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Study of Procalcitonin as a Marker of Severity of Renal Lesions in Children with Urinary Tract Infection

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Abstract

Background: *In up to 40% of the cases of infection of the upper urinary tract, pyelonephritis, renal scar develops and the scarring process may occasionally lead to chronic renal insufficiency. Moreover, UTI has a high tendency of recurrence and recurrent UTI's even increases the risk of renal scarring. Occurrence of UTI below 2 years of age, delay in starting treatment and presence of VUR or obstruction are chief risk factors associated with renal scarring. Renal cortical scintigraphy is used for the early detection of the cortical defects of acute pyelonephritis and scarring related to chronic pyelonephritis.*

Objective: *Procalcitonin as a marker of severity of pyelonephritis in children.*

To show procalcitonin is superior to other infectious markers (CRP) in detecting UTI.

To differentiate upper and lower UTI in children.

Methodology:

- *Place of study- Manipal hospital, Bangalore*
- *Study design – Observation study (Prospective)*
- *Period of study – 30 months*
- *Study population- 100 cases which includes first attack of UTI and recurrent attacks of UTI.*

Results: *Hundred children with culture proven UTI were followed over two years and 99m Tc DMSA scintigraphy was done once after diagnosis of UTI and repeated after 6 month – 2 years. The male to female ratio of incidence of UTI in children less than 1 year is 2.4: 1 and in children more than 5 years the ratio is 1:2. The prevalence of renal scarring after UTI is 31.2%, after first episode of UTI is 24 % and after recurrent UTI, the prevalence is 42%. 9.6% of children with VUR had renal scarring after first attack of UTI and 53% of children with VUR developed renal scarring after recurrent UTI.*

Conclusion: *Our study provides a useful data on childhood UTI in terms of demographical data, imaging abnormality and confirms the importance of PCT levels in the assessment of renal scar and reflux Our data indicate that PCT is an accurate biological marker with high sensitivity and specificity for the prediction of acute pyelonephritis among infants and children, compared with the low specificity of CRP measurements.*

Abbreviations

APN- Acute Pyelonephritis

CI- 95% Confidence Interval

CRP-c Reactive Protein

CT- Computer tomography

Deg C- Degree Celsis

Deg F- Degree Fahrenheit

DF- Degree of Freedom

Div- Divided

DMSA – Dimercaptosuccinic acid

DTPA- Diethylenetriamine Penta acetic Acid

E. coli- Escherichia coli

ECM- Extracellular Membrane

Eg- Example

GHA- Gluco Heptonate

G6 PD- Glucose 6 Phosphate Deficiency

HPF- High Power Field

Hr- Hour

IL- Interleukin

IVP- Intravenous Pyelography

LPS- Lipopolysaccharide

LK- LEFT Kidney

MBq- Milli Becqueral

Mci- Milli curie

MCU- Micturating Cystourethrogram

Mon- Month

NM- Nanometer

P value- Probability value

PCT-Procalcitonin

PUJ- Pelvi Urethric Junction

RK- Right Kidney

SPECT- Single Photon Emission Tomography.

Strep- Streptococcus

99 m Tc- 99m – Technicium

TGF- Transforming Growth Factor.

UTI- Urinary Tract Infection

VUR- Vesico Urethral Reflux

Introduction

Urinary tract infection (UTI) is the most common bacterial infection. In up to 40% of the cases of infection of the upper urinary tract, pyelonephritis, renal scar develops and the scarring process may occasionally lead to chronic renal insufficiency. Moreover, UTI has a high tendency of recurrence and recurrent UTI's even increases the risk of renal scarring.

Urinary tract infection implies invasion of urinary tract by pathogens, which may involve upper or lower tract depending on infection in kidney or bladder and urethra. UTI causes acute morbidity and result in long term complication including hypertension and chronic renal failure.

Urinary tract infection is the third most common bacterial infection in children in developing countries after those of gastrointestinal and respiratory tract. The commonest age for occurrence of first symptomatic UTI is first year of life in both sexes, boys are more susceptible to UTI than girls and thereafter incidence is substantially higher in girls than boys. Occurrence of UTI below 2 years of age,

delay in starting treatment and presence of VUR or obstruction are chief risk factors associated with renal scarring.

The risk of renal damage secondary to UTI is highest in children below 2 years. VUR is an important predictor of renal damage in children.

Renal scars occur in children within 1 year of their first diagnosis of UTI.

Review of Literature

Introduction

Urinary tract infection (UTI) is one of the most common bacterial infection in children. Although most patients with UTI have a good prognosis, there is a risk of serious complications in a group of them. In up to 40% of the cases of infection of the upper urinary tract, pyelonephritis, renal scar develops and the scarring process may occasionally lead to chronic renal insufficiency. Moreover, UTI has a high tendency of recurrence and recurrent UTI's even increase the risk of renal scarring.

The incidence of symptomatic UTI in term neonates is approximately 1% and in the preterm 3%, both with male preponderance (male to female ratio 5:1). During infancy, the risk is equal in both boys and girls, after that girls have a higher risk of developing UTI. The risk of developing symptomatic UTI before the age of 14 years is 1.1- 1.6 % in boys and 3- 7.8% in girls. UTI depends on the region that is infected, it is necessary to localize the infection to the upper or lower urinary tract. Upper UTI (pyelonephritis or febrile UTI) is usually associated with fever of greater than 38.5 deg C. Lower UTI in which the bladder (cystitis) and urethra (urethritis) are involved is characterized by dysuria, urgency and frequency of micturition with no or low-grade fever. Asymptomatic bacteriuria describes the presence of bacteria in the urinary tract without symptoms and is diagnosed by screening. Since infected children often feel better after eradication of the bacteria, the term 'covert bacteriuria' might be more appropriate (1,2).

Although most patients with UTI have an excellent prognosis, there is risk of complication in a group of them. Renal scarring develop in 10- 40% of cases of pyelonephritis, depending on which method is used to detect the scar, renal scintigraphy (Stokland 1996), Urography (Stokland 1998), CT (Saxton 1995) or MRI (Kavanagh 2004).

The clinical relevance of all detected scars has been widely debated. Renal scars have been correlated with long term problems, such as hypertension and in most severe cases end stage renal disease. Other

studies, in contrast indicate that the risk could be overestimated and that infection per se does not cause renal scarring. However, UTI is still one of the main causes leading to end stage renal disease mainly in children. (4). Urinary tract infection also carries a high risk of recurrence. Approximately 30% to 40% of patients develop a repeat infection within one year after a first UTI. This rate becomes even higher after subsequent infection. In order to identify individuals at risk of recurrence, different radiological tests have been introduced after first episode of pyelonephritis. Still, more than one half of the patients have normal radiographic studies (Jodal 1987), and also these patients have high probability to develop consequent infections (5)

Etiology

Majority of UTI is due to Gram-Negative bacteria. The Candida Albicans infections are seen particularly in preterm infants and among community acquired UTI, also Staphylococcus Saprophyticus (1).

In healthy girls, periurethral flora is dominated by lactobacilli and other commensals, whereas in those with recurrent UTI, the colonization is with uropathogens.

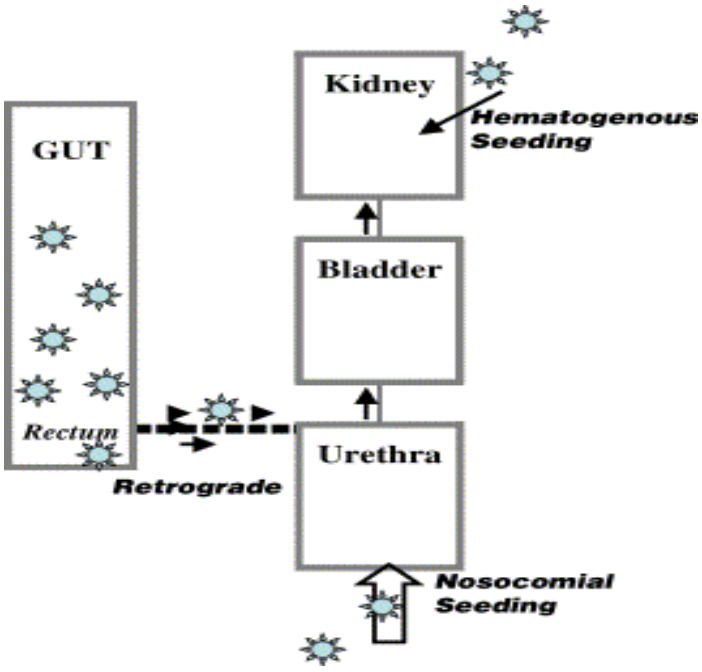


Figure 1: Major pathways of pathogen spreading in urinary tract infection

Pathogenesis of UTI

Bacterial factors

In the neonatal period, renal parenchymal infection is due to hematogenous spread. Bacteria under the prepuce in boys reach the bladder by ascending the urethra, which explains why circumcised boys have fewer UTI than those who are not circumcised. In absence of such factors, UTI depends on bacterial virulence or host resistance (2).

Escherichia coli (E. coli) is the most commonly isolated pathogen, both in community- acquired and hospitalized patient UTI (3). E. coli clones can acquire specific virulence attributes with increased ability to adapt to new niches. These phenotypic characteristics include specific adhesions, toxins, siderophores, proteases and the capsule, as well as hydrophobicity and serum resistance coli use a multi-step scheme of pathogenesis, which consists of adhesion and colonization, invasion, survival, multiplication and host damage (3)

Adhesions and colonization

E. coli is characterized by type 1 fimbriae, P fimbriae, S fimbriae, F1C fimbriae and Dr adhesions E. coli express mainly one fimbrial type at a time E. coli attach to mannose moieties of the uroplakin receptors that coat transitional uroepithelial cells. In strains that cause cystitis, type 1 fimbriae are continually expressed and the infection is confined to the bladder (4). In pyelonephritic strains, on the other hand, the type 1 fimbriae expression turns ‘off’. This may allow the organism to ascend through the ureters to the kidneys, where the bacterium can attach by P fimbriae to digalactoside receptors that are expressed on the kidney epithelium. S fimbriae and F1C fimbriae have also been shown to bind to epithelial and endothelial cells from the kidney and lower urinary tract. Dr Fimbriae, on the other hand, bind to type IV collagen and decay-accelerating factor, and enable E.Coli persist longer in the renal interstitium. Curli fimbriae belong to a class of fibers known as amyloids (5,6)

Survival and immune escape

Adhesion to the cells could be a function of physicochemical surface properties of bacteria as determined by a specific composition of lipopolysaccharides (LPS) and the capsule. Aerobactin, an example of a siderophore, enhances iron uptake and thus promote the survival and growth of bacteria within the urinary tract (Jacobson et al. coli is able to produce a polysaccharide capsule, which substantially increases bacterial survival within the urinary tract and increases resistance to serum and to phagocytosis (6)

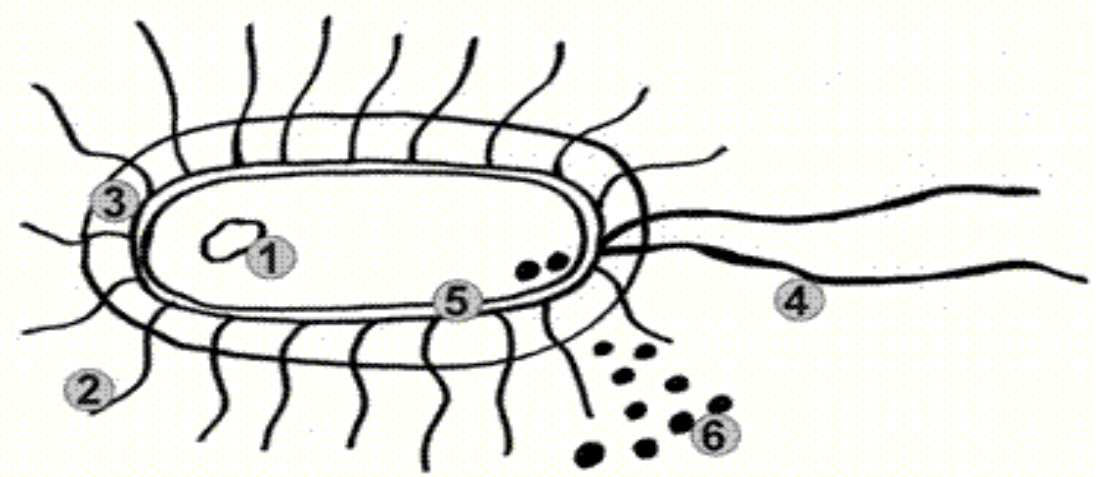


Figure 2. Uropathogenic E. coli: (1) Bacterial chromosome with pathogenicity island (-s), (2) Fimbriae, (3) Capsule, (4) Flagella, (5) LPS as a constituent of cytoplasmic membrane, (6) Secreted toxin

Toxins

LPS, bacterial endotoxin, a principal component of the bacterial cell membrane is recognized by the immune system as a pathogen associated molecular pattern and initiates local and systemic response.

Host factors

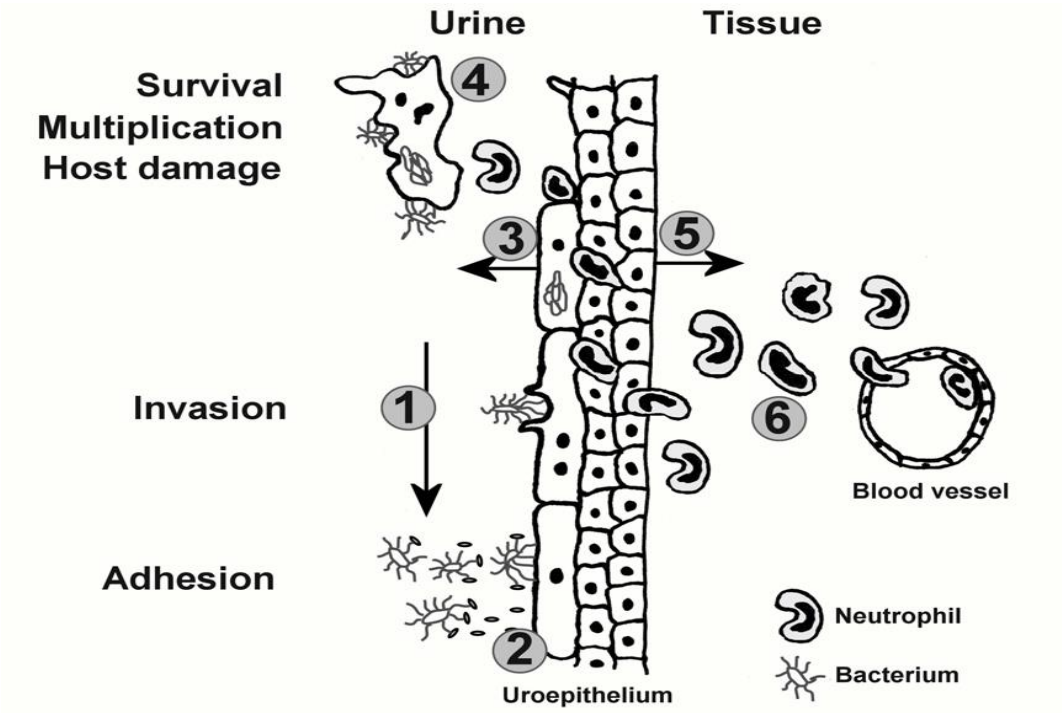
The urinary tract is one of the exclusive areas of the body, which normally resists microbes' growth despite its close proximity to the outside environment and frequent bacterial entry (4). Various factors are involved in bacterial clearance, both constitutive and those inducible by the presence of a pathogen.

Constitutive Host mechanisms

coli to uroplakin receptors (Bates et al. Secretory IgA (Bueler et al. 1986) and low molecular weight sugars inhibits the growth of bacteria by decreasing the accessibility of iron, and antimicrobial peptides directly kill bacteria by their membrane.

Inducible host mechanism

Bladder superficial epithelial cells express toll-like receptor-4 (TLR-4) on their membrane (1). During pyelonephritis, renal tubular epithelial cells are the main cells to react the presence of bacteria (Brauner et al. 2001).After contact with bacteria, epithelial cells react by different ways. They produce substances toxic to bacteria, like nitric oxide . Epithelium can also engage other cells by production of chemokines and proinflammatory cytokines. Amongst them, CXCR1 receptor on renal epithelial cells has been shown to be of importance for transepithelial migration of neutrophils granulocytes and bacterial clearance during urinary tract infection (8)



(1) Urine flow, (2) Antiadherence factors (e.g. Tamm-Horsfall protein), (3) Antimicrobial factors (e.g. nitric oxide, antimicrobial peptides), (4) Exfoliation of cells, (5) Production of chemokines and cytokines, (6) Migration of neutrophils.

Figure 3: Host factors in the protection against bacteria.

Pathogenesis of Renal Scarring

Interstitial fibrosis is the final common end-point of progressive renal diseases. Despite its clinical significance, the mechanisms of scar formation in the kidney are still not fully understood. The risk of renal scarring increases with each new episode of UTI. Factors predisposing for recurrence of UTI are therefore also risk factors of renal factors of renal scarring.

Bacterial factors

The presence of P fimbriae was proposed as a risk for renal scarring in some studies. E. coli in children developing renal scars as compared with those without scarring. Studies using mouse UTI model systems and cell cultures demonstrated that E.coli can invade bladder superficial cells. E. coli is promoted by distinct virulence factors, including cytotoxic necrotizing factor Afa/Dr adhesins (6), type 1 fimbriae, and curli fimbriae. As the urinary bladder fills and empties, extensive exocytic and endocytic traffic of membrane domains of epithelial cells may facilitate entry of bacteria bound to membrane uroplakins. (9)

Dysfunction Elimination

Functional abnormalities of the lower urinary tract or dysfunctional elimination syndrome denote a group of abnormal voiding patterns, such as bladder instability, infrequent voiding, lazy bladder and the Hinman syndrome. Voiding dysfunction was clearly associated with recurrent UTIs. The clear association between VUR and dysfunctional elimination syndrome in children may also explain in part, the relationship between VUR, recurrent UTI and renal scarring. (10)

Immune Response during acute Pyelonephritis

Clinical observations have suggested a link between increased urinary levels of interleukin-6, acute kidney damage and postinfective renal scar development. On the other hand, persisting high urinary levels of IL-1a were associated with less inflammation and scarring (8). Both blocking of polymorphonuclear leukocytes chemoattraction and migration resulted in excessive scarring. During acute pyelonephritis, many resident renal cells die as a result of toxic effect of bacteria as well as due to hypoperfusion and tissue hypoxia. Thus, oxygen radicals originating from both immune cells and tubular epithelium may participate in tissue injury during acute inflammation and reperfusion. Okur et

al. Progressive apoptosis of renal cells, on the other hand, has been implicated in the renal scarring process (10).

Mainly in non-infectious causes of renal fibrosis, a connection with growth factors such as transforming growth factor beta (TGF-ß1), platelet derived growth factor and connective tissue growth factor have been suggested (11). The pro-fibrotic state could be a consequence of excessive or prolonged increase of ECM protein synthesis and/or a decrease of proteolytic degradation with accumulation of collagen.

DNA polymorphism

The role of several genetic polymorphisms has been studied in the pathogenesis of renal scarring. Genetic variability in the gene for intercellular adhesion molecule-1 and TGF-ß1 have been related to the presence of renal parenchymal scarring following UTI.

Risk Factors for UTI

Many factors have been shown to influence the risk of renal scarring following acute pyelonephritis, including patient age, bacterial virulence properties, treatment delay and VUR. Role of VUR- VUR is an important entity for UTI and especially pyelonephritis. In 1960, Hodson and Edwards demonstrated renal scarring in patients with VUR, some of whom had no previous history of VUR suggesting the water hammer effect of VUR as a causative factor.

Recent studies have however questioned the role of VUR in renal scarring and in several, scarring occurred more often in the absence of VUR. Acquired renal scarring correlates best with recurrent UTI and not with VUR and primary VUR is neither sufficient nor essential for renal damage. Gordon et al, performed a meta- analysis to determine the value of diagnosed VUR as the predictor of renal damage in hospitalized children with UTI (Dave et al 2007). They evaluated 12 studies including 537 children with 1032 kidneys and showed that primary VUR was a poor indicator of renal damage in children hospitalized with UTI. Also infected refluxing urine does not always lead to renal scarring and that renal damage often occurs without demonstrable VUR. VUR grade 2 and higher was detected in 19% of patients and at 2 years follow up only 3 of the 12 patients with scarring had VUR.

The role of VUR, especially lower grades, as a predisposing factor for recurrent UTI is controversial. Nuutinen and Uhari noted a higher rate of recurrent UTI's in children with grade 3-5 VUR in comparison with children with grade 1-2 VUR (13, 14).

Faust et al from Washington, D.C conducted an extensive meta- analysis of all peer reviewed articles between 1980- 2006. Patients with VUR demonstrated an increased likelihood of having a scar after acute pyelonephritis than those without VUR (Odds ratio 2.8: 95% CI 1.9, 4.2).

Clinical Features

The manifestations of UTI are related to the age and the severity of the infection.

In the neonates, acute pyelonephritis presents with features of sepsis such as lethargy, seizures, shock, unstable temperature and persistence of physiological jaundice.

Non- specific symptoms including failure to thrive, vomiting, and diarrhoea may be caused by UTI. In older infants, recurrent fever, diarrhoea, vomiting, poor weight and abdominal pain are the usual symptoms.

Older children complain of burning, urgency, frequency and pain in the lower abdomen. Gross haematuria may occasionally occur.

The presence of UTI should be strongly considered in infants and young children, below 2 years of age, with unexplained fever. with 3 UTI, the risk of scarring is approximately 15%, with 4 infection- it approaches 40%, with 5 infections- the risk of renal scarring is approximately 60% (3, 15)

Diagnosis

UTI should be suspected in a child with unexplained fever persisting beyond 2-3 days. In young children, it is usually not possible to differentiate upper from lower UTI.

Presence of fever >39 deg C, marked toxicity, persistent vomiting and renal angle tenderness suggest complicated UTI, where the treatment should be aggressive. If the degree of illness warrants initiation of antimicrobial therapy, a urine specimen should be immediately obtained for culture before antimicrobial therapy is administered.

Urine Examination: One study has also shown that bacterial contamination rate for urine collected by the bag techniques is not significant (16).

However, for verification of its usefulness in the documentation of UTI “Suspicious or positive” growth in a urinary specimen collected with the “bag technique” should be confirmed as reflecting true

bacteriuria by means of suprapubic aspiration or catheterization. A negative culture from a bag specimen, however, helps to exclude UTI.

A clean catch midstream specimen is the most widely used method. A urine specimen can also be safely obtained, in infants, by bladder catheterization but requires some skill and experience.

The specimen should be transported to laboratory as early as possible, or stored at 4 deg C.

URINALYSIS: The findings of any bacteria on a Gram stained urine specimen have a very high sensitivity and specificity for predicting a positive urine culture (17).

The urine specimen may be centrifuged in standard manner (10 ml spun at the rate of 5000 rmp for 5min, most of the supernatant decanted off and the sediment resuspended in the remaining 0.5 ml). Febrile UTI is usually associated with pyuria (greater than 5 white cells per high power field in a centrifuged urine sample or more than 10 white cells in uncentrifuged urine sample.

DIPSTICK TESTS: Dipstick tests based on nitrite reduction and measurement of leucocytes esterase are satisfactory as screening tests. Any of the following are suggestive (not diagnostic) : Bacteria present on an unspun Gram stained specimen , positive result of a nitrite or leukocyte esterase test, more than 5 white blood cells per high power field of a spun specimen.

Method of collection	***Colony count (per ml)***	***Probability of Infection***
Suprapubic	Any number	99%
Urethral catheterization	$>10^5$	95%
	10^4- 10^5	Very likely
	10^3- 10^4	Suspicious repeat
	$<10^3$	Unlikely
Midstream Void		
Boy	$>10^4$	Very likely
Girl	$>10^5$	90- 95%
	10^4- 10^5	Suspicious repeat
	$<10^4$	Unlikely

Table 1: Diagnosis of UTI

Urine Culture: On culture, a colony count of more than 105 per milliliter organisms of a single species is considered confirmatory of UTI. The colony count may be lower if the child has increase frequency or polyuria or has received antibiotics. Infants have a lower bladder capacity and void frequently and therefore may have lower colony counts.

Upper Verses Lower UTI: The distinction between lower UTI (cystitis) and upper UTI (Pyelonephritis) is difficult in children clinical or laboratory findings are not accurate in distinguishing pyelonephritis from cystitis. Moreover, the risk of detecting the underlying reflux is similar in all patients with UTI.

Haematological Investigations:

This rapid and specific induction of PCT after an adequate stimulus, and the high and reliable production of PCT in patients with bacterial infections or sepsis, suggests a pathophysiological function of PCT in the acute immune response, even though it is not clear whether PCT is a cytokine, a hormone, or an acute-phase protein since it has characteristics of all these mediators.

PCT can be measured with a quantitative immunoluminometric assay (LUMItest PCT, progressively replaced by PCT sensitive KRYPTOR, both from Brahms Diagnostica, Berlin, Germany) in 2 hours, with a maximum interassay variation of approximately 0.3 ng/mL. Plasma concentrations respond rather specifically to bacterial infection, and PCT has been demonstrated to be a better or at least of equal value for diagnosis of sepsis when compared with markers like CRP, lactate, proinflammatory cytokines, leukocytosis, and PCT not only diagnosis of sepsis but also diagnosis of specific infection can be improved by measuring PCT, as demonstrated by the meta-analysis comparing PCT and CRP in patients with bacterial versus viral or nonbacterial infections. summarised most of these studies in a systematic review and meta-analysis (10 studies,) and demonstrated that the pooled diagnostic odds ratio (OR) measuring the association between DMSA-proven APN and PCT was 14.3 (95% confidence interval—CI, 4.7–42.2), after having pooled results from studies using close PCT threshold (0.5 and 0.6 ng/mL) . Before clinical use of PCT to identify children at high risk of renal scarring after UTI and selectively perform late DMSA-scan, validation studies and threshold analyses are needed to derive an evidence-based clinical decision rule.

PCT has been demonstrated to be correlated to both APN and late renal scars on one hand, and on another hand VUR is thought to be related to a higher risk of APN and late renal scar . Based on indirect relationships between VUR, scar and PCT, and statistical work, they ended up with a clinical

tool combining PCT with renal ultrasonography that may be useful for clinicians to predict high-grade VUR in children with UTI and then selectively prescribe them a cystography.

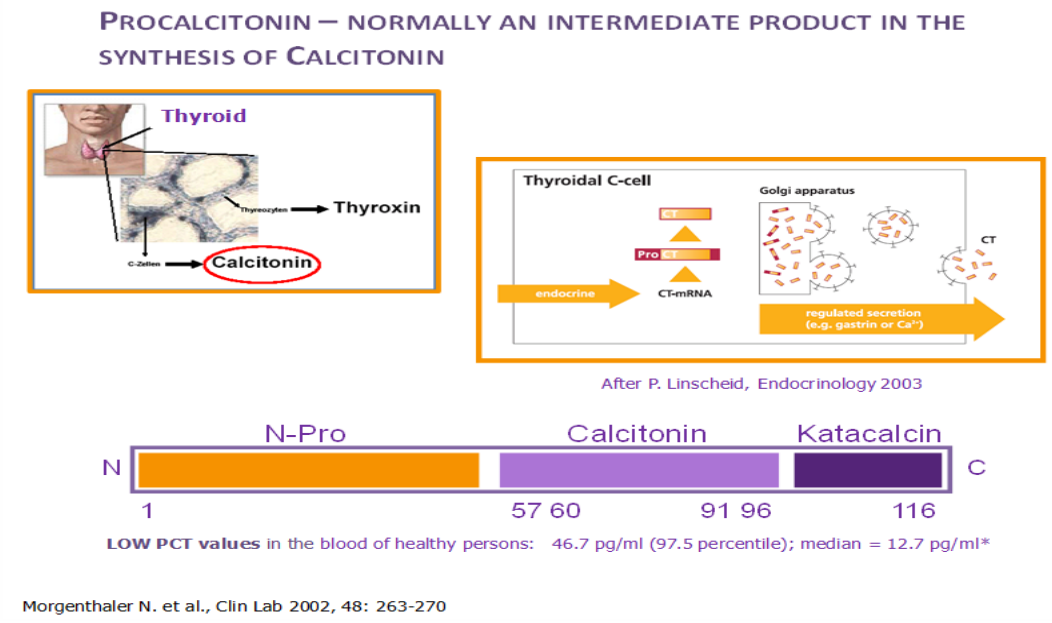


Figure 5: PCT Synthesis

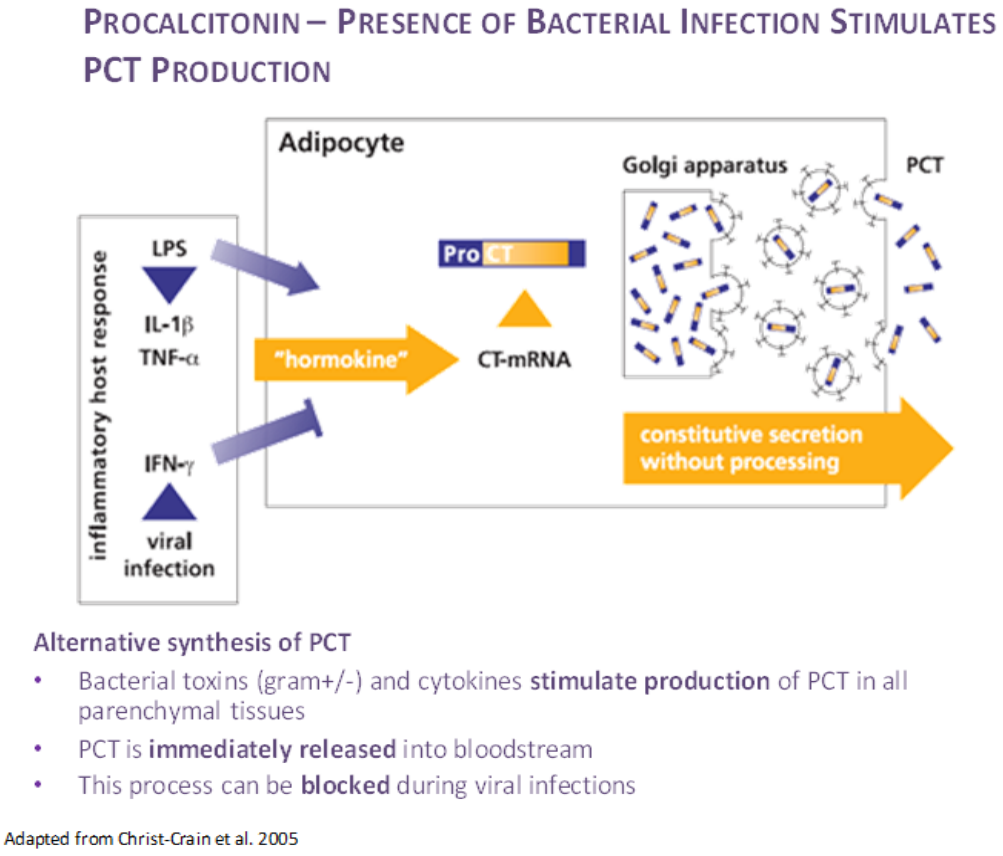


Figure 6: Alternative synthesis of PCT

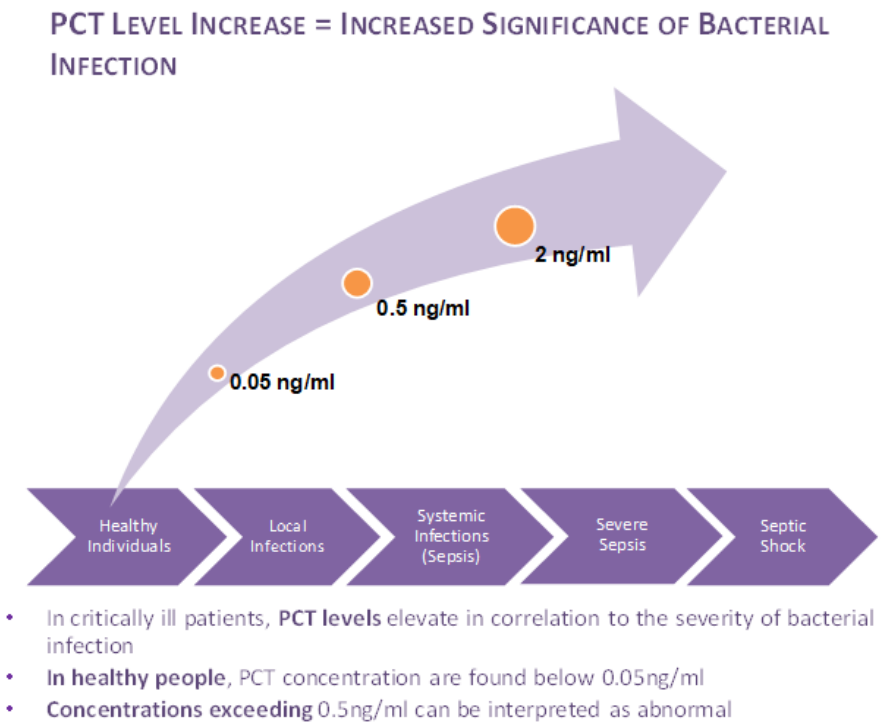


Figure 7: PCT levels

Treatment and Evaluation

Initial Evaluation: Once UTI is suspected, the patient is examined for complications and the risk of recurrence. The blood pressures should be recorded and history regarding bowel and bladder habits elicited straining during micturition, dribbling, poor urinary stream and ballooning of the prepuce suggest obstruction. In such children, examination of perianal sensation, deep tendon reflexes in the lower extremities and inspection of the lower back for sacral dimpling or other abnormalities is useful.

Therapy: Initially, it is necessary to consider the organism most frequently responsible for UTI in choosing the anti microbial agent: 80 – 90% of the first time UTI in children is due to E. Careful monitoring and repeated clinical examinations are required in children with clinical urosepsis or bacteraemia.

Parenteral antibiotics therapy may be required, initially, even in older children who have complicate UTI. Once the clinical condition improves and the child is accepting by mouth, oral antibiotics are started.

Children > 1 yrs of age, who are accepting by mouth and not toxic, may be given oral antibiotics (Amoxicillin, Amoxicillin and clavulanic acid). Symptomatic treatment for fever and pain should be given and liberal fluid intake ensured.

In a multi center, randomized clinical trial, evaluated the efficacy of oral versus initial intravenous therapy in 306 children 1 to 24 months old with fever and UTI, in terms of short – term clinical outcomes and long term morbidity. Children received either oral Cefixime for 14 days or Cefotaxime initially intravenous for 3 days followed by oral Cefixime for 11 days. Additionally, children with first time UTI's who need imaging studies, should be on low- dose prophylactic antibiotic therapy until their work-up is completed.

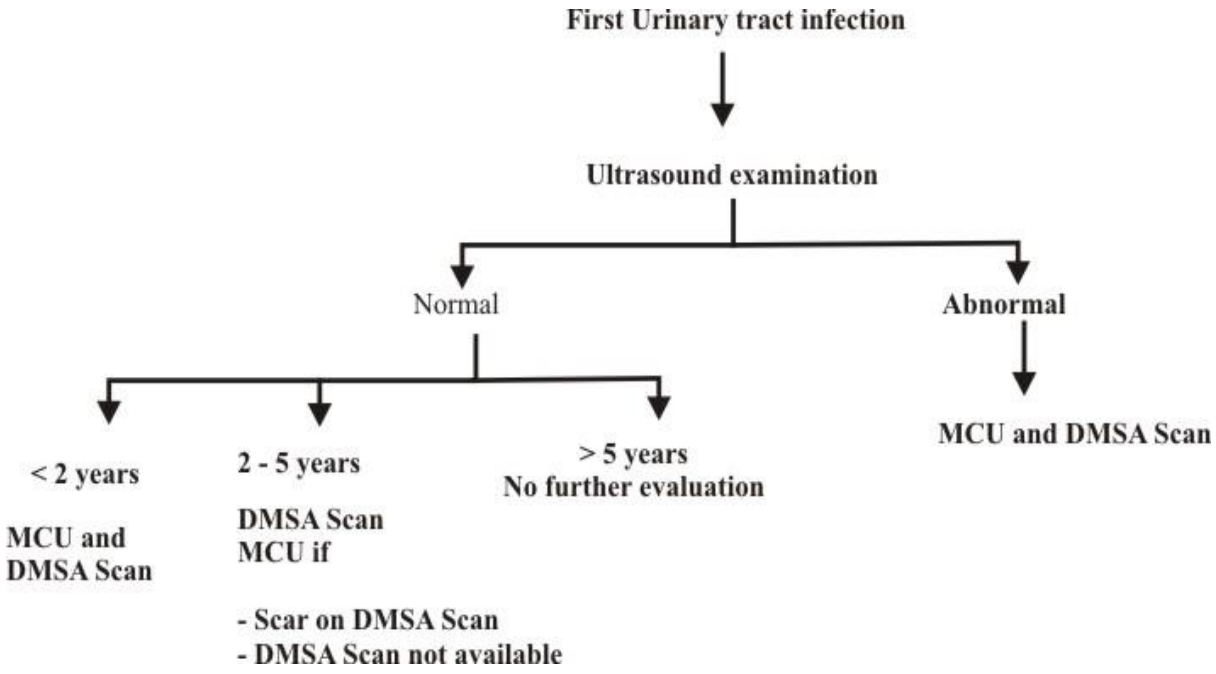


Figure 9: Evaluation of UTI in children

Evaluation following initial UTI: Detailed evaluation with ultrasound, MCU and DMSA scan should be done in boys before the age of 5 years and girls below 2 years with even one confirmed UTI. Between the ages of 2 – 5 years a MCU is not immediately required, unless the symptoms suggest an underlying obstruction.

Children over the age of 5 years can be reliably screened with USG performed by an expert.

Measures to reduce recurrent UTI: Circumcision is not recommended routinely but may be considered for infants with recurrent UTI (17). Constipation predisposes to recurrent – UTI and improvement in bowel habits reduces the incidence of UTI.

Materials and Methods

Hundred patients both admitted or treated as outpatients at Manipal hospital, Bangalore between October 2010 to April 2013 with culture positive urinary tract infections both first and recurrent attacks was studied and followed over 2 ½ years.

Diagnostic Criteria

1. Unexplained fever for more than 5 days.
2. Frequent micturition or dysuria.
3. Abnormal urine stream.
4. Urine routine positive for suprapubic bladder aspiration or clean catch urine in a sterile container. Uncentrifuged urine specimen examined in counting chamber showing > 10 pus cells/ high power field is considered abnormal.
5. Urine Culture Positive- Diagnostic of UTI. Growth showing colony > 105 bacteria per ml in clean catch urine or 103 in suprapubic aspiration in sterile container.
6. DMSA scan- For demonstration and monitoring of renal scarring.

Inclusion Criteria

1. Age- new borns to 10 years
2. Sex- Male and Female
3. Fever- 5 days or more.
4. Urine routine & microscopy showing more than 10 pus cells/ high power field
5. Urine Culture- Positive (105 colony forming units/ ml).

16.4 Exclusion Criteria

1. Age more than 10 years.
2. Clinical and laboratory parameters suggestive of obstructive urological disorders.
3. Children without clear laboratory evidence.
4. Major urinary tract congenital anomaly.
5. Urine culture negative.

Method of Statistical Analysis

In the chi-square test for independence the degree of freedom is equal to the number of columns in the table minus one multiplied by the number of rows in the table minus one, Where Oi is Observed frequency and Ei is Expected frequency with (n-1) df

The Assumptions of Chi-square test

The chi square test, when used with the standard approximation that a chi-square distribution is applicable, has the following assumptions:

- Random sample – A random sampling of the data from a fixed distribution or population.
- Sample size (whole table) – A sample with a sufficiently large size is assumed. If a chi square test is conducted on a sample with a smaller size, then the chi square test will yield an inaccurate inference. The researcher, by using chi square test on small samples, might end up committing a Type II error.
- Expected Cell Count – Adequate expected cell counts. When this assumption is not met, Fisher Exact test or Yates' correction is applied.

The Fisher Exact Test looks at a contingency table which displays how different treatments have produced different outcomes.

	Class1	Class2	Total
Sample1	A	b	a+b
Sample2	C	d	c+d
Total	a+c	b+d	N

2x2 Fisher Exact Test statistic= $\sum p = \frac{(a+b)!(c+d)!(a+c)!(b+d)!}{n!}\frac{1}{\sum a!b!c!d!}$

Observation And Analysis

A total of 100 children with culture proven urinary tract infection of age group newborn to 10 years were studied. The diagnosis of urinary tract infection was confirmed with urine microscopy and urine culture. Procalcitonin ,CRP ,ultrasonography of abdomen and 99mTc- DMSA scan were done for all the children. All the children in the study group were followed up over 30 months and results were tabulated and interpreted as below.

Age in years	Number of patients	%
<1	30	30.0
1-2	15	15.0
2-5	31	31.0
>5	24	24.0
Total	100	100.0

Table 2: Age distribution of patients

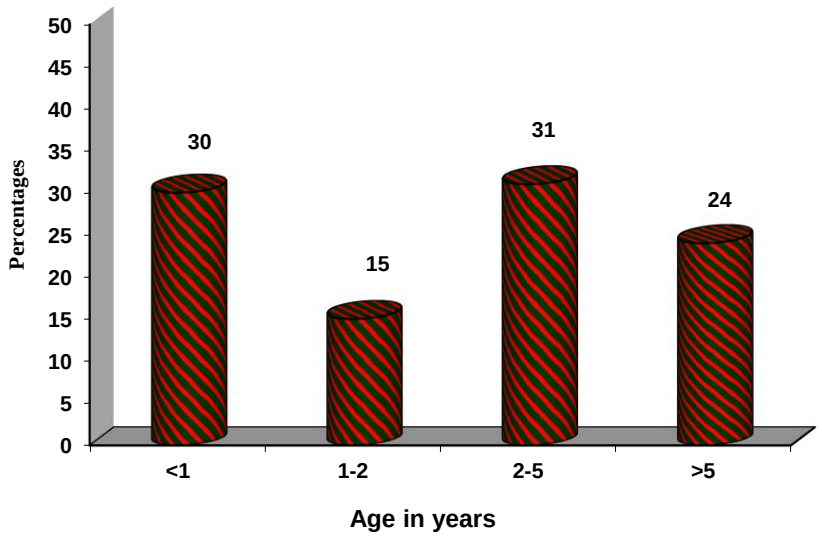


Figure 10: Age distribution of patients

The study group included both inpatient and outpatient children with symptoms and signs of urinary tract infection.

Based on Indian Pediatric Nephrology group criteria, urinary tract infection was diagnosed and child was treated with antibiotics. Children with urine culture showing more than 105 colony count were included in the study group and ultrasonography of kidney and urinary tract and 99m Tc- DMSA scan was done , data was analyzed. According to Indian Pediatric Nephrology group criteria, in children less than 2 years of age, ultrasonography of abdomen and 99m Tc- DMSA scan was done between 7-10 days.

The children in the study group were regularly followed upto 9 months after the diagnoses of UTI and on follow- up 99m Tc DMSA scan USG abdomen and MCU scan were done and results were analyzed.

Gender	Number of patients	%
Male	62	62.0
Female	38	38.0
Total	100	100.0

Table 3: Gender distribution of patients

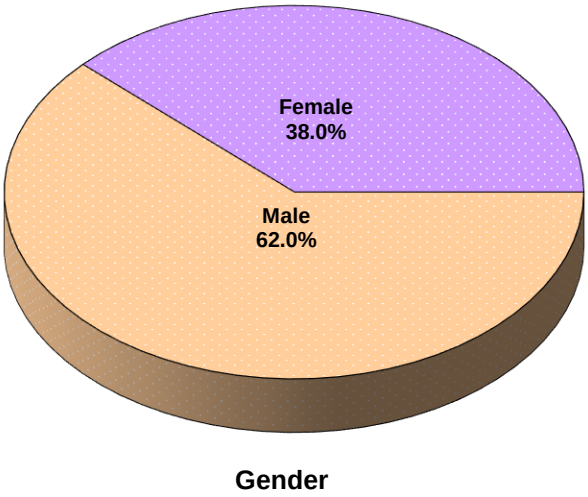


Figure 11: Gender distribution of patients

Duration in days	Number of patients	%
5 days	37	37.0
6-10 days	61	61.0
>10 days	2	2.0
Total	100	100.0

Mean ± SD: 6.24±1.60

Table 4: Duration of Fever

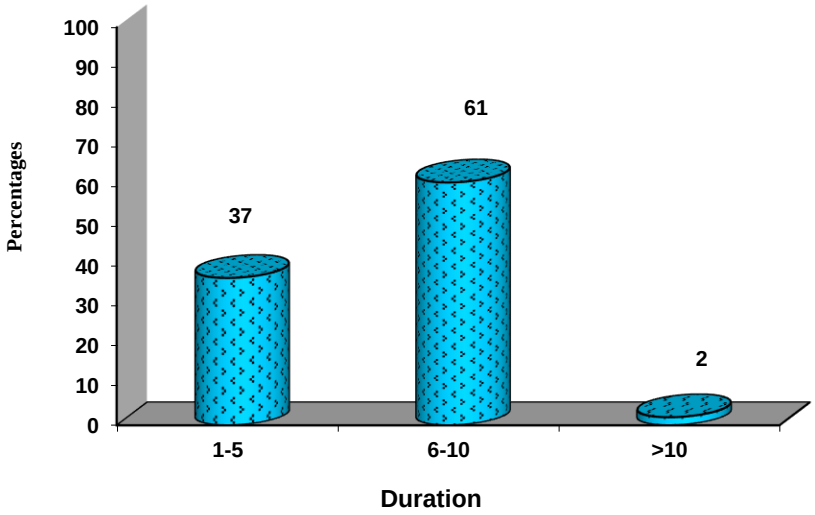


Figure 12: Duration of Fever

Clinical presentation	Number of patients (n=100)	%
Increased frequency of Urination	32	32.0
Dysuria	54	54.0
Vomiting	44	44.0
Abdominal pain	36	36.0

Table 5: Clinical presentation of UTI

Spectrum of the presenting symptoms in the study population were analyzed , out of 100 children in the study group, all presented with fever, 54% presented with dysuria ,44% presented with vomiting,36% presented with abdominal pain and 32% presented with increased frequency of Urination.

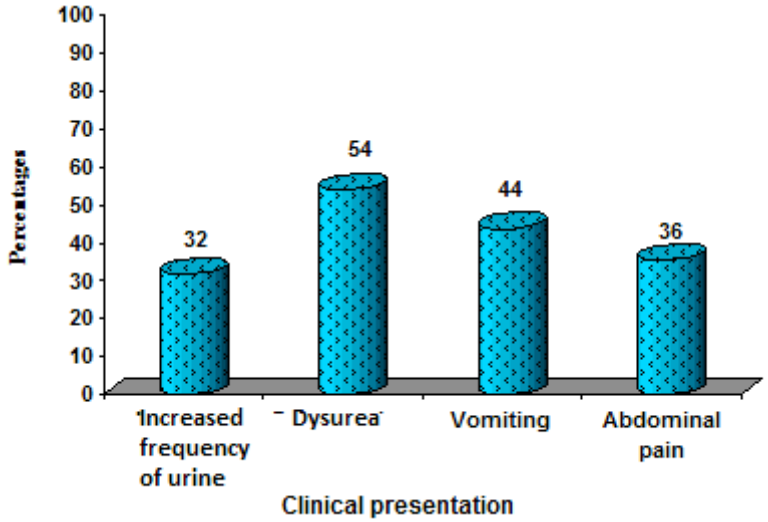
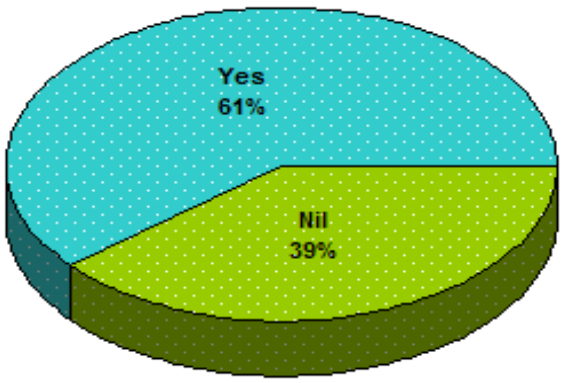


Figure 13: Clinical presentation of UTI

UTI past	Number of patients	%
Nil	39	39.0
YES	61	61.0
• 1 episode	32	32.0
• 2 episodes	21	21.0
• 3 episodes	6	6.0
• 4 episodes	2	2.0
Total	100	100.0

Table 6: Previous episodes of UTI

In the study group, 39 children (39%) had UTI for the first time and 61 children (61%) had more than one episode of UTI in the past.



Previous episodes of UTI

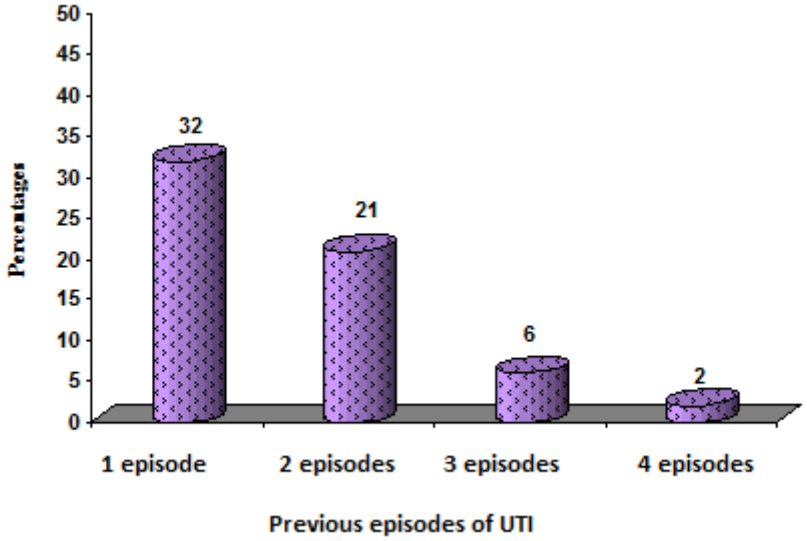


Figure 14: Previous episodes of UTI

Total count	Number of patients	%
<4000	0	0.0
4000-11000	8	8.0
>11000	92	92.0
Total	100	100.0

Mean ± SD: 16557.10±2795.33

Table 7: Total Leucocyte count

In the study group, 92% children had total leucocyte count more than 11000 and (8%) children between 4000 to 11000.

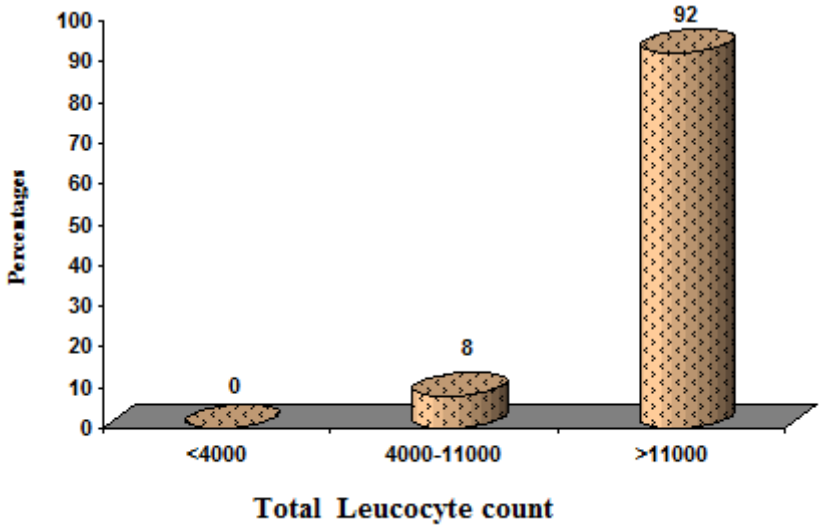


Figure 15: Total Leucocyte count

Method collection	Number of patients	%
Catheter	34	34.0
Midstream	44	44.0
Suprapubic	22	22.0
Total	100	100.0

Table 8: Method of collection of urine samples

In the study group, in 44 children urine culture were done by midstream clean catch technique, in 34 children through catheter and in 22 children by suprapubic aspiration.

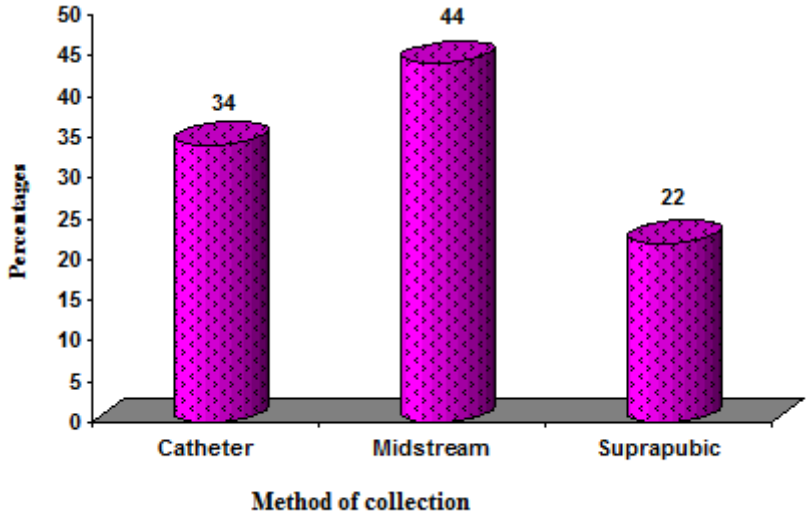


Figure 16: Method of collection of urine samples

Urine	Number of patients	%
E.coli	88	88.0
Klebsiella	11	11.0
Proteus	1	1.0
Total	100	100.0

Table 9: Results of urine culture

E.Coli is the most common cause of UTI (88%) in the study group, followed by Klebsilla pneumonia (11%) and proteus is (1%).

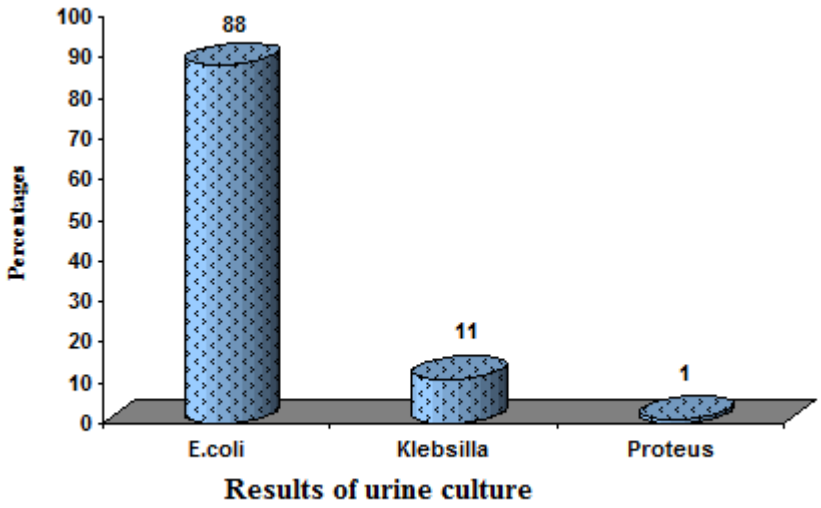
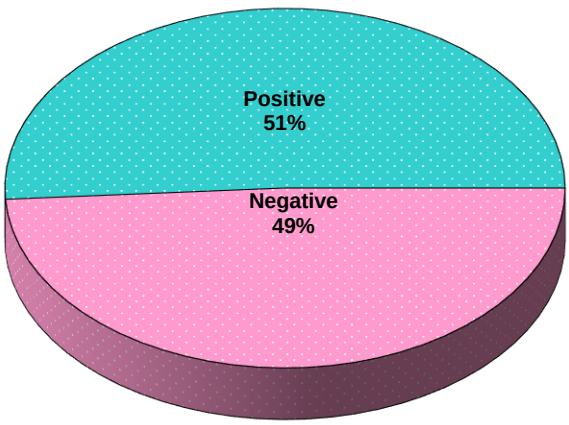


Figure 17: Results of urine culture

Procalcitonin levels	Number of patients	%
Negative(< 0.5 ng/ml)	49	49.0
Positive(≥ 0.5 ng/ml)	51	51.0
Total	100	100.0

Procalcitonin levels in patients studied

Out of 100 children 51 % had raised PCT and49% had low PCT values.



Procalcitonin levels

Procalcitonin (ng/ml)	Number of patients	%
<0.5	49	49.0
0.5-2	7	7.0
2-5	3	3.0
5-10	6	6.0
10-20	15	15.0
>20	20	20.0
Total	100	100.0

Mean ± SD: 19.08±26.81

Table 10: Serum Procalcitonin Levels (ng/ml)

In the study group 49 children (49%) PCT value is less than 0.5 ng/ml , 20 children (20%) value is more than 20ng/ml and remaining 31children (31%) value is between 0.5 to 20 ng/ml.

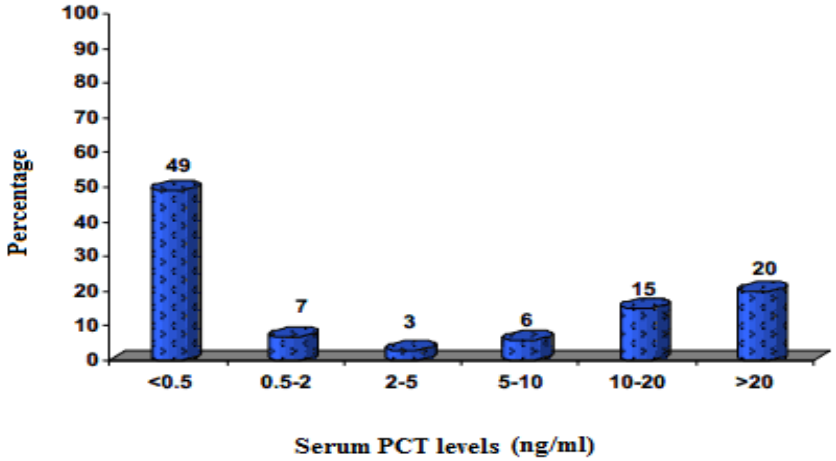


Figure 18: Serum Procalcitonin levels

CRP	Number of patients	%
<10	37	37.0
10-20	19	19.0
20-40	19	19.0
>40	25	25.0
Total	100	100.0

Mean ± SD: 33.11±40.04

Table 11: CRP levels of patients

In the study group 37 children (37%) CRP value less than 10 mg/dl , 25 children (25%) value more than 40mg/dl and remaining 38 children (38%) value between 10 to 40 mg/dl.

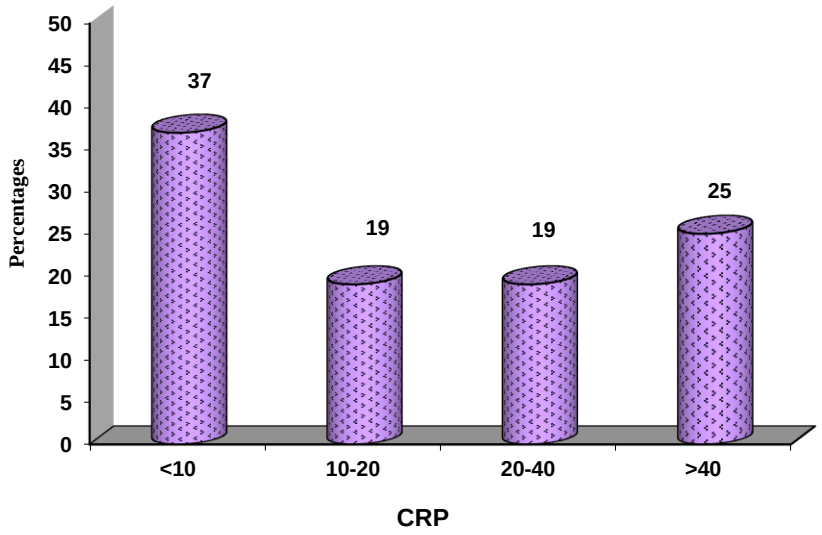


Figure 19: CRP Levels

MCU	Number of patients (n=100)	%
No reflux	60	60.0
Reflux	40	40.0
• Grade 1	18	18.0
• Grade 2	14	14.0
• Grade 3	6	6.0
• Grade 4	2	2.0

Table 12: MCU

In the study group all children underwent MCU , 40 children (40%) had VUR and remaining 60 children (60%) had no VUR .Grading was done and results were analyzed, 18 children (18%) had grade 1 VUR, 14 children (14%) had grade 2 VUR, 6 children (6%) had grade 3 VUR and 2 children (2%) had grade 4 VUR.

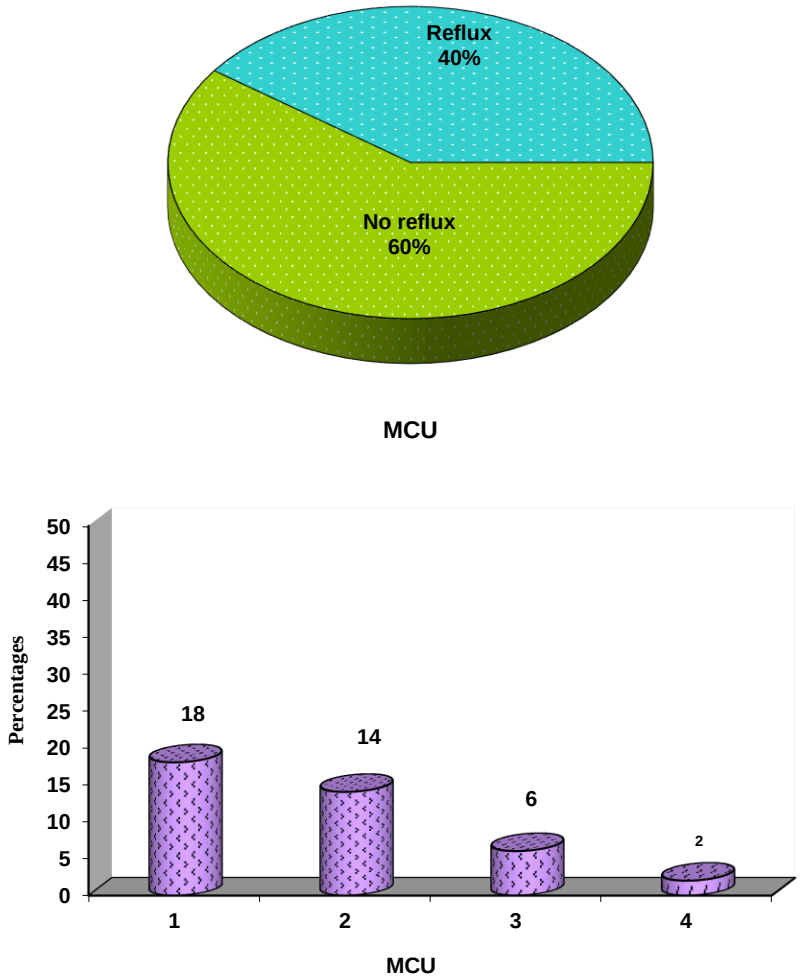


Figure 20: MCU Grades

Renal Scar	Number of patients	%
NO	56	56.0
Yes	44	44.0
Total	100	100.0

Table 13: Renal Scar (DMSA)

In the study group 44 children (44%) had renal scar and remaining 56 children (56%) had no renal scar.

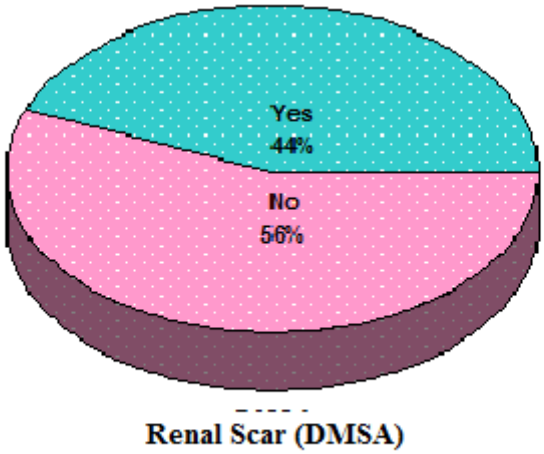


Figure 21: Renal Scar Percentage in patents studied

Procalcitonin	CRP		Total
	<10	≥10	
Positive (≥ 0.5ng/ml)	20(54.1%)	31(49.2%)	51(51.0%)
negative (<0.5 ng/ml)	17(45.9%)	32(50.8%)	49(49.0%)
Total	37(100.0%)	63(100.0%)	100(100.0%)
Inference	Levels of PCT is not statistically associated with CRP levels with P=0.640		

Table 14: Comparison of PCT with CRP levels

Renal Scar	Procalcitonin levels		Total
	Positive	Negative	
No	8(15.7%)	48(97.9%)	56(56.0%)
Yes	43(84.3%)	1(2.1%)	44(44.0%)
Total	51(100.0%)	49(100.0%)	100(100.0%)
Inference	Incidence of renal scar is Significantly associated with Procalcitonin levels with χ^2=68.6; P<0.001**		

Table 15: Correlation of incidence of Renal scar (DMSA) with PCT levels

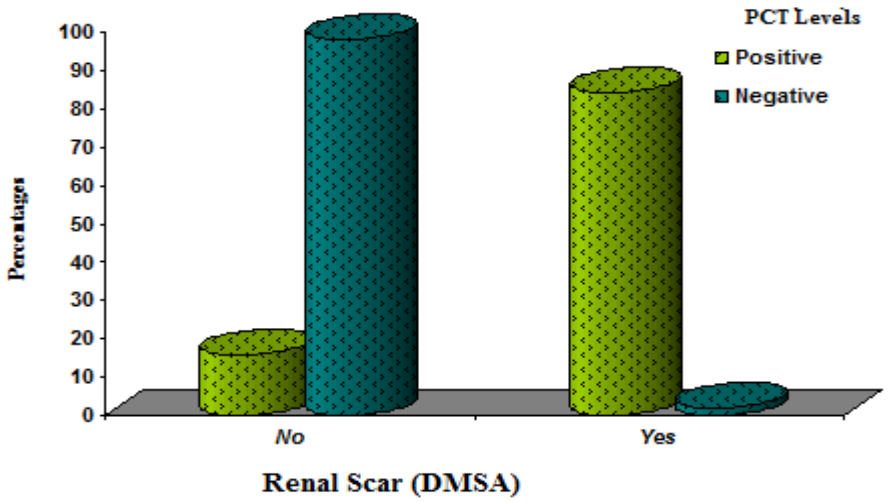


Figure 22: Correlation of incidence of Renal scar with PCT levels

Incidence of renal scar is significantly associated with high Procalcitonin levels with □2=68.6; P<0.001**

Reflux	Procalcitonin levels		Total
	Positive	Negative	
No	6(11.8%)	48(97.9%)	54(54.0%)
Yes	45(88.2%)	1(2.1%)	46(46.0%)
Total	51(100.0%)	49(100.0%)	100(100.0%)
Inference	Incidence of reflux is significantly associated with higher Procalcitonin levels with χ^2=74.7; P<0.001**		

Table 16: Correlation of incidence of Reflux with Procalcitonin levels

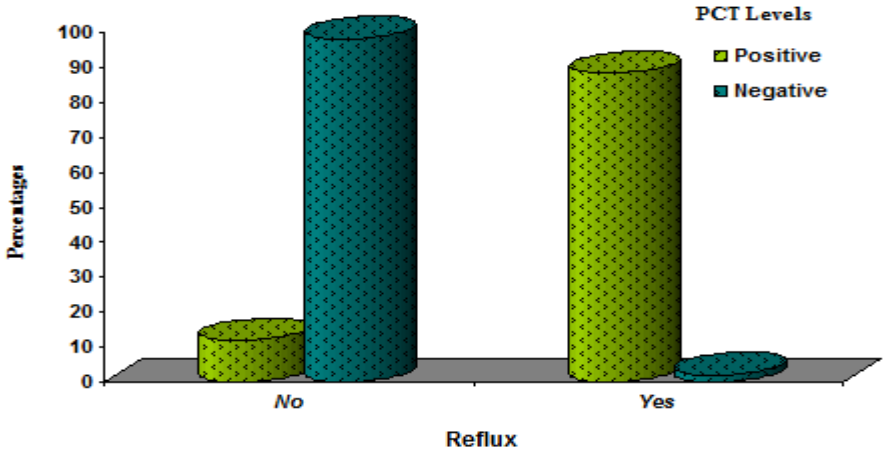


Figure 23: Correlation of incidence of Reflux with Procalcitonin levels

Incidence of reflux is significantly associated with higher levels of Procalcitonin levels with χ^2=74.7; P<0.001**

Comparision with Other Studies

S.NO	STUDY	COUNTRY	n	RESULT
1	Karavanaki,2007	Athens, Greece	58	PCT values(3.08 mg/L versus 5.3 mg/L;P=0.05)were Significantly lower in the group with totally reversible renal scar.
2	Kotoula,2009	Thrase, Greece	57	The PCT level was significantly greater in the patients with persistent renal scar(median PCT level of 10.4 ng/ml,range 1.6-13.0) then in those with total regression (1.9 ng/ml,range 0.7-10.0;p=0.005).
3	Bressan,2009	Padova, Italy	72	Patients with persistent lesions had significantly higher PCT values(2.3 ng/ml,IQR:1.0-11.6)than those without permanent renal lesions(0.5 ng/ml,IQR:0.2-1.4;P=0.007).
4	JC Singh et al, 2010	Vellore, India	100	The PCT levels were significantly correlated with severity of renal lesions (value of 0.8 ng/ml was considered as abnormal) with p=0.428
5	Present study,2013	Bangalore, India	100	The PCT levels were significantly correlated with severity of renal scar (>0.5 ng/ml was considered as abnormal) with p<0.001

S.NO	STUDY	COUNTRY	n	VUR	
				Sensitivity	Specificity
1	Prevur ll study	Paris, France	136	92%	44%
2	Purevur lll Study	Multicentre	398	100%	43%
3	Prevur lllb study	Multicentre	526	83%	43%
4	Prevur v study	Multicentre	494	86%	47%
5	Present study	India	100	98%	90%

Table 18: Studies on prediction accuracy of PCT for VUR in children with UTI

Our study done in 100 patients who are presented with febrile UTI and patients followed up over 6 months . We found out that high PCT (≥ 0.5 ng/ml) levels are strongly associated with incidence of renal scar (P <0.001) and VUR (P<0.001).

Discussion

Our study showed that children with Grade 1 VUR are more (18%) compare with other studies and Grade 3 & 4 VUR children are less .

We identified a new predictor for renal scar and VUR in children with a first febrile UTI, a high serum PCT concentration (≥0.5 ng/mL) at admission. A high PCT level predicted renal scar and VUR with high sensitivity . In light of its specificity, this PCT test could avoid a lot of MCUs.

The results of our study confirm that high procalcitonin levels detects, significantly higher number renal cortical abnormalities like renal scar and VUR than CRP.

Age group	Nammalvar et al (n= 42)	Fong & Wong (n= 188)	Present study (n=100)
< 1 years	19 (45%)	97 (46%)	30(30%)
1-5 years	13 (31%)	69 (32%)	46(46%)
>5 years	10 (24%)	22 (27%)	24(19%)

Table 19: Studies showing incidence of UTI

Symptoms and signs:

Fever (>100 deg F) was the major symptom in 100% of older children, 54 % presented with dysuria,44% presented with vomiting and 32% presented with increased frequency of urination.

	Theodoras et al	**Fong & Wong**	**Present Study**
Fever	83%	86%	100%
FTT	15%	36%	10%
Poor feeding	28%	19%	19%
Vomiting	11%	7.4%	44%
Dysuria	22%	20%	54%
Increased frequency of urination	23%	11%	32%

Table 20: Studies showing symptoms of the study group

Organism

The common microorganism is E.Coli (88%) which is comparable to other studies (Nammalvar 2005, Rasoul 2009). Klebsilla was the causative organism for UTI in 11%; this is higher than other study (Najid 2009).

Organism	Fong & Wong et al	Cecil et al	Nammalvar et al	Present study
E.Coli	78%	80.6%	88.1%	88%
Klebsilla	9%	4.2%	4.8%	***11%***
Proteus	8%	4.2%	--	1%
Pseudomonas	--	8.3%	7.1%	-
Other	4%	2.8%	--	-

Table 21: Studies showing organism causing UTI

	Hadi et al	**Boris et al**	**Howard et al**	**Present study**
Grade 1	3 (7.3%)	15 (7%)	**17 (31%)**	18 (18%)
Grade 2	14 (34.1%)	88 (41.3%)	**8 (14.5%)**	**14 (14%)**
Grade 3	17 (41.5%)	57 (26.8%)	12 (21.8%)	6 (6%)
Grade 4	2 (4.9%)	33 (15.5%)	**12 (21.8%)**	2 (2%)
Grade 5	5 (12.2%)	20 (9.4%)	6 (10.9%)	-

Table 22: Studies showing grading of VUR

The prevalence of renal scarring in our study (41%) is higher than other Indian study done by Nammalvar et al and by Sen et al (34%) ; also other western studies done in UK, Sweden, Italy and other meta analysis studies (36- 42%).

The prevalence of renal scarring is more after recurrent episodes of urinary tract infection than after first episode of urinary tract infection.

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