The urobags (Fig.11) nowadays have a tap at the bottom to letout the urine easily. Both the collection devices can be sterilised in the similar way as described earlier. Large drains can be disinfected in chlorine bleach in the dilution of one tablespoon bleach with ten ounces of tap water, soaked for 30 minutes.

Urinary diversions

4(a)Tube diversions-Nephrostomy/ Suprapubic catheters

Urinary diversions can be tube diversions or tubeless diversions. Tube diversions include suprapubic catheter drain and percutaneous nephrostomy drain. The common indications for percutaneous nephrostomy include supravesical obstruction - pelviureteric junction obstruction with septicemia, upper moiety obstruction in duplex kidney, pelvic or ureteric calculus, postoperative edema, ureteric stricture / stenosis, azotemia in a single kidney, stent placements, retroperitoneal fibrosis or malignancies and other individual surgical causes. In an uncertain functional capacity of an obstructed kidney, a percutaneous nephrostomy drainage allows assessment of maximum recoverable renal function to guide the choice between nephrectomy or reconstructive surgery. Percutaneous nephrostomy represents one of the most rewarding therapeutic urinary diversions for

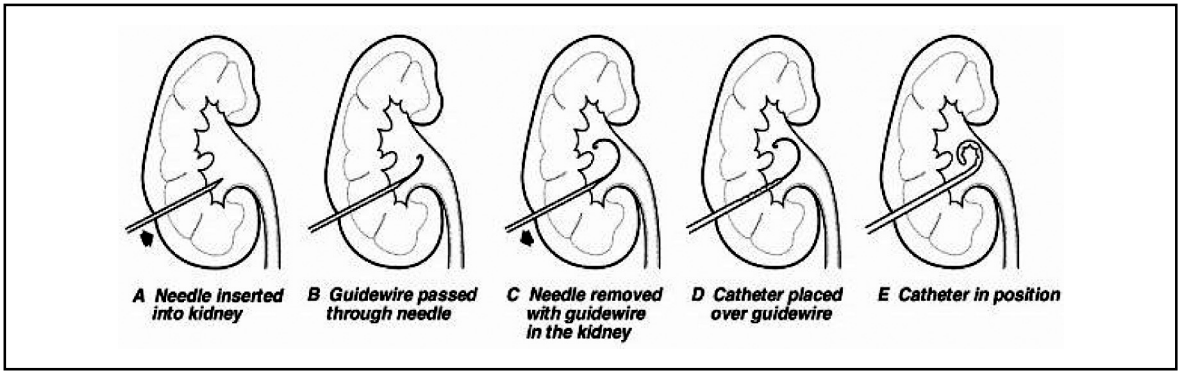


Fig.12. Steps of percutaneous nephrostomy drain insertion (reproduced from uwhealth.org)

surgically unfit patients as a temporary measure. This procedure is safer, quicker, easier and less expensive than surgery.

Percutaneous nephrostomy drain is generally carried out under the guidance of image intensifier (C arm) with contrast instilled in the system with needle. Now a days, ultrasound has become a simpler non invasive modality to guide the site of percutaneous approach for nephrostomy drain. Procedure is done under sedation or short general anesthesia in children.

It is usually safe to introduce the nephrostomy drain by seldinger technique as depicted in the picture (Fig.12). Nephrostomy drains are always self retaining ones - Malecot (flower tip) or Pig tail stent (one sided coil) (Fig.13).

Percutaneous suprapubic cystostomy has long been used for the treatment of acute urinary retention, regardless of cause, when standard urethral catheterization of the bladder is either impossible or contraindicated. Although effective in urgent situations, potential complications after suprapubic cystostomy placement include perivesical hemorrhage, hematuria, bowel injury, perforation of posterior wall of bladder and catheter fragmentation resulting in an intravesical foreign body.

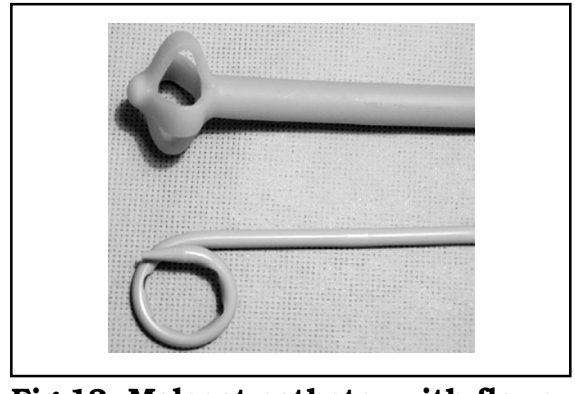


Fig.13. Malecot catheter with flower tip / coiled tip of pig tail catheter

Suprapubic catheters[3] are the same as nephrostomy drains in handling and insertion into the bladder for continuous urine drainage from the bladder.

Foley catheter can be introduced supra-pubically as self retaining - cost effective ones. A special suprapubic trocar is used to puncture the distended bladder for insertion of Foley. Once urine escapes, the inner metal trocar is removed leaving the outer metal sheath inside the bladder. Through the metal sheath, the Foley of required size is inserted into the bladder. After ensuring urine flow, metal sheath is removed and balloon is inflated. This requires formal suturing of the skin opening which is bigger than the Foley because of the metal sheath.

Tube diversions can be retained for 4-6 weeks depending on the need of the child's condition.

4(b)Tubeless diversions and stoma care

Tubeless diversions[4] include vesicostomy and ureterostomy which are incontinent diversions commonly done in children. As the indications and complications of these diversions are beyond the scope of this article, the management of these stomas alone is detailed below.

Vesicostomy was the primary diversion done for newborn in the initial days of posterior urethral valves before valve fulgration at one year of age. As smaller size cystoscopes are available now to tackle posterior urethral valves in newborn period, this procedure has faded away from pediatric urology.

Ureterostomy has gained popularity among pediatric surgeons and nephrologist in stabilising the renal function. Increasing trend in ureterostomies warrants the knowledge of stoma care.

As both stomas are incontinent diversions, stoma management should be taught to the parents well in advance. It is easily handled in infants similar to diaper handling. When the child grows, it is difficult for them to socialise among the peer group because of the odour of urine.

Stoma is always fleshy, moist, painless to handle. Long standing stoma will keratinize (Fig.14) and get the skin colour. Any trivial trauma over the stoma will bleed and it can be arrested by simple saline compression. Child can be given bath with the stoma. Stoma if unwashed with soap and water shows crystallisation or encrustation over it, which needs vinegar douches or washes for one minute to remove the crystals.

Prolapse of stoma, retraction, infection, parastomal hernia, extensive skin excoriation are the complications encountered.

Peristomal excoriation (Fig.15) is very painful and should be attended as day to day problem. Skin around the stoma should be always kept dry. Absorbant dressing like cotton pad, sanitary pads, cotton or mull cloth or diapers should be applied over the stoma to absorb urine. If affordability is a problem, cloth napkins can be used with a lubricant (xylocaine jelly / coconut oil) so that the stoma doesn't bleed on frequent change.

Fig.14. Keratinised ureterostomy stoma with no excoriation

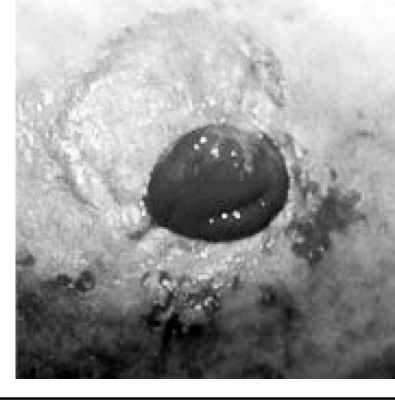


Fig.15. Ureterostomy with extensive peristomal excoriation

Peristomal excoriation[5] should be attended with topical zinc preparations, vitamin E and aloe vera creams which prevent denudation of skin along with protective re-epithelialisation. Severe inflammation require topical steroid preparations. Ulceration with persistent moisture can result in candida growth warranting antifungal applications as well. Few ayurvedic ones like tribala powder / karaya powder,[6] paste or gel (Indian tragacanth) does wonders in some children. Amphogel or milk of magnesia is also used for the purpose. Expensive shields are available in the form of stomadhesive paste[7] which is applied over the peristomal region preventing urine spill onto the skin. It is made of

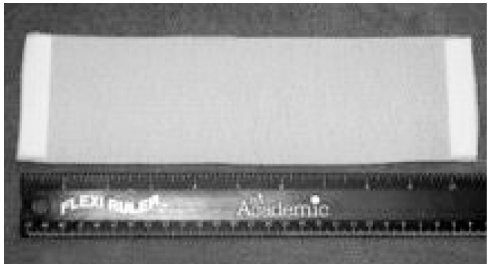


Fig.16. Waist band made individually according to child's abdominal girth at the stoma site with velcro at the ends as shown

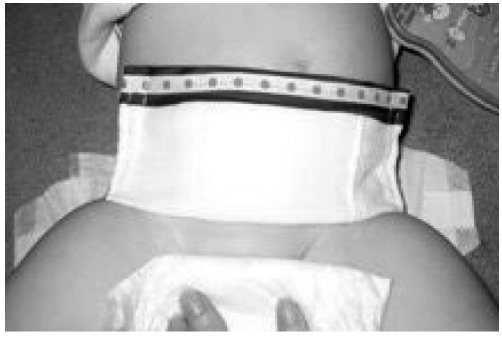


Fig.16a. Waist band secured over a cloth napkin on a vesicostomy

One-piece adhesive system

Figs.17,18,19. Urostomy pouches single system or two piece system is available. Single system has an adhesive in the pouch itself as seen in the right side one. The two piece system has a diaphragm to be adhered on stoma, over which the ring adaptation of the urostomy pouch is available

gelatine, pectin, sodium carboxy methyl cellulose and polyisobutylene which has same pH as skin and protects skin . Topical sucralfate[8] has been tried in few trails which gives pain relief and healing in 2-3 days in few patients.

- Home made cloth napkins along with the waist band (Figs.16 and 16a) to hold the napkin in place should be taught to the parents.Waist band can be prepared with velcro or nappy pins can be applied.
- Grown up children who can attend to their needs have the comfort of urostomy pouches. Though expensive, it can be fixed around the stoma which helps in dry peristomal region , easy emptying of urine as in urobag, quantifying of urine output, odour free in public places with no frequent change of cloth napkins or diapers.
- Urostomy pouches have a common T valve at the end for easy disposal of urine from the bag (Figs.17,18,19). They are available in two models. One is a single system as shown in the right side bag, which has a flexible washable thin bag with a hole for the stoma accommo-dation around which a circumference of adhesive peel is available. Once a day it can be applied after bath and peeled off in toto.
- The two piece system of urostomy bag has a diaphragm as shown above which has to be fitted around the stoma with or without stomadhesive paste. This has a white plastic groove to accommodate the ring fixation from the disposable bags available as shown in the picture. This diaphragm can be retained for 2-3 days or even more by patient compliance on which only the urostomy bags can be dismantled and changed as frequently as necessary. Some patients feel two piece systems are more economical. These urostomy bags can still be sterilized and reused if required.

4(c)Continent diversion-mitrofanoff principle

Permanent continent diversions are required in the pretransplant period for a child in chronic renal failure due to high pressure bladders due to various reasons. This procedure is often clubbed with an augmentation cystoplasty (increase in bladder volume by a segment of intestine or ureter) which increases the bladder capacity and reduces the bladder pressures. This is the protective mechanism for the upper tracts from failing further. This continent diversion is proposed in children who are noncompliant with clean intermittent catheterization through a sensate urethra.

In 1980, Mitrofanoff[9] proposed a technique of creating a insensitive continent urinary channel by tubularised segment of intestine that could be catheterized. The commonest technique is called appendico - vesicostomy which utilizes the appendix as a conduit connecting the skin to the bladder to facilitate catheterization. Variations and refinements of this procedure have since been made by Mitrofanoff and others using alternative conduits such as gastric segments, ileum, and even the ureter and fallopian tube . The appendix still remains the best source of catheterisable continent stoma.

This stoma is usually flushed with the skin level and hence management is quite easy. Clean intermittent catheterization through a insensate conduit is favoured by children as well.

Science and technology are improving day by day to provide better quality of life to pediatric patients. Hence the latest appliances in pediatric urology also finds its way very often in the market with different clinical trials.

Points to Remember

- ***Urine sampling technique has to be instructed properly to the parents.***

- ***Any invasive procedure like catheterization, suprapubic aspiration should be done by the physician himself with informed consent.***
- ***Stoma care / tube diversions should be maintained according to the surgeon's advice.***
- ***Surgeon and physician should work as a team in managing complicated ones with a common advice given to a parent regarding any ailment – As each patient is individualized !***

References

1. Rogers. J, Saunders C. Urine Collection In Infants And Children. Nursing Times, 2008;104: 5, 40–42 .
2. Canning DA. Teaching children Clean Intermittent Self-Catheterization(CISC) in a group setting. J Urol 2011 May;185(5): 1905.Epub 2011 Mar21.
3. Vasdev N, Kachroo N, Mathur S, Pickard R. Suprapubic bladder catheterisation using the seldinger technique. Int J Urol 2007; 5: ISSN: 1528-8390.
4. Merenda LA, Duffy T, Betz RR, Mulcahey MJ, Dean G, Pontari M. Outcomes of Urinary Diversion in Children With Spinal Cord Injuries. J Spinal Cord Med 2007;30:S41–S47.
5. Louise Foulds, Annalyn Manalastas, Specialist Sister, Stoma Care: Stoma Care Guidelines: Guidelines for nurses caring for patients with a stoma, April 2011, royal free hampstead NHS TRUST.
6. Brewster L, Rgn, Dn. Ensuring correct use of skin care products on peristomal skin. Nurs pract Clin Res 2004; 100: 34 .
7. Black P. Peristomal Skin Care: An Overview Of Available Products. Br J Nurs. 2007; 16:1048-1050.
8. Hayashi AhH, Lau HY, Gillis DA. Topical Sucralfate: effective therapy for the management of resistant peristomal and perineal excoriation. J Pediatr Surg 1991; 26:1279-1281.
9. Wilcox DT, Prasad P. Godbole, Koyle MA. Appendicovesicostomy and ileovesicostomy. In: Pediatric Urology: Surgical Complications And Management; Martin Kaefer; Blackwell Publishing Ltd; 2008; pp315-323.

NEWS AND NOTES

National Midterm CME on Airway Disease by

IAP Respiratory Chapter, West Bengal

Date: 29th April, 2012

For details contact

Beladi: IAP Office, Kolkata, India: 9830866712

Dr Subhasis Roy: 9830036761

Dr Pallab Chatterjee: 9830178987

Dr Monideepa Banerjee: 9831170932

NEPHROLOGY

VITAMIN D IN HEALTH AND RENAL DISEASE

**** Ashima Gulati***
***** Arvind Bagga***

Abstract:*Vitamin D is an important prohormone in health and disease. Vitamin D deficiency is common among the normal population as well as in patients with chronic kidney disease. Activated vitamin D, a hormone produced by the proximal convoluted tubule of the kidney, appears to have beneficial effects beyond suppressing parathyroid hormone. In the recent past, there have been numerous reports associating vitamin D with the pathogenesis of various chronic diseases including cancer, hypertension and diabetes. While the benefit of supplementation is known for patients with chronic kidney disease, the role of widespread supplementation in the apparently healthy population remains to be determined.*

Keywords: *Calcitriol, Chronic kidney disease, Deficiency, Supplementation.*

Vitamin D is a prohormone which has been known to play an important role in maintaining calcium and phosphorus homeostasis. There is recent interest in the pathophysiological role of vitamin D in various key regulatory processes related to health. Vitamin D receptors (VDR) exist in a variety of cells and thus there are perhaps many more biological effects than on mineral metabolism alone.[1] While there is improved understanding of the diverse functions of vitamin D, evidence based causal relationship remains to be determined. This review highlights the current understanding of the role of vitamin D in the normal healthy population and in patients with chronic kidney disease (CKD).

* Prof of Pediatrics

** Senior Research Officer,
Department of Pediatrics,
All India Institute of Medical Sciences, New Delhi.

Mechanism of action and metabolism

Vitamin D is a group of fat-soluble prohormones namely vitamin D2 (ergocalciferol; plant derived) and D3 (cholecalciferol; animal derived) compounds and their derivatives. Hydroxylation of vitamin D is required for its biological action and leads to formation of 25-hydroxyvitamin D2 [25OHD2] and 25-hydroxyvitamin D3 [25OHD3] which are known as ercalcidiol and calcidiol, respectively. The production of 25OHD occurs mainly in the liver and is substrate dependent, without any negative feedback control of this step. It is released from the liver and circulates in the blood stream with a biological half-life of approximately 3 weeks. The second hydroxylation by 25- hydroxyvitamin D-1 hydroxylase enzyme leads to the production of 1, 25-dihydroxyvitamin D2 [1, 25$(OH)_2$D2] and 1, 25-dihydroxyvitamin D3 [1, 25$(OH)_2$D3], ercalcitriol and calcitriol respectively (Fig.1). The proximal renal tubule is the major site of 1-α hydroxylation. Circulating 1, 25$(OH)_2$D levels are thus almost exclusively the result of renal production but there is an extra renal component (skin, colon, macrophages, vascular smooth muscle cells, pancreatic β-cells, bone and parathyroid glands) also. The renal conversion

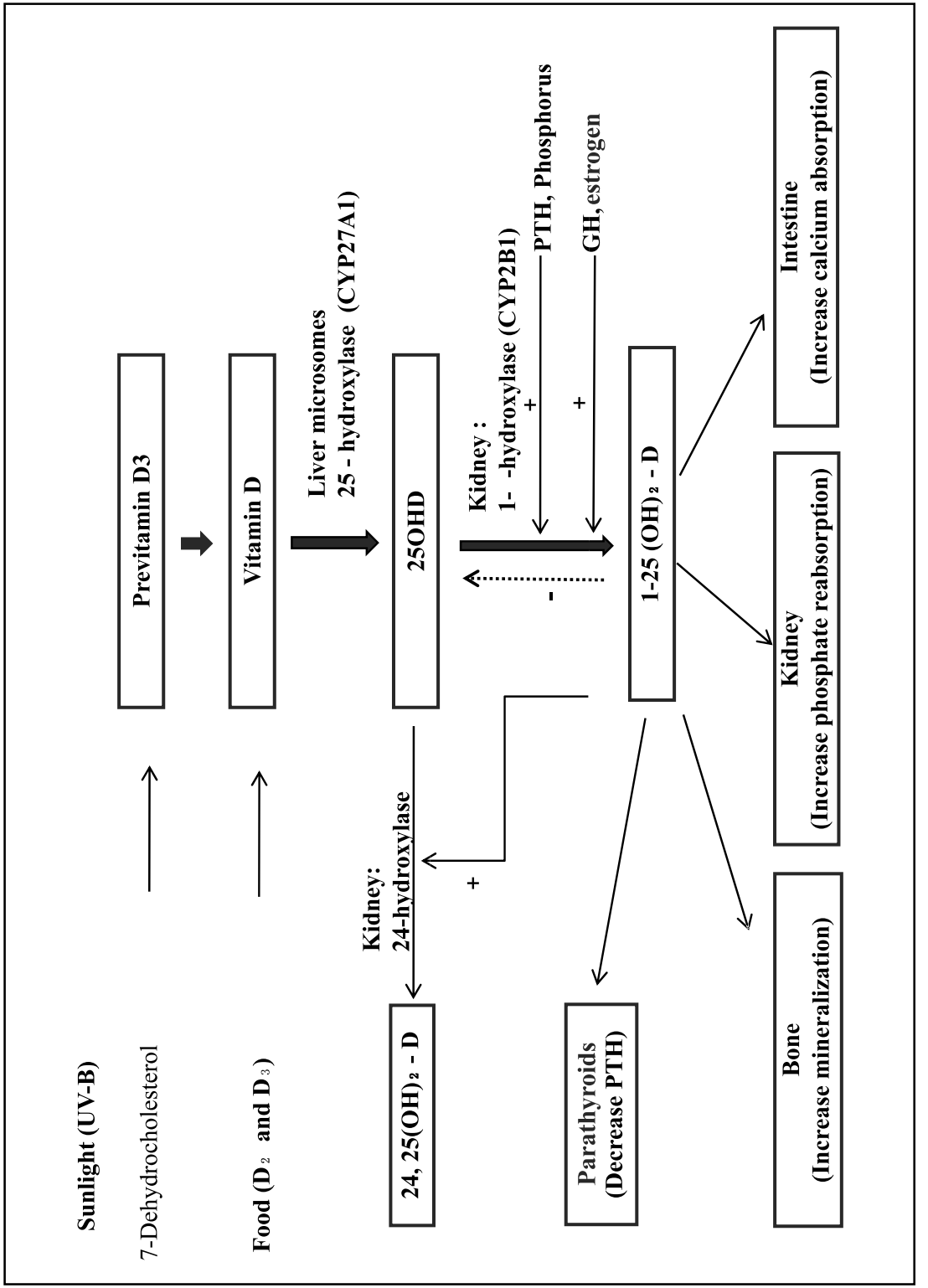


Fig.1. Vitamin D Synthesis and metabolism

of 25OHD to 1, 25$(OH)_2$D is regulated by parathyroid hormone (PTH), calcitonin, calcium and phosphate and is inhibited by calcitriol and the phosphaturic hormone fibroblast growth factor 23 (FGF-23). A negative relationship exists between serum 25OHD and PTH levels. Vitamin D supplementation suppresses serum PTH and increases bone mineral density. The regulatory processes for extrarenal conversion are not clear and this is also not sufficient to maintain adequate circulatory levels of 1, 25 $(OH)_2$D in patients with advanced stages of CKD.

Sources

The major natural source of vitamin D is its synthesis in the skin after exposure to ultraviolet B (UV-B) solar irradiation which has a shorter wavelength (290–315 nm). The concentration of melanin in the skin regulates the amount of UV-B, which penetrates to reach the epidermal layers (stratum basale and spinosum) with the highest concentrations of the substrate, 7-dehydro- cholesterol. While the time required for adequate sun exposure remains to be determined, it depends on skin pigmentation, timing of the day, season and clothing. UVR exposure to the skin is measured as the minimum erythema dose (MED) or the amount of UVR exposure that will cause minimal erythema (slight pinkness) of the skin. The amount of UVR exposure that is equivalent to 1 MED depends on skin pigmentation and duration of exposure is factored into the MED. An entire body exposure to 1 MED is estimated to result in release of 10000 to 20000 IU of vitamin D into the circulation in 24 hours. Exposure of 40% of the body to one-forth MED will result in generation of 1000 IU of vitamin D per day, the minimum amount of vitamin D synthesis necessary to maintain concentrations in the target reference range.[2] Excessive exposure to sunlight does not further increase vitamin D production as previtamin D3 is degraded into inert products such as lumisterol-3 and tachysterol-3, and vitamin D3 photo isomerizes to suprasterol and other inert products.

Dietary vitamin D usually accounts for 5-10% of the total vitamin D. The most significant dietary sources are fish and fish oils, egg yolk, supplemented cereals and margarine. The amount in most vegetable sources is negligible and in the absence of food fortification policies dietary intakes can be low.

Vitamin D adequacy and deficiency

Sufficient vitamin D levels are required to optimize calcium absorption from the gut with up to 30-50% of calcium getting absorbed and also for maximal reabsorption of phosphate. The best index describing the body vitamin D status is the concentration of the hepatic metabolite, 25OHD in the serum. This is because the production of 25OHD does not have a negative feedback mechanism and it is not stored in liver to any significant extent. The second hydroxylation is a tightly regulated step and its product, 1, 25$(OH)_2$D normally circulates at concentrations that are 100- to 1000-fold less abundant than 25OHD and has a short half-life of 4-6 hours.

There is no consensus on an optimal serum level of 25OHD. The most widely accepted reference ranges for serum 25OHD concentrations define vitamin D deficiency as a serum level <15 ng/mL and insufficiency as 15-20 ng/mL. While 25OHD levels >20 ng/mL are indicative of vitamin D sufficiency, levels >30 ng/mL are considered optimal for calcium handling.[3] These reference ranges are based on studies correlating 25OHD levels with calcium absorption and bone density. To be universally applicable, 25OHD assays need to be accurate, reproducible and internationally standardized. Although serum levels of 25OHD reflect

nutritional intake and endogenous synthesis, there is seasonal, geographic, ethnic and age-related variation in levels. Variation in collection and processing of samples and the type of assay can also affect measurement of vitamin D. The current definitions of vitamin D status do not take these factors into consideration. The implication of low vitamin D levels in a significant proportion of normal individuals and the reason for inter-individual variations is not clear.

Vitamin D deficiency is a significant healthcare problem in children. Observational studies have demonstrated that vitamin D insufficiency is widespread in the apparently healthy normal population. Clinical and subclinical vitamin D deficiency is common in all age groups in India with up to 70% of subjects from rural areas and 87% of urban Indians showing low 25OHD levels.[4,5] Risk factors for vitamin D deficiency include premature birth, skin pigmentation, low sunshine exposure, obesity, malabsorption, advanced age, renal and liver disease and anticonvulsant use. Different stages of vitamin D deficiency manifest as biochemical perturbations of varying severity. Less severe vitamin D deficiency causes an increase of serum PTH leading to bone resorption, osteoporosis and fractures. Rickets in children and osteomalacia in adults are the classic manifestations of profound vitamin D deficiency.

Extraskeletal effects of vitamin D including cardiovascular disease, type 2 diabetes, several cancers and autoimmune conditions have recently been associated with vitamin D insufficiency.[1] The role of vitamin D in renin regulation, podocyte function and limiting proteinuria has also been shown. However these observations mainly imply associations and well designed randomized controlled trials are needed to establish a truly causal relationship.

Vitamin D requirement and supplementation

Recent recommendations from the American Academy of Pediatrics state that all infants, children and adolescents should receive a minimum daily intake of 400 IU (10 μg) of vitamin D beginning soon after birth. A recent report from the Pediatric Endocrine Society in US reviewed recommendations for sun exposure and vitamin D intake.[2] The Society opined that vitamin D should be supplemented in all children beginning in infancy as breast milk is deficient in vitamin D. Current recommendations for vitamin D intakes do not take into account skin pigmentation or the effects of geography. Dietary requirements for vitamin D may be higher in northern latitudes, especially in winter and it is for this reason that the Canadian Pediatric Society recommends 800 IU/day of vitamin D for breastfed infants during the winter months. These recommendations for vitamin D supplementation are based on achieving levels so as to prevent rickets and osteomalacia but have no correlation with the other possible functions of vitamin D. A vitamin D intake of 400 IU/day will only cause a modest increase in 25OHD levels by 2.8–4.8 ng/mL.[3] These recommendations in the absence of skin synthesis will however not provide an optimal status and would also be insufficient to treat vitamin D deficiency. Individuals with vitamin D deficiency need higher daily supplementation, up to 3000-6000 IU/day.

Both vitamin D2 (plant derived) and D3 (animal derived) are used in supplements. Vitamin D supplements with 200 to 1000 IU per tablet are available. Several therapeutic options are available to correct vitamin D deficiency, including pro-hormones [ergocalciferol (D2) and cholecalciferol (D3)] and active hormones (calcitriol). Though there is some evidence that

D3 might be more efficacious than D2, there is no conclusive benefit of recommending one over the other. Vitamin D therapy is necessary for infants and children who manifest vitamin D deficiency or rickets. Treatment regimens vary from 600,000 IU of D2 or D3 as a single dose every 3 months (Stoss regimen), 2000–4000 IU daily for 3-6 months or 50,000 IU three times per week. While all these regimens have been shown to increase circulating 25OHD levels, regimens using at least 600,000 IU ergocalciferol are favorable as they achieve adequate 25OHD levels.

Alfacalcidol (1α-hydroxycholecalcidol) and active hormones (calcitriol) are inappropriate for routine supplementation as they do not replace vitamin D stores. They should only be used when there is an abnormality in renal hydroxylation of vitamin D, 1-α hydroxylase deficiency and in patients of CKD with raised PTH.

Toxicity

Vitamin D in its active form, especially calcitriol is a highly potent molecule capable of producing toxic effects. Though there is a comfortable margin of safety between the intakes required for optimization of vitamin D status and those associated with toxicity, vitamin D has a therapeutic window with hypercalcemia being associated with 25OHD levels >150 ng/mL. Individuals with 25OHD levels >100 ng/mL are usually considered to have vitamin D excess and are at risk for vitamin D intoxication[3].

Vitamin D and Chronic kidney disease (CKD)

Vitamin D deficiency is widely prevalent in patients with CKD and may contribute to mineral bone disease. It has been shown that up to 99% of adults with CKD stages 4-5 in north India have vitamin D insufficiency.[6] A prospective study examining the effect of cholecalciferol supplementation in children with CKD showed that vitamin D insufficiency is highly prevalent in children with CKD stages 2-4 with only 11.9% having 25OHD levels >30 ng/mL. Further, 45.2% patients had levels between 16 and 30 ng/mL, and 42.8% had levels <16 ng/mL with severe deficiency (25OHD <5 ng/mL) seen in three patients.[7] Median 25OHD levels increased significantly following high-dose (600,000 IU) cholecalciferol supplementation. The study showed that high-dose cholecalciferol is safe and effective in correcting vitamin D insufficiency and results in a significant reduction in PTH levels in vitamin D-insufficient children with CKD.

Patients with CKD are much more likely to have low levels of 25OHD due to decreased exposure to sunlight, low endogenous synthesis of vitamin D3 in the skin and reduced intake of foods that are natural sources of vitamin D and urinary or peritoneal dialysis fluid loss of vitamin D binding protein and vitamin D metabolites.[8] Reduced serum 25OHD levels result in secondary hyperparathyroidism in individuals with normal kidney function and may aggravate it in those with decreased kidney function. Progressive loss of intact renal parenchyma, low 25OHD levels and increased FGF-23 release from the bone result in low circulating $1,25(OH)_2D3$ levels and thus reduced intestinal calcium absorption and hypocalcemia. Subsequently, plasma PTH levels increase to maintain calcium homeostasis and to stimulate 1- α hydroxylase. Hence, in the presence of hyperparathyroidism even normal levels of $1, 25(OH)_2D3$ must be considered inappropriately low.

Abnormalities of 1, 25(OH)$_2$D metabolism in CKD

When the GFR falls to <50 ml/min/1.73 m^2, the kidney cannot convert 25OHD to $1,25(OH)_2D$. This is because of reduced renal mass and low availability of 1-α hydroxylase.

Raised phosphate and FGF-23 further downregulate renal 1-α hydroxylase which is already suppressed in an acidic and uremic milieu. Secondary hyperparathyroidism depletes body stores of vitamin D by promoting the enzyme 24,25-dihydroxy vitamin D to cause rapid degradation of 25OHD. The low levels of $1,25(OH)_2D$ in CKD patients have even lower biological effects as the binding of VDR to the response element in the DNA is compromised in uremia and may account for the resistance to vitamin D therapy seen in CKD patients.

Supplementation and monitoring in CKD

The doses of ergocalciferol or cholecalciferol required to correct vitamin D insufficiency and to maintain normal plasma levels have not been established in children with CKD. Opinion based guidelines from the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI) recommend that in children with CKD stages 3-5, serum 25OHD levels be measured once a year and supplementation with ergocalciferol or cholecalciferol is required if the serum level is <30 ng/mL (Table I). The use of active vitamin D analogues is only recommended if PTH levels are raised in pre-dialysis CKD patients. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines, have only suggested the use of vitamin D analogues for the treatment of secondary hyperparathyroidism in predialysis CKD[9]. Vitamins D2 (ergocalciferol) and D3 (cholecalciferol) can be used interchangeably in most treatment regimens and there are no recommendations to favor one over the other. There are also no recommendations for the combined use of ergocalciferol or cholecalciferol with active vitamin D analogs.

Table.I. Oral cholecalciferol supplementation in CKD[1]

Blood 25OHD level	Severity of deficiency	Oral Calciferol dose* [IU]		Frequency of administration	Duration of administration
<5 ng/mL	Severe	Initially	60000	Weekly	4 weeks
	deficiency	Later	60000	2 times a month	2 months
5-15 ng/mL	Mild deficiency	60000		2 times a month	3 months
16-30 ng/mL	Insufficiency	60000		Once a month	3 months
>30 ng/mL		1000-2000		Daily maintenance	

* Daily maintenance with 1000-2000 continued; available cholecalciferol preparations [CALCIROL™, CALDIKIND™, PHOSITE™, D-GAIN™, D3-60™] contain 60 000 IU per sachet

[1] K/DOQI guidelines accessed at www.kidney.org 17 May 2011

Therapy with active forms of vitamin D (calcitriol) is started if hyperparathyroidism persists despite lowering of serum phosphorus to below 5.5 mg/dL. In patients with CKD stages 2-4, such therapy should be considered only if these abnormalities persist despite repletion of 25 OHD levels (>30 ng/mL). The dosing of 1, 25$(OH)_2$D in patients with CKD stage 2-4 is based on body weight: <10 kg: 0.25 µg twice a week; 10-20 kg:0.25 µg on alternate days, >20 kg: 0.25 µg daily. In patients on dialysis, the dose is titrated to serum PTH levels: 300-500 pg/mL: 0.0075 µg/kg (maximum dose 0.25 µg/day), 500-1000 pg/mL: 0.015 µg/kg (maximum 0.5 µg/day); >1000 pg/mL: 0.025 µg/kg (maximum 1 µg/day).

Close monitoring and frequent dose adjustments are required while patients are receiving active forms of vitamin D. In patients with CKD stages 2-4, serum calcium and phosphate should be measured monthly for the first 3 months, and every 3 months thereafter. In patients with CKD stage 5, these levels are measured every 2 weeks for 1 month and then monthly thereafter. Blood PTH level should be measured every 3 months. Determinations of plasma 1, 25$(OH)_2$D concentration are expensive, and provide limited information as they have not yet been correlated with the incidence of hypercalcemia or vascular calcifications in CKD patients. However they may be occasionally helpful to demonstrate or rule out nonadherence to calcitriol therapy.

The mode of calcitriol administration whether intermittent or daily is of minor importance. Prospective randomized studies comparing daily versus intermittent oral calcitriol in healthy children and children with CKD stages 2-4 did not reveal any differences in PTH suppression, or in intestinal calcium absorption, the incidence of hypercalcemia and hyperphosphatemia or longitudinal growth rates.[10] The response to calcitriol depends on the degree of secondary hyperparathyroidism and hyperphosphatemia and on the degree of parathyroid gland autonomy. Active vitamin D treatment increases not only the intestinal absorption of calcium but also of phosphate and therefore calcitriol use is often limited by hyperphosphatemia and hypercalcemia which contribute to extraosseus tissue calcifications and decreased survival in children with end stage renal disease. With prolonged treatment there is a risk of developing adynamic bone disease which is associated with a reduced growth rate and frequent episodes of hypercalcemia.

Synthetic vitamin D analogs have been developed to reduce intestinal calcium and phosphate absorption at equipotent PTH suppressive action. These are 22-oxacalcitriol, 19-nor-1, 25 dihydroxyvitamin D2 (paricalcitol), and 1α-hydroxyvitamin D2 (doxercalciferol). Treatment with these is associated with a more rapid achievement of PTH control and fewer episodes of sustained hypercalcemia and increased calcium-phosphate product than calcitriol therapy in adult hemodialysis patients. However there is very limited pediatric experience with these compounds.

Vitamin D and reduction of proteinuria

Active vitamin D has been shown to inhibit multiple pathogenic pathways in renal fibrosis including down-regulation of renin-angiotensin system by inhibiting renin production. There is recent interest in the potential role of vitamin D and its analogues in the reduction of proteinuria and consequently retardation of the progression of CKD. Recent trials have shown a promising effect of vitamin D in ameliorating proteinuria in rat and human models. The antiproteinuric effect of paracalcitol was shown in a double blind randomized controlled trial in patients with CKD stage 3 and 4. The study showed a reduction of

proteinuria in 51% patients in the paracalcitol group as compared to 25% in the placebo group.[11]

Vitamin D and survival in CKD patients

There is adult data to support the effect of vitamin D deficiency on survival in CKD patients. Large epidemiological studies on hemodialysis (HD) patients have shown that vitamin D deficiency adversely affects all-cause and cardiovascular mortality. It has been shown that HD patients receiving any activated vitamin D treatment have a 25% survival advantage.[12] Further, the survival advantage of vitamin D has been shown irrespective of calcium, phosphorus and PTH levels suggesting that vitamin D has important effects beyond its role in mineral metabolism. However, all of these studies are non-randomized and so far only suggest rather than provide any robust evidence of survival advantage.

Conclusions

While the utility of routine vitamin D supplementation in the apparently normal population needs to be determined, vitamin D sterols are indispensable therapeutic agents in the management of CKD with beneficial effects not only on the bone but also on cardiovascular and potentially other systems. There is observational evidence for a survival benefit associated with the use of vitamin D sterols in general. This may be related to the beneficial immunologic and cardiovascular effects of active vitamin D compounds. However these observations need to be proved in prospective trials.

Points to Remember

- ***Vitamin D functions in the body through an active circulating hormone, calcitriol (1, 25 dihydroxy vitamin D).***
- ***The best index describing the body vitamin D status is the concentration in blood of the hepatic metabolite, calcidiol (25-hydroxy D) in the serum.***
- ***Optimal blood levels of 25-hydroxy D are required for the functioning of vitamin D.***
- ***While dietary vitamin D usually accounts for 5-10% of the total vitamin D, the major source is its synthesis in the skin.***
- ***Vitamin D deficiency is widely prevalent in population studies and in patients with chronic kidney disease.***

References

1. Holick MF. Vitamin D: a D-lightful health perspective. Nutrition Rev2008; 66:S182-S194.
2. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 2008; 122:398-417.
3. Pearce SH, Cheetham TD. Diagnosis and management of vitamin D deficiency. Br Med J 2010; 340: b5664.
4. Goswami R, Marwaha RK, Gupta N, Tandon N, Sreenivas V, Tomar N, et al. Prevalence of vitamin D deficiency and its relationship with thyroid autoimmunity in Asian Indians: a community-based survey. Br J Nutr 2009; 102:382–386.
5. Goswami R, Kochupillai N, Gupta N, Goswami D, Singh N, Dudha A. Presence of 25(OH) D deficiency in a rural North Indian village despite abundant sunshine. J Assoc Physicians India 2008; 56:755–757.
6. Jabbar Z, Aggarwal PK, Chandel N, Kohli HS, Gupta KL, Sakhuja V, et al. High prevalence of vitamin D deficiency in north Indian adults is exacerbated in those with chronic kidney disease. Nephrology (Carlton) 2009;14: 345-349.

7. Hari P, Gupta N, Hari S, Gulati A, Mahajan P, Bagga A. Vitamin D insufficiency and effect of cholecalciferol in children with chronic kidney disease. Pediatr Nephrol 2010;25: 2483-2488.
8. Shroff R, Knott C, Rees L. The virtues of vitamin D-but how much is too much? Pediatr Nephrol 2010;25:1607–1620.
9. KDIGO Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease Related Mineral and Bone Disorders (CKD-MBD). Available at: http://www.kdigo.org/clinical practice guidelines1.php. accessed 17 May 2011.
10. Geary DF, Hodson EM, Craig JC. Interventions for bone disease in children with chronic kidney disease. Cochrane Database Syst Rev 2010;20:CD008327
11. Agarwal R, Acharya M, Tian J, Hippensteel RL, Melnick JZ, Qiu P, Williams L, Batlle D. Antiproteinuric effect of oral paricalcitol in chronic kidney disease. Kidney Int 2005;68:2823-2828
12. Wolf M,Betancourt J, Chang Y, Shah A, Teng M, Tamez H,et al. Impact of activated vitamin D and race on survival among hemodialysis patients. J Am Soc Nephrol 2008; 19: 1379-1388.

CLIPPINGS

Bharat Ramakrishna, Stephen M Graham, Ajib Phiri, Limangeni Mankhambo, Trevor Duke. Lactate as a predictor of mortality in Malawian children with WHO-defined pneumonia. Arch Dis Child Jan 2012.

The study was done to determine whether blood lactate measured at the time of presentation to hospital predicted outcome in children with pneumonia in Malawi and to understand the factors associated with high blood lactate concentrations in pneumonia.

Analysis of data was done from a prospective study of children presenting to Queus Elizabeth Central Hospital, Blantyre, with WHO-defined severe or very severe pneumonia. Multivariate analysis showed that hypoxemia, hyperlactataemia and age < 12 months were independent risk factors for death from pneumonia.

Used in conjunction with clinical risk factors and pulse oximetry for measuring oxygen saturation, lactate could play an important role in identifying the sickest patients with pneumonia in developing countries.

NEWS AND NOTES

PG CME ON DEMONSTRATION OF CLINICAL SKILLS

Date: 4thMay, 2012

Venue: Kanchi Kamakoti CHILDS Trust Hospital, Chennai

For details contact

Mrs.Pechiammal 044-42001800 ext 159, **Dr.Janani Sankar** 9841078101

NEPHROLOGY

APPROACH TO RENAL TUBULAR DISORDERS

**** Mehul A Shah***

Abstract:*Renal tubular disorders are not uncommon and can be due to a genetic / inherited defect or an acquired cause. The most common presenting feature is failure to thrive characterized by delayed physical milestones and growth. In majority of children, a carefully obtained detailed history along with focussed physical examination findings and selected, not so expensive, investigations can confirm the type of renal tubulopathy. Treatment is often easy, affordable and improves the condition in a significant number of patients. If untreated or with delayed diagnosis, renal tubulopathies can cause significant morbidity as well as mortality.*

Keywords:*Renal tubular disorder, Tubulopathy, Renal tubular acidosis.*

The human kidney has several important functions including excretion of solutes (waste products such as urea, creatinine, organic acids, uric acid, etc), regulation of electrolyte and acid-base balance and synthesis of hormones such as renin, active Vit D, prostaglandins and erythropoietin. To achieve the primary function of waste excretion, we need to have high glomerular filtration rate of 100 mL/min/1.73 m^2 (that translates in to 100 x 1440 mins/day = 144000 mL i.e. 144 Liters of ultrafiltrate is generated at the level of Bowman's space every day). The electrolytes present in the ultrafiltrate have to be reabsorbed leaving behind the unwanted waste solutes. This reabsorption of electrolytes is achieved by various segments of the renal tubules. The renal tubule is responsible for the reabsorption of more than 99% of the water and sodium in the ultrafiltrate. Approximately 65% of sodium and water is reabsorbed by the proximal tubule, 25% by thick ascending limb of Loop of Henle, 5% by distal convoluted tubule and 2-3% by the cortical collecting tubule. The renal tubule also has to regulate acid-base balance, mineral homeostasis, and the excretion of organic acids and drugs. To fulfill these functions, a large number of specialized transporters and channels are specifically located in the tubular cell membranes, some on the apical and others on the basolateral side (interstitial side). In the past decade and a half, advances in the molecular genetic research have enabled us to identify the structure, function and effects of mutations in these transporters. These gene mutations result in a variety of functional defects in the transporter/channel proteins, including decreased activity, impaired gating, defective trafficking, impaired endocytosis and degradation or defective assembly of the channel subunits. A number of clinical disorders of renal tubules were described several decades earlier such as Bartter's syndrome, renal tubular acidosis (RTA), Liddle's syndrome, etc. but the underlying defect in the specific transporter was identified only in the past decade.[1, 2] The identification of the molecular defects in inherited tubulopathies has

* Consultant Pediatric Nephrologist,
Apollo Hospitals and
Little Stars Children's Hospital, Hyderabad

not only solved the puzzle of confirming the patho-physiology of several disorders but may also provide a basis for future design of targeted therapeutic interventions and possibly, strategies for gene therapy of these complex disorders.

Most renal tubular disorders are due to a genetic / inherited defect in one of the transporter protein usually transmitted as an autosomal recessive mode (Renal tubular disorder, Bartter's syndrome, Nephrogenic diabetes insipidus, DI, Inherited rickets, Liddle's syndrome, etc) (Table I) and occasionally due to an acquired cause such as medications (Ifosphamide, Cysplatin, Amphotericin B, Lithium, etc), obstructive uropathy (Posterior urethral valves, Neurogenic bladder) or auto-immune disorders (such as SLE, Sjogren's syndrome). The presentation of these tubular disorders is usually non-specific, with failure to thrive being the most common feature. They are associated with profound morbidity as well as mortality. Morbidity can be minimized by early diagnosis and prompt treatment which is not only effective but also inexpensive in most cases.

When to suspect renal tubular disorders?

The following features can be pointers towards renal tubulopathy:

1) Failure to thrive (FTT) is the sine qua non of salt wasting renal tubulopathies which constitute a majority of renal tubular disorders. FTT defined as inadequate weight and height gain (most children are below the 5th percentile on growth chart especially height) is due to several factors including chronic intravascular volume depletion related to NaCl wasting, chronic metabolic acidemia, and poor intake of proteins and calories. Decreased appetite is related to metabolic acidemia, vomiting, and polydipsia that makes children fill up the stomach with water.

2) Delayed physical milestones and weakness: This is related to hypokalemia, hypomagnesemia, chronic volume depletion and muscle wasting with chronic metabolic acidemia.

3) Polyuria: Polyuria is defined as excessive urine output, usually greater than 4 mL/kg/hour and is caused by increased NaCl loss that carries water along with it or diabetes insipidus (related to primary defect or secondary to hypokalemia, and hypercalciuria). Polyuria has to be differentiated from frequent urination seen in children with UTI's, voiding dysfunction, or physiological in infants due to small bladder capacity. A child with polyuria will continue to void large volumes of urine at night (associated nocturia) and will have polydipsia (volume contraction stimulates thirst center that increases water intake). In contrast, children with voiding dysfunction / UTI's will usually sleep through the night with out waking up to void urine or drink water. For practical purpose, absence of nocturia and polydipsia usually rules out polyuria.

4) Polydipsia: The average physiologic intake of 1500 mL/m^2/day of water is required to replace loss of water through urine, skin, GI and respiratory tract. Polydipsia is defined as increased intake of liquids > 3000 mL/m^2/day. It is characterized by increased irritability in infants (that resolves after feeding water) and drinking of liquids even at night time. Nocturnal polydipsia is always significant and pathological as compared to polydipsia during daytime alone could be due to behavioral or excessive dilution of bottle feeds.

In children, polyuria is usually the primary event (due to renal tubulopathy) and polydispia follows polyuria due to increased thirst. Primary or psychogenic polydipsia causing secondary polyuria is uncommon in children.

Table.I. Some of the common renal tubular disorders[1,2,4]

Renal Tubular Disease	*MOI*	*Characeteristic features*	*Gene product*	*Tubule segment*	*Manage-ment*
Proximal RTA	AR	Proximal RTA with extrarenal abnormalities	CA2, cytosolic carbonic anhydrase; SLCA4A,NaHCO3 cotransporter (on basolateral membrane)	PT	Oral Bicarbonate, Potassium, Thiazides
Bartters's syndrome	AR	Hypokalemic, metabolic alkalosis, hypercalciuria, polyuria, polydipsia, failure to thrive	NKCC2; ROMK; ClCKb; Barttin	mTAL, + DCT	Oral KCl, Oral salt, Indomethacin /COX2 inhibitor
Gitelman syndrome	AR	Delayed presentation, weakness, hypokalemia, mild metabolic alkalosis, hypomagnesemia	Thiazide sensitive NaCl cotransporter on apical membrane	DCT	KCl, Magnesium supplements
Liddle syndrome	AD	Hypertension, hypokalemia, mild metabolic alkalosis	ENaC, Sodium channel on apical membrane (Gain of function mutation)	CCD	Amiloride, Salt restricted diet
Pseudo-hypoaldosteronism Type1a (renal limited)	AD	Failure to thrive, salt wasting state, hyponatremia, hyperkalemia	Minerlaocorticoid receptor	CCD	High Salt intake, K binding resins
Pseudo-hypoaldosteronism Type 1b (systemic)	AR	Failure to thrive, salt wasting state, hyponatremia, hyperkalemia, respiratory infections	ENaC, Sodium channel on apical membrane (Loss of function mutation)	CCD, colon, skin, lungs	High salt & low K diet, K binding resins
Distal RTA	AR AR	FTT, features of RTA, hypokalemic, hyperchloremic, metabolic acidosis +/- deafness	Vacuolar H-ATPase on apical membrane Anion Exchanger 1 protein on Basolateral membrane	CCD	Oral bicarbonate + Potassium (Potassium citrate)
Diabetes Insipidus	AR AR/AD	Polyuria, polydipsia, FTT, recurrent fever, seizures	AVP2 receptor AQP2 Aquaporin-2 channel	CCD	Unrestricted intake of water, low salt diet, Thiazides

[AR: Autosomal Recessive, AD: Autosmomal Dominant, XR: X linked Recessive, PT: Proximal Tubule, mTAL: medullary Thick Ascending Loop of Henle, DCT: Distal Convoluted Tubule, CCD: Cortical Collecting Duct, ENaC: Epithelial Sodium Channel]

5) Resistant rickets: Rickets not responding to 1 or 2 doses of Vitamin D3 (3 lacs units) or rickets associated with failure to thrive/polyuria/ polydipsia or in siblings should always make one look for underlying renal tubulopathy (RTA, Hypophosphatemic rickets), Vitamin D Dependant rickets or chronic kidney disease (PUV).

6) Unexplained hypertension, especially when diagnosed at an early age, associated with hypokalemic, metabolic alkalosis and with strong

family history of hypertension especially in young members should make one suspect underlying monogenic forms of hypertension (such as Liddle's syndrome, Syndrome of Apparent Mineral Corticoid Excess (AME).

Approach to a child with suspected renal tubulopathy

As with any other medical problem, evaluation of a child with renal tubular disorder begins with a carefully obtained, detailed history followed by physical examination and appropriate investigations to confirm the disorder.[3]

1) History: The most common complaint with which a parent approaches the pediatrician is failure to thrive / "my child is not growing". Often, the inadequate growth is present since early infancy. The other specific complaints that needs to be enquired about include:

a) Polyuria

b) Polydipsia

c) Constipation (due to volume depletion, hypokalemia, hypoamagnesemia)

d) Episodic weakness (hypokalemia)

e) Gross hematuria and recurrent UTI's (due to hypercalciuria observed in dRTA and Bartter's syndrome)

f) Seizures and recurrent fevers (with hypernatremic dehydration in Nephrogenic Diabetes Insipdus)

g) Antenatal and birth history: Enquiry about amniotic fluid index (polyhydramnios is suggestive of fetal polyuria as observed in some forms of Bartter's syndrome and Nephrogenic diabetes insipidus) and premature delivery (due to polyhydramnios) can be important pointers towards fetal polyuria.

h) Family history of similar complaints in siblings, renal stones and hearing impairment.

2) Physical examination: The following specific points on physical examination have to be observed:

a) General appearance: Most children with renal tubulopathy have volume depletion and appear "dehydrated" with sunken eyes as well as malnourished with muscle wasting (Fig.1). Bartter's phenotype is characterized by sunken eyes, triangular facies and small lower jaw.

b) Weight and height percentiles (often below 5th percentile). A child with height above the 5th percentile is less likely to have an inherited / genetic tubular disorder

c) Blood pressure: Majority of children with tubulopathy will have salt wasting and hence, BP would be low normal. Rare causes of hypertension (monogenic) such as Liddle's syndrome will have hypertension (Stage II).

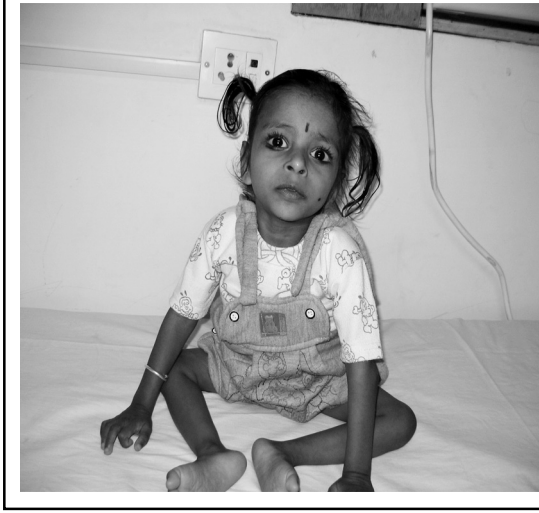


Fig.1. 3 year boy with nephrogenic diabetes insipidus

d) Rickets: Generalized signs of rickets including frontal bossing, rachitic rosary, pot-belly, widened wrists and genu deformity can be observed in children with dRTA or Vitamin dependant rickets. Children with hypophosphatemic rickets usually have signs of rickets limited to lower limbs and develop the changes after 1-2 years of age (related to increased phosphate loss with physiological increase in GFR).

e) Abdomen should be examined for presence of renal or bladder mass in boys with posterior urethral valves

f) Ambiguous genitalia and hyperpigmentation of skin are noted in children with salt-wasting congenital adrenal hyperplasia (CAH).

g) Generalized hypotonia due to hypokalemia, hypomagnesemia, hypophosphatemia, and associated nutritional Vitamin D dediciency, is very often present and contributes to the delay in physical milestones.

3)Investigations: Following simple, inexpensive, and easily available investigations help in confirming renal tubulopathy (Fig.2).

a) Complete urine examination: First morning, freshly collected, urine sample for physical and microscopic examination is the first step in evaluation.

Specific gravity: Most children with salt wasting tubulopathy and chronic kidney disease due to PUV will have hyposthenuric specific gravity of < 1010 (dilute urine, corresponding to urine osmolality of < 300 mOsm/Kg H_2O related to impaired medullary concentration gradient as well as hypokalemia related secondary nephrogenic diabetes insipidus). In contrast, children who can concentrate their urine and have

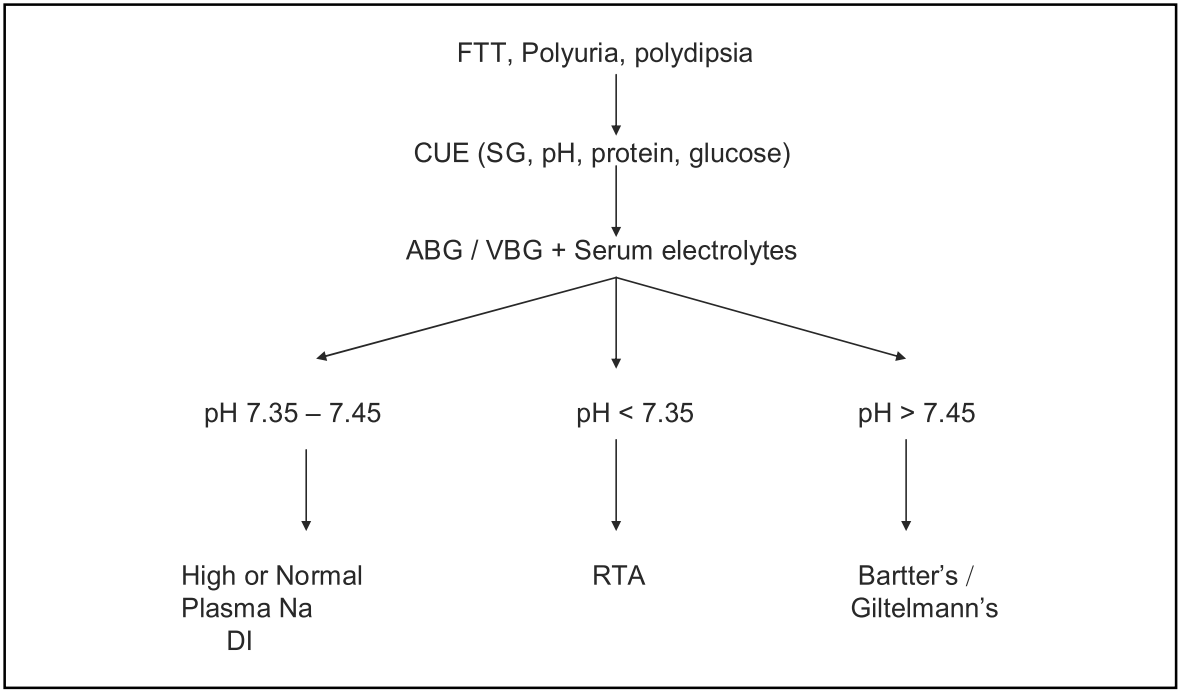


Fig.2. Approach to suspected tubulopathy

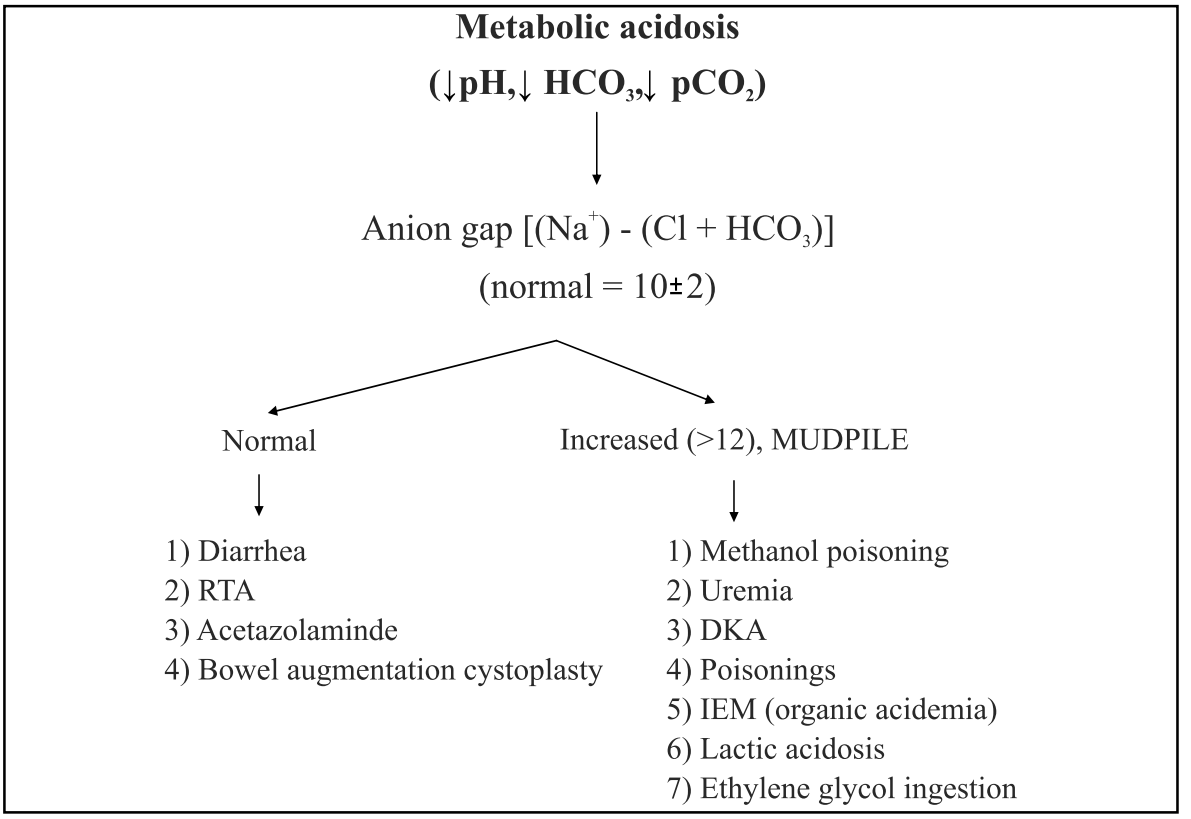


Fig.3. Differential diagnosis of metabolic acidosis

a specific gravity of > 1020 usually will not have a renal tubulopathy (can be essentially rule out).

Urine pH: Urine pH should be measured with a pH meter in a freshly collected urine sample in a syringe to avoid CO_2 loss from the urine that can give a falsely high urine pH. Urine pH < 6.0 indicates intact distal acidification mechanism and can be observed with proximal RTA. Urine pH > 6.0 is noted in children with diarrhea, distal RTA, Proteus UTI or if there is delay in measurement.

Proteinuria: Even 1+ proteinuria in a dilute urine is significant and can be seen in Fanconi's syndrome, Dent's disease or with associated UTI

Glucosuria in absence of hyperglycemia indicates proximal tubular dysfunction (as seen in Fanconi's syndrome).

Microscopic examination for RBC's and calcium oxalate crystals observed with hypercalciuria as well as pyuria that may indicate associated UTI are also important.

b) Blood gas analysis: This is the second important investigation that needs to be performed. A venous sample is usually adequate for pH measurement and to define acidemia/ alkalemia (Fig.3) (venous pH is 0.03 units lower than arterial pH due to slightly higher pCO_2 concentration in venous blood).

c) Serum electrolytes including sodium, potassium, chloride and if possible, measured bicarbonate concentration. Hypokalemia is present in renal tubular acidosis, Bartter's syndrome and some monogenic forms of hypertension such as Liddle's syndrome.

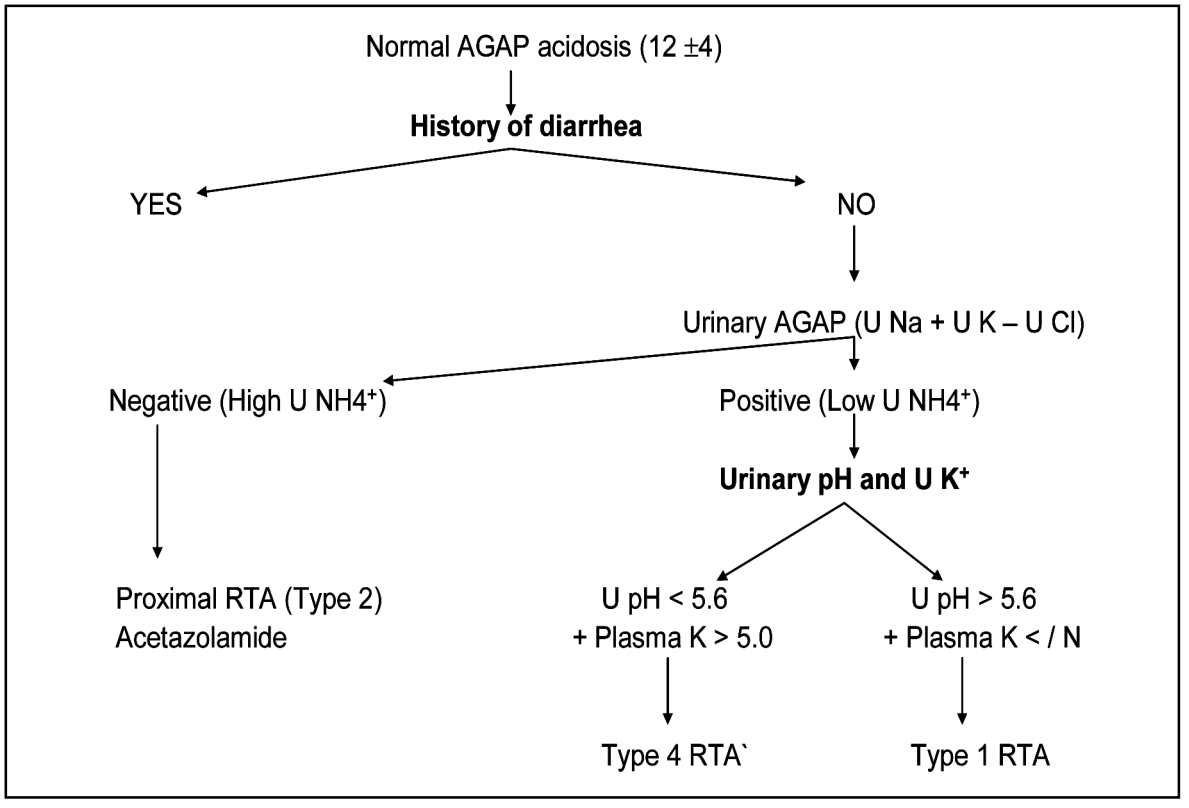


Fig.4. Evaluation of normal AGAP metabolic acidosis

Hypochloremia is observed with renal chloride wasting state in Bartter's syndrome and hyperchloremia with RTA.

Plasma Anion Gap (pAGAP) is calculated by following method: $Na^+ - (Cl^- + HCO_3^-)$. Normal pAGAP is 8 + 2 mEq/L. Metabolic acidemia can be classified based on anion gap in to normal AGAP acidemia (as observed in diarrhea and RTA) or high AGAP acidemia (Fig.4).

d) Serum calcium, phosphate and alkaline phosphatase: as biochemical indicators of rickets

e) Serum creatinine and blood urea concentration.

f) Spot urine electrolytes - Most laboratories can measure urine for Na^+, K^+, and Cl^- using the same electrodes used for plasma electrolyte measurement. Urinary bicarbonate loss is generally minimal and its measurement difficult, hence it is not routinely measured.

Urinary anion gap (uAGAP) is calculated using the following formula: $(U\ Na^+ + U\ K^+) - U\ Cl^-$. Normal uAGAP is 0 +/- 5 mEq/L and reflects the urinary concentration of ammonium (Fig.4). In distal acidification defect of dRTA, urinary ammonium excretion is decreased and hence, the uAGAP will be positive.[4,5] In contrast, a negative uAGAP indicates presence of ammonium and an intact distal acidification mechanism as seen with diarrhea (urinary chloride excretion is higher than the sum of sodium and potassium since the increased urinary ammonium in urine has to bind with negatively charged chloride ions to be excreted).

Spot urine for calcium and creatinine ratio can assist in evaluation of hypercalciuria (as observed in dRTA, some forms of Bartter's syndrome, and Dent's disease). Normal ratio is age dependant and is < 0.8 in infants below 6 months, less than 0.5 in 6 months – 18 months children, and < 0.20 in children older than 18 months age.[6]

g) Abdominal ultrasonography for nephrocalcinosis (noted in dRTA, Bartter's syndrome, hypomagnesemic Hypercalciuric nephrocaclcinosis) and hydronephrosis, hydro-ureter, post void residual urine noted in obstructive uropathy (PUV, neurogenic bladder).

h) Additional investigations may be required such as serum magnesium concentration, serum PTH assay (selected cases of Rickets) and urinary acidification tests.

In summary renal tubular disorders are an inherited or acquired defect in reabsorption or secretion of one or more solutes and / or water along the tubule length resulting in salt and water loss. They present with failure to thrive, and often associated with polyuria, polydipsia, and constipation. A careful and detailed history, focused physical examination, and appropriate investigations can confirm the underlying tubulopathy. Early diagnosis and prompt treatment can correct the metabolic abnormalities in majority of children with renal tubulopathies, leading to improved well-being and decreased morbidity and mortality. Treatment of these disorders is usually life-long.

Points to Remember

- ***Children with renal tubular disorders present with polyuria, polydipsia, delayed physical milestones, and inadequate growth***
- ***Detailed history along with appropriate investigations can often lead to a specific diagnosis***
- ***Majority of children can be treated with simple medications***
- ***Early diagnosis (preferably before 2 years age) can minimize the morbidity and improve growth of these children***

References

1. Van't Hoff WC. Molecular developments in renal tubulopathies. Arch Dis Childr 2000; 83: 189-191.
2. Hildebrandt F. Genetic kidney diseases. Lancet. 2010; 375: 1287-1295.
3. Bianchetti MG, Bettinelli A. Differential diagnosis and management of fluid, electrolyte, and acid-base disorders. In: Denis F. Geary and Franz Schaefer, editors. Comprehensive Pediatric Nephrology. USA: Mosby, 2008; pp 395-432.
4. Pereira PCB, Miranda DM, Oliveira EA, Simoese Silva AC. Molecular pathophysiology of renal tubular acidosis. Current Genomics. 2009; 10: 51-59.
5. Fry AC, Karet FE. Inherited Renal Acidoses. Physiology. 2007; 22: 202-211.
6. So NP, Osorio AV, Simon SD, Alon US. Normal urinary calcium / creatinine ratios in African American and Caucasian children. Pediatr Nephrol 2001; 16: 133-139.

NEPHROLOGY

CHRONIC KIDNEY DISEASE – NEWER CLASSIFICATION AND PRIMARY PREVENTION

** Nammalwar BR*
*** Vijayakumar M*

Abstract: *Chronic kidney disease (CKD) in children is frequently due to congenital anomalies in infants and young children, followed by hereditary diseases inclusive of metabolic and structural abnormalities in older children and chronic glomerular nephropathies in adolescents and is based on the time of presentation of CKD in them. Children with CKD often do not manifest clinically until their renal failure is advanced. Pediatricians have a unique role in primary prevention. Screening for CKD in children in developing countries can be implemented with simple, cheap and reliable tests, such as measurement of body weight, blood pressure and urine analysis for protein or albumin, glucose and blood by using a scale for body weight, a sphygmomanometer for blood pressure and a dipstick for urinalysis.*

Keywords: *Chronic kidney disease, Screening, Primary prevention, Multidisciplinary approach.*

Chronic disease of the kidney (CKD) has been described since the fifth BC. Until recent times it was labeled as chronic renal failure or chronic renal insufficiency (Table I).[1]

* Director, Medical Education

** Consultant Pediatric Nephrologist, Mehta Children's Hospital, Chennai.

Table.I Staging of chronic renal disease

Description	Renal function % of normal
Normal renal function	>75%
Decreased renal reserve	75-50
Renal insufficiency	50-20
Renal failure	20-15
Uremia	<15

These terms were ill defined, implying an unspecified degree of reduced function, present for an unspecified time, lacking specific and consensus of management profile. In 2002, the Kidney Disease Outcomes Quality Initiative (KDOQI) of the USA National Kidney Foundation (NKF) published a classification of chronic kidney disease with explicit definitions.[2] By establishing a common nomenclature and staging, it has been helpful for physicians and nephrologists to define and identify early stages of kidney damage, consensus to initiate measures for prevention of progression, institute appropriate counter measures for the metabolic decompensation, depending on the grade of CKD, anticipate comorbidities, plan treatment and for comparative universal evaluation of their outcomes.

Definition

The NKF KDOQI guidelines define CKD as kidney damage with a GFR <60 ml/min

Table. II. Stages of chronic kidney diseases

Stage	Description	eGFR(ml/per 1.73 m^2)
1	Kidney damage with normal or increased GFR	> 90
2	Kidney damage with decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	< 15 for dialysis

per 1.73m^2 for more than 3 months (Table II). The guidelines define kidney damage as either functional abnormalities of the kidneys such as proteinuria, albuminuria, or abnormalities of the urinary sediments, such as dysmorphic RBCs or structural abnormalities as noted in imaging studies. The definition would appear to be inappropriate for children because it would include infants and young children whose normal GFR is <60 ml/min per 1.73m^2 but who have no kidney damage or children with relatively benign anatomical anomalies like horse shoe kidney or MCNS or PSGN. Hence GFR ranges that define the five CKD stages apply only to children 2 years of age and older. However in practice the Schwartz equation is helpful in estimating eGFR in children less than 2 years and stratifying the kidney damage.[3]

Etiology

The etiology of CKD in children is significantly different from that in the adult population. Studies from international data suggest that congenital abnormalities of the kidney and urinary tract are the cause of end stage renal disease (ESRD) in 50%; glomerular nephropathies (GN) in 20%, inherited disease in 20%, unknown in 5%. In half of the children with GN is due to focal segmental glomerulosclerosis (FSGS). The ESRD caused by polycystic kidney diseases develops past childhood years.

In the CRI Registry arm of the North American Pediatric Renal Transplant Co-operative Study, almost one half of the patients is with the diagnosis of obstructive uropathy (22%), aplasia/hypoplasia/dyplasia (18%) and reflux nephropathy (8%). Structural causes predominant in the younger children and the incidence of glomerulonephritis increases in those older than 12 years. Among the individual glomerular causes only FSGS accounts for a significant percentage of children (8.7%) whereas all other glomerulonephritides combined contribute less than 10% of the causes of childhood CKD.[4]

Data from the ItalKid Project revealed that hypoplasia with or without urological malformations accounts for 57.7% of all cases of CKD in Italy, whereas glomerular diseases account for as few as 6.8% of cases of CKD in children.[5] When the analysis was restricted to the patient population that had reached ESRD and was in need of dialysis or renal transplant, the relative percentage of glomerular diseases increased from 6.8% to 15%, whereas that of hypoplasia decreased from 57.6% to 39.5%, underscoring the discrepancy between the rates of progression of these two entities.[6]

In the ESRD population reported by the European Dialysis and Transplant Association Registry, hypoplasia/dyplasia and hereditary diseases were the most common causes for ESRD

in the 0-4 year age group, whereas GN and pyelonephritis became progressively more common with increasing age.[7]

Hereditary disorders are more common in countries where consanguinity is common. One third of CKD in Jordanian children was due to hereditary renal disorders such as polycystic kidney diseases, primary hyperoxaluria and congenital nephrotic syndrome.[8] In Iranian children with CKD, hereditary diseases due to cystinosis, cystic kidney diseases, Alport syndrome and primary hyperoxaluria was diagnosed in one fifth of children.[9]

In summary, CKD in children is frequently due to congenital anomalies in infants and young children, followed by hereditary diseases inclusive of metabolic and structural abnormalities in older children and chronic glomerular nephropathies in adolescents.

Prevention

Children with CKD often do not manifest clinically until their renal failure is advanced. The number of children and adolescents who have less severe kidney disease (Stage 1 to 4) is much higher than ESRD (Stage 5). The major health consequence of CKD is associated with increased risk of cardiac morbidity and mortality which often precedes mortality due to the renal cause. Pediatricians have the advantage to recognize children who are at risk for CKD and potential for ESRD. Pediatricians have the opportunity to screen at-risk children, identify affected children, prevent renal damage and ameliorate the impact of CKD by initiating early therapy and monitoring disease progression. Prevention of CKD constitutes three important aspects, primary, secondary and tertiary prevention. Pediatricians have a unique role in primary prevention. Prevention of progression of renal damage from stage 1 to stage 5 by introducing appropriate measures at various stages of CKD, constitutes secondary prevention. Tertiary prevention strategies are focused on to reduce or delay long-term complications, impairment or disability in established disease needing renal replacement therapy. This discussion is confined to primary prevention. Adequate details on secondary and tertiary prevention are available for the interested readers from 'Management of chronic kidney disease' in Pediatric Nephrology.[10]

Primary prevention

Primary prevention begins well before conception and aims to eliminate or reduce exposure to factors, which cause renal disease. For CKD, this involves prevention of inheritable renal disease by appropriate genetic counseling, strategies to reduce antenatal exposure to infections, drugs, prevention of obesity, dyslipidemia and early detection and appropriate management of hypertension.

Genetic counseling: Genetic kidney disease (GKD) has been estimated to be the cause of 16% of ESRD which increases to 38% in an inbred community.[11,12] In India, particularly in South India, consanguineous marriage is a common entity. Hence CKD should have a higher frequency. Heredofamilial and congenital renal diseases are inherited in a variety of patterns: X-linked, Autosomal dominant or Autosomal recessive. Among them are Alport syndrome, thin basement membrane nephropathy, Fabry's disease, lecithin cholesterol Acyl transferase deficiency, lipoprotein glomeruloropathy, Finnish type of congenital nephrotic syndrome, diffuse mesangial sclerosis and familial FSGS. Structural tubulointerstial diseases such as polycystic kidney disease, nephronopthisis, medullary cystic disease have a genetic predisposition. Metabolic tubulointerstitial diseases such as distal renal tubular acidosis, chronic hypokalemic disorders, hypercalciuric syndrome, Fanconi syndrome,

hypophosphatemic rickets can lead to renal parenchymal damage and CKD. Congenital anomalies such as vesicoureteral reflex (VUR), posterior uretheral valve (PUV), mega ureters have Mendelian inheritance. Atypical hemolytic uremic syndrome has a genetic basis. Pre-marital genetic evaluation and counseling can probably play an important role in reducing such diseases which contribute to a significant number of ESRD. Until high-tech gene therapy are available, simple prevention and correction of metabolic abnormalities can delay or prevent CKD. For example, prevention of calcium deposition in the kidney in hypercalciuric syndrome, Fanconi syndrome, renal tubular acidosis can go a long way in preventing interstitial damage and renal failure. Renal stone disease (RSD) is one of the causes of ESRD in adults. The commonest metabolic abnormality namely hypercalcuria and other urinary metabolites manifest from infancy and present as RSD in second or third decade of life. Early detection and appropriate preventive measures including alkali therapy can reduce the burden of RSD in adults. Prevention of chronic hypokalemic states can prevent interstitial fibrosis and renal failure. Likewise, control of proteinuria in glomerular diseases can prevent renal damage. Antenatal ultrasonogram, amniotic fluid cytology, chorionic villus sampling, maternal serum alpha-feto protein estimation can detect early renal disorders and congenital anomalies. These finding can lead to possibility of fetal surgery or termination of pregnancy depending on the gravity of abnormality and irreversible renal failure.

Antenatal preventive measures: Intrauterine infections are a cause of acquired congenital nephrotic syndrome or malformation syndromes. Toxoplasmosis, congenital rubella and cytomegalo virus have been reported to cause renal damage. Preventive measures include appropriate immunizations before marriage to prevent rubella infection and screening and treatment of cytomegalo virus and toxoplasmosis. Adverse functional effects occurs when fetuses are exposed to NSAIDs, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). Studies have shown long-term adverse effects, including renal dysfunction and arterial hypertension in adulthood. In addition in utero exposure to drugs affect renal structure itself and produce renal congenital abnormalities, including cystic dysplasia, tubular dysgenesis, ischemic damage and reduced nephron number. Such findings stress the importance of long-term follow-up of infants exposed in utero to certain drugs that have been administered to the mother.[13] Nephrotoxic medication particularly aminoglycosides, ACEI, non-steroidal anti-inflammatory and antifungal drugs taken during postnatal nephrogenesis particularly in preterm infants could interfere with nephron generation contributing to renal damage. Such adjunctive damage could further increase the risk of renal failure in the adulthood of children born prematurely.[14] The prevention of renal damage and CKD in spina bifida is through prevention of spina bifida itself by folic acid supplementation before pregnancy.[15]

Low birth weight (LBW): It is an important determinant of renal disease risk. The long-term renal consequences of LBW are generally attributed to the noxious effect of malnutrition on renal organogenesis resulting in a lower than normal number of nephrons. Many of these children would have mild to moderate renal failure, hypertension and cardiovascular events in adult life. The concurrent risk of low nephron endowment may be the 'first hit' while the 'second hit' would be imposed by the development of obesity and insulin resistance. Adequate maternal nutrition, serial antenatal evaluation and therapeutic interventions for

improved birth weights can significantly reduce LBW. In infants, especially those born preterm and/or of LBW, the growth projectory should be plotted with attention to weight:length ratios. Special hypercaloric formulae and carbohydrate supplements should be discouraged and the rate of weight gain and 'catch-up' growth modulated. Postnatal monitoring of these children for proteinuria, albuminuria and hypertension can detect early renal dysfunction and prevent the progression or delay the progress to grade 5 CKD. After 6 months of age, angiotensin-blocking agents may be used to control blood pressure, glomerular hyperfiltration and proteinuria.[16]

Prematurity: This is an important factor for CKD later in childhood. Prematurity was significantly more frequent in children with congenital CKD (hypoplasia/dysplasia) than in children with hereditary (nephronophthisis) and acquired CKD (diarrhoea-associated haemolytic uremic syndrome, idiopathic focal and segmental glomerulosclerosis). Prematurity could be the effect of the congenital CKD. Pediatricians taking the medical history of their patients should ask for gestational age and other birth parameters.[17]

Familial CKD: The clustering of CKD in families is strongly suggestive of genetic or familial predisposition in some cases. Familial clustering of disparate causes of ESRD in adults has been reported by several groups, including families with members having nephropathy associated with type 1 and 2 diabetes mellitus, hypertension, chronic glomerulonephritis, systemic lupus erythematosus and HIV infection.[18] Low birth weight in some ethnic communities might be associated with a reduction in the number of nephrons and subsequent predisposition to hypertension and renal disease in later life. A case control study by Lei et al concluded that familial clustering of renal disease occurred in excess of that which could be accounted for by the clustering of hypertension and diabetes mellitus within families.[19] Children from such families are to be evaluated at frequent intervals for microalbuminuria, proteinuria, renal function and ultrasonogram of abdomen, if indicated.

Congenital anomalies: Initially, many of the congenital anomalies of the kidneys and urinary tract have normal renal functions at birth, until early childhood. With growth, particularly the puberty seems to be a critical stage for patients with renal impairment, as steep decline in renal function often occurs during puberty and the early post puberty period. Renal aplasia, hypoplasia/dysplasia, posterior uretheral valve, vesicoureteral reflux co existing with renal hypoplasia/dysplasia are a few of the well known clinical disorders.[5,20] A considerable risk to develop proteinuria, glomerular scelorosis, and renal failure has been documented in patients with unilateral renal agenesis. Subtle nephron deficit in renal/hypoplasia has increased risk of hypertension or susceptibility to acquired renal disease in later life. It is observed that overweight plays a fundamental role in the appearance of proteinuria and renal damage in patients with severe renal mass reduction.[21]

Antenatal diagnosis of these congenital anomalies can direct the introduction of uroprophylaxis and appropriate postnatal evaluation including renal function test, ultrasonogram of abdomen, voiding cystourethrogram, urodynamic studies and isotope evaluation for structural and parenchymal abnormalities (dysplastic kidney), and obstructive disorders. These can determine preventive measures such as correction of metabolic abnormalities namely polyuria, salt loosing states, hyperkalemia and bicarbonaturia. Early diagnosis can ensure the need for anticholinergic therapy, adequate drainage of urine with clean intermittent catheterization

(CIC) technique and surgical intervention in obstructive uropathy.[15] These measures can prevent renal damage or the effects of the metabolic abnormalities on functions of kidney and its growth. Use of urodynamic studies can decide the need for drug therapy with or without CIC and prevent the damaging effects of retrograde pressure. The utility of ACEI and ARB for its renoprotective effects in these situations have not been universally accepted.[22] But is being tried in many pediatric nephrology centers with adequate biochemical monitoring.

Obesity: It is on the rise among children and adolescents. Obesity with the body mass index of >27 kg/m^2 has been associated with microalbuminuria, proteinuria, poor renal function and histologically characterized by glomerulomegaly, mesangial expansion and/or sclerosis, which has been termed 'obesity related glomerulopathy'. The risk seems to be especially evident in cases of abdominal obesity, a powerful risk determinant. Obesity alone does not appear to be the sole mediator of this nephropathy. Rapid catch-up growth, early obesity and insulin resistance are major contributors to the emergence of obesity-related glomerulopathy in children and adolescents.[16] These troubling factors are fueled in part by diets high in partially hydrogenated vegetable oil and low in fresh produce, consumption of carbonated drinks, fast foods as well as by increase in sedentary lifestyles, as children spend an average of four to six hours per day watching television**.** Consequences of sub-fertility and high pre-pregnancy BMI include higher birth weight, increased perinatal mortality and an increased risk of congenital abnormalities. The increased pre-pregnancy BMI is also associated with higher BMI and a higher BP in the off spring; thus a potential risk factor for future CKD. Targeting a healthier weight prior to conception may reduce the risk of CKD in the offspring.[23] Primary prevention will rely on controlling the global epidemic of obesity and associated type 2 diabetes as well as hypertension. Improved public health education on life style modifications such as weight reduction, exercise, and dietary manipulations can be effective. Approach to control hypertension by means of dietary salt restriction <5-6 g/day in adolescents and less than 3-4 g/day in younger children and prescribing diet rich in fruits, vegetables and low in saturated fat have been recommended.[24]

Infections: In developing countries the high incidence of post-infectious glomerulonephritis, HIV/AIDS, Hepatitis B, Hepatitis C (rare in children) and other uncommon viral infection such as Parvovirus, Coronavirus, BK virus (in immunocompromised individuals) hepatitis A with hepatorenal syndrome secondary to acute fulminant hepatitis, Ebstein-Barr virus and dengue fever with multiorgan failure are the causes of acute kidney injury (AKI).[25] Parasitic infestations such as malaria both falciparum and vivax, schistosomasis can cause renal damage. Incomplete recovery of renal damage from these illness can predispose to CKD later in life.

Metabolic diseases: In addition to the above mentioned inherited tubulointerstitial metabolic disorders, there are other systemic disorders which predispose to systemic and renal vessel artherosclerosis and glomerulosclerosis. Diabetes mellitus, hyperlipidemic conditions and Syndrome X are a few of them. The Metabolic Syndrome (Syndrome X) is defined as a clustering of obesity, dyslipidemia (high triglycrides and low high-density lipoproteins), elevated blood pressure, impaired glucose metabolism and insulin resistance. The duration of diabetes in type 1 and 2 seems to be a major factor with renal complications occurring on an average 10 to15 years after of the onset of diabetes. Tight control of blood glucose with preventive measures against renal damage with

ACEI or ARB or both will play a significant role in reducing the incidence of diabetic nephropathy.

