UROