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September 2014 | Newsletter | Year 2014 | Volume 7 Issue: 1

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Allopurinol for prevention of progression of kidney disease with hyperuricemia

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Hyperuricemia is associated with hypertension and progressive chronic kidney disease (CKD). Many studies have shown that increase in the serum uric acid levels were positively associated with CKD. Strategies to reduce the serum uric acid (UA), including dietary changes such as lower intake of fructose, and sugar , sweetened beverages and red meat and uric acid lowering drugs like allopurinol may be useful in preventing or arresting the progression of kidney disease . Recent randomized controlled trials reported that UA lowering medication with allopurinol was associated with a lower serum creatinine level in the treatment group compared to controls.

We therefore conducted a study to analyze the renal effects of allopurinol treatment in CKD patients with hyperuricemia. This study is a retrospective cohort analysis of CKD patients with hyperuricemia, attending out‑patient department (OPD) of Nephrology at Nizam's Institute of Medical Sciences, Hyderabad from 1998 to 2008. With a margin of error of 10 and confidence interval of 95% and 50% of response distribution the sample size was calculated to be 192. The inclusion criteria were presence of renal disease, defined as having an estimated GFR (eGFR) lower than 90mL/min, hyperuricemia of value more than7.0 mg/dL in men and more than 6.5 mg/dL in women, at least 2 years of follow-up.

We divided the patients into 2 groups: treatment group who received allopurinol in a dose of 100 mg/dL and the control group who did not receive allopurinol. Subjects were followed up at monthly intervals. Patient's clinical outcome was analyzed at 6 months, 1 and 2 years study period. Men were more than females in both the groups. There was no difference in the age distribution in both the groups. The commonest age group was 51 – 60 years in both the groups. There was no significant difference in the baseline characteristic of CKD patients in both the groups. The most common cause of CKD was type 2 diabetes mellitus in both the groups. The most common staging of CKD was stage 3 in both the groups.

There was a significant fall in the mean systolic and diastolic blood pressure at the end of 2 years in allopuinol group when compared to control group (p value <0.0001and 0.03 respectively). In allopurinol group there was significant decrease in the mean systolic and diastolic blood pressure at 6 months, 1 year and 2 years when compared to baseline. But in control group there was no change in the systolic and diastolic blood pressure at 6 months, 1 year and 2 years when compared to the baseline. There was no significant difference in the proteinuria in both the groups at baseline, 6 months and 1 year. However, at the end of 2 years control group had significant increase in proteinuria compared to allopurinol group. At the end of 2 years, proteinuria increased in control group whereas, it was decreased in allopurinol group but, were not significant in both the groups . Though there was no significant difference in serum uric acid at baseline, there was significant fall in seum uric acid at 6 months (P value 0.0001), 1 year (P value < 0.0001) and 2 years (P value 0.0001) in allopurinol group when compared to control group. There was significant increase in serum creatinine in control group when compared to allopurinol group at 1 year (p value 0.006) and 2 years (p value <0.0001). At the end of 2 years, significantly higher number of patients in allopurinol group reached end point (50% increase in in serum creatinine) compared to control group (p value <0.0001,OR=52). Odds ratio in favour of allopurinol is 52. In allopurinol group serum creatinine was maintained at 6 months, 1 year and 2 years when compared to baseline. Where as in control group there was significant increase in serum creatinine in at 6 months ,1 year and 2 years compared to baseline creatinine. In control group there was significant fall in e GFR at 6 months (P value< 0.0001), 1 year (P value <0.0001) and 2 years (P value< 0.0001) when compared to baseline. Whereas, in allopurinol group there was no change in the e GFR at 6 months, 1 years and 2 years when compared to baseline. There was no significant difference in the therapeutic medication used in both the groups except for the calcium channel blockers. Significantly higher percentage of patients in control group used calcium channels blockers.

Conclusions

1. Allopurinol significantly decreases the serum uric acid in CKD patients with hyperuricemia
2. Allopurinol decreases the systolic and diastolic blood pressure in hyperuricemic CKD patients; this is probably due to the reduction of serum uric acid levels.
3. Though, allopurinol may not decrease the amount of proteinuria significantly, it definitely prevents the rise in proteinuria and thereby , the progression of CKD with hyperuricemia.
4. Allopurinol slows down the progression and rate of fall of GFR in CKD patients with hyperuricemia
5. However, further randomised control studies are required to know the role of high uric acid in progression of CKD and role of allopurinol in halting the rate of progression of CKD

NAIL – PATELLA SYNDROME – A NOVEL

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Nail-patella syndrome (NPS) is a rare autosomal-dominant genetic disorder (1 in 50 000 live births) due to heterozygous mutations in the LMX1B gene resulting in symmetrical nail, skeletal, ocular and renal abnormalities. This gene is a transcription factor involved in the normal dorso-ventral patterning of limb and development of glomerular basement membrane (GBM) in the kidney.

Renal involvement is found in 60% of patients, of which 15% progress to end-stage renal disease (ESRD). We report a patient of NPS complicated by severe ocular anomalies and ESRD caused by a de novo mutation in the LMX1B gene; the patient underwent successful renal transplantation. A 29-year-old male was referred to our hospital with end-stage renal failure. At 6 months of age he was diagnosed with sclerocornea and congenital glaucoma; he had a progressive loss of vision and became blind by eight years of age. He had limited extension of the elbows and recurrent subluxation of both knee joints since birth. He was found to have proteinuria at 9 years of age and later developed progressive renal failure.

A renal biopsy showed severe glomerulosclerosis and interstitial fibrosis and was initiated on hemodialysis at the age of 28years. Neither of his parents nor his younger sister have similar clinical features. DNA analysis with direct sequencing of the eight coding exons and flanking introns of the LMX1B gene was carried out. In this patient, a new missense mutation in the homeodomain of LMX1B was identified, presumed to abolish DNA binding (c.725T>C, p.Val242Ala). The patient had a missense mutation at codon 725 where thymine was replaced by cytosine. This missense mutation led to a replacement of valine by alanine at position 242. This mutation was not detected in either parent. A live-related donor renal transplantation with his mother as donor was performed for this patient at the age of 29 years. He had an uneventful postoperative period and the graft function is normal 5 years after transplantation. Our patient with NPS had a de novo missense mutation in the homeodomain of LMXIB, not previously described in the literature; he had severe ocular and renal complications. The LMX1B gene is involved in the correct binding of DNA in the transcriptional regulation of key eukaryotic developmental processes. Both parents of the patient have been tested to exclude the possibility of a rare polymorphism, and found not to have this mutation, proving that this is a de novo mutation. A significant association described in literature between the presence of clinically relevant renal involvement in an NPS patient and a positive family history of nephropathy was, however, lacking in our case .Renal transplantation is a viable therapeutic modality in the treatment of ESRD in patients with NPS, and the disease does not recur in the kidney grafts. Whether the denovo mutation identified here is consistently associated with severe renal involvement and progression to ESRD remains to be studied in future. Nuclear genotype–phenotype association was apparent for extrarenal manifestations as phenotype is highly variable, and this is one sporadic case only. Further studies on modifier factors are needed to understand the mechanisms underlying phenotypic heterogeneity. A careful evaluation of potential living kidney donors for features of the disease is essential.

CHARACTERISTICS OF BIOFILMS FORMED ON NON-TUNNELED HEMODIALYSIS CATHETERS

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Microbial biofilms are mechanisms used by microorganisms that cause chronic infections in humans. Tunneled dialysis catheters are important source of infection through biofilm formation. The incidence of catheter related bacteremia is reported be 0.8-5.5/1000 catheter days.[1] Staphylococcal species particularly *S.aureus* is the predominant cause for tunneled dialysis catheter infection.[2] In India, non-tunneled catheters are commonly used a source of temporary vascular access for the initiation of hemodialysis in end-stage renal disease patients. This study analyzed the characteristics of biofilms formed on non-tunneled hemodialysis catheters.

50 adult patients with end-stage renal disease receiving hemodialysis through non-tunneled catheters, whose catheters were removed for catheter-related bacteremia, are studied. Catheter-related bacteremia was defined as the presence of bacteremia in an HD patient with a non-tunneled catheter and in whom no other obvious source of infection was evident. Peripheral-blood cultures were obtained from patients with catheter-related bacteremia before starting systemic antibiotic therapy. The decision to remove the HD catheter was made by the Nephrologist after obtaining positive peripheral blood culture reports. Catheter cultures were obtained from the surfaces of the removed HD catheters.The tip of the catheter is rolled across the surface of a blood agar plate and the resulting colonies are counted after overnight incubation. A statistical association of >15 CFU with catheter-associated sepsis was considered as significant.[3]

Blood cultures were positive in all 50 patients. Gram-positive organisms were isolated in 82%, Gram-negative bacteria in 12% and both gram positive and gram-negative in 6% of the cultures. *Staphylococcus aureus* was the most common pathogen (61%), followed by *Staphylococcus epidermidis* (27%).Catheter cultures were positive in only 32 patients. Staphylococcal biofilm was found in 25 out of 32 patients. All 25 biofilm producers belong to *S.aureus*.

Our study was the first of its kind in detecting the biofilm formation on non-tunneled HD catheters from patients with bacteremia. Passerini*et al.* detected biofilms in 100% of central venous catheters (CVC) removed from 26 intensive care unit patients; bacteria were present in the biofilms of 88% of CVCs.[4] In our study catheter culture were positive in only 32 patients. All patients with bacteremia had received systemic antibiotics for a few days prior to catheter removal. Subsequently, when the catheter was removed and processed, catheter cultures were positive in only 32 patients. We also tested 25 catheter isolates of staphylococci by three in vitro screening procedures for their ability to form biofilm. We found that tissue culture plate method was more sensitive than tube method and congo red agar method in detecting biofilm formation by *S.aureus.*

Our study has certain limitations. First, only 50 patients were studied. This is a small number considering high prevalence of catheter related bacteremia among the HD patients. Second, catheter cultures were positive in only 32 patients, owing to the use of systemic antibiotics prior to catheter removal. Third, only patients with catheter related bacteremia were studied. Fourth, this is only an observational study.
Our study concludes that staphylococcus species are the most common bacteria isolated from patients with catheter related bacteremia and *S. aureus*is the predominant microorganism responsible for biofilm formation in the non-tunneled HD catheters.

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ACUTE KIDNEY INJURY IN SCRUB TYPHUS

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Rickettsioses of the scrub typhus group are caused by Orientia tsutsugamushi an intracellular gram negative bacterium. The name scrub typhus comes from vegetation harbouring the vector. It was first observed in Japan and called tsutsugamushi (tsutsuga = dangerous mushi = insect or mite). It is an acute infectious disease that is emerging in South-East Asia transmitted by bite of infected Trombiculid mite larvae called chiggers. The disease is endemic in the Tsutsugamushi triangle bordered by Japan, Australia, India and Siberia. In India outbreaks have been reported from the sub-Himalayan belt from Jammu to Nagaland, Himachal Pradesh, Pondicherry, Tamil Nadu, Sikkim and Darjeeling occurring in rainy season and in cooler season in southern India. Scrub typhus is probably underdiagnosed and underreported in our country. Absence of definitive signs and symptoms and a general dependence upon serological tests makes differentiation from other common febrile diseases such as typhoid fever and leptospirosis difficult.

The disease results from endothelial infection, vasculitis and increased vascular permeability. After 10 to 12 days of Chigger bite a “punched-out” skin ulcer or eschar results at the site of bite followed by acute fever, headache, profuse sweating, conjunctival injection, lymphadenopathy and cough followed by a self-limiting dull red maculopapular rash on the trunk extending to extremities. Eschar may be absent and rash may be overlooked in the dark skinned. The disease is usually mild and self-limiting. Multi organ involvement may be seen manifesting as interstitial pneumonia, meningoencephalitis, progressive hypotension, multi-organ failure and death. With treatment defervescence occurs in 36 hours. Mortality is up to 30% if untreated usually by end of second week due to primary infection or secondary complications (e.g., pneumonitis, encephalitis, circulatory failure). Febrile illness, history of exposure to mites, travel to endemic areas, typical eschar, rash and laboratory evidence of low platelets, low to normal white blood count, mild transaminitis and hyponatremia point to the diagnosis. Laboratory diagnosis is by detection of specific IgM for 56 KDa antigen at 1:100 or higher by Enzyme Immunoassay (EIA) which becomes positive by 3 to 4 days, 1:32 dilution or higher by Immunoperoxidase (IP) or 1:10 dilution or higher by Indirect Immunofluorescence (IF). The classical Weil-Felix agglutination test using Proteus vulgaris OX-K antigens at a titre of 1:80 has also been recommended but is less sensitive and becomes positive by the second week. Doxycycline is the recommended treatment continued for three days after fever subsides. Chloramphenicol and rifampin may also be used. Scrub typhus has emerged as an important differential diagnosis in the setting of acute febrile illness with acute kidney injury (AKI). Kidney involvement in scrub typhus is probably due to renal hypo perfusion resulting from shock or hypovolemia, rhabdomyolysis, vasculitis, acute interstitial nephritis or direct microbial invasion of the renal tubules causing acute tubular necrosis. We studied the kidney related abnormalities in a large series of diagnosed scrub typhus over a 2 year period and followed for 3 months or till kidney recovery. Diagnosis was by Weil-Felix test or scrub typhus IgM ELISA. In our series of 259 patients 22.3% had AKI and 56.7 % urinary abnormalities such as proteinuria, pyuria, granular casts and haematuria. All patients of AKI had urinary abnormalities indicating intrinsic kidney involvement. One patient had acute interstitial nephritis and acute tubular necrosis on kidney biopsy. Eschar was seen in about 20%, altered sensorium in 7.7% and most had mild transaminitis (93%), mild rise in creatine phosphokinase (65.3%) and thrombocytopenia (73%). Mechanical ventilation was required in 7.3% and intensive care in 22%. Most had mild AKI with RIFLE category risk in 38.3 %, injury in 28.7%, most were nonoliguric (72.8%) and only 10% required haemodialysis for 1 to 9 sessions. Most recovered kidney function with only one having a creatinine of 1.8 mg/dl at 3 months. The final median creatinine and duration of hospital stay were not significantly different between the non AKI and AKI groups. Two patients died both having AKI. Thrombocytopenia and intensive care requirement were predictors of AKI. Other series from South India have shown myocarditis to be a predictor of AKI and delayed presentation, acute respiratory distress syndrome and shock to be the determinants of mortality. We wish to highlight the importance of scrub typhus as a cause of acute febrile illness and AKI in South India especially in the presence of thrombocytopenia and intensive care requirement. Due to a nonspecific presentation there may be a role for empirical doxycycline in this setting. The AKI is usually mild and recovers completely in most patients if diagnosed and treated early.

EMPHYSEMATOUS PYELONEPHRITIS – THE TAMING OF THE BEAST

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Emphysematous pyelonephritis (EPN) is a septic involvement of the kidneys by gas forming organisms classically seen in diabetic individuals. In the past, it is known to have been fatal in 60-80% of cases.[1] This condition has seen a paradigm shift in its management protocols from a primarily surgical option of nephrectomy to a more conservative kidney-preserving medical management. The advancement in imaging modalities like Ultrasonography (USG) and computerized tomography (CT) scan, broad spectrum antibiotics and supportive critical care has contributed to this improvement in survival with conservative management.

In this retrospective study, we evaluated 22 consecutive cases managed at a centre with a uniform protocol with a primarily medical approach and a rescue surgical management (Percutaneous drainage or nephrectomy) in those showing poor initial response.[2] Comparison was made between those who responded to medical management alone and those who needed surgical rescue procedure. The overall mortality was lower than described in the literature in this small study. The clinical triad of shock, altered sensorium and thrombocytopenia marked poor prognosis and mortality. No single laboratory parameter was predictive of poor prognosis or higher mortality. Studies have shown that Class IV EPN, renal parenchymal necrosis with either no fluid content or a streaky/mottled gas pattern on imaging, conservative therapy defined as fluid resuscitation and antimicrobials without PCD, and thrombocytopenia are markers and associated with greater mortality.[3] Studies have shown that mortality associated with medical management plus percutaneous catheter drainage was significantly lower than medical management plus emergency nephrectomy. However such studies may be confounded by the fact that more severe cases underwent nephrectomy and hence greater mortality in them.[4]This study demonstrates the results of a series of cases managed by a uniform protocol in a real life practice situation. Improved survival and success of conservative management over a primary surgical approach highlights the improvement in diagnostic modalities like USG and CT scan, better antibiotics, critical care protocols and supportive measures like renal replacement therapy in intensive care settings. Such improved survival has also been replicated in other Indian studies.[5]

This study as the earlier ones, underlines the markers of poor prognosis like presentation with obtunded sensorium, thrombocytopenia and extensive renal involvement represented by grade IV or V EPN on a CT Scan. These markers may be used to select cases for a primary surgical approach like a percutaneous drainage or nephrectomy as a life saving measure. Any evidence derived out of retrospective analysis of a case series is fraught with bias and week strength. In a rare condition like EPN, which is getting even rarer now with early and effective management of urinary tract infections and better approaches to glycemic control, to have a randomized controlled trial may be hard to design. Evidence such as that derived from similar studies, albeit weak, will be a reasonable means to assign treatment protocols and case selection for various modalities of treatment for EPN.

EPN is a rare, potentially fatal complication of urinary tract infection, classically seen in diabetic patients. Good glycemic control and early, effective treatment of lower urinary tract infections is the best way to prevent this dreaded complication. Strong clinical suspicion and use of imaging like USG or CT Scan is an effective modality to diagnose this condition early for an effective medical management. In those presenting late, with a more severe involvement of the kidneys and multi-systemic dysfunction should be addressed with a primarily surgical approach under cover of broad spectrum antibiotics and effective critical care.

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Finger nail creatinine and its role in confirming chronicity of renal failure

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Indian J Nephrol. 2013 Mar-Apr; 23(2): 114–118. doi: 10.4103/0971-4065.109413

Creatinine enters the nail during the formation of the nail and is localized in nail plate. Once it is incorporated into the nail, it cannot be further added or removed. So, the concentration of nail creatinine will be proportional to the serum creatinine at the time of nail formation. The amounts of creatinine from the clippings at the tip of the nails represent the creatinine levels 4-6 months earlier. If the creatinine level in the nail clippings is higher than the normal, it may suggest elevated serum creatinine 4-6 months earlier thereby confirming chronicity. Just as HbA1c helps us to assess the status of diabetic control that existed 2-3 months earlier, nail creatinine helps us to get an idea about the elevation of creatinine that existed 4-6 months earlier. The test requires streamlining and standardization of the procedure in the laboratory. Once done, the question of acute versus chronic in a given patient can be established within 48 hours. The effort required is minimal if the procedure can be streamlined. The steps are, clipping finger and or toe nails, washing and drying them before pulverization. Liquid nitrogen which is now available makes the process of pulverization simpler. Creatinine can be extracted from the pulverized nails and assessed by the conventional Jaffe's reaction.

This paper has tried to standardize the methodology for extraction and assay creatinine from nail clippings and shown that it is useful for assessing the level of serum creatinine that existed at the time of formation of the nail. The study also shows that the nail creatinine level of patients with established chronic renal failure was higher than normal volunteers and those with acute kidney injury and the difference was statistically significant (figure: 1).

Figure 1 Showing the nail creatinine values in all the groups studied

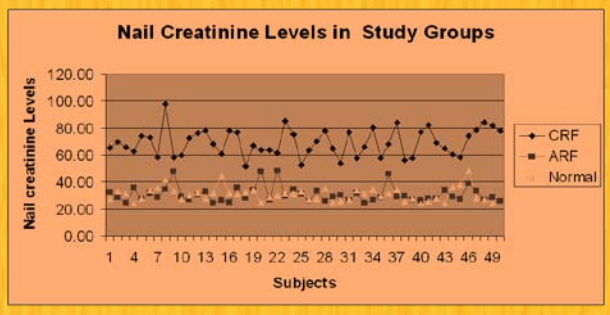
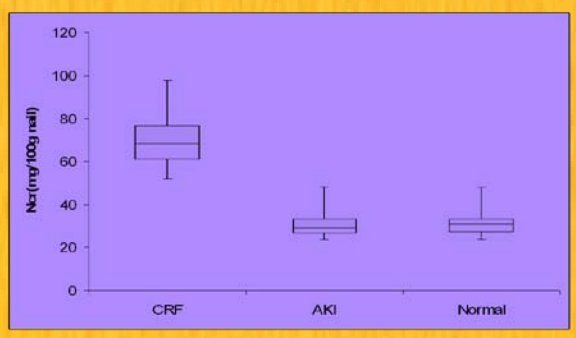


Figure 2 Showing the nail creatinine values in the 3 groups studied



Comparison of peritoneal transport characteristics at the second week and at six months of peritoneal dialysis commencement.

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Indian Journal of Nephrology, September 2013/ Vol 23/ Issue 5, page 347-350.

Peritoneal Equilibration test (PET) defines the transport nature of the patient's peritoneal membrane. Understanding this helps in giving a proper dialysis prescription to the patient. It also helps to prognosticate the outcome and helps in managing a patient with ultra filtration failure.

The current recommendation by NKF-KDOQI towards performing the first 'peritoneal equilibration test' is 4-8 weeks after the catheter insertion. This suggestion is based on the recommendation by Rocco et al and Johnson et al who studied the peritoneal transport profile within 2 weeks of catheter placement and found it differed from the subsequent PET performed later. The reasons believed to be responsible for the change in the membrane character in the initial days are due to the dialysate induced changes in the local inflammatory cytokine production, dextrose induced changes in the peritoneal blood flow, and peritoneal vascularity.

They also observed that PET done at 4 weeks correlated with later PET tests – done at six months and one year. Unfortunately not many studies are available in this context. Also no study is available where the peritoneal transport characteristics are performed between the second and fourth week that was compared it with the subsequent assessment.
Our protocol is to start small volume exchanges without break-in period and the dwell volume is increased every 2-3 days and 2 liters are achieved by 10th day after initiation. In this study we performed the PET test at 2nd week after catheter placement in our patients and compared it with a similar test done at six months. Patients with peritonitis were excluded. This is a single center, prospective study performed between March 2007 and December 2011. PET was done by the standard procedure described by Twardowski for sugar and creatinine. The study included 126 patients – 102 men (81 %) and 24 women (19%). The first PET revealed 'Low Average' was the commonest transport character seen in 87 (69%) followed by 'High Average' in 20 (15.9%).

Comparison of second week PET and sixth month PET were similar in 115 patients (91.2 %) and only 11 patients (8.8%) had a different PET at sixth month – 4 changed from High Average to Low Average, three changed from Low Average to Low and four changed from Low Average to High Average.
Comparison of the 4th hour D/P creatinine and D4/D0 sugar between the first and the sixth month PET values between the 'unchanged' PET group (115 patients) and the 'changed' PET group(11patients) did not show statistically significant variation. In the 'unchanged PET' group of patients the 4th hour D/P creatinine and D4/D0 sugar between both the PET were 0.59 + 0.14 vs 0.62 + 0.12 for creatinine (p= 0.26, NS) and 0.46 + 0.12 vs 0.46 + 0.11 for sugar (p=0.65 NS).
Even in the changed PET group these values were statistically insignificant (0.56 + 0.1 vs 0.67 + 0.1 for creatinine, p=0.243 NS, and 0.44 + 0.1 and 0.37 + 0.1, p = 0.29 NS). This is basically because all patients with changed transport status, did so within the adjacent transport status. No patient changed their transport characteristics drastically – from Low to High and vice versa.

The major advantage of this study is the large patient numbers (126) compared to the studies done by Rocco et al (34 patients) and Johnson et al (50 patients). In conclusion, we have proven for the first time that PET can be done as early as 2 weeks (EARLY PET) after catheterization and this allows the patient to get a proper prescription from the onset of peritoneal dialysis.

DIAGNOSIS OF IRON DEFICIENCY IN CHRONIC KIDNEY DISEASE: VALIDITY OF IRON PARAMETERS, RETICULOCYTE HEMOGLOBIN CONTENT (CHR) AND HYPOCHROMIC RED CELLS IN INFLAMMATORY STATE

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International Journal of Current Research and Review 5:21; Sept 2013, 83-91.

Iron deficiency is the major cause of inadequate response to erythropoeitin therapy in patients with chronic kidney disease. The accurate and early detection of iron deficiency is the most essential step in the management of the patients with chronic kidney disease. However, the diagnosis of iron deficiency in patients with chronic kidney disease is rendered difficult as the currently available tests are less reliable in presence of uremia (inflammatory state).Measuring reticulocyte hemoglobin content (CHr) and hypochromic red cells(Hypo%) has been proposed as a measure of available iron stores that could be superior to the available tests in various studies.

On hundred and twenty two consecutive chronic kidney disease (CKD III, IV, V-non dialysis) patients were enrolled. Complete hemogram, iron studies, Reticulocyte hemoglobin content (CHr) and percent hypochromic red cells (%Hypo), high sensitive CRP(hs-CRP) levels were done. In the study group of 122 patients screened, 103 patients were found to be iron deficient by Kidney Dialysis Outcome Quality Initiative (KDOQI)criteria. In the iron deficient patients, intra venous iron(i.v iron sucrose 1000mg) was administered in divided doses followed by erythropoetin and the tests were repeated after 4 weeks of completing i.v iron therapy . If the rise in Hb> 1gm%, at the end of 4 weeks , the patient were grouped into responders (iron deficient subjects). The rest were grouped as non-responders (Iron replete).The value of the tests, individually or in combination, was determined in the subgroups and categorized based on hs-CRP levels (<5mg/L).

There were 64 males with mean age of 45.32±12.23 years and 39 females with mean age of 41.23±10.34 years were iron deficient. A total of 103 patients were iron-deficient by KDOQI criteria (TSAT < 20% or Serum ferritin <100mg/dl) According to the response criteria mentioned in the study methods,58 (56.31%) patients were iron deficient and 45 (43.68%) were Iron replete

TABLE: Sensitivity, specificity of chosen cut off values of various parameters in the absence of inflammation and presence of inflammation

Test criteria	Sensitivity (%)		Specificity (%)		Positive predictive value (%)		Negative Predictive Value (%)	
	CRP mg/L		CRP mg/L		CRP mg/L		CRP mg/L	
BASE LINE	<5	>5	<5	>5	<5	>5	<5	>5
TSAT<20 %+S Fer <100 ng/ml	57.55	60.66	66.67	80.87	25.54	60.00	78.59	80.00
CHr<29 pg+ Hypo>2.5 %	55.25	80.00	88.86	60.00	40.21	40.00	80.00	80.00
TSAT<20 %+ CHr <29 pg	60.54	80.00	77.78	60.00	25.24	50.54	77.78	85.71
TSAT<20%+ Hypo>2.5%	75.78	60.64	77.74	70.00	50.50	50.00	91.36	77.72
CHr <29 pg+ Fer <100 mg/ml	50.80	100.00	85.11	80.85	50.55	50.56	85.18	100.00
CHr <29 pg+ Hypo>2.5 %+ S Fer <100 ng/ml	57.58	100.00	88.56	80.00	50.00	71.25	82.24	100.00
TSAT<20 %+ CHr <29 pg+ Hypo>2.5 %	55.25	60.65	88.85	80.00	40.25	60.68	80.00	80.00
TSAT<20 %+ CHr <29 pg+ S Fer <100 ng/ml	55.69	100.00	85.68	80.00	33.65	71.15	79.96	100.00
TSAT<20%+ Hypo>2.5 %+ S Fer <100 ng/ml	50.56	60.68	92.26	90.95	66.67	75.58	86.68	81.56
TSAT<20 %+ CHr <29 pg+ Hypo>2.5 % +S Fer <100 ng/ml	56.56	60.64	88.65	80.00	40.56	60.00	80.00	80.25

Studies evaluating the combination of CHr with %hypo with iron studies parameters in predialysis chronic kidney disease patients are very few.
The base line mean MCV, CHr, TSAT, Serum ferritin, Reticulocyte count, were significantly lower in iron deficient in comparison to iron replete subjects. Patients with inflammation had higher mean serum ferritin, low TIBC and Higher %Hypo when compared to absence of inflammation.

Newer parameters like CHr and % Hypo, have variable sensitivity and specificity when used alone in CKD patients. The combination of CHr (<29) and %hypo (>2.5%) with iron parameters like serum ferritin or TSAT increases specificity in presence of inflammation. We recommend the tests for diagnosis (iron parameters, CHr, % Hypo) should be correlated with hs CRP(a marker of inflammation) before iron therapy.

A miniseries of spontaneous intramural esophageal hematoma in hemodialysis patients: A rare cause of dysphagia

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Hemodial Int. 2014 Apr;18(2):558-61. doi: 10.1111/hdi.12143. Epub 2014 Feb 12.

We reported a case series of three patients on hemodialysis, who presented with dysphagia and later found to have intramural esophageal hematoma (IEH) which is an uncommon clinical condition, though essentially benign. Esophageal injury may be divided broadly into mechanical and chemical injuries. Mechanical injury is further classified into traumatic and spontaneous types; the former is caused by accidental ingestion of foreign objects or medical procedures such as endoscopic procedures, nasogastric intubation and dilatation of constrictions; the latter accompanies increased intraluminal pressure in the esophagus due to nausea, emesis, and/or blood coagulation abnormalities.

Multiple predisposing factors were noted in our patients like heparin anticoagulation during dialysis, thrombocytopenia and prolonged prothrombin time in one of our patient who had associated liver disease. Also all three patients had recurrent vomiting and retching due to uremia and probably would have raised the intraluminal pressure.

Most commonly they presents with acute chest pain, hematemesis and dysphagia and clinicians should have high index of suspicion for esophageal hematoma in the presence of such symptoms. Our patients had varied clinical presentation but the common factor in all of them was, they had dysphagia and hematemesis. Cardiac evaluation was normal in all three patients.

It can be diagnosed by doing upper GI endoscopy and can be confirmed by contrast CT scan of the chest and/or gastrograffin swallow study which shows a 'double barrel' sign.

We had difficulty in managing these patients as they were kept on liquid diet for as long as 8 to 10 days. Also they were receiving heparin free dialysis during this period in spite of the requirement of blood and blood products transfusion during dialysis. Spontaneous IEH's generally have a benign course and resolve within three weeks of conservative management as is seen in our patients also. However, on rare occasions, the hematoma can progress to cause complete esophageal obstruction and severe dysphagia, and in some cases, spontaneous drainage of hematoma with massive bleeding, leading to hemodynamic instability and death. Rare cases of esophageal perforation has been reported, which carries a mortality of 10% to 20%.

Well documented cases of spontaneous Intramural esophageal hematoma in hemodialysis patients is sparse in worldwide literature. No such reports are available from India. This case series was reported so that the treating physician should suspect the possibility of Intramural esophageal hematoma (IEH) in a dialysis patient presenting with dysphagia, as continued anticoagulation during hemodialysis would possibly lead to life threatening complications, the course of which is otherwise benign.

Acute interstitial nephritis due to proton inhibitors

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Indian J Nephrol. 2013 Jul-Aug; 23(4): 304–307

Kidneys provide the excretory route for majority of drugs and their metabolites. Renal concentrating, secreting and metabolizing pathways result in manifold changes to the chemical and antigenic structure of parent compound. Both Antigen antibody and cell mediated immunity have been implicated in Acute Interstitial Nephritis with resultant renal damage. In developing countries where free access to medical care through medical practicioners may not be universal , public at large take recourse to non prescription pattern of drug ingestion. Since dyspepsia and indigestion constitute one of the most common symptoms in the community, drugs to alleviate these have been ingested regularly. Proton pump Inhibitors have come to occupy a preeminent space in the management of upper gastrointestinal symptoms. Generally these drugs are safe .But of late , instances of allergic interstitial nephritis has been reported as adverse effect for these drugs. We present here the first case series reported from India. Unless a high index of suspicion is entertained about this condition, it is likely to be missed. Permanent and irreversible fibrosis may ensue in kidneys. It is important that early diagnosis is made with the help of renal biopsy and immunosuppressive medications in the form of corticosteroids instituted to arrest the progression of inflammation in the kidneys.

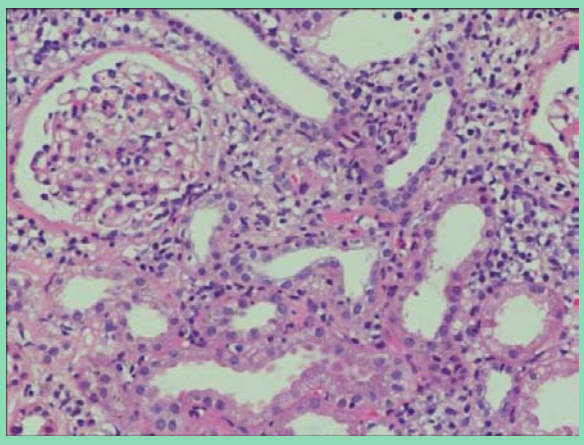

Figure of renal biopsy showing inflammation in and around renal tubules with infiltrating lymphocytes and eosinophils

Pharmacokinetics of concentration-controlled mycophenolate mofetil in proliferative lupus nephritis: an observational cohort study

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Therapeutic Drug Monitoring. 2014 Aug;36(4):423-432. doi:10.1097/FTD.0000000000000031.

Lupus nephritis (LN) is a major organ involvement in systemic lupus erythematosus (SLE). Mycophenolate mofetil (MMF) is the prodrug of mycophenolic acid (MPA) and is recommended for induction therapy in LN in fixed doses. LN patients have altered serum albumin, proteinuria, renal impairment, and increased inflammatory markers, all of which may affect the drug's kinetics.This was an observational study conducted in the Departments of Nephrology and Clinical Pharmacology, Christian Medical College, Vellore, India. Thirty four patients with biopsy proven class III or IV LN were started on induction regimen with oral steroids and MMF. Eight patients received the innovator product CellCept (Roche pharmaceuticals, Basel, Switzerland) and the remaining 26 received generic formulations, either Mofilet (Emcure pharmaceuticals, Pune, India) or Mycept (Panacea Biotec pharmaceuticals, New Delhi, India). The initial dose of MMF was empirical at 30mg/kg/day. The area under the concentration–time curve (AUC) for MPA was measured by limited sampling strategies (LSS) within three weeks of initiation, and dosing was adjusted to achieve an AUC of 30–60 mg.h/L. In this study, the majority of the measurements were 6-hour extrapolated AUCs with 9 sampling points. Renal response was defined as a decrease in 24-hour urine protein collection to <3.5 g/d in patients with baseline nephrotic range proteinuria (≥3.5 g/d) or by >50% in patients with subnephrotic proteinuria (<3.5 g/d) and stabilization (±25%) or improvement in serum creatinine. This definition was taken from the Asperva lupus management study (ALMS). Complete renal response was defined as improvement of serum creatinine to previous baseline and a decline in proteinuria to <0.5 g/d as per the KDIGO clinical practice guidelines on glomerulonephritis. We assessed outcomes at the end of one year and correlated it with clinical features and MPA pharmacokinetics.

The median follow-up time was 264 (IQR, 180–324) days. 27 (79.4%) patients achieved renal response by one year (median dose, 2 g/d). 50% of them reached the end-point within four months (111 days) of induction therapy and 75% by approx. five months (157 days). The proportion of patients who achieved complete renal response at 1 year was 23 (67.6%). Patients with an AUC >30 mg.h/L had better renal response at 1 year. We found that 21(61.8%) of patients had lower than target AUC at first testing and required upward titration of MMF dose. Those with serum albumin >3.5 g/dL had a greater chance of having an AUC >30 mg.h/L. There was only a weak correlation of MMF dose per body weight with AUC. There was a weak but significant correlation (r = 0.561, P = 0.001) of MPA trough concentrations and AUC. The coefficient of variability between patients of dose normalized MPA AUC was 37.9% at baseline. MPA exposure was not significantly associated with adverse events.

In the largest ALMS, the target MMF dose used in 185 patients was 3 g/d (median dose, 2.6 g/d) for a 24-week induction period, with much lower response rates of 56.2% (n = 104). About 33.5% (n = 62) of patients in the MMF arm were Asians in this study and had a response rate of 53.2% (n = 33). In this study, the median concentration-controlled dose was 1.5–2 g/d during the induction phase. The recent KDIGO guidelines recommend MMF up to 3 g/d during the induction phase. This may need to be relooked especially in South Asian patients. Whether therapeutic drug monitoring (TDM) contributed to the higher response rates in our cohort needs to be tested with randomized controlled trials. There is large inter-patient variability in MPA pharmacokinetics. Factors reported in the literature responsible for this variability are serum albumin, serum bilirubin, hemoglobin, renal and hepatic impairment, co-medications, co-morbidities, body weight, gender, race, age, and genetic polymorphisms of metabolizing enzymes. This study showed that higher 24-hour urine protein excretion and lower serum albumin produced lower MPA exposures in LN patients. The lower MPA exposure in our cohort of Asian LN patients could be explained by the greater MPA metabolism contributed by the severe hypoalbuminaemia (2.7 ± 0.8 g/dL).

High inter-patient variability precludes fixed dosing schedule in patients especially in the setting of hypoalbuminaemia in LN. Therapeutic drug monitoring of MMF can achieve optimum response for each patient with the least possible dose thus ensuring long term cost reductions in most cases.This observational study reflects every day practice for the treatment of LN in a center with facilities for TDM of MMF. There was no control arm with fixed-dose MMF

Cardiovascular disease in peritoneal dialysis: A review

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Published in Clinical Queries -Nephrology,Dec 2013

Cardiovascular disease accounts for the highest percentage of mortality in renal failure- a fact that is accentuated in this uremia. Indeed it follows that better PD outcomes mandate more attention to this factor. Atherosclerotic CVD and its higher preponderance in uremic patients is well described. However non atherosclerotic disease like LVH, volume overload and CHF also contribute significantly to propagation of CVD. In addition, factors unique to PD are thought to play a part. This includes hypoalbuminemia, malnutrition, and transport status .

Uremia is also associated with changes in calcium, phosphorus and Vit D metabolism which leads to vascular calcification. Better management of the PD prescription, attention to the volume status, treatment of hyperlipidemia, smoking cessation, BP control, anti platelets, etc are important parts of the management of CVD in PD.Glucose loading associated with PD may also contribute. It increases insulin resistance with its attendant complications. Though not as coninflammation Thorpeoved as in HD, infection (peritonitis) is also thought to propagate CVD by predisposing to chronic inflammation.

While several yet putative risk factors also may contributed ,till conclusively proven by RCTs the cornerstone will remain age old strategies like diet and lifestyle modification, smoking cessation and lipid management. Clever PD prescriptions and meticulous attention to calcium/phosphorus, anemia, nutrition and peritonitis prevention cannot be understated.