Acute kidney injury: Acute renal failure (ARF) or AKI results from complications of other systemic diseases resulting from the advancements in congenital heart surgery, neonatal care, bone marrow and solid organ transplantation. In a longitudinal follow-up study after AKI, it was shown that 68% of the survivors recovered complete renal function, 13% had improved renal function, 12% sustained renal failure, and 5% progressed to ESRD.[26] As the risk for long-term renal injury is high, children should be evaluated periodically for signs of renal injury for years after the initial insult. In developing countries, the frequency of AKI following acute gastroenteritis and acute bacterial infections continue to be high in the list of etiology. Natural calamities such as earth quakes, man made disasters contribute a large population with trauma and crush injuries leading to AKI. The inevitable delay in management in these situations leads to residual renal damage and CKD. Appropriate education to the health care professionals and to public will help to institute early interventional therapies namely intravenous fluid administration at the site of accident, measures to prevent loss of blood and hypovolemia, appropriate wound care and prevention of sepsis can reduce a large amount of AKI or its severity. Hemolytic uremic syndrome (HUS) particularly the non-diahorreal is associated with residual renal damage, hypertension and progression to CKD. Early recognition and intervention with dialysis as per need and/or plasma infusion / exchange therapy is associated with less residual renal damage.

Nephrotoxic drugs: Use of combination of nephrotoxic drugs particularly aminoglycosides, NSAIDs and contrast are to be avoided wherever possible. Particular care should be taken to assess for presence of renal insufficiency, hypovolemia and low cardiac output states and extremes of age before administration of these drugs. Avoidance of these drugs or its combination would be a preferred choice and use of modified doses as per renal function would be a second choice.

Screening procedures for early detection of renal disease

Early identification: Prompt and early identification of children with CKD is desirable because interventions can then be implemented to alter the progression to kidney failure and to reduce the risk of cardiovascular events. Consequently, detection of CKD should be a priority for primary pediatricians. Blood pressure measurement is mandatory in all children above three years during any medical examination and in children less than 3 years when admitted for serious renal or non-renal disease. Primary hypertension among children is on the increase co-incidence with the epidemic of obesity.[27] Hypertension is often the only presenting sign of CKD in children and adolescents. ACEI and ARB are more effective than other antihypertensive drugs in preventing the progression of kidney disease. These agents not only lower systemic blood pressure and thereby the intraglomerular pressure but also have a direct effect on intraglomerular pressure and proteinuria. When ACEI therapy is started, some patients with CKD may have a mild increase in the serum creatinine and potassium level. Therefore, serum creatinine and potassium levels should be monitored one to two weeks after the initiation of therapy and monitored once in 3 months thereafter..

The American Academy of Pediatrics recommends that urine screening tests be conducted on 2 occasions during childhood, once before starting school and then again during adolescence.[28] Proteinuria is a marker of kidney injury, severity of CKD and a powerful

independent predictor of its progression. Patients with persistently high rates of urinary protein excretion have a much faster rate of progression than those with mild or moderate proteinuria. Hypertension together with proteinuria has been shown to be an important risk factor for progression of primary renal disease in children and adults. The control of proteinuria is important in slowing the progression to ESRD. ACEI or ARB is advocated for their antihypertensive and protein lowering effect. Children with a positive dipstick test (1+ or greater) should undergo confirmation of proteinuria by a quantitative measurement preferably protein-to-creatinine ratio. Children with 2 or more positive quantitative tests temporally separated by 1 to 2 weeks should be diagnosed as having persistent proteinuria and undergo further evaluation for glomerular disease. Most children who have proteinuria that does not persist on repeated testing may be considered to have transient proteinuria, a benign condition that is often associated with fever, stress, or exercise.[29] Proteinuria screening for children done in Japan represents an effective mass screening technique for detection of asymptomatic glomerular disease and has been observed to prevent ESRD in children with MPGN and IgA nephropathy.[30] Pediatric school screening initiative program, developed by National Kidney Foundation, Singapore in collaboration with the Ministry of Health and the National University of Singapore was initiated in 1999 as part of the School Health Screening Program. This targeted the early adolescent age group and was introduced as an additional component of the government's school health screening services. In a pilot study of 2083 children, the overall prevalence of proteinuria (dipstick protein 1+) was 2.0% and the prevalence of age and gender calibrated hypertension was 13.0%. The analysis also identified a trend for an association between LBW and proteinuria, consistent with prior studies that suggest LBW and therefore low renal mass may be a risk factor for CKD. The pediatric program also detected a prevalence of clinically significant isolated hematuria of 6.8%, arguing for the continued screening for renal disease and proteinuria among pediatric populations with a high background prevalence of kidney disease and other chronic diseases.[31]

Microalbuminuria: Refers to albumin excretion above the normal range but below the level of detection by dipstick for total protein. The test measures albumin, which is in very small quantities, hence the term microalbuminuria. It is a sensitive test for early detection of parenchymal damage particularly glomerular injury. In recent times determination of microalbuminuria has been indicated as evidence of glomerular damage in many nondiabetic conditions such as polycystic kidney and urinary tract infection. Microalbuminuria screening should be confined to children known to have renal parenchymal damage but have a normal renal function test including absence of proteinuria.[29]

Dyslipidemia: Screening of children with obesity and with family history of dyslipidemia and institution of antilipidemic measures can prevent or delay atherosclerotic process. Dyslipidemia is a systemic disease that predisposes diffuse atherosclerosis including the renal vessels. This could lead to renal artery stenosis and renal ischemia and consequent renal dysfunction. In addition, it is a risk factor for cardiovascular disease, a complication of CKD. The goals are for total cholesterol level <170 mg/dL, LDL cholesterol level <100 mg/dL and a triglyceride level <100 mg/dL.[32] Statins can lower cholesterol levels safely and effectively in these children. Atorvastatin is the recommended statin for use in children. Bile acid sequestrants appear to be safe and effective in improving

dyslipidemias in children. Cholestryamine a bile sequestrant is also recommended.

Conclusion

Chronic kidney disease is many times more prevalent than end-stage renal disease, and its incidence is increasing. Consequently, detection of CKD should be a priority for pediatricians.[33] Screening in developing countries can be implemented with simple, cheap and reliable tests, such as measurement of body weight, blood pressure and urine analysis for protein or albumin, glucose and blood by using a scale for body weight, a sphygmomanometer for blood pressure and a dipstick for urinalysis.

Points to Remember

- ***Chronic kidney disease (CKD) in children is frequently due to congenital anomalies in infants and young children, followed by hereditary diseases inclusive of metabolic and structural abnormalities in older children and chronic glomerular nephropathies in adolescents.***
- ***Children with CKD often do not manifest clinically until their renal failure is advanced.***
- ***Primary, secondary and tertiary prevention steps are needed for reducing the morbidity and mortality in childhood CKD. Pediatricians have a unique role in primary prevention.***
- ***Primary prevention involves proper genetic counseling and antenatal preventive measures. Prevention of LBW babies and prematurity as well as adequate and appropriate care of them, reduce the problem of CKD in adulthood. Familial CKD and congenital anomalies should not be forgotten. Prevention of obesity, anticipating and treating infections, identification and managing metabolic diseases and AKI play a major role in the preventive aspects. Use nephrotoxic drugs only when needed with proper renal monitoring***
- ***Detection of CKD should be a priority for pediatricians. Screening in developing countries can be implemented with simple, cheap and reliable tests, such as measurement of body weight, blood pressure and urine analysis for protein or albumin, glucose and blood, using a scale for body weight, a sphygmomanometer for blood pressure and a dipstick for urinalysis.***
- ***Secondary prevention done through pediatric nephrologist, wherein prevention of progression of renal damage from stage 1 to stage 5 is done by introducing appropriate measures at various stages of CKD***
- ***Tertiary prevention is done by a multidisciplinary integrated approach involving pediatricians, pediatric nephrologist, urologist, psychiatrist, social workers, teachers, law makers, insurance companies and personnel involved in the delivery of health care system in the society by strategies that are focused to reduce or delay long-term complications, impairment or disability in established disease, needing renal replacement therapy***

References

1. Knochel JP, Seldin DW. The Pathophysiology of uremia. In: The Kidney. 2nd Edn, Eds Brenner BM, Rector FC. WB Saunders, Philadelphia, 1981;pp 2137-2183
2. Hogg RJ, Furth S, Lemley KV, Portman R, Schwartz GJ, Coresh J, et al. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease in Children and

Adolescents: Evaluation, Classification, and Stratification. Pediatrics 2003; 3: 1416-1421.

3. Schwartz G, Haycock GB, Edelmann CM Jr, Sptizer A. A simple estimation of glomerular filteration rate in children, derived from body length and plasma creatinine. Pediatrics 1976; 58: 259-263.
4. North American Pediatric Renal Transplant Co-operative Study 2005 Annual report. The EMMES Corporation. Rockville, MD.
5. Ardissino G, Dacco V, Testa S, Banaudo R, Claris-Applani A, Taioli E, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. Pediatrics 2003; 111:e382-e387.
6. Pope JC IV, Brock JW III, Adams MC, Stephens FD, Ichikawa I. How they began and how they end: classic and new theories for the development and deterioration of congenital anomalies the kidneys and urinary tract, CAKUT. J Am Soc Nephrol 1999; 10: 2018-2028.
7. van der Heijden BJ, van Dijk PC, Verrier-Jones K, Jager KJ, Briggs JD, Renal replacement therapy in children: data from 12 registries in Europe . Pediatr Nephrol 2004; 19: 213-221.
8. Hamed RMA. The spectrum of chronic renal failure among Jordian children. J Nephrol 2002; 15:130-135.
9. Madani K, Otoukesh H, Rastegar A, Why SV. Chronic renal failure in Iranian children. Pediatr Nephrol 2001; 16:140-144.
10. VanDeVoorde RG. Warady BA. Management of chronic kidney disease. In: Pediatric Nephrology, 6th Edn, eds Avner ED, Harmon WE, Niadudet P, Yoshikawa N, Springer Verlag, Berlin, Heidelberg, 2009; pp 1661-1692.
11. Foreman JW, Chan JC. Chronic renal failure in infants and children. J Pediatr 1988; 113:793-800.
12. Finer G, Shalev H, Landan D. Genetic kidney diseases in the pediatric population of Southern Israel. Pediatr Nephrol 2006; 21: 910-916.
13. Boubred F, Vendemmia M, Garcia-Meric P, Buffat C, Millet V, Simeoni U Effects of maternally administered drugs on the fetal and neonatal kidney. Drug Saf 2006; 29:397-419.
14. Zaffanello M, Bassareo PP, Cataldi L, Antonucci R, Biban P, Fanos V. Long-term effects of neonatal drugs on the kidney. J Matern Fetal Neonatal Med 2010; 3: S87-S89.
15. Filler G, Gharib M, Casier S, Lodge P, Ehrich JHH, Dave S. Prevention of chronic kidney diseases in spina bifida. Int Urol Nephrol DOI 10, 1007/s11255-010-9894-5
16. Abitbol CL, Rodríguez MM. Obesity-Related Nephropathy in Children. Pediatr Health 2009; 3:141-153.
17. Franke D, Völker S, Haase S, Pavicic L, Querfeld U, Ehrich JH, et al. Prematurity, small for gestational age and perinatal parameters in children with congenital, hereditary and acquired chronic kidney disease. Nephrol Dial Transplant 2010; 25: 3918-3924.
18. Satko SG, Freedman BI, Moossavi S. Genetic factors in end-stage renal disease. Kidney Int 2005; 94: S46-S49.
19. Lei HH, Perneger TV, Klag MJ, Whelton PK, Coresh J. Familial aggregation of renal disease in a population based case control study. J Am Soc Nephrol 1998; 9:1270-1276.
20. Seikaly MG, Ho PL, Emmett L, Fine RN, Tejani A. Chronic renal insufficiency in children: The 2001 Annual Report of the NAPRTCS. Pediatr Nephrol 2003; 18: 796-804.
21. Gonzalez E, Gutierrez E, Morales E, Hernandez E, Andres A, Bello I, et al. Factors influencing the progression of renal damage in patients with unilateral renal agenesis and remnant kidney. Kidney Int 2005; 68: 263-270.
22. Hilgers KF, Dostsch J, Rascher W, Mann JFE. Treatment strategies in patients with chronic renal disease: ACE inhibitors, angiotensin receptor antagonists or both? Pediatr Nephrol 2004; 19: 956-961.
23. Filler G, Rayar MS, Orlando de Silva, Buffo I, Poelassis D Sharma AJ. Should prevention of CKD start before pregnancy? Int. Urol nephrol 2008; 40:483-488.

24. He FJ, Jenner KH, MacGregor GA. WASH-World Action on Salt and Health. Kidney Int 2010; 78, 745-753

25. Lai ASH, Lai KN. Viral Nephrology. Nature Clin Prac Nephrol 2006; 2: 254-262.

26. Askenazi DJ, Feig DI, Graham NM, Hui-Stickle S, Goldstein SL. 3-5 year longitudinal follow-up of pediatric patients after acute renal failure. Kidney Int. 2006; 69: 184-189.

27. Liao CC, Su TC, Chien KL, Wang JK, Chiang CC, Lin CC et al. Elevated blood pressure, obesity and hyperlipidemia. J Pediatr 2009; 155: 79-83.

28. Hogg RJ, Portman RJ, Milliner D, Lemley KV, Eddy A, Ingelfinger J. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk, Assessment, Detection, and Elimination (PARADE). Pediatrics 2000; 105: 1242 –1249.

29. Prabha S. Approach to Proteinuria. Indian J Pract Pediatr 2012;14:

30. Murakami M, Hayakawa M, Yanagihara T, Hukunaga Y. Proteinuria screening for children. Kidney Int 2005; 67: S23-S27.

31. Ramirez SP. Chronic Kidney Disease Prevention in Singapore. Clin J Am Soc Nephrol 2008;3: 610-615.

32. Daniels SR, Greer FR, Committee on Nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics 2008;122:198-208.

33. Vijayakumar M, Nammalwar BR, Prahlad N. Prevention of chronic kidney disease. Indian J Nephrol 2007;17:47-52.

CLIPPINGS

Statins for the primary prevention of cardiovascular disease

Cardiovascular disease (CVD) is ranked as the number one cause of mortality and is a major cause of morbidity world wide. Reducing high blood cholesterol which is a risk factor for CVD events is an important goal of medical treatment. Statins are the first-choice agents. The aim of this systematic review is to assess the effects, both in terms of benefits and harms of statins for the primary prevention of CVD. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE until 2007. We found 14 randomised control trials with 16 trial arms (34,272 patients) dating from 1994 to 2006. All were randomised control trials comparing statins with usual care or placebo. Duration of treatment was minimum one year and with follow up of a minimum of six months.

Reductions in all-cause mortality, major vascular events and revascularisations were found with no excess of cancers or muscle pain among people without evidence of cardiovascular disease treated with statins. Other potential adverse events were not reported and some trials included people with cardiovascular disease. Only limited evidence showed that primary prevention with statins may be cost effective and improve patient quality of life. Caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.

Taylor F, Ward K, Moore THM, Burke M, Davey Smith G, Casas J-P, Ebrahim S. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD004816. DOI: 10.1002/14651858.CD004816.pub4.

NEPHROLOGY

APPROACH TO PROTEINURIA

**** Prabha Senguttuvan***

Abstract: *Proteinuria is common in primary care practice The incidence of proteinuria in school children is 0.6- 6.3% Besides hypertension, proteinuria is the second key modifiable risk factor to preserve GFR. Proteinuria is classified as nonpathological and pathological proteinuria. Massive proteinuria is the hallmark of glomerular disease. Algorithm can help to identify between benign and pathological proteinuria. Asymptomatic proteinuria with no hematuria or renal failure can be followed up by pediatricians. Persistent proteinuria, active urine sediments, hematuria and elevated renal function tests indicate a major renal problem and require a pediatric nephrology consult.*

Keywords*: Children, Dipstick, Microalbuminuria Proteinuria.*

Proteinuria is a marker of parenchymal injury in kidney disorders of diverse etiologies and an early sign of kidney disease. Although the proteinuria is the result of kidney disease, it also plays a role in the progression of kidney damage. During a time when uroscopy was the only diagnostic tool for detecting renal diseases, Hippocrates described the association between "bubbles on the surface of the urine" and kidney disease. In the seventeenth century Frederick Dekkers described that urine samples became caseous after exposure to heat and it took another 200 years until Richard Bright associated proteinuria with kidney disease. Presently proteinuria is routinely and easily assessed in clinical practice.

* Professor of Nephrology,
Sri Ramachandra Medical College and
Research Institute, Chennai.

Epidemiology

The prevalence of isolated asymptomatic proteinuria in children has been estimated to be between 0.6 and 6.3 percent. Proteinuria is usually transient and intermittent, so that much higher prevalences are observed when a single urine specimen is tested. Most children who test positive for proteinuria on initial evaluation "lose" the proteinuria at follow-up. Less than one percent of children have persistent proteinuria after six to 12 months.

Normal urinary protein excretion in infants and children

Healthy children excrete small amounts of protein in their urine, described as physiologic proteinuria. When corrected for body surface area, the protein excretion is highest in newborn infants, decreasing with age until late adolescence, when adult level of 150 mgs per day is reached. In neonates, normal urinary protein excretion is higher, up to 300 mg/m^2/day, because of reduced reabsorption of filtered proteins reflecting the immaturity of their renal tubular function. Physiological proteinuria varies with the age and size of the child, but when expressed as mg/m^2/24 hr, is relatively constant after the first year of life. The normal rate of protein excretion is less than 4 mg/m^2/hr or less than 100 mg/m^2/24 hr throughout childhood in both boys and girls. Nephrotic range proteinuria

is more than 40 mg/m^2/hr in an overnight specimen of urine or more than 50 mg/kg body weight per 24 hour. In children over two years of age, a urine protein by urine creatinine ratio (PCR) of less than 0.2 on a random urine specimen obtained during the day is considered normal. In children aged six months to two years, the upper limit of normal is extended to 0.5. A PCR above 3.0 is consistent with nephrotic-range proteinuria. A ratio in between these two values is termed as abnormal proteinuria. Albumin accounts for about 15% of the total protein in urine, which is less than 30 mgs per day. Immunoglobulins and low molecular weight proteins, such as β-2 microglobulin and amino acids account for about 35%. Approximately 50% of urinary protein is Tamm-Horsfall protein, referred to as uromodulin, secreted by proximal tubules.

Measurement of proteinuria

Qualitative methods

The dipstick method is an inexpensive test that is used for screening of urinary proteins which is actually a test for albumin among the various proteins in urine. The standard dipstick measures albumin concentration in the urine via a colorimetric reaction between albumin and tetrabromophenol blue, causing different color shading depending on the albumin concentration in the sample. The amount of protein in the urine is assessed as 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL) or 4+ (1,000 mg/dL). False-positive results can be obtained when the urine is alkaline (pH greater than 7) or when it contains heavy mucus, blood, pus, semen or vaginal secretions. In the dilute urine, the urine albumin concentration is decreased and may not be detected by dipstick. A positive urinary dipstick is a useful screening test for proteinuria but should be remembered that it reacts preferentially with albumin and are insensitive to other proteins such as gamma globulins and Bence Jones protein.

A positive dip-stick test can be verified with sulfosalicylic acid turbidometry. In the latter test, three drops of a 20% solution of sulfosalicylic acid are added to 5 ml of urine to cause acidic pH and precipitation of proteins. The turbidity of the urine is noted by visual inspection. Sulfosalicylic acid test detects all types of urinary proteins and hence useful in the diagnosis of multiple myeloma, which is characterized by urinary excretion of immunoglobulin light chains that are not detected by urine dipstick testing.

Quantitative methods

Spot or random urine analysis for UPr/UCr and urine albumin-to-creatinine ratio (UA/UCr) are currently preferred to the 24-hour urine collection for quantification of daily proteinuria because of the greater convenience of spot urine sampling. The UA/UCr is used to assess for albumin excretion of 30-300mg/day/dL in an adult whereas the PCR can be used when proteinuria of more than 300 mg/day is suspected. First morning specimens are preferable. The UACR is a more sensitive screening test for glomerular injury than the PCR. PCR is less expensive and can be used to followup therapeutic efforts to reduce proteinuria. Clinicians should be aware that the accuracy of estimating proteinuria from a random urine specimen is diminished if creatinine excretion is substantially different from expected normal levels. Steady-state daily creatinine excretion is 20 mg/kg/day in children from one to 12 years of age and 22 to 25 mg/kg/day in older children, with the lower value corresponding with creatinine excretion in girls. Thus, the albumin-to-creatinine ratio will underestimate protein excretion in a muscular individual with a high rate of creatinine excretion and will overestimate urinary protein excretion in a cachectic patient

with low muscle mass and low creatinine excretion.

The **24 hours urine protein excretion** is considered as the 'gold standard' for quantitative evaluation of proteinuria but technically it is difficult in children. Several colorimetric laboratory methods are available to quantitate protein concentration in 24 hours voided urine. In children, however, physiologic proteinuria varies with age and the size of the child (see above). In children a way of quantitating urinary protein excretion has been to measure protein in a urine sample collected over a 12 hour period. Quantitative estimates of proteinuria performed at clinical laboratories reflect several classes of proteins and yield a result greater than the actual amount of albumin in the specimen. Urinary protein electrophoresis and direct measurements of low-molecular-weight proteins such as β2 microglobulin are performed in special circumstances and are not part of the routine evaluation of a child with proteinuria.

Selectivity index (SI) of protein clearance is estimated by immunonephelometry This is calculated by the ratio of the clearance of IgG (molecular weight 160,000) to the clearance of transferrin (molecular weight 88,000).

$$SI = \frac{U\ IgG}{S\ IgG} \times \frac{S\ Transferrin}{U\ Transferrin.}$$

In children with nephrotic syndrome when the ratio is less than 0.1 the proteinuria is highly selective and indicates minimal change diseasse (MCNS) responsive to corticosteroids. The response is moderate if the ratio is between 0.11 and 0.20 and anything more than 0.21 is nonselective proteinuria and indicates steroid resistance as seen in focal segmental glomerulosclerosis. Currently this investigation is not in vogue. Steroid responsiveness in MCNS is a simple and equally reliable indicator of treatment out come.

Mechanisms of Proteinuria

Glomerular proteinuria: In the normal kidney, the glomerular basement membrane allows for passage of small molecules into the renal tubule while restricting the passage of macromolecules. The glomerular capillary wall and its adjacent structures constitute the main barriers to the passage of macromolecules, which includes globulins and albumin. Proteinuria indicates an alteration in the permeability and selectivity properties of the glomerular filtration barrier, which encompasses the 3 major components: visceral epithelial cell foot processes, glomerular basement membrane, and endothelial cell layer lining the capillary loops. Albumin which is negatively charged are repelled by negatively charged glomerular basement membrane and endothelial cells coated with heparan sulphate proteoglycans and the glomerular epithelial cells by sialoproteins.The slit diaphragm a zipper like scaffold between the podocyte foot processes, act as the primary site for size barrier to protein filtration. Mutations in the slit diaphragm genes called Nephrin alters the permselectivity. Podocyte foot processes are a contractile apparatus composed of actin, myosin and á Actinin 4. Podocytes injury leads to foot process swelling and injury to slit diaphragm. Earlier foot process fusion was thought to occur secondary to proteinuria but now it is recognized as a primary manifestation of podocyte injury. Filtration is reduced at sites where foot processes fuse and massive proteinuria occurs where glomerular epithelial cells are detached from GBM.

Reduced podocyte number contributes to glomerulosclerosis. Podocytes located on the outer aspect of GBM and its main function is to provide tensile support to underlying capillary

loops by opposing hydrostatic pressure. The podocyte loss leads to a localized bare GBM at that site. Lack of tensile support at that area leads to bulging of capillary loop, and increased hydrostatic pressure in glomerular diseases worsens the process. Expanding capillary loop causes the denuded GBM to abut on the Bowman's capsule leading to synechae formation and development of focal segmental glomerulosclerosis, and proteinuria.

The glomerular injury can be mediated by immune deposits as in post streptococcal nephritis or complement activation as in membranous nephropathy or due to cytokines as in minimal change nephrotic syndrome. Mutation in Actinin 4 gene leads to autosomal dominant focal segmental glomerulosclerosis and proteinuria. The movement of proteins across the glomerular capillary wall in addition to molecular size and charge, is also regulated by several factors like glomerular plasma flow rate, hydrostatic and oncotic forces and configuration of proteins.

Tubular proteinuria: In healthy children low-molecular-weight proteins (LMW) are freely filtered through the glomerulus and subsequently absorbed and catabolized by the proximal tubule and returned to the circulation. They include, lysozyme, light chains of immunoglobulin, α_1 microglobulin, β_2-microglobulin, retinol binding protein and hormones such as vasopressin, insulin, growth hormone and parathyroid hormone. Injury to the proximal tubular epithelium leads to inability of the tubule to reabsorb low-molecular-weight proteins and thus to their loss in urine.

Overflow proteinuria: It occurs when the plasma concentration of certain LMW proteins exceeds the capacity of the tubules to reabsorb the filtered protein. Examples include the presence of immunoglobulin light chains in the urine in multiple myeloma, hemoglobinuria in intravascular hemolysis, myoglobulinuria in rhabdomyolysis and amylasuria in acute pancreatitis.

Classification of proteinuria

Non pathological proteinuria

Transient proteinuria can occur with strenuous exercise, abdominal surgery or congestive heart failure. It can also occur during febrile illnesses and after seizures. The proteinuria is less than 2+ and not associated with edema, hematuria, hypertension or renal failure. It is benign and disappears on subsequent urine examination when the basic condition abates. Hence no further investigations and treatment are required.

Orthostatic proteinuria occurs as an isolated proteinuria, without hematuria, in an asymptomatic individual in a random day time collected specimen. This must be confirmed by repeating the test on a specimen collected immediately upon the patient's awakening in the morning. Recumbent urine sample is protein free but in the upright sample proteinuria is present. To ensure that no residual urine originating from the previous day is in the bladder, the child must completely empty his or her bladder before going to bed the night before the collection. Orthostatic proteinuria is not a kidney disease; it is a benign condition without clinical significance. However testing for proteinuria on an annual basis is prudent until the third decade of life. Children with orthostatic proteinuria commonly excrete less than 1 g of protein in 24 hours or PCR less than 1.

Pathological proteinuria

There are three main mechanisms of increased protein excretion: glomerular, tubular and overflow proteinuria.

Glomerular proteinuria: The main function of the glomerulus is to restrict the filtration of

proteins across the glomerular capillary wall. Glomerular proteinuria are large molecular weight proteins mostly albumin. Glomerular proteinuria is defined as urinary protein excretion >100 mg/m^2/day or > 4 mg/m^2/hour and this is abnormal in children. If it persists for more than 3 months it is called persistent proteinuria. Nephrotic range proteinuria is defined as urine protein excretion > 40 mg/m^2/hour or a PCR greater than 3.0. Often there is associated hematuria either visible or non visible.

Causes of glomerular proteinuria are:

1) Primary glomerular diseases: congenital nephrotic syndrome, minimal change nephrotic syndrome, focal segmental glomerulosclerosis, mesangiocapillary GN, membranous, rapidly progressing GN, IgA Anephropathy.

2) **Secondary glomerular diseases:** Post infective glomerulonephritis, Henoch schonlein purpura, hepatitis B nephropathy, Hemolytic uremic syndrome, HIV nephropathy, while chronic interstitial nephritis and renal dysplasia or hypoplasia lead to secondary glomerular sclerosis.

3) **Hereditary glomerular diseases**: Inherited disorders of glomerular basement eg. Alport syndrome.

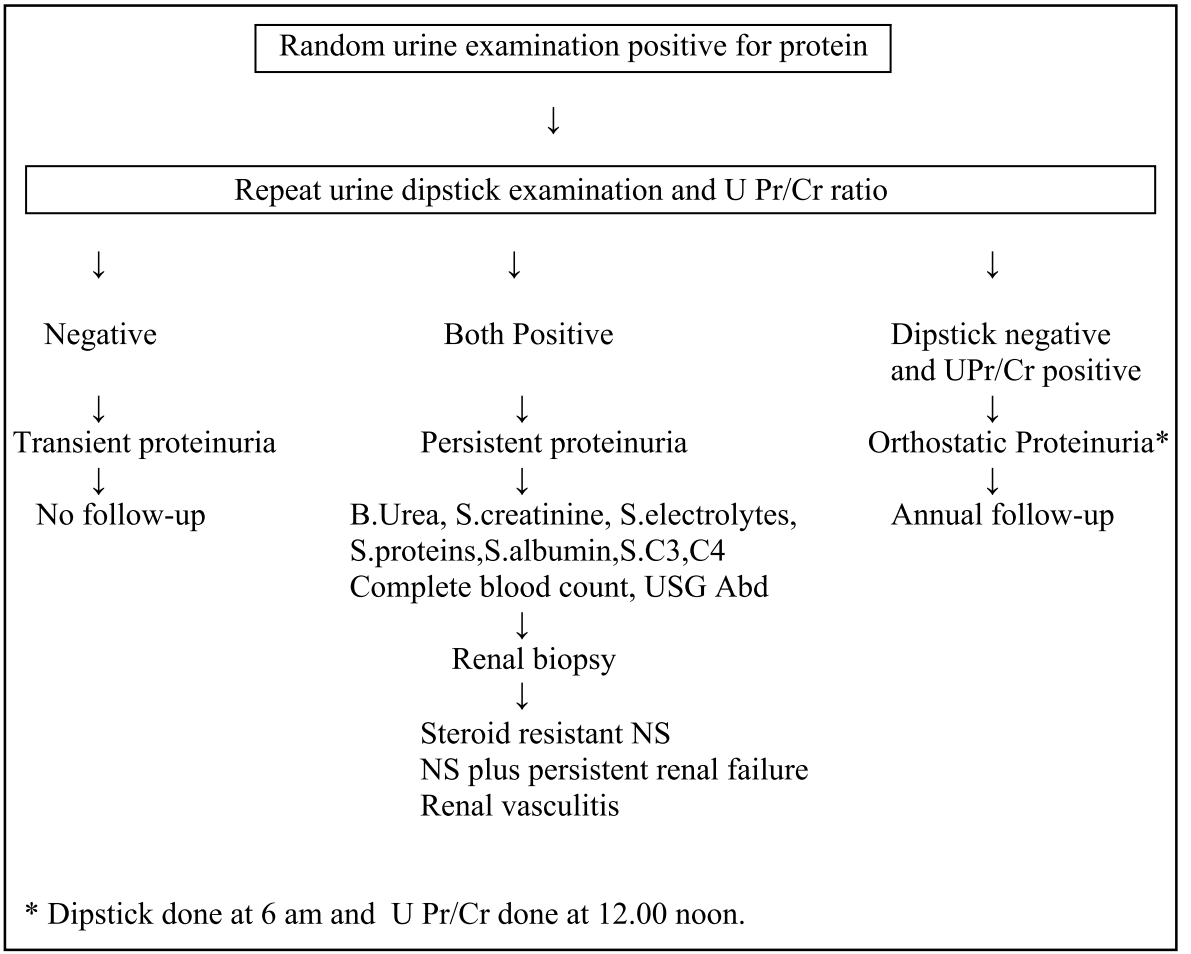
4) **Acquired:** May occur due to drugs like pencillamine, NSAID, heavy metal poisoning like gold, mercury and lead.

Tubular proteinuria: Normally the proximal tubules reabsorb the freely filtered LMW proteins. Injury to the proximal tubules results in diminished reabsorptive capacity and the loss of these LMW proteins in the urine and no or little albumin. Such proteinuria may show trace or 1+ and rarely exceeds 1g/day or <40mg/m^2/hour and is not associated with edema glomerular and tubular proteinuria can be distinguished by electrophoresis of the urine. In tubular proteinuria, the LMW proteins migrate primarily in the alpha and beta regions and little or no albumin is detected, whereas in glomerular proteinuria the major protein is albumin tubular proteinuria may be seen in acquired and inherited disorders and be associated with other defects of proximal tubular function,such as glucosuria, phosphaturia, bicarbonate wasting, and aminoaciduria. Tubular proteinuria rarely presents a diagnostic dilemma because the underlying disease is usually detected before the proteinuria. It occurs in tubulo interstitial diseases like reflux nephropathy and polycystic kidney disease. It may also occur due to drug toxicity like NSIADs, aminoglycosides and heavy metals, in ischemic injury due to shock and acute tubular necrosis and in transport defects like Fanconi syndrome.

Overflow proteinuria: LMW proteins filtered by the glomerulus are almost entirely reabsorbed in the proximal tubule. During states of overproduction of a particular LMW protein and hyperfiltration, the amount of filtered protein exceeds the normal proximal tubular reabsorptive capacity, leading to proteinuria. Overflow proteinuria is not common in children but could occur in myoglobinuria, hemoglobinuria, repeated albumin transfusions, myeloma and paraproteinemia disorders.

Microalbuminuria is a level of albuminuria at which the dipstick is not sensitive enough for detecting albumin. It is an early marker of systemic vascular endothelial cells dysfunction and kidney disease than overt proteinuria. A sensitive and specific assay for albumin is used for the quantitation of albuminuria in the microalbuminuric range. Specialized test strips are there to specifically detect microalbuminuria. The 24 hour urine collection is considered the 'gold standard' method for the measurement of microalbuminuria. Microalbuminuria is defined as daily excretion of 30 to 300 mg of albumin/ day in adults. The PCR on random urine samples

Table.I. Evaluation of asymptomatic proteinuria in children



can also be used. With this method microalbuminuria is defined as a ratio of >0.03mg albumin/mg creatinine and this is abnormal. The importance of asymptomatic microalbuminuria as a risk factor for progressive kidney and cardiovascular diseases was emphasized by the initiation of proteinuria, albuminuria, risk assessment, detection and elimination. (PARADE) program by National Kidney Foundation of United states. Microalbuminuria has been documented in adults to independently predicts poor cardiovascular and renal outcome and the benefits of early interventions. The Causasians PREVEND IT study suggested that treatment of microalbuminuria with ACEI in subjects with normal blood pressure and cholesterol effectively lowered cardiovascular morbidity and mortality and was cost effective. Congenital structural abnormalities and tubular disorders occur much more commonly in children than in adults, while diabetes and hypertension are rare. Structural and tubular diseases may be characterized by significant excretion of LMW proteins that would not be detected by testing exclusively for albumin. It is recommended that total protein be measured for those children with renal disorders other than diabetes.

Clinical evaluation of proteinuria

Children with initial proteinuria, (particularly if 2 + and less) in the absence of a any identifiable source or cause for proteinuria, should have one additional urinalyses be performed and a PCR ratio on the first morning specimen. If the urinalysis and PCR ratio are normal, then it is likely the patient has transient proteinuria (Table 1). A large proportion of children show disappearence of proteinuria subsequently and need no further evaluation. A negative urine protein in the first morning void and a positive urine protein in the mid morning specimen is indicative of orthostatic proteinuria. If both subsequent test results are positive, the child should be considered as persistent proteinuria and subjected to clinical and laboratory evaluation particularly in the presence of renal symptoms, or systemic clinical features and investigations favouring renal involvement.

Once persistent proteinuria is documented, evaluation should begin with history and physical examination focusing on the presence of signs of and symptoms of systemic diseases that can affect the kidney. Manifestations of renal disease such as hematuria, both visible and non visible, edema, hypertension, oliguria, polyuria and urinary symptoms is a strong basis for further evalution even if there is no renal dysfunction. Consanguinous marriage, family history of childhood renal disease, renal anomalies, renal cause of death, deafness, visual defects, (Alport syndrome) and polycystic kidney disease is to be enquired into. Diabetes, eclampsia and hypertension during pregnancy can injure the developing kidney in the fetus. Angiotensin converting enzyme inhibitor(ACEI), angiotensin receptor blockers (ARB), non steroidal anti inflammatory drugs (NSAIDS) during early and late pregnancy injure the fetal kidney. Infants born to mothers receiving ACEI during the second and third trimesters of pregnancy develop oligohydramnios, pulmonary hypoplasia, hypocalvaria, postnatal hypertension, anemia and on postmortem examination found to have severe glomerular and tubular malformations. Perinatal morbidities needing NICU care can be associated with neonatal acute kidney injury and compromised renal function in later life. Presence of early morning facial edema, rapid weight gain, reduced urine out put, hematuria, history of skin infection, infectious fevers like typhoid, mumps, measles and chicken pox, persistent erythematous maculopapular rashes over the face or lower limbs, joint pains (vasculitis), hypertension indicate glomerular origin of proteinuria. Recurrent UTI, polyuria, nocturia, preceding drug intake like NSAID's, aminoglycosides. most frequently prescribed cephalosporins indicate tubular etiology. Vigorous exercise may cause transient proteinuria. Presence of failure to thrive, growth failure, anemia, bony deformities denote chronic kidney injury of early age onset.

Investigation

All the investigations need not be performed for all the patients. For asymptomatic children step by step investigations can be done as per the algorithm (Fig.1). If the child is symptomatic all the tests should be performed.

Urinalysis: (first void morning sample) is rewarding for the presence of proteinuria and the amount of proteinuria reflects the severity glomerular damage. Microscopic presence of RBC casts and dysmorphic RBCs confirm the glomerular origin while large amount lecocytes and its casts with positive bacterial growth in urine cultures indicate pyelonephritis. Persistent crystaluria suggests renal stone disease and tubulo interstitial origin of proteinuria.

Blood chemistry: Blood urea nitrogen, serum creatinine, serum electrolytes , serum cholesterol, serum total proteins-albumin and globulin are the basic investigations in glomerular disease.

Immunlogical profile: Serum complements C3 and C4, anti nuclear antibodies, anti double stranded DNA antibodies, anti nuclear cytoplasmic antibodies for a diagnosis of systemic vasculitis. An elevated serum globulins in the serum electrophoresis is a reliable screening test for immunologically mediated glomerular injury. Anti streptococcal enzyme antibodies is for post infectious glomerular diseases.

Microbiology: Throat, urine and blood cultures if infections are a possibility.

Imaging: Ultrasonography of the urinary tract is an appropriate, noninvasive screening test for the size and anatomic abnormalities of the kidneys and urinary tract and should be considered in patients with chronic kidney disease. A dimercaptosuccinic acid scan is the preferred study to detect renal scars and preferably a pediatric nephrologist concurrence is obtained.

Audiometry: The possibility of Alport syndrome is considered in the presence of family history of nephritis, renal failure, deafness or visual defects.

Renal biopsy is not routinely indicated in the proteinuria work-up. A biopsy should be considered when proteinuria is accompanied by active urinary sediments, persistent and gross hematuria, hypertension, hypocomplementemia, persistent renal insufficiency (CKD > Stage 2) for more than three months with a normal or enlarged kidneys or signs and symptoms suggestive of vasculitic disease. A renal biopsy should also be considered in selected patients with nephrotic syndrome associated with a later age of onset or unresponsiveness to corticosteroid treatment

Management

The family can be reassured if the proteinuria is transient or orthostatic, asymptomatic, no hematuria, has normal blood pressure and glomerular filtration rate. A child with persistent proteinuria should initially receive a blood pressure measurement, urinalysis and serum creatinine estimation at least once in a year until the child is free of proteinuria. The child can have normal diet and physical activity.

Diet: Avoid excessive sodium intake as it will contribute to fluid retention and edema. It is resonable to avoid an excess of dietary protein in children with proteinuric renal diseases, because high dietary protein intake may worsen proteinuria, without achieving higher serum albumin level. It is recommended that children with proteinuria receive the recommended daily allowance of protein for age.

Medications: Certain classes of antihypertensive agents, the ACEI and the ARB, in addition to reducing systemic blood pressure, exert other beneficial effects, such as reducing urinary protein excretion and decreasing the risk of renal fibrosis. Combination ACEI and ARB therapies have additive antiproteinuric activity but proportionately have an increase in adverse effects as cough, hyperkalemia and a rise of serum creatinine particularly in CKD children which requires indicates withdrawal of the drug. The need for serial monitoring of serum potassium and creatinine levels needs to be emphasized. NSAIDs acts by reducing intrarenal prostaglandin production. Dipyridamole acts through adenosine-mediated efferent arteriolar vasoconstriction. However their usage in children is limited by lack of controlled studies.

Summary

The presence of proteinuria can have different significance depending on the underlying cause. At one end are children with false positive, transient or intermittent proteinuria in whom the proteinuria is a harmless finding. At the other end are children with persistent

proteinuria, hematuria and renal failure who are at considerable risk for serious renal disease. In between are children with asymptomatic proteinuria, without hematuria or renal failure who are at no or mild risk of renal disease. The Pediatrician's responsibility remains in recognizing these clinical situations and then planning evaluation, therapy and further referral to a pediatric nephrologist.

Points to Remember

- ***Proteinuria is an early marker of renal disease.***
- ***Quantification of proteinuria is mandatory.***
- ***Pathological proteinuria requires further work up.***
- ***Asymptomatic <2+ isolated proteinuria requires annual surveillance.***

Bibliography

1. Bergstein JM. A practical approach to proteinuria. Pediatr Nephrol 1999; 13: 697-700.
2. Jafar TH, Chaturvedi N, Hatcher J, Levey AS. Use of albumin creatinine ratio and urine albumin concentration as a screening test for albuminuria in an Indo-Asian population. Nephrol Dial Transplant 2007; 22: 2194-2200.
3. Tomlinson PA. Low molecular weight proteinuria in children with renal disease; Pediatr Nephrol 1992; 6: 565-571.
4. Litwin M, Grenda R, Sladowska J, Antoniewicz J. Add-on therapy with Angiotensin II receptor I blocker in children with chronic kidney disease already treated with ACE inhibitor. Pediatr Nephrol. 2006; 11: 1716-1722.
5. Williams JD, Coles GA. Proteinuria – a direct cause of renal morbidity. Kidney Int 1994; 45:443–450.
6. Dodge WF, West EF, Smith EH, Bruce Harvey III. Proteinuria and hematuria in schoolchildren: epidemiology and early natural history. J Pediatr 1976; 88: 327–347.
7. Vehaskari VM, Rapola J. Isolated proteinuria: analysis of a school-age population. J Pediatr 1982; 101: 661–668.
8. Bergstein JM. A practical approach to proteinuria. Pediatr Nephrol 1999;13:697–670.
9. Alt JM, Von der Heyde D, Assel E, Stolte H. Characteristics of protein excretion in glomerular and tubular disease. Contrib Nephrol 1981; 24: 115–121.
10. Hogg RJ, Portman R J, Milliner D, Lemley KV, Eddy A, Ingelfinger J. Evaluation and Management of Proteinuria and Nephrotic Syndrome in Children: Recommendations From a Pediatric Nephrology Panel Establishedat the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk, Assessment, Detection, and Elimination (PARADE) Pediatrics 2000; 105; 1242-1249.
11. Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, et al. Prevention of renal and vascular end stage disease Intervention Trial (PREVEND IT). Effects of Fosinopril and Pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation 2004;110: 2809-2816.

NEPHROLOGY

APPROACH TO MANAGEMENT OF PEDIATRIC STONE DISEASE

** Tamilarasi V*

Abstract: *Renal stone disease among children is usually associated with biochemical abnormalities and need evaluation for detecting the cause. Renal dysfunction is also common. Calcium containing stones are the predominant type. Clinical features of urolithiasis include abdominal or flank pain and hematuria and the presenting symptom varies with age. CT scan of abdomen is a useful imaging tool for confirmation of diagnosis and planning treatment. Management of pediatric urolithiasis includes treatment of acute event and prevention of recurrence of stone. Technical advances have greatly helped the endourological interventions possible for stone disease. Hydration and tackling the underlying disorder is the main stay of medical management for prevention of stone recurrence.*

Keywords: *Pediatric, Renal stone, Urolithiasis, Calcium, Oxalate, ESWL*

Urolithiasis in the pediatric age group is associated with significant morbidity, particularly if stones recur. Although progress has been made with regard to the better understanding of the aetiology, pathophysiology, therapy and prevention of stone disease, still many aspects are controversial. Renal stone disease is less common in children than adults. Though many aspects of pediatric renal stone disease are similar to that of adults, there are unique concerns regarding the presentation, diagnosis and management. Among children and adolescents, boys show a mild preponderance for stone disease overall. Urolithiasis in children is usually secondary to systemic disease or renal disease. Establishing the diagnosis, finding out the etiology and medicosurgical management are three important aspects in urolithiasis. Overall management depends on obstruction (unilateral or bilateral), associated hypertension, renal failure and infection.

Types of stones and stone promoting factors

Stones are classified depending on the content in them. Most common is calcium stones containing a) calcium oxalate b) calcium oxalate and phosphate c) calcium phosphate or calcium oxalate and d) uric acid. Cystine stones contain cystine or cystine and calcium. Infection or struvite stones contain ammonium magnesium phosphate. Uric acid stones are relatively less common. Low intake of fluids causes increased supersaturation of stone forming salts. Dairy products cause hypercalciuria and animal proteins increase the uric acid production. Increased oxalate intake in vegetarian diet and hence increased urinary excretion of oxalate should be remembered. Hypercalcemia and hypercalciuria following immobilization can become a problem. Hypocitraturia is an important factor, which results in reduced complexing of calcium with citrate, and can cause increased

* Professor of Nephrology,
Christian Medical College and Hospital,
Vellore.

calcium oxalate supersaturation. Hypomagnesiuria results in reduced magnesium oxalate complexing, producing calcium oxalate supersaturation.

Essential features of renal stone disease

Evaluation for metabolic causes in children with renal stone disease becomes very important in the following conditions; 1) Renal calculi in children < 5 years, 2) presence of systemic features like acidosis, failure to thrive, 3) Multiple stones and 4) Recurrence of stones within one year. Normal 24-hours urine values for various stone related substances are given in Table 1.

Table.I. Normal 24 hours urine values

Calcium	< 4 mg/kg/24h
Uric acid	< 11 mg/kg/24h
Oxalate	< 0.7 mg/kg/24h
Creatinine	Newborn 8 to 10 mg/kg
	Children 10 – 12 mg/kg
Cystine	<75 mg/G creatinine
Citrate	< 180 mg/G creatinine
Magnesium	> 88mg/1.73 m2/day

Hypercalciuria: This condition is diagnosed with a spot urine calcium/creatinine ratio of more than 0.21 and 24 hours urine calcium of more than 4 mg/kg/day. It can be normocalcemic or hypercalcemic. The common causes of hypercalcemic hypercalciuria include vitamin D intoxication, hyperparathyroidism and immobilization. While normocalcemic hyper calciuria can occur due to frusemide toxicity, renal tubular acidosis and idiopathic autosomal dominant hypercalciuric syndrome. Two types of hypercalcuric syndrome include absorptive hypercalciuria and renal hypercalciuria. In absorptive variety fasting urine Ca/Cr ratio is normal with normal serum paratharmone level. There is increased Ca/Cr ratio on calcium load. Whereas in renal variety there is high fasting urine Ca/Cr ratio with elevated serum paratharmone level and very mild increase on calcium load.

Infection (Struvite) stones : It essentially results from infection. It usually occupies the entire pelvis and is irregular. Urease producing organisms (Proteus, Klebsiella, Pseudomonas) split urea to ammonia and CO_2 which is converted into ammonium and hydroxyl ion. Hydration of CO_2 produce HCO_3- which increases the urinary pH (alkaline). This increased pH causes precipitation of magnesium, ammonium, calcium and phosphate leading to struvite formation. E. coli is also noted in infected stones as they reduce urokinase and increase sialidase activity resulting in increased matrix substance and crystal adherance.

Renal tubular acidosis: Type I RTA can present with nephrocalcinosis and nephrolithiasis. Stones essentially result from hypercalciuria and hypocitraturia. Stones are also rarely being documented in proximal RTA.

Oxalate stones: This condition results from hyperoxaluria and may be inherited or acquired. Primary Type I is due to deficiency of liver-peroxisomal glyoxylate aminotransferase. Pyridoxine is a cofactor to convert glyoxylate to glycine in liver peroxisomes. Enzyme deficiency leads to conversion of glyoxylate to oxalate and glycolate with deposition of oxalates in various tissues resulting in organ damage. Infantile variant of type I will have nephrocalcinosis and CRF; Nephrolithiasis is rare. It is termed metabolic malignancy. Primary type II is a rare disease and is due to deficiency of cytosolic enzyme D-glycerate dehydrogenase. Acquired hyperoxaluria can occur due to GI disorders like

blind loop syndrome and biliary and pancreatic disease. Excessive dietary intake of oxalate and excessive intake of oxalate precursors like ascorbic acid can be a factor. Pyridoxine deficiency is an added factor in them. Acquired enteral variety is due to fat malabsorption. Normally good amount of oxalate is excreted as Calcium oxalate in stools. Here calcium combines with fatty acids to form insoluble soaps, reducing calcium and hence reduced complexing with oxalate resulting in increased absorption of oxalate in colon.

Cystinuria: Cystines are detected by sodium nitroprusside test or by urinary aminoacid screening. Usually cystine crystals are not readily seen in urine as urine is alkaline. Usually cystine stone is non-radiopaque unless the sulfur content and calcium makes it radio-paque. It is due to autosomal recessive metabolic disease of defective cystine transport across renal tubules and GI tract. Cystine is usually insoluble more so in acid medium and hence crystal precipitation occurs leading to urolithiasis.

Hyperuricosuria: Low urine pH favours uric acid stones. Increased uric acid production (Gout due to enzyme defect, myelo or lympho proliferative diseases or excessive purine intake) and decreased urinary volume as in chronic diarrhoea and ileostomy are the common etiologies. Uric acid forms the nidus for calcium oxalate stone or it decreases the concentration of inhibitors of calcium oxalate lithiasis in urine. Relatively less common in children.

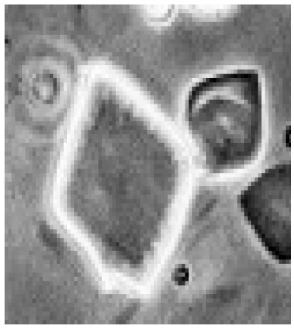
Clinical features

Symptoms of renal colic and gross hematuria, pathognomonic of urolithiasis in adults, are seen less commonly in children. Flank or abdominal pain or hematuria accounted for initial presenting features in 94% of adolescents,72% in school age children, and accounted for presenting features in just 56% of those from birth to 5 years of age in one series.[1,2] Stones from the upper urinary tract are comprised of calcium oxalate in 40-60%, calcium phosphate in 15-25%, mixed (usually calcium oxalate and calcium phosphate) in 10-25%, magnesium ammonium phosphate (struvite) in 17-30%, cystine in 6-10%, and uric acid in 2-10%.[1,3,4]

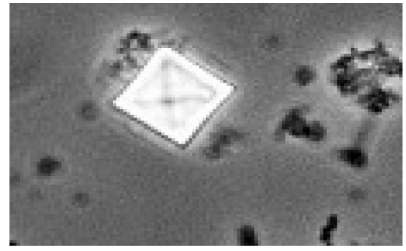
Diagnosis

History of passage of stones or mud in the urine should make one supect renal stone disease. Essential clinical features mentioned should be looked into. Radiology is an important diagnostic tool. Radiopaque stones by plain radiograph of abdomen can be identified with calcium oxalate and calcium phosphate stones. Radiolucent stones (uric acid, xanthine and cystine) will be usually missed. Mixed uric acid and calcium oxalate stones and cystine stones with more sulfur content can be radioopaque. Infection stones exhibit varying radiopacity. USG abdomen is important for identification of stones and to detect hydronephrosis or ureterohydronephrosis, the secondary effects. Intravenous urogram may be useful in radiolucent stones and it also iidentifies abnormalities of the tract. CT abdomen with or without contrast is an important modality in this context. It is useful as a last resort to confirm the presence and the position of the stones. Nimkin compared imaging modalities for detection of stones in the pediatric population, and reported a sensitivity of 57% for plain films, and 77% for ultrasonography when compared with stone detection by CT.[5] Others have reported better overall sensitivity for ultrasonography, but it may miss 30% of small papillary or calyceal stones and may miss ureteral calculi.

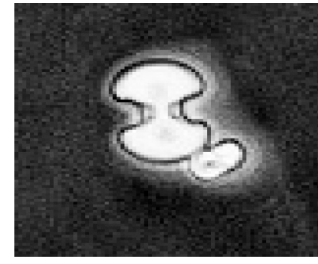
Urine analysis is done for RBCs and pus cells in the urine. Crystals by their shapes can also give pointers towards the cause (Fig.I). Calcium oxalate crystals can be seen as pyramid or envelope shaped crystals. Magnesium



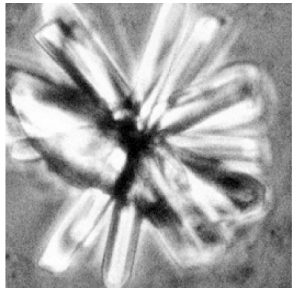
Uric acid crystals; rhomboid shape.



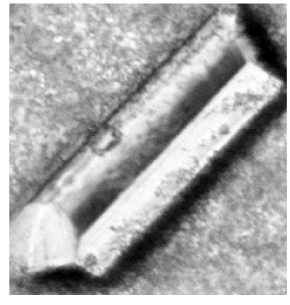
Bihydrated calcium oxalate, crystals letter envelope.



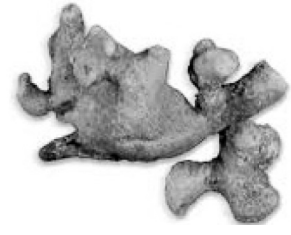
Monohydrated calcium oxalate crystals.



Star-like calcium phosphate Crystal.



Triple phosphate crystal with massive amount of amorphous phosphate particles.



Struvite stones [magnesium ammonium phosphate hexahydrate].

Fig.1. Various types urinary crystals

ammonium phosphate crystals appear as coffin lids. Cystine crystals are seen as flat hexagonal plates. Urate crystals are usually diamond or trapezoid shaped. Urine culture is needed to rule out UTI which is primary or secondary in urolithiasis. Basal renal evaluation is necessary and acute renal failure signifies the urgency in the management of obstruction. Chronic renal failure can be due to infantile oxaluria, a variant form of Type I primary oxaluria. Serum electrolytes and ABG should be done. Normal anion gap hyperchloremic acidosis is seen in Type I RTA and look for hypo and hyperkalemia. Always look for hypercalcemia and hypercalciuria. In most of the renal stone diseases in children the initial evaluation is for hypercalciuria. Parathormone assay as per need is mandatory. Later look for hyperuricemia, hyperuricosuria, hyperoxalauria and hypocitraturia. Nitroprusside test for cystine should be done. Stone analysis for the type of stones may guide us towards the casue.

Managament

Management is mainly aimed at the cause. Cause of stone is basically due to supersaturation and hence treatment is aimed at reducing the supersaturation. General management include

increased fluid intake to increase urine amount and we should make the child to avoid unwanted vitamin D, vitamin C and calcium containing antacids. Child should be encourage to take the daily recommended allowance of milk. Avoidance of oxalate rich substances is adviced. Narcotic analgesics for renal colics and surgical care for obstruction should be done. Liberal use of USG for monitoring the disease progress will be needed.

Renal hypercalciuria is treated with hydrochlorothiazide for increasing the tubular reabsorption of Ca++ In a dose of 2-3 mg/kg/day in 2-3 doses. Low sodium intake is needed for better action of thiazide. In absorptive hypercalciuria decreasing the calcium intake is useful but impossible in children. Cellulose phosphate to bind Ca++ in the gut can be tried but there is reduced calcium to complex with oxalate leading to increased oxalate absorption and oxaluria. Renal tubular acidosis is treated with correction of acidosis. Potassium citrate is better than sodium citrate in practice. Hydrochlorothiazide is also tried for hypercalciuria.

In hyperoxaluria the child should reduce the intake of oxalate rich food. Administration of high dose pyridoxine is advised. Normal calcium diet should be encouraged which will bind oxalate in the gut. Increasing the fluid intake is an important step. In primary oxaluria large doses of pyridoxine, good hydration, haemodialysis to reduce oxalate burden and combined liver and renal transplantations are the various steps. In enteric hyperoxaluria, treatment of GI conditions and reducing the fat intake will help the child. In uric acid stones reduction in dietary purine intake and urinary alkalinisation with potassium citrate or acetazolamide will be useful. Increasing the fluid intake again is very useful. Allopurinol is used if hyperuricemia is present. In cystine stones increasing the water intake and oral alkali therapy are useful. D-penicillamine is used with caution. It reduces the excretion of cystine and makes the cystine more soluble.

In infection stones treatment of infection with antibiotics and long-term chemoprophylaxis are useful. Regular acidification of urine is tried by some. Less than 2.5 cm stone are treated with extra corporeal shortwave lithotripsy (ESWL) whereas more than 2.5 cm stone are treated with ESWL with percutaneous nephrolithotomy or ureteroscopic removal and pyelolithotomy. Ureteral stenting to avoid obstruction before ESWL for large stones is usually done.

The management of pediatric nephrolithiasis is divided into two parts. 1) Acute episode - During the acute episode the aim of treatment is to control the pain and measures to facilitate the removal of calculus and 2) Prevention of recurrent disease - After the acute episode, management is directed towards prevention of recurrent stone disease.

Stones causing obstruction, acute renal colic, stones with a high potential for acute obstruction (e.g., a large stone in the renal pelvis), and infected stones should be evaluated. Majority of stones less than 5 mm in diameter will pass spontaneously.

Recently alpha adrenergic antagonists or calcium channel blockers are being used to facilitate passage of ureteral stones.The proposed mechanism is relaxation of ureteral smooth muscle, with subsequent inhibition of ureteral spasms and dilatation of the ureter. Tamsulosin is a frequently used agent. In adult patients meta-analysis of available studies suggests benefit when either of these agents are added to standard therapy, and the mean time to stone expulsion of less than 14 days in those receiving alpha-

adrenergic antagonists.[6,7] This approach has been most successful with distal ureteral stones. There is little information available in pediatric stone patients. Use of corticosteroids or non-steroidal anti-inflammatory agents to reduce ureteral edema, either alone or in combination with alpha adrenergic antagonists has shown mixed results.[6]

Dissolution of cystine, uric acid, or struvite stones can sometimes be accomplished but is challenging and best reserved for selected situations. Calcium stones are not amenable to dissolution. Larger symptomatic stones are likely to require surgical intervention.

The best treatment for infection related stones involves eradication of the infectious agent. Since stone material is often not well penetrated by antibiotics, removal of infected stone material is often required.Urease inhibitors such as acetohydroxamic acid (AHA) can be helpful but have a high incidence of adverse effects.[4,5] Patients with infected stones requiring ESWL, percutaneous ultrasonic lithotripsy, or an open procedure require attentive antibiotic management as bacteria may be released rapidly from stone material on fragmentation during lithotripsy orinstrumentation. Struvite stones may be soft and friable,with particular vulnerability to stone fragment retention following ESWL. Any stone fragments remaining mayharbor bacteria in the interstices of the fragments, making eradication of the infection very difficult. In addition, stone fragments provide a nidus for new struvite stone formation, which can occur rapidly. It is for this reason that percutaneous nephrolithotomy is still sometimes required to assure complete removal of stone material. Stones that are not infected and not causing symptoms or associated with impending or established obstruction may be managed medically.

Surgical management of renal stones in children

Management of renal stones has significantly evolved due to technological advances and miniaturization of endourological instruments. Currently, the majority of stones in children can be managed with shock-wave lithotripsy (SWL), percutaneous nephrolithotomy (PCNL) or ureterorenoscopy (URS), or a combination of these modalities while open surgery is currently needed in a limited number of cases.

Extracorporeal shock-wave lithotripsy (ESWL): ESWL is least invasive and most simple, safe and effective so it has become the preferred treatment alternative in the minimally invasive management of stones in children, with satisfactory stone-free rates. Following treatment, residual fragments after ESWL should be followed closely with regular visits in the light of the higher incidence of metabolic and anatomical abnormalities in this specific age group. Renal pelvic stones or calyceal stones up to 2cm in diameter are ideal indications for SWL and success rates tend to decrease as the size of the stone(s) increases. Currently, depending on the size, number, location and chemical composition of the stones, more than 90% of all urinary stones in adults and nearly 80% of all stones in children are successfully treated with ESWL. Following ESWL, stone-free rates ranging from 57 to 97% during short-term follow-up and 57 to 92% during long-term follow-up have been reported in the literature.[8,9] Re-treatment rates range from 13.9 to 53.9% in different series, while ancillary procedures and/or additional interventions range from 7 to 33%.[10]

No irreversible serious side effects of high-energy shock waves have been seen during short- or long-term follow-up. Although ESWL is the first treatment modality in the majority of stones located in the upper ureter, the success rates

decrease as the stone passes to the more distal parts of the ureter. Currently, larger stones (>1cm), impacted stones, Ca-oxalate monohydrate and cysteine stones, stones in children with unfavourable anatomy and in whom localization difficulties exist are the cases in which SWL is likely to be unsuccessful.

Ureteroscopy: Traditionally, the standard treatment for ureteral stones in children was open surgical removal but now open surgery is needed rarely in such cases. Today, ureteroscopy may be applied for diagnostic and/or therapeutic purposes, and with the clinical introduction of fine, smaller-calibre instruments this modality has become the treatment of choice in middle and distal ureteric stones in children. The success rate of ureteroscopy has been reported to be 87-100% for removal of lower and mid ureteric calculi whereas it is 78%for upper ureteric stones.Regarding the efficacy of ESWL and URS, stone-free rates in patients with calculi of >10mm were 93% with ureteroscopy and 50% with SWL, while for calculi of <10mm the stone-free rates were 100 and 80% for ureteroscopy and SWL, respectively. Ureteroscopy should be preferred for distal ureteral stones, larger stones and impacted stones. Complications such as ureteral avulsion, perforation, haematuria, infection and ureteral stricture, may occur after ureteroscopy in 0-7% of the patients.

Percutaneous nephrolithotomy (PCNL): Major concerns for using this technique in pediatric population were regarding long-term renal damage, small kidney size, relatively large instruments, radiation exposure and the risk of major complications such as bleeding. However, as the experience in this field grew, large studies demonstrated that there can be only minimal scarring and insignificant loss of renal function after PCNL. Thus, the same techniques are used in this population as in adults and age is not considered to be a limitation. Indications for PCNL in children are a large stone burden, significant renal obstruction with urinary infection, failure of ESWL and significant volume of residual stones after open surgery. Typically PCNL has been advocated as a suitable treatment for children with significant stone burdens to avoid numerous ESWL sessions under anaesthesia and the prospect of repeated open surgery. Concerning the efficacy of the technique, stone-free rates of about 90% (ranging from 67 to 100%) and no significant complications have been reported in many series.

Cystolithotomy: The principles of management of bladder calculi are similar to those for upper urinary tract calculi. Approaches for bladder stones are the endoscopic, suprapubic percutaneous access and open surgery routes. The majority of the stones located in the bladder are usually large and hard, and can be treated by either transurethral or percutaneous suprapubic lithotripsy or litholopaxy. The major concern with the transurethral approach is the posssible damage to the male urethra, explaining the rare and judicious use of this technique.

In recent years suprapubic cystolithotomy has evolved as a safe and effective alternative technique in such cases. After removing the stone intact, one option will be closing the bladder primarily, or, in small openings, the bladder may be drained for several days to let the opening close.

Laparoscopic surgery: The role of laparoscopy in the management of pediatric stone disease remains to be explored. Despite the limited data reported in the literature, we believe that further studies including larger series of children are needed.

Retrograde intra-renal surgery: With increasing experience of retrograde intra-renal surgery (RIRS) in adults, recently a

few reports of successful ureterorenoscopic management of inferior calyceal stones in children have been published. In future, RIRS may be used more frequently to treat residual stones after SWL, inferior calyceal stones and cystine.

Points to Remember

- ***Urolithiasis in children is usually associated with underlying disorders and hence needs evaluation.***
- ***Commonest are the calcium containing stones***
- ***Clinical features vary with age of presentation***
- ***Management of pediatric renal stone disease involves both the treatment of acute episode and also prevention of stone recurrence.***

References

1. Milliner DS, Murphy ME. Urolithiasis in pediatric patients. Mayo Clinic Proc 1993; 68:241-248.
2. Stapleton FB. Clinical approach to children with urolithiasis. Semin Nephrol 1996;16:389-397.
3. Walther PC, Lamm D, Kaplan GW. Pediatric urolithiasis: a 10-year review. Pediatrics 1980; 65:1068-1072.
4. Sarkissian A, Baloyan A, Arikyants N, et al. Pediatric urolithiasis in Armenia: a study of 198 patients observed from 1991 to 1999. Pediatr Nephrol 2001;16:728-732.
5. Nimkin K, Lebowitz RL, Share JC, Teele RL. Urolithiasis in a children's hospital: 1985-1990. Urol Radiol 1992;14:139-143.
6. Singh A, Alter HJ, Littlepage A. A systematic review of medicaltherapy to facilitate passage of ureteral calculi. Ann Emerg Med 2007;50: 552-563.
7. Parsons JK, Hergan LA, Sakamoto K, Lakin C. Efficacy of alpha-blockersfor the treatment of ureteral stones. J Urol 2007; 177:983-987.
8. Rizvi S, Nagvi S, Hussain Z, Hashmi A, Hussain M, Zafar MN, et al., Management of pediatric urolithiasis in Pakistan. Experience with 1,440 children, J Urol 2003;169:634–638.
9. Landau E, Gofrit O, Shapiro A, Merety KS, Katz G, Shenfeld OZ,et al. Extracorporeal shockwave lithotripsy is highly effective for ureteral calculi in children, J Urol 2001; 165:2316–2318.
10. Tan AH, Al-Omar M, Watterson JD, Nott L, Denstedt JD, Razvi H. Results of shockwave lithotripsy for pediatric urolithiasis, J Endourol, 2004; 18:527–530.

NEWS AND NOTES

3rd Spring Summer National Pediatric Neurology Workshop (EEG-EMG-NCV-EP (BAER-VEP), Hubli, Karnataka.

Date: **1st to 3rd June, 2012**

For details contact

Dr KMP Suresh,

Child Neurology and Epilepsy Referral Centre,

1 & 2 – 2nd Floor, Mallikarjun Avenue, Koppikar Road, Hubli 580 020, Karnataka, India. Mobile: 09448272428, E-mail: drkmpsuresh@hotmail.com.

NEPHROLOGY

APPROACH TO OLIGO- ANURIA IN NEONATES

**** Arpana Iyengar***

Abstract: *Neonatal kidneys are vulnerable to perinatal stress in the form of hypoxia, hypoperfusion and hypovolemia. Oliguria and anuria are manifestations of pre-renal and intrinsic renal failure secondary to perinatal asphyxia, drug toxicity and obstructive disease. Early recognition of precipitating factors for oligo-anuria, timely detection of underlying renal anomalies and prompt management go a long way in preventing oligo-anuric renal failure and its complications. The clinical approach to oligo-anuria and management with fluid challenge, diuretic challenge, fluid restriction and renal replacement therapy are discussed in this article.*

Keywords: *Oligo-anuria, Neonates, Acute renal failure, Acute kidney injury.*

The 'stressed' newborn kidney: Neonates have vulnerable, immature kidneys with the following characteristics: (a) low glomerular filtration rate, (b) limited ability to concentrate urine, (c) inability to excrete large amounts of free water (d) poor capacity to reabsorb solutes and (e) limited ability to auto regulate renal blood flow. The neonatal kidney is particularly vulnerable to the effects of hypoperfusion since the renal vascular resistance and plasma renin activity are high. The incidence of nonoliguric, oliguric and anuric renal failure in asphyxiated neonates are reported to be 60%, 25% and 15% respectively.[1]

* Associate Professor
Division of Pediatric Nephrology,
St John's Medical College Hospital,
Bangalore.

Oliguria is defined as urine output less than 1mL/kg/hr and anuria as urine output of less than 0.5mL/kg/hr. Acute kidney injury (AKI)/Acute renal failure is an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL, a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg per hour for more than six hours).

The time of first voiding is dependent on the infant's state of hydration and therefore indicates adequacy of intake as much as renal function. Generally the first void occurs in the delivery room in 20% and within the first 24hours in 90% of neonates. Premature infants may void even earlier than term infants unless they are unwell. Improved maternal hydration during labour and early initiation of feeding in the newborn could prevent delay in the first void of urine. A decrease in urine output is a common clinical manifestation of acute renal failure but many forms of acute renal failure are associated with normal urine output.

Pathophysiology

Prerenal ARF is the most common form of ARF in newborn. The cause of prerenal ARF is renal hypoperfusion due to systemic hypotension or to selective decreases in renal blood flow in response to tissue hypoxia without significant systemic hypotension. Under these

circumstances, renal autoregulation fails to maintain renal blood flow (RBF) and glomerular filtration rate(GFR) in the physiologic range. Correction of the underlying condition immediately restores normal renal function unless renal hypoperfusion has been so severe and prolonged that renal parenchymal damage has already developed. One parenchymal damage occurs, prerenal ARF evolves into intrinsic ARF.

Severe perinatal asphyxia is most common cause of intrinsic renal failure. The severity of intrinsic ARF ranges from mild tubular dysfunction to acute tubular necrosis. The course of intrinsic ARF may be subdivided into initiation, maintenance and recovery phases. Changes in renal hemodynamics brought about by the excessive production and release of vasoconstrictive hormones, including the renin-angiotensin system, epinephrine, norepinephrine, endothelin, adenosine, vasoconstrictive prostaglandins, and vasopressin, play an important role in the development and maintenance of intrinsic renal failure. In addition, alterations in the function and ultrastructure of the nephron, including the decrease in the permeability and surface area of the glomerular capillary, intratubular obstruction to tubular flow by cellular debris, and tubular back leak, contribute to the impairment or renal function in intrinsic renal failure. Finally , the deterioration of hemodynamic and tubular functions is associated with intracellular events, such as enhanced free radical injury with reperfusion of the kidneys and accumulation and sequestration of intracellular calcium in mitochondria, resulting in phospholipase activation and ensuing deterioration of mitochondrial structure and function.

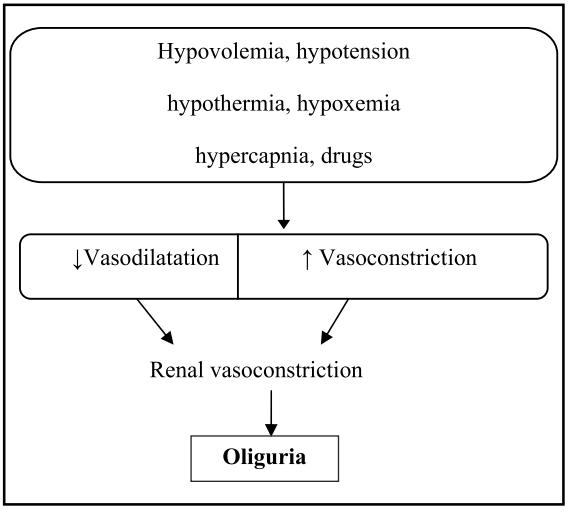


Fig.1. Etiopathogenesis of oliguria[3]

Obstructive renal failure can be caused by a variety of congenital malformations of the kidneys and urinary collecting system. Some of the newborns have reversible renal failure, whereas others have renal dysplasia with irreversible intrinsic renal failure at the time of diagnosis. Although prognostication of long term outcome of renal function in obstructive renal failure is extremely difficult, in new borns with prune belly syndrome, a nadir serum creatinine greater than 0.7 mg/dL, bilateral renal abnormalities on renal ultrasound scan, and clinical pyelonephritis are prognostic for development of CRF.

Etiology

Newborns with prerenal failure or acute renal failure due to hypoxic/ischemic insults or corticonecrosis are more likely to have oligo-anuria. Sepsis, acute tubular necrosis, aminoglycoside nephrotoxicity and contrast nephropathy are more likely to have acute renal failure with normal urine output.

The common causes of oligo-anuria are listed in Table.I.

Pre-renal failure

This is the commonest (85%) cause for acute kidney injury in the newborn.[2] It results from renal hypoperfusion due to true volume

Table.I. Causes likely to present with oligo-anuric acute renal failure in neonates

1. Prerenal acute renal failure - Loss of effective circulating blood volume

Absolute loss

- Hemorrhage
- Dehydration

Relative loss

- Increased capillary leak (sepsis, NEC, RDS, asphyxia, ECMO)

Renal hypoperfusion

- All of above
- CCF, cardiac surgery
- Pharmacological agent (indomethacin, ACE inhibitors)

2. Intrinsic acute renal failure

Acute tubular necrosis (severe renal ischemia, nephrotoxins)

Congenital malformations (bilateral renal agenesis, renal dysplasia, polycystic kidneys)

Infections

- Congenital infections like syphilis, toxoplasmosis
- Pyelonephritis
- Bacterial endocarditis

Renal vascular causes

- Renal artery thrombosis
- Renal vein thrombosis
- DIC

Nephrotoxins

- Amino glycosides, indomethacin, amphotericin B, methicillin, dyes

Intrarenal obstruction

- Uric acid nephropathy, myoglobinuria, hemoglobinuria

3. Obstructive renal failure

Congenital malformations

- Imperforate prepuce, urethral stricture, PUV, urethral diverticulum, primary VUR, ureterocoele, megaureter, UPJ obstruction

Extrinsic compression

- Sacrococcygeal teratoma, hematocolpos

Intrinsic compression

- Renal calculi, fungal balls

Neurogenic bladder

contraction or from a decreased effective blood volume. Volume contraction results from hemorrhage, diarrhea, phototherapy, salt wasting renal or adrenal diseases, diabetes insipidus and in disease states associated with third space losses such as sepsis or traumatized tissue with capillary leak syndrome. Decreased effective blood volume occurs when the true blood volume is normal or increased but renal perfusion is decreased like in congestive cardiac failure and cardiac tamponade.

Ischemic renal failure

This comprises of 11% of AKI and can evolve from pre-renal failure if the insult is severe enough to result in vasoconstriction and acute tubular necrosis. This form of AKI results from perinatal asphyxia and septic shock.

Nephrotoxic renal failure

Nephrotoxic renal failure is commonly associated with aminoglycosides, nonsteroidal anti- inflammatory drugs (NSAIDs), ACE (angiotensin converting enzyme) inhibitors, amphotericin B and contrast media. Among these, NSAIDs and ACE inhibitors can cause oligo-anuric AKI whereas aminoglycosides typically cause non-oliguric AKI.

Vascular injury

Renal artery thrombosis and renal vein thrombosis will result in renal failure if bilateral or if it occurs in a solitary kidney and can result in oliguria. Cortical necrosis is associated with hypoxic/ischemic insults due to perinatal anoxia, placenta abruption and twin to twin, twin - maternal transfusion resulting in hematuria, oliguria and hypertension.

Obstruction

This forms 3% of AKI in neonates. Though the quantity of urine formed is optimal, due to obstruction of the urinary tract, there is reduced urine output. Some forms of urological problems like posterior urethral valves can be associated with renal dysplasia/ hypoplasia.

The etiopathogenesis can be sumarised as in Fig.1[3]

Evaluation

Prenatal evaluation

1. Maternal history: Ingestion of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs and selective COX-2 inhibitors. Maternal exposure to ACE inhibitors in second / third trimester causes ACE fetopathy (renal failure, limb deformities, hypotension, pulmonary hypoplasia and hypo calvaria).

2. Antenatal ultrasonography: Fetal renal anomalies should be identified in the antenatal period as shown in Table II.

3. Amniocentesis:Amniotic fluid serves as a surrogate marker of the fetal renal function as it is composed of foetal urine. Foetal urine markers associated with favourable renal prognosis[4] are depicted in Table III.

Post natal evaluation

Examination

Gestational age assessment: preterm neonates are at higher risk for renal insults.

Congenital anomalies: Single umbilical artery, external ear defects, aniridia, microcephaly, Potter's facies, pulmonary hypoplasia, absence or laxity in abdominal wall (prune belly syndrome), ambiguous genitalia, spinal and skeletal defects.

Edema, hypertension, palpable kidneys, palpable bladder, volume status: fluid overload or dehydration

Table.II. Ultrasonographic findings

Kidneys	:	Agenesis, cysts, hydronephrosis, nephrocalcinosis
Bladder	:	Dilation with thickened wall (posterior urethral valves), exstrophy
Hydrops fetalis	:	Bilateral renal cystic disease, urinary tract obstruction and congenital nephrotic syndrome
Oligohydramnios	:	Renal dysfunction, urinary tract obstruction
Placental edema	:	Finnish type of congenital nephrotic syndrome

Table.III. Amniocentesis markers for favourable fetal renal function

Fetal urine	Value
Sodium (mmol/L)	<100
Chloride (mmol/L)	<90
Calcium (mmol/L)	<1.2
Osmolality (mOsm/L)	<200
Total protein (mg/dL)	<20
Cystatin C (mg/L)	<1

Investigations

Renal functions: (serum creatinine, blood urea). As urine output alone may not reflect renal functions in the newborn, serial measurements of renal functions especially in high risk neonates is mandatory. The expected finding of high creatinine in the neonate in the first 72 hours due to maternal reflection should be kept in mind during evaluation.

Biochemistry: Serum electrolytes (sodium, potassium, chloride), serum bicarbonate, calcium, phosphorous, albumin and uric acid.

Renal ultrasound: The size of the kidneys, bladder anatomy, hydronephrosis and features of nephrocalcinosis need to be noted.

Urine analysis: The presence of granular casts, hyaline casts, RBC, proteins and tubular cells suggest an intrinsic cause.

Differentiating pre renal from intrinsic renal failure[5]: Obtaining urine sample may be difficult in babies who are oliguric. The urinary indices are not reliable after fluid challenge or use of diuretics, making their utility limited in clinical practice. The urinary diagnostic indices are listed in Table IV.

Medical management

The approach to manage a newborn with oligo-anuria is depicted in Fig.2.

Urinary bladder catheterisation: It is vital to ensure bladder drainage in all newborns with oligo-anuria.

Regime for fluid restriction

Having ensured necessary fluid resuscitation, in the presence of persisting oligo-anuria, fluids must be restricted to insensible water loss along with urinary loss. The fluid should be electrolyte free10% dextrose water. Fluids should be restricted to insensible losses (500mL/m^2 perday or 30mL/kg/day) plus urine out put and other measured losses.[6] It is important to revise fluid requirement every eight hours based on urine output and ongoing losses.

Table.IV. Urinary diagnostic indices

Parameters	Pre-renal AKI	Intrinsic AKI
BUN/Creatinine ratio(mg/mg)	>30	<20
*Fractional excretion of sodium (FENa%)	<2.5	>3.0
Urinary sodium (mEq/l)	<20	>50
Urinary osmolality (mOsm/kg)	>350	<300
Urinary specific gravity	>1.012	<1.014
**Renal failure index	<1	>4
Response to volume challenge	Urine output >2mL/kg/h	No increase in urine output

* Fractional excretion of sodium: $\frac{\text{urine Na X plasma creatinine}}{\text{plasma sodium X urine creatinine}}$ X 100

** Renal failure index: $\frac{\text{urine Na X plasma creatinine}}{\text{urine creatinine}}$ X 100

Electrolyte imbalances

Hyponatremia in oligo-anuria: Hyponatremia is most often due to dilution secondary to water retention, hence has to be corrected with fluid restriction. Babies with non-oliguric ARF may have very large urinary sodium losses of up to 10 mmol/kg/day, and this must be replaced. In asymptomatic mild hyponatremia (Serum Na+ 120-135 mEq/L), restriction of fluids will suffice with close monitoring of serum sodium. In symptomatic severe hyponatremia (S Na <120mEq/l) prompt correction with 3% hypertonic saline in a dose of 5 mL/kg over 4-5 hours is indicated. Hyponatremia unresponsive to above therapy or associated with refractory hyperkalemia, acidosis is an indication for dialysis.

Hyperkalemia

Hyperkalemia (Serum potassium more than 6 mEq/L) is one of the most dangerous complications that develops in babies with ARF. Following cessation of all potassium containing fluids, an ECG is done to look for characteristic changes secondary to hyperkalemia. If ECG changes are evident calcium gluconate 10% is given (0.5 to 1 mL/kg over 5-10 min). This will decrease the myocardial excitability but will not lower the potassium levels. This should immediately be followed by other methods to decrease the potassium levels such as

1. Cation exchange resin(Na/Ca polystyrene sulphonate): 1g/kg intrarectal every 6 hourly.
2. Glucose and insulin infusion: 0.5 g/kg/hour of glucose and 0.2 U of regular insulin per g of glucose over 2 hour.
3. Hyperkalemia which is unresponsive to medications is one of the most common indications for instituting dialysis. Remember to use a dialysate with low concentration.

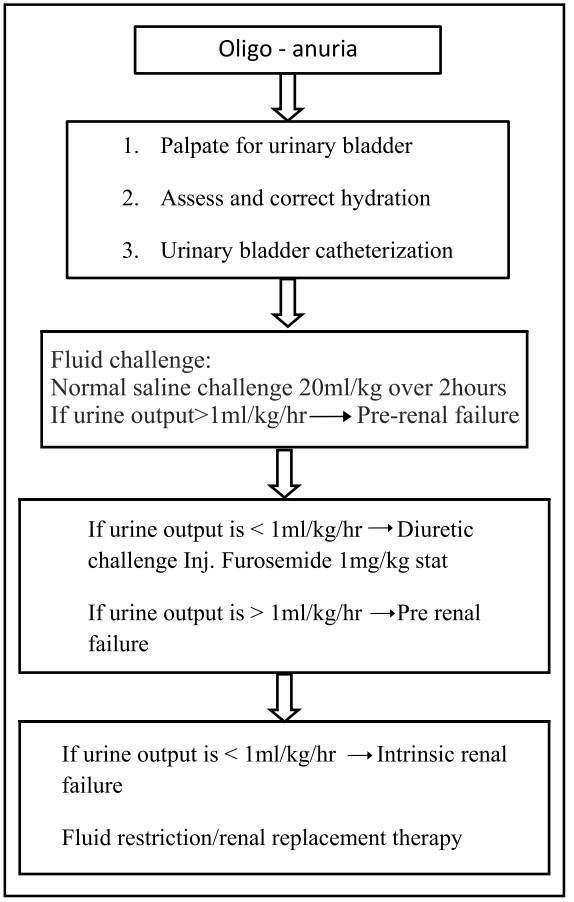


Fig.2. Approach to managing oligo-anuria in neonates

Hypocalcemia

It may result from hyperphosphatemia and skeletal resistance to parathyroid hormone. Symptomatic hypocalcemia should be corrected by infusing 10% calcium gluconate at a dose of 0.5-1 mL/kg over 5-10 min under cardiac monitoring. Injection is available as 10% calcium gluconate (0.45 mEq of calcium/mL). The maintenance dose for neonates is 200-800 mg/kg/day, 24h q6h.

Antibiotic therapy

Prompt initiation of antibiotics in situations of sepsis or urinary tract infection is mandatory.

Avoid nephrotoxic drugs

One should be cautious regarding the use of nephrotoxic drugs (ibu profen, indomethacin and diuretics) in the presence of renal failure. Antibiotics, antifungals when indicated need to be adjusted to renal corrected doses with close monitoring of renal functions. For modifying drug dosage, the creatinine clearance has to be calculated.

Creatinine clearance = (k x length in cm)/ serum creatinine (where k in term babies is 0.44 and in preterm babies is 0.33)

Metabolic acidosis

Sodium bicarbonate is indicated only if pH is < 7.2. Sodium bicarbonate can be used for correction of acidosis. Calculate the patient's dose with the following formula :

HCO_3(mEq)= 0.3X weight (kg)x base deficit (mEq/L).

Dilute to a maximum concentration of 0.5 mEq/mL in dextrose or sterile water for injection and infuse over 2 hour with a maximum rate of 1 mEq/kg/hour. Remember sodium bicarbonate should not be mixed with or be in contact with calcium, norepinephrine or dobutamine. Administration should be done carefully as it can cause fluid overload, hypernatremia, intracranial hemorrhage and intracellular acidosis. Babies with persistent acidosis require dialysis.

Hypertension

Fluid overload in neonatal oliguric renal failure can result in mild hypertension, which can be controlled with fluid restriction and antihypertensive agents. The development of severe hypertension in the setting of neonatal ARF should raise the suspicion for renal artery or venous thrombosis.

Role of furosemide

Furosemide is a potent loop natriuretic agent commonly used to improve urine output in oliguric neonates in the hope of increasing diuresis and improving renal blood flow and glomerular filtration rate by stimulating the production of vasodilator prostaglandins. However, use of furosemide should be limited to treat oliguric neonates presenting with edematous states and congestive heart failure. The dose of furosemide in neonates is 0.5mg/kg/dose q8hr-24 hours max dose 2mg/kg/dose. Bioavailability by oral route is poor, doses of 1-4 mg/kg/dose QD or BID have been used. Remember ototoxicity may occur in the presence of renal disease, especially when used with amino glycosides. Prolonged use in premature infants may result in nephrocalcinosis.

Role of dopamine, dopexamine, theophylline

Dopamine and dopaminergic agents are not recommended for routine use in oliguric renal failure with the aim of improving GFR and urine output.[7] Though there is some evidence of theophylline improving renal functions in asphyxiated neonates,[8] its administration is not recommended in the routine care of neonates with renal failure.

Renal replacement therapy

Acute kidney injury with oligo-anuria persisting after adequate fluid resuscitation is an indicator to initiate dialysis. Fluid removal through dialysis would help fluid overload and also allow required fluid and blood products to be transfused in the presence of oligo-anuria. Dialysis would also control uremia and treat associated problems like hyperkalemia and metabolic acidosis. The modality used most often to dialyse neonates worldwide is peritoneal dialysis though hemofiltration or diafiltration is a feasible option in the best of centres.[9,10]

Dialysis and filtration techniques are the available modalities. Dialysis is a process of removal of plasma solutes by diffusion down their concentration gradients across a semipermeable membrane. The membrane may be a synthetic one (hemodialysis) or peritoneum separating the splanchnic blood from fluid instilled into the peritoneal space (peritoneal dialysis). Filtration involves removal of protein free plasma water across a membrane by convection. The filtered water contains other plasma solutes at a concentration similar to plasma and can be thought of as glomerular filtrate equivalent. Hemo diafiltration involves both dialysis and filtration. hemofiltration and hemo diafiltration are effective in neonates with ARF in whom Peritoneal Dialysis is contraindicated.

Peritoneal dialysis has traditionally been preferred over hemodialysis in the newborn. With peritoneal dialysis, the peritoneal catheter may be placed either percutaneously or surgically. The common sites of insertion are in the midline below umbilicus, right or left lower quadrant of the abdomen. Urinary bladder must be emptied before insertion of the catheter. The abdomen is distended with 20ml/kg of peritoneal dialysis fluid before inserting catheter. Later 20-30ml/kg of dialysis fluid (1.7% dextrose with lactate) is infused over 10 min. after a dwell period of 20-30 min, the fluid is drained over 10 min. the dwell time may be reduced in case of respiratory compromise. Blood sugar and serum electrolytes have to be monitored every 6 hrly and serum creatinine every 24 hrly. If baby has hypokalemia, add 1.5 ml of KCl to one litre of dialysate fluid. The contraindications for PD are necrotising enterocolitis, babies who underwent abdominal surgery and in those with severe respiratory compromise as it may worsen with abdominal

distension. The complications of PD are as follows:

1. Hyperglycaemia
2. Bleeding
3. Perforation of abdominal viscera
4. Peritonitis
5. Adhesion of catheter tip to omentum

The use of CRRT in the neonatal patient requires a close attention to the potential for adverse events. Due to the small intravascular blood volume of neonates, careful attention must be paid to their volume status and the percent of intravascular blood volume to be contained in the extracorporeal circuit.

The blood flow rate in the neonatal and young infant is targeted at 5-10 ml/kg/min. However, this may lead to too slow blood flow through the extracorporeal CRRT circuit, and result in clotting of the CRRT circuit, and the need for its frequent replacement. In order to overcome these problems, our recommendation is to run the CRRT blood flow at a minimum speed of 50 ml/min in neonates, irrespective of body weight.

Prognosis

The mortality from acute kidney injury is associated with multiorgan failure, hypotension, need for mechanical ventilation and dialysis. In neonates maintained by peritoneal dialysis for acute kidney injury, mortality is more in oligoanuric neonates compared to neonates with adequate urine output.[1]

Follow up

All babies who develop ARF need follow up. Adequacy of growth and nutrition, blood pressure and renal function status have to be monitored. Newborns who have ARF are predisposed to the development of chronic renal failure in the future. Long term follow up of ELBW infants who had neonatal ARF has shown that prominent risk factors for progression of renal disease at 1 year of age included a spot urinary protein/creatinine ratio of greater than 0.6 and serum creatinine greater than 0.6 mg/dL.

Points to Remember

- ***Newborns could present with physiological oliguria in the first 24-48hours after birth.***
- ***Antenatal and perinatal history is useful in the approach to oligo-anuria***
- ***Urine output alone is not a reliable marker of underlying renal function in neonates***
- ***Pre-renal causes are commonly associated with acute renal failure and oliguria in the newborn***
- ***Adequate fluid resuscitation, use of diuretics and peritoneal dialysis in selected situations form the main stay of therapy for oligo-anuria in neonates.***

References

1. Karlowivz MG, Adelman RD. Non oliguric and oliguric acute renal failure. Pediatr Nephrol 1995, 9:718-722.
2. Hentschel R, Lodige B, Bulla M. Renal insufficiency in the neonatal period. Clin Nephrol 1996, 46:54-58.
3. Seri I, Tulassay T, Evans JR, Friedlich PS. Acute and chronic renal failure. In: Avery's Diseases of the newborn. Eds. H. William Taeusch, Roberta A. Ballard, Christine A. Gleason. 8th Edn. 2005; pp1298-1306.
4. Chevalier RL. Obstructive uropathy: assessment of renal function in the fetus. In: Nephrology and fluid electrolyte physiology. Neonatology questions and controversies. Eds. William OH, Guignard JP, Baumgart S. 2nd Edn. Elsevier 2008.p234.
5. Bruder F, Stapleton, Jones DP, Green RS. Acute renal failure in neonates: incidence, etiology and outcome. Pediatr Nephrol 1987; 1: 314-320.

6. Vogt BA, Katherine MacRae Dell. The kidney and the urinary tract. In: Eds, Neonatal-Perinatal Medicine, Diseases of the fetus and infant, Richard JM, Avroy AF, Michele CW, 9th Edn, Elsevier Mosby, 2011;p 1681.
7. Lynch SK, Lemley KV, Polak MJ. The effect of dopamine on glomerular filtration rate in normotensive, oliguric premature neonates. Pediatr Nephrol 2003;18:649.
8. Bakr AF.Prophylactic theophylline to prevent renal dysfunction in newborns exposed to perinatal asphyxia, a study in a developing country. Pediatr Nephrol 2005;20:1249.
9. Mathews DE, West KW, Rescorla FJ, Vane DW, Grosfeld JL, Wrapper RS, et al. Peritoneal dialysis in the first 60 days of life. J Pediatr Surg 1990;25:110-116.
10. Zobel G, Rod S, Urlesberger B, Kuttring-Hojm M, Ring E, et al. Continous renal replacement therapy in critically ill neonates. Kidney Int 1998;53:S169-S173.

DRUG PROFILE

ANTIFUNGAL THERAPY IN CHILDREN

* ***Ramya Uppuluri***
** ***Ira Shah***

Abstract: *Fungal infections are on the rise in children. Drug resistance is now emerging for various antifungals. Infections by unusual fungi such as non-albicans candida, invasive aspergillosis are now appearing. Newer antifungals such as echinocandins and third generation azoles have revolutionized the treatment of fungal infections in children. Various antifungals and their uses in children are discussed in this article.*

Keywords: Anti fungals, Children

With the ever increasing incidence of fungal infections in children and the emerging drug resistance, it is prudent that specific indications, dosages and duration of treatment for the existing antifungals be defined. Major predisposing factors for development of fungal infections include prematurity, low birth weight, irrational and prolonged use of antibacterials, use of histamine-2 blockers, steroids, mucoepithelial infections, central vascular catheters, hyperglycemia, total parental nutrition and intralipids.[1,2,3] It is important to have a high index of suspicion for the timely diagnosis due to the non-specific signs and symptoms that fungal infections present with.

* Resident, Department of Pediatrics
** Incharge, Pediatric HIV, TB Clinic
B.J.Wadia Hospital for Children, Mumbai.

Classification of antifungals

The available antifungals can be classified as given in Table I based on pharmacological properties:[4,5]

Polyenes

Mechanism of action: Susceptibility to these compounds depends on the presence of sterols in the fungal cell membrane. These drugs produce pores or channels in the cell membrane leading to altered permeability of the membrane and leaking of vital cytoplasmic contents with death of the organism. Notable exception to this is the effect on Candida albicans which depends on the oxidative damage caused by polyenes.[6]

Drugs commonly used in pediatric practice

Amphotericin B

Obtained from Streptomyces nodosus. Liposomal Amphotericin B, Ampho- tericin B lipid complex (ABLC), amphotericin B colloidal suspension (ABCD). Advantages of liposomal amphotericin B and lipid formulations over conventional amphotericin B is that efficacy is the same but it leads to fewer breakthrough fungal infections, less infusion related toxicity and less nephrotoxicity.[7]

Dose: Amphotericin B is not absorbed orally, hence is given intravenously. Sixty percent of the drug is metabolized in the liver. It is active against most candida species except C. lusitaniae and occasionally C. glabrata and C. krusei. It is the drug of choice for systemic candidiasis including neonatal candidiasis.[8,9]

Table I. Types of antifungals[4,5]

Antifungals	Subgroups	Site of action	Drugs
Antibiotics	Polyenes	Cell membrane agents	Amphotericin B, Nystatin, Hamycin, Natamycin
	Heterocyclic benzofuran		Griseofulvin
Antimetabolites			Flucytosine
Azoles	Imidazoles	Cell membrane agents	Topical: Clotrimazole, Econazole, Miconazole, Oxiconazole Systemic: Ketoconazole
	Triazoles	Cell membrane agents	1st generation: Fluconazole, itraconazole 2nd generation: Voriconazole, ravuconazole, posaconazole
Allylamine		Affect ergosterol pathways	Terbinafine
Echinocandins		Cell wall active agents	Caspofungin, Micafungin, Anidulafungin
Other topical agents			Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, Ciclopirox olamine, Butenafine, Sodium thiosulfate

Conventional amphotericin B : 0.8-1.2mg/kg/day IV. Liposomal amphotericin B:1-5mg/kg/day IV, ABCL: 5mg/kg/day IV, ABCD: 4-6mg/kg/day IV

Drug interactions Rifampicin potentiates its action. Aminoglycosides, vancomycin, cyclosporine and other nephrotoxic drugs enhance its renal toxicity.

Adverse effects a) Acute reaction: fever, chills, aches, nausea, vomiting, dyspnea lasting for 2-5 hours [(due to release of interleukins and tumor necrosis factor alpha (TNF-a)], intensity decreases with continued medication. Injection of hydrocortisone 0.6mg/kg with infusion and use of normal saline bolus prior to infusion can decrease the intensity.

b) Long term: nephrotoxicity with azotemia, reduced GFR, hypokalemia, acidosis[10]. These reverse slowly and sometimes incompletely after stoppage of the drug. It can cause slowly progressive anemia and also central nervous system (CNS) toxicity if used intrathecally.

Nystatin

In view of its significant systemic toxicity, it is used only as topical use for superficial candidiasis such as corneal, conjunctival and cutaneous candidiasis. It is also effective in preventing oral candidiasis due to use of corticosteroid aerosols.[4]

Griseofulvin

This mitotic inhibitor can be used orally only for dermatophytosis. It is not commonly used in

children and use in adults has also shown a declining trend. However as per few studies and recommendations by dermatologists, oral griseofulvin can be used effectively for tinea capitis in children.[11]

Antimetabolites

5-Flucytosine

It is a fluorine analog of cytosine (normal constituent of cell). It causes interference with pyrimidine metabolism, inhibiting nucleic acids, disrupting protein synthesis.[5] Its advantage is that concentration in cerebrospinal fluid (CSF) is 74% that of serum. It also penetrates into aqueous humor, joints, bronchial secretions, peritoneal fluid, brain, bowel and bone.[6] Flucytosine plus amphotericin B is the gold standard for treatment of cryptococcal meningitis.[12] It has also been studied for cryptococcosis in combination with azoles such as posaconazole, and has shown promising results.[13] It is not to be used as monotherapy due to likely development of resistance.[6]

Dose: It is available as capsules or liquid formulations. It is not currently available in India

Adolescents: 150mg/kg/day in 4 divided doses

Children: 100-150mg/kg/day in 4 divided doses

Neonates: 50-100mg/kg/day once daily or two divided doses

Dose reduction is required in those with elevated serum hepatic enzymes. Serum levels should be maintained between 25 and 80 μg/mL. Blood levels should be measured in patients with renal failure 2 hours after the last dose and before the next dose.

Adverse effects: rash, diarrhea, hepatic dysfunction, bone marrow suppression, nephrotoxicity.[5]

Azoles

It consists of imidazoles: miconazole, ketoconazole, clotrimazole and triazoles: fluconazole, itraconazole, voriconazole, ravuconazole (both structurally similar to fluconazole) and posaconazole (structurally similar to itraconazole). Newer triazoles have been developed in order to increase the spectrum of antifungal activity, provide fungicidal activity against molds and decrease adverse effects. Clotrimazole, Miconazole, Oxiconazole are used in the topical treatment of tinea infections like ringworm, athletes' foot, oral or cutaneous candidiasis, and also used in skin infections caused by Corynebacterium.[4]

Mechanism of action: They inhibit cytochrome P450 (CYP) dependant lanosterol 14-á-demethylase[14], required for synthesis of ergosterol which is a major constituent of cell membrane working as a bioregulator of membrane fluidity and integrity.

Fluconazole

It is used for treatment of systemic candidiasis (most commonly oropharyngeal), cryptococcal meningitis, especially in patients who are HIV positive for lifelong maintenance therapy to prevent relapses[6]. It is used as prophylaxis to improve survival in patients undergoing allogeneic bone marrow transplantation. It is not indicated for treatment of aspergillus, mucor or scedosporium.

Dose: It is available as tablets and IV preparation. It is given as 12mg/kg/day once daily for 28 days (for μg systemic candidiasis), for 10-12 weeks (for cryptococcal meningitis). Dose reduction is needed in renal failure.

Advantages: concentrations in CSF are 70% of simultaneous blood levels, irrespective of meningeal inflammation, penetrates into the brain and other organs and body fluids.

Drug interactions: H_2 blockers and proton pump inhibitors do not affect its absorption. Increased plasma levels of phenytoin, cyclosporine, warfarin, zidovudine have been found when used concomitantly.

Adverse effects: elevated liver enzymes, hepatotoxicity, a few cases of ventricular tachycardia have been reported when used along with cisapride.[15]

Itraconazole

It is used in the treatment of histoplasmosis, blastomycosis, coccidiodomy- cosis, paracoccidiodomycosis, sporotrichosis, ringworm, onychomycosis, tinea versicolor and aspergillosis[16]. It has excellent activity against most dimorphic pathogens in vitro.[17,18,19] Itraconazole with flucytosine has shown good activity against aspergillosis including spondylodiscitis.[13]

Dose: It is available as capsules in India. It is given as 3-5mg/kg/dose OD or BD. Dividing into 2 doses improves tolerance and absorption. Oral absorption is enhanced by food when given as capsule. Steady state concentration is reached only after 13-15 days, tissue and secretion concentrations are generally higher than plasma concentrations. However, CSF concentrations are immeasurable.

Adverse effects: They are dose related and cause nausea and abdominal discomfort. Higher doses can cause hypokalemia.

Drug interactions: Drug levels reduced by half if taken along with H_2 blockers or proton pump inhibitors, rifampicin, rifabutin, isoniazid, phenytoin, carbamazepine and phenobarbital.

Voriconazole

It is a broad antifungal with activity against Candida including C. krusei and glabrata[20] (which are intrinsically resistant to fluconazole). It has fungistatic, at times fungicidal activity against aspergillus. It has good oral bioavailability and low toxicity.

Dose: Pharmacokinetic data in children is lacking. However it is given as 6-10mg/kg/day divided every 12 hours in children <25 kg and loading with 200mg every 12 hours for 2 doses then 100 mg every 12 hours for those weighing >25kg. Dose adjustment is required in renal insufficiency. If taken with high fat meals, drug levels are reduced. It gets extensively distributed in tissues including CSF.

Adverse effects: elevated liver function tests, skin rash, visual abnormalities like photophobia, blurred vision, torsades de pointes[21]. It should not be given to neonates predisposed to retinopathy of prematurity[22].

Drug interactions: Rifampicin, long-acting barbiturates and carbamazepine decrease levels. Voriconazole increases levels of cisapride, cyclosporine, tacrolimus, quinidine, omeprazole and warfarin

Ravuconazole

It is an extended spectrum antifungal with activity against candida and aspergillus that are resistant to fluconazole, It has in-vitro activity against cryptococcus, histoplasma and penicillium. Cross resistance between ravuconazole and fluconazole is most common with candida glabrata. Dosing is not adequately studied in children.

Posaconazole

It has extended spectrum activity against candida (including fluconazole resistant strains), aspergillus, cryptococcus, coccidiodes, histoplasma, trichosporon, fusarium, scedosporium, zygomycetes. It inhibits only

hepatic CYP3A4 and no other cyp 450 enzymes. Doses, adverse effects are not adequately studied in children.

Allylamine

Terbinafine

It acts as a non-competitive inhibitor of squalene epoxidase, an early step enzyme in ergosterol biosynthesis, used topically or orally for tinea infections. Few studies have shown a combination of terbinafine with fluconazole or voriconazole to be effective in treating drug resistant candidiasis.[23,24]

Echinocandins

They are lipopeptide agents inhibiting β-1, 3-glucan synthase which is required for forming glucan polymers in the fungal cell wall leading to disruption of cell wall with osmotic stress, lysis and death of the organism. These drugs mainly exert their effect by destabilizing the fungal cell wall.[25,26] Echinocandins are fungistatic against aspergillus, but due to their excellent safety profile they may be used as combination therapy in cases of invasive aspergillosis or as broad spectrum empiric antifungal therapy in immuno-compromised patients.[5] They lack activity against cryptococcus spp.[13], but have shown in vitro and in vivo activity against P.jiroveci, histoplasma, blastomyces, scedosporium and some black molds. Some positive results have been observed when used in combination therapy for zygomycosis.[28]

Caspofungin

It is the first to be licensed for use. It is used for the treatment of refractory invasive aspergillosis, resistant isolates of C.albicans, C.glabrata, C.krusei. It is active in vitro against coccidiodes, blastomyces, histoplasma. One study found the combination of caspofungin with terbinafine to show some promising activity against candida.[27]

Dose: It is available only as IV formulation. **Neonates:** 1mg/kg/day for 2 doses then 2mg/kg/day. **2-11 years:** 70mg/m^2/day on day1 then 50mg/m^2/day. **>12 years:** 70mg OD on day 1 then 50 mg OD

Drug interactions: interacts with cyclosporine, tacrolimus and other inducers or inhibitors of hepatic metabolism.

Adverse effects: hypokalemia, hyperbilirubinemia, elevated hepatic enzymes, anemia

Micafungin

It has been currently approved for antifungal prophylaxis in hematopoietic stem cell transplant recipients.[29,30] Spectrum of activity is similar to caspofungin. Dose is not defined for pediatric age group, few studies have shown effective activity at 10-12mg/kg/day.

Anidulafungin

It has similar spectrum as caspofungin and micafungin but has not been studied adequately in pediatric population. In a recent study, combination of anidulafungin with voriconazole was shown to decrease pulmonary injury in cases of invasive aspergillosis.[31]

It exhibits linear kinetics in children between 2-17 years of age.[32]

Combination therapy for drug resistant fungal infections

With increasing resistance among various fungi, broad spectrum antifungals with enhanced rate or extent of killing (through synergy) are used in combinations. This leads to decreased chances of development of resistance and reduced toxicities.[33] However, combination therapies increase cost and one has to be careful about drug

interactions. Current recommendations as per the published practice guidelines of the Infectious Diseases Society of America (IDSA)[12,16-19,25,34] has stated that for HIV associated cryptococcal meningitis in developed countries, combination of amphotericin B and flucytosine is preferred as first line therapy. Other alternatives albeit with lesser efficacy are amphotericin B plus fluconazole and fluconazole plus flucytosine. For candida infections routine use of combination therapy is not recommended,[34] except invasive candidiasis which may be difficult to treat. Amphotericin B plus flucytosine are recommended to be used for the first few weeks of CNS candidiasis. This combination can also be used for candidial endophthalmitis and for candida endocarditis. More recently combinations of echinocandins with polyenes, azoles or flucytosines are showing good outcomes. For initial treatment of invasive pulmonary aspergillosis, combination therapy is not the first line. It is considered for salvage therapy.[12] Caspofungin plus voriconazole is a promising combination for CNS aspergillosis. For endemic mycosis, there are no recommendations at present. Amphotericin B plus an azole can be considered for coccidiodomycosis.

Conclusion

With newer antifungals in the clinician's armamentarium, there is a wide range of drugs that can be used for treatment of fungal infections. However with increase in drug resistance and increase in non-albicans candida infections that are inherently resistant to azoles, antifungal therapy is becoming more complex and costly.

Points to Rembember

- ***Major predisposing factors for development of fungal infections include prematurity, low birth weight, irrational and prolonged use of antibacterials, use of histamine-2 blockers, steroids, mucoepithelial infections, central vascular catheters, hyperglycemia, total parental nutrition and intralipids.***
- ***Among the polyenes, advantages of liposomal amphotericin B and lipid formulations over conventional amphotericin B is that efficacy is the same but it leads to fewer breakthrough fungal infections, less infusion related toxicity and less nephrotoxicity***
- ***Azoles consist of imidazoles: miconazole, ketoconazole, clotrimazole and triazoles: fluconazole, itraconazole, voriconazole, ravuconazole (both structurally similar to fluconazole) and posaconazole (structurally similar to itraconazole).***
- ***Voriconazole is a broad antifungal with activity against Candida including C. krusei and glabrata (which are intrinsically resistant to fluconazole) and is drug of choice for invasive aspergillosis***
- ***Among the echinocandins, caspofungin is approved for use in children with candidiasis.***

References

1. Kaufman, D. Strategies for prevention of neonatal invasive candidiasis. Semin Perinatol. 2003; 27: 414–424.
2. Makhoul IR, Kassis I, Smolkin T, Tamir A, Sujov P. Review of 49 neonates with acquired fungal sepsis: further characterization. Pediatrics 2001; 107: 61–66.
3. Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality, and neurodevelopmental outcomes at 18–22 months. Pediatrics 2005; 116: e241–e246.
4. Antifungal drugs. In: Tripathi KD, editor. Essentials of medical pharmacology.6th ed. New Delhi. Jaypee. 2008:757-766.

5. Johnson MD, Perfect JR. Use of Antifungal Combination Therapy: Agents, Order, and Timing. Curr Fungal Infect Rep 2010; 4: 87–95
6. Ferrieri P. Principles of antifungal therapy. In:Kleigman RM, Behrman RE, Jenson HB, Stanton BF, editors. Nelson textbook of pediatrics. 18th ed.Philadelphia. Saunders; 2008: 1303-1306.
7. Juster-Reicher A, Flidel-Rimon O, Amitay M, Even-Tov S, Shinwell E, Leibovitz E. High-dose liposomal amphotericin B in the therapy of systemic candidiasis in neonates. Eur J Clin Microbiol Infect Dis 2003; 22: 603–607
8. Minari A, Hachem R, Raad I. Candida lusitaniae: a cause of breakthrough fungemia in cancer patients. Clin Infect Dis. 2001; 32: 186–190
9. Rowen JL, Tate JM. Management of neonatal candidiasis. Neonatal Candidiasis Study Group. Pediatr Infect Dis J 1998; 17: 1007–1011.
10. Linder N, Klinger G, Shalit I, Levy I, Ashkenazi S, Haski G, et al. Treatment of candidaemia in premature infants: comparison of three amphotericin B preparations. J Antimicrob Chemother 2003; 52: 663–667.
11. Bennett ML, Fleischer AB, Loveless JW, Feldman SR. Oral Griseofulvin Remains the Treatment of Choice for Tinea Capitis in Children. Pediatric Dermatology 2000; 17: 304–309.
12. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2010; 50: 291–322.
13. Johnson MD, MacDougall C, Ostrosky-Zeichner L, Perfect JR, Rex JH. Combination antifungal therapy. Antimicrob Agents Chemother 2004; 48: 693–715.
14. Sanglard D. Clinical relevance of mechanisms of antifungal drug resistance in yeasts. Enferm Infec Microbiol Clin 2002; 20: 462–469
15. Hill SL, Evangelista JK, Pizzi AM, Mobassaleh M, Fulton DR, Berul CI. Proarrythmia associated with cisapride in children. Pediatr 1998,101: 1053-1056.
16. Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 2007; 45: 807–825.
17. Kauffman CA, Bustamante B, Chapman SW, Pappas PG. Clinical practice guidelines for the management of sporotrichosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 2007; 45:1255–1265.
18. Chapman SW, Dismukes WE, Proia LA, Bradsher RW, Pappas PG, Threlkeld MG, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis 2008; 46: 1801–1812.
19. Galgiani JN, Ampel NM, Blair JE, Catanzaro A, Johnson RH, Stevens DA, et al. Coccidioidomycosis. Clin Infect Dis 2005; 41: 1217–1223.
20. Müller FM, Weig M, Peter J, Walsh TJ. Azole cross-resistance to ketoconazole, fluconazole, itraconazole and voriconazole in clinical Candida albicans isolates from HIV-infected children with oropharyngeal candidosis. J Antimicrob Chemother 2000; 46: 338–340.
21. Walsh TJ, Karlsson MO, Driscoll T, Arguedas AG, Adamson P, Saez-Llorens X, et al. Pharmacokinetics of Intravenous Voriconazole in Children after Single and Multiple Dose Administration. Antimicrob Agents Chemother. 2004; 48: 2166-2172.
22. Smith PB, Steinbach WJ, Cotton CM, Schell WA, Perfect JR, Walsh TJ et al. Caspofungin for the treatment of azole resisitant candidemia in a premature infant. J Perinat 2007; 27:127–129.
23. Cantón E, Pemán J, Gobernado M, Viudes A, Espinel-Ingroff A. Synergistic activities of fluconazole and voriconazole with terbinafine against four Candida species determined by checkerboard, time-kill, and Etest methods.

Antimicrob Agents Chemother 2005; 49: 1593–1596.

24. Ghannoum MA, Elewski B. Successful treatment of fluconazole resistant oropharyngeal candidiasis by a combination of fluconazole and terbinafine. Clin Diagn Lab Immunol 1999; 6: 921–923.
25. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008; 46: 327–360
26. Sucher AJ, Chahine EB, Balcer HE. Echinocandins: the newest class of antifungals. Ann Pharmacother 2009; 43: 1647–1657.
27. Gil-Lamaignere C, Muller FM. Differential effects of the combination of caspofungin and terbinafine against Candida albicans, Candida dubliniensis and Candida kefyr. Int J Antimicrob Agents 2004; 23: 520–523.
28. Ibrahim AS, Gebremariam T, Fu Y, Edwards JE Jr, Spellberg B. Combination echinocandin-polyene treatment of murine mucormycosis. Antimicrob Agents Chemother 2008; 52: 1556–1558.
29. Mora-Duarte J, Betts R, Rotstein C, Lopes Columbo A, Thompson-Moya L, Smietana J, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 2002; 347: 2020–2029
30. Van Burik JA, Ratanatharathorn V, Stepan DE, Miller CB, Lipton JH, Vesole DH, et al. Micfungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 2004; 39: 1407–1416
31. Petraitis V, Petraitiene R, Hope WW, Meletiadis J, Mickiene D, Hughes JE, et al. Combination therapy in treatment of experimental pulmonary aspergillosis: in vitro and in vivo correlations of the concentration- and dose- dependent interactions between anidulafungin and voriconazole. Curr Fungal Infect Rep 2010; 4: 87–95
32. Benjamin DK Jr, Driscoll T, Seibel NL, Gonzalez CE, Roden MM, Kilaru R, et al. Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. Antimicrob Agents Chemother. 2006; 50: 632-638.
33. Lewis RE, Kontoyiannis DP. Rationale for combination antifungal therapy. Pharmacotherapy 2001; 21:149S–164S.
34. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48: 503–535
35. Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics 2006; 117: 84–92.

NEWS AND NOTES

The 2nd Global Congress for Consensus in Pediatrics & Child Health, Moscow, Russia

Date: 17th to 20th May, 2012

For details contact

Sarah Krein, CIP 2012 Congress, Marketing and Sales Coordinator, Paragon Conventions, Moscow, Russia.
Tel: +41 225330 948; Fax: +41 225802 953, E-mail: skrein@paragon-conventions.com.

DERMATOLOGY

CUTANEOUS MANIFESTATIONS OF RICKETTSIAL INFECTIONS

**** Anandan V***

Abstract: *Rickettsial infections are infrequently thought of and frequently under diagnosed in the past as evidenced by increasing incidence of this disease as of now. Many of the diseases caused by Rickettsia will have dermatological findings which might give a clue to suspect the disease and to arrive at a definitive diagnosis with the help of higher investigatory tools.*

Keywords: *Rickettsia, Epidemic typhus, Endemic typhus, Scrub typhus, Rocky mountain spotted fever.*

Rickettsial infections are named in honour of Dr.H.T.Ricketts who recognised and described Rocky mountain spotted fever and its life cycle in 1910 and died of Typhus fever while investigating this illness in Mexico.[1]

Rickettsial diseases are caused by non-motile,gram negative, cocco bacilli that are obligate intracellular parasites which cannot be cultured on ordinary media.They are highly sensitive to drying,heat and sunlight during their transmission and the only exception to this is Coxiella burnetii which causes Q fever.[2]

Mammals usually are infected only via blood sucking arthropods such as body louse, flea, ticks and mites which can serve as vector and reservoir.

* Professor and HOD,
Department of Dermatology,
Chengelpet Medical College Hospital,
Chengalpattu.

Rickettsiosis is quite common in temperate and tropical climates and they fall into four major groups such as

(1)Typhus group, (2) Spotted fever group, (3) Scrub Typhus and (4) Q fever

Rickettsia have a predilection for the endothelial cells of small blood vessels in which they replicate causing the host cell to swell and divide producing microangiitis and widespread vasculitis.[3] This is pathogenesis of rash and eschar of Rickettsial infections.

All Rickettsial infections, will have a rash except for Q fever and Ehrlichiosis[4] and hence these two diseases will not be discussed in this article.

1. Typhus group

a) Epidemic typhus (louse - borne typus)

Epidemic typhus has a cosmopolitian prevalence but has an higher prevalence in Africa, South America, Asia and Afganisthan.[5]

The causative agent has been identified as R.prowazekii which gets transmitted through human body louse called Pedicuius humanus var corporis.

The infectious organisms which get excreted in the feces of the infected louse gains entry into the host either through an abrasion or by

scratching the bite site of the louse. Commonly occurs in over crowded and high louse infested population.

The incubation period ranges from 10-14 days and the onset of the disease will be with high fever, headache, photophobia, conjunctivitis, flushing and chills.

A centripetal pinhead sized maculopapular erythematous blanchable rash occurs on the 4-6th day of illness commonly near the axilla and spreads to trunk and extremities, usually sparing the face, palms and soles. It starts as macules which blanches, become maculo papules and then becomes petetichiae and hemorrhagic to leave back a brownish exfoliation at the end of the second week.

The diagnosis is confirmed by isolation of the organism, elevated antibody titres which peaks at the end of second week.Agglutination reaction to Proteus OX19 antigen is often positive, ELISA assay and latex agglutination tests are found to be sensitive. PCR is helpful in the diagnosis by 48 hours of infection.

Patient should be deloused with a thorough wash with soap water and delousing agent such as malathion will help in clearing off the louse.Proper institution of antibiotic therapy is mandatory.[6]

b) Brill-Zinsser disease

This is a recrudescent form of epidemic typhus which occurs due to reactivation of dormant organism following stress or provocation.

The presentation is similar to epidemic typhus but with shorter incubation period with or without a rash.The importance of this disease lies in the fact that the source person may be a nidus for an epidemic.[7]

c) Endemic typhus

It is cosmopolitian in distribution but, relatively rare. It is common in all ages and sex incidence is equal.

The causative agent has been identified as R.mooseri also known as R.typhi transmitted by a rat flea Xenopsylla cheopsis. Infection is either by bite of the flea or by scratching the infected feces through the abraded skin.

The incubation period is 6-14 days with gradual onset of the disease associated with centripetal maculo papular rash mainly involving the face, palms and soles lasting for 9-13 days. Rash occurs in mild form but can be evanescent.

Management is similar to that of epidemic typhus and dermatological intervention is not required.

2. Spotted fever group

This group includes Rocky mountain spotted fever, Mediterranean spotted fever, Siberian tick typhus, Queensland tick typhus. Rocky mountain fever has been reported from Asia and hence only this will be discussed in this article.

a) Rocky mountain spotted fever [RMSF]

Rocky mountain spotted fever is caused by R.rickettsii and transmitted by ticks. It has worldwide distribution. But frequently reported from American countries and less commonly reported from Europe, Asia, Africa and Australia where humans are incidental victims.

The disease can be transmitted by the a bite of an infected tick or by contamination of skin when the infected arthropod vector has been crushed.Occasionally the disease is transmitted by transfusion.[8] The disease can occur any age but common under 15 years of age.[9] Sex incidence are equal.

The incubation period is 2-12 days and presents with headache, malaise, anorexia, chills, photophobia, low grade fever, and joint and muscle pain especially of the gastronemius. Azotemia and jaundice are poor prognosticators.[10]

The most common triad of clinical features are rash,edema and fever of which the rash is present in 90% of the cases and is the earliest dependable most diagnostic sign which can appear between 1-4 days of the illness.Commonly the rash starts over the ankles and feet which spreads to involve wrists, hands,head,trunk ,palms and soles. Characteristic of rash is that it is almost always seen in palms and soles.

The rash starts as small, discrete, blanchable and rose colured macule which soon becomes papular and within 2-3 days, occasionally delayed till sixth day or later it turns out to petechiae or parpura. If untreated it becomes confluent and hemorrhagic rarely to massive skin necrosis.[11] Gangrene has been reported in the scrotum, fingers, toes and ear lobes. The rash may finally desquamate and leave back long standing hyperpigmentation. Eschars unique of other rickettsial diseases are rarely reported in RMSF.[12] Occasionally there may not be almost any rash at all.[13] Jaundice is also observed in RMSF. Diagnosis is by isolation of the organism, detection of the antibodies late in the second week, by indirect immunofluroscent techniques, ELISA could be both specific and sensitive. More rapid diagnosis is possible by rickettsial identification in monocytes of a buffy coat preparation.[14]

Newer investigations like frequency pulsed electron capture-gas liquid chromatography [FPEC-GLC] may detect the illness on the very first day. The mortality of RMSF is 5-7% and death usually occurs between 9-12 days of illness.

b) Mediterranean spotter fever

(Boutonneuse fever, Kenya tick bite fever, African tick typhus, India tick typhus Isreli spotted fever, Marseilles fever).

Caused by Rickettsia conorii. Reservoir and vector is brown dog tick. It is seen in all ages and both sex with a peak occurrence between June to October, Incubation period is 6 to 10 days. A painless, rarely pruritic primary lesion called tachenoire (blck spot) seen at the site of tick bite[15] observed mostly over head in children and legs in adults. This lesion gets necrosed leading to eschar formation, gives rise to regional lymphadenitis.Lesion heals with out scarring in 10 to 20 days, can leave residual pigmentation indefinitely. This is pathognomonic but seen in 30 to 90% of patients only. Occasionally multiple lesions occur. Predominant mononuclear infiltrates can be demonstrated in the site.

On the fifth day of fever maulo papular rash is almost always observed initially over the extremities which then spread to trunk, neck, face, buttocks, palms and soles.To start with pink macular within hours become maculo papular measuring 1 to 4mm. Rash persists for subside. May be pruritic petechial, purpura or papulo vesicular lesions occur occasionally.

c) Rickettsial pox

It is caused by Rickettsia akari where the vector is mouse mite. Males and females are susceptible. The incubation period is 9 to 14 days. Primary lesion at the site of mite bite is, a papule which passes through a vasicular stage measuring 6.5 to 2 cms, ruptures leading to eschar with surrounding induration, which is pathognomonic. Invariably there is regional lymphadeopathy. The lesions which are few to usually seen over face and trunk-, extremities and spare palms and soles.

3. Scrub typhus group

Scrub typhus is caused by Orientia tsutsugamushi and is transmitted by bite of trombiculid mites. Recently there had been reports from India also.[16-17] Marked stain differences in scrub typhus rickettsiae, leads to differences in severity of disease. It occurs usually from June to November. Incubation period is 1 to 2 weeks. Two third develop necrotic eschar and is seen over trunk in adults and in intertriginous areas of genitals and perineum. Scar can persist even up to 25 years. Maculopapular rash appear between the 5th and 8th day of illness. Generalised lymphadenopathy, hepatosplenomegaly, myocarditis, DIVC are other manifestations observed.

Antibiotic and supportive management is the same as for other typhus diseases and is effective.

Conclusion

It is essential that every astute physican should be aware of the infrequently touched Rickettsial infections in which the dermatological rash could be the presenting sign of the disease. In future with increasing awareness and knowledge and with the available advanced diagnostics tools these diseases could find a place in the literature as travelling now a days has become un imaginably easier to reach the required destinations whch could be an endemic area for Rickettsiosis. Hence it is mandatory for the treating physician to be aware of Rickettsiosis.

Points to Remember

- ***It is not the constitutional symptoms but the rashes which will be the eye opener for the diagnosis.***
- ***The rashes do not require treatment but the primary disease should be treated with appropriate antibiotics for optimum period to reduce the morbity and mortality.***

References

1. Feigin RD,Snider RL,Edwards MS. Rickettsial disease.In:Textbook of Pediatric Infectious Disease. 4th Edn,Feigin RD,Cherry JD,eds. Philadelphia: WB Saunders, 1998;pp 1847-1865.
2. Riley HD Jr. Rickettsial Diseases. In:Infections in Children,Wedgewood RJ,Davis SD,Ray CG,Kelley VC, Eds.Philadelphia:Harper & Row,1982;pp.1027
3. Rapmund G. Rickettsia. In:Infectious Diseases and Medical Microbiology,2nd edn,Braude Al,Davis CE,Fierer J,Eds.Philadelphia: WB Saunders,1986;pp.443
4. Murray ES. Rickettsial diseases. In: Textbook of Pediatric Infectious Diseases, Feigin RD, Cherry JD, Eds. Philadelphia: WB Saunders, 1981;pp1437
5. Brezina R. Epidemic (louse borne) typhus.In:Infectious Diseases and Medical Microbiology, 2nd Edn,Braude AL,Davis CE,Fierer J, Eds.Philadelphia:WB saunders,1986;pp1231
6. Riley HD Jr. Typhus fevers.In: Infections in Children, Wedgewood RJ, Davis SD, Ray GG et al. eds.Philadelphia: Harper & Row,1982;pp1032
7. Murray ES,Baehr G,Schwartzman G et al. brill's disease.I.Clinical and laboratory diagnosis.JAMA 1950;142:1059
8. Wells GM,Woodward TE,Fiset P et al. Rocky Mountain spotted fever caused by blood transfusion. JAMA 1978;239:2763.
9. Walker DH (1989) Rocky Mountain spotted fever: A disease in need of microbiological concern.Clin Microbiol Rev 2:227-240.
10. Mc Murray JF Jr (1966) Review of Rocky Mountain spotted fever.J Okla State Med Assoc 59:165.
11. Edwards MS, Feigin RD. Rickettsial diseases. In: Feigin and Cherrys textbook of pediatric Infectious diseases, 6th Edn, James Cherry, Sheldon Kaplan, Gail Demmler-Harrison, William Eds. Saunders Philadelphia, 2009;pp2669-2683.

12. Wallur DH, Gay RM, Valdes Dapers M. The occurrence of eschars in Rocky Mountain spotted fair J Am Acad Dermotol 1981;4:571-576.
13. Sexton DJ, Corey GR. Rodey Mountain "Spotless" and "almost spotless" fever: A wolf in shapes clothing clin infect Dis 1992;15:439-448.
14. De Shazo RD,Boyce JR,Osterman JV et al.(1976) Early diagnosis of Rocky Mountain spotted fever:use of primary monocyte culture technique.JAMA 235:1353.
15. Montenegro MR, Mansueto S, Hegarry BC, et al. The histology of "tachenoir" of boutonneuse fever and demonstration of Rickettsia conori in them by immune fluorescences. Virchows Arch 1983;900:309-317.
16. Rathi N, Rathi A. Rickettsial Infections, Indian Pediatr 2010; 47: 157-164.
17. Vivekanandan M, Mani A, Priya YS, Singh AP, Jayakumar S, Purty S. Outbreak of scrub typhus in Pondicherry. J Assoc of phys India 2010; 58: 24-28.

RADIOLOGIST TALKS TO YOU

CEREBELLOPONTINE ANGLE MASSES

**** Vijayalakshmi G***
***** Malathy K***
****** Venkatesan MD***
******* Elavarasu E***

The cerebello-pontine area is a rare location for lesions in children. It is the site of the cerebellopontine cistern that is a CSF containing space bound by the the pons and cerebellum medially and the petrous temporal bone laterally. The roof of the cistern is the tentorium and below is the occipital dura. The 5^{th},6^{th},7^{th} and 8^{th} cranial nerves are in the superior part while the 9^{th}, 10^{th}, 11^{th} nerves lie in the lower part. It therefore follows that the commonest tumor here is the schwannoma arising from the schwann cells in the myelin sheath of these nerves before they enter the brain. The commonest schwannoma is that arising from the vestibular nerve. The next common cranial nerve to be involved is the trigeminal nerve. Sporadic vestibular schwannomas present in middle age. But the ones associated with type neurofibromatoses present early in the second decade. Fig.1 is that of a boy aged 16. This is a T2 weighted image showing a hyperintense mass in the left CP angle. It is a schwannoma arising in the internal auditory canal and growing out into the cerebellopontine cistern. The larger part of the tumor is in the cistern but there is a small cone of mass projecting into the internal auditory canal. This appearance strongly favours a vestibular nerve schwannoma. In CT, schwannomas are iso or hypodense and enhance with contrast. Small schwannomas are homogenous, larger ones show a heterogenous pattern with areas of cystic necrosis and in homogenous enhancement. Fig.2 is a sagital section of the same patient showing another mass superiorly. This is a meningioma from the falx. Meningiomas are hypointense and give similar intensity in both T1 and T2 images. Schwannomas tend to give lower signal intensity than gray matter on T1-weighted images and higher signal intensity on T2-wighted images. Other tumors that can occur in neurofibromatoses and ependymomas (MISME- multiple inherited schwannomas, meningiomas and ependymomas)

CP angle lesions also include meningiomas, epidermoid and arachnoid cysts. We have seen the appearance of meningiomas earlier. Meningiomas are slow growing, well-defined masses. In CT, they are homogenously hyperdense and very well enhancing masses with a wide base towards the meninges(Fig.3). When meningiomas occur in the CP angle they are not centred on the internal auditory canal. They usually do not extend into the internal auditory canal and if they do they do not expand the canal. Hyperostosis is a feature of meningiomas.

* Associate Professor,
*** Professor,
**** Asst. Professor,
Chengalpat Medical College Hospital,
Chengalpattu
** Associate Professor
Department of Radiology,
Madras Medical College, Chennai

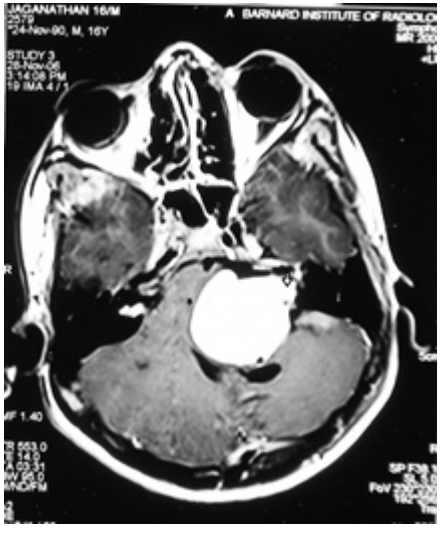


Fig.1 Vestibular schwannoma in the left CP angle. Note the cone like extension(arrow) into the Internal acoustic meatus.

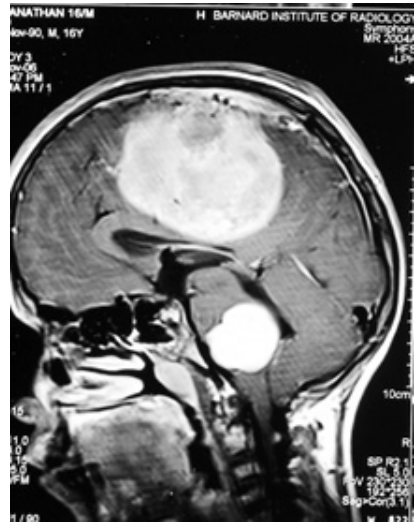


Fig. 2 Vestibular schwannoma and falcine meningioma.- NF type2

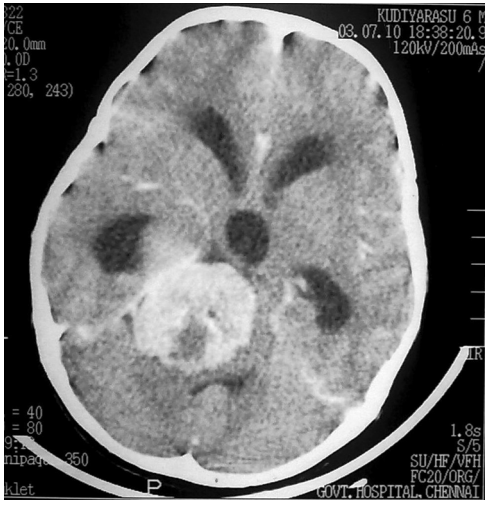


Fig.3 Meningioma in the right CP angle. Note displaced pons and 4th ventricle.

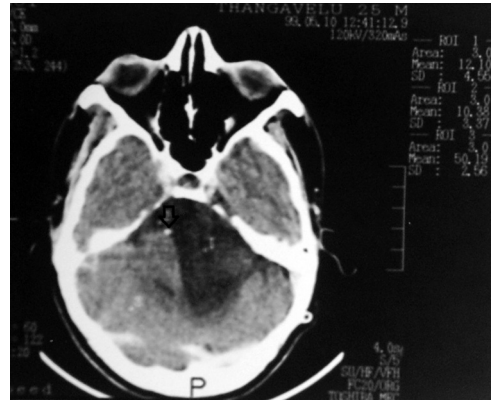


Fig. 4 Epidermoid in left CP angle. Note the displaced pons and basilar artery (arrow)

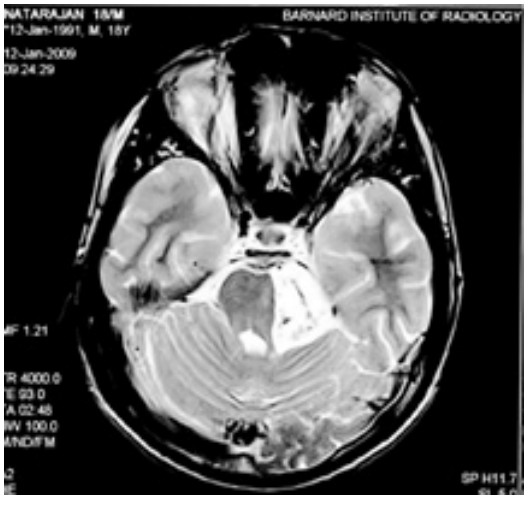


Fig. 5 MRI -Epidermoid. Note the density similar to CSF and inhomogeneity within mass

Epidermoids are inclusion cysts arising out of ectodermal inclusion during the closure of the neural tube. They are not true neoplasms but they form masses as they slowly grow due to continued desquamation of the squamous lining of the cyst. Debris accumulating within consists of lipids and proteinaceous keratin. The CP angle is the commonest intracranial site for epidermoids. On CT, epidermoids (Fig.4) are hypodense (almost water density) homogenous masses. They rarely show calcification. They are avascular and hence do not enhance with contrast. Although homogenous in CT they show inhomogeneity or lamellated pattern in MRI due to periodic layering of desquamated material. On T1 images they are hypointense and on T2 images (Fig.5) they are hyperintense. Like in CT, they do not enhance on gadolinium administration. Sometimes they do not displace adjacent structures but insinuate around and in between structures so that resection is incomplete. The acquired epidermoid or cholesteatoma is centred on the petrous apex or middle ear cavity and is associated with chronic otitis media.

Arachnoid cysts are incidental findings and rarely cause symptoms. They are of the same density as CSF. They do not enhance. So they are like epidermoids in both CT and MRI. But inhomogeneity of epidermoids in MRI is a distinguishing feature.

An aneurysm of the posterior-inferior cerebellar artery can be visualized in the CP angle. Aneurysms enhance on contrast CT if they are not filled with thrombus. In MRI they are seen as signal voids(black). Thrombus can also be seen within. Other tumors to be remembered are gliomas, ependymomas, metastases and brain masses that extend to the CP angle.

With this issue we conclude neoplasms and mass lesions in the brain.

NEWS AND NOTES

XXXII Annual Convention of National Neonatology Forum,

New Delhi, India

Date: 13-16 December, 2012

Contact:

Dr Ajay Gambhir, Organizing Secretary, XXXII Annual Convention of National Neonatology,
M: 09811557085, 9311557085, Email: secnnf@nnfi.org, drajaygambhir@rediffmail.com,
Website: www.nnfi.org

FAMILY BENEFIT SCHEME
INDIAN ACADEMY OF PEDIATRICS

Enroll in the Scheme and provide financial security to your family.

Family Benefit Scheme of IAP

Mutual Benefit Scheme

- To provide immediate substantial financial aid to the family members on death of the IAP members who are in this scheme
- Scheme is only for Life Members of IAP who have not completed the age of 55 years at the time of joining the Scheme
- In the First Year of inception (till 26-03-2012) relaxation of age for 55 to 65 years will be taken under as founder member in the same slab of 45 to 55 years

Joining Fee

For Age between 25+ to 30 Years – ₹ 5,000/-
For Age between 30+ to 35 Years – ₹ 7,500/-
For Age between 35+ to 40 Years – ₹ 10,000/-
For Age between 40+to 45 Years – ₹ 12,500/-
For Age between 45+ to 55 Years – ₹ 15,000/-
Caution Deposit ₹ 1,500/-

Total amount to pay is Joining fee (as per age slab) + Caution deposit + Annual Administration fee.

For Eg : A Member 32 years old has to pay
₹ 7,500 + ₹ 1,500 + ₹ 400 = ₹ 9,400/-

How to apply for membership

IAP Life Members will have to apply in the prescribed Application Form which can be obtained from the FBS IAP Office Hyderabad or can be downloaded from www.iapindia.org or www.fbsiap.org. The Application Form should be submitted to the Scheme office with relevant fee by cheque / D.D in favor of **" Family Benefit Society"** payable at Hyderabad · Copy of IAP Life Membership Certificate and a copy of Proof of Age i.e. SSC Certificate/ Passport and along with the relevant documents are to be submitted with the Application Form to the Hon. Secretary of the Scheme.

Fraternity Contribution

Every Member of the Scheme shall pay ₹ 300/- per each member in the event of death of IAP Members who are in the Scheme. The amount calculated according to the number of Members who expired in a six month period. The amount thus collected from the Members of the Scheme will be paid after verifying the claim to the family members of the persons who have expired.

Voluntary Retirement

A Member can voluntarily retire from Membership of the Scheme by giving a written request to the Hon. Secretary of the Scheme.

Termination of Membership

The Membership from the Scheme will be terminated on the following grounds:

1. If a Member furnishes wrong information.
2. If a Member fails to pay his/her share of fraternity contribution within six months after the demand by the Hon. Secretary, he/she is treated as a defaulter and Membership will be terminated.
3. If he/she ceases to be a Member of IAP, his/her Membership of this Scheme shall automatically cease.

New Beneficial Amendments in FBS bye-laws after AGM FBS IAP, Gurgaon held on 21-01-2012

1) A revised Age and slab structure introduced from 27-3-2012 as: 55+ to 60 years joining fees Rs 30,000/- and 60+ to 65 years Rs 45,000/- for senior IAP members. Old structure of 55+ to 65 years will continue up to 26-3-2012.
2) Now FBS Membership is also open for Associate life members of IAP
3) All who apply within one year of launch 27-3-2011 to 26-3-2012 will be known as "Founder Members".
4) Founder Members have to pay Fraternity Contribution for 20 years only.
5) Those who apply and become members of FBS IAP after 26-3-2012 will be paying for 25 years as "Regular members".
6) A "Future Liability Fund" is ear marked which will consists of corpus plus 20% of enhanced Death Fraternity Contribution (i.e Rs 300 + 20%(Rs.60/-) total FC Rs 360/- per death)
7) FC bill will be raised once in a year ie on 30th September.
8) Advance Fraternity of Rs 10,000/- can be paid for future adjustments.

Dr Rohit C Agrawal
President IAP

Dr. George F. Moolayil
Chairman FBS IAP

Dr Sailesh Gupta
Hon. Secretary IAP

Dr Ajoy Kumar
Hon. Secretary FBS IAP

Dr Praveen J Mehta
Hon. Treasurer IAP

Dr M Surendranath
Hon. Joint Secretary & Treasurer FBS IAP

For any other details contact Hon. Secretary of FBS IAP

6-3-598/1, 1st Floor, Navata Castle, Venkatramana Colony,
Khairatabad, Hyderabad Andhra Pradesh – 500 004 Mobile : +91 9848034599
Office Tel: +91 40 23332666 Mobile: +91 8978311651 (Rajashekar) Office In-charge
E-mail:fbs.iap@gmail.com Website: www.fbsiap.org

GIVE THIS EXTRA FINANCIAL SECURITY ADDITIONALLY EVEN IF YOU ARE IN IMA's SECURITY SCHEME

The Institute of Child Health and Hospital for Children-Egmore, Chennai

Madras Medical College

Under the auspices of the

Tamil Nadu Dr. MGR Medical University

Invites applications for one year Post Doctoral Fellowships

1) Pediatric Emergency Medicine: 2 seats (1 reserved for Tamil Nadu Service)

2) Pediatric Intensive Care: 2 seats (1 reserved for Tamil Nadu Service)

The Pediatric Emergency Department of the Institute of Child Health-Madras Medical College receives and resuscitates over 10,000 critically ill children every year. A post graduate training program which incorporates a systematic, structured approach to handle a wide variety of pediatric emergencies has been in vogue for the past 15 years. Manned by expert faculty a fully equipped 15 bedded PICU provides post resuscitative care for children and training.

Applications for fellowship training are invited from motivated pediatricians who wish to train in a large volume public children's hospital known for providing emergency and critical care for children from socio economically backward communities.

Eligibility: MD/DNB Pediatrics

Course fee: Rs 50,000.Registeration and exam fee has to be paid separately to the university.

Age: <35 for private candidates; <40yr for service candidates

Last date for submission of application : May 30th 2012, 5 pm

Date of examination : June 7th 2012, 10 am

Course commences on **July 1st 2012**.

Application can be down loaded from the : **www.tnmgrmu.ac.in**

Entrance examination will be conducted for selection of candidates.

Interested candidates should apply with relevant certificates and complete CV

Contact for details: Dr. Poovazhaghi : 9840033020 (poomuthu@yahoo.com)

Dr. Sivaraman : 9884238721 (drmani_76@yahoo.com)

Dr. Ellilarasu : 9841021018 (elilarasu@yahoo.com)

Applications should be sent by registered post to the following address and superscribed as 'APPLICATION FOR FELLOWSHIP IN PEDIATRIC EMERGENCY MEDICINE/INTENSIVE CARE'

Director and Superintendent,

Institute of Child Health & Hospital for Children, Halls Road, Egmore, Chennai - 600008.

Dr.MEHTA'S HOSPITALS Pvt Ltd

A Centre for DNB Pediatrics, Neonatology, Family Medicine &
Fellowship in Pediatric Nephrology
recognized by ISPN

Now Invites applications for

1) Fellowship Programme in Pediatric Intensive Care
Accredited by The Tamilnadu Dr MGR Medical University Since 2011.

Eligibility : MD/DNB in Pediatrics

No. of seats : 2

Duration : 1 year

Application can be downloaded from : www.tnmgru.ac.in

Eligible candidates may apply before : **01/06/2012**

Course commences from : **01/07/2012**

Contact persons: 1) Dr.V.P.Anitha : 9884394885

2) Dr.Shrishu kamath : 9884220588

3) Dr.S.Thangavelu : 9790970772

Apply to:

The Medical Director,
Dr.Mehta's Hospitals,
No.2, Mc.Nicholas Road, 3rd lane,
Chetpet, Chennai – 600031.

Email: hr@mehtahospital.com

INDIAN JOURNAL OF PRACTICAL PEDIATRICS

SUBSCRIPTION TARIFF

JOURNAL OFFICE
1A, Block II, Krsna Apartments,
50, Halls Road, Egmore,
Chennai 600 008, Tamilnadu, India.
Phone: +91-44-28190032, 42052900.
Email: ijpp_iap@rediffmail.com

Official Journal of the Indian Academy of Pediatrics
A quarterly medical journal committed to practical pediatric problems and management update

Enter Subscription for [ONE] year / [TEN] years

For office use
Ref. No.
Cash / DD for Rs.
DD No.
Receipt No. & Date

Name .....

Address .....

.....

City .....State .....

Pin ..... Phone (R) ..... (O).....

Mobile ..... Email .....

Designation ..... Qualification.....

I am enclosing a DD No. …….. dated …… drawn on ……..…….....

favoring **Indian Journal of Practical Pediatrics** for Rs…….....

Signature

Subscription rate

Individual	Annual	Rs.500/-
	Ten Years	Rs.5000/-
Institution	Annual	Rs.600/-
	Ten Years	Rs.6000/-
Foreign	Annual	US $ 65/-

(Subscription period is between January and December only)

Send your subscription, only by crossed demand draft, drawn in favour of **INDIAN JOURNAL OF PRACTICAL PEDIATRICS**, payable at **Chennai** and mail to **Dr. K. NEDUNCHELIAN,** Editor-in-Chief, 1A, Block II, Krsna Apartments, 50, Halls Road, Egmore, Chennai 600 008, Tamilnadu, India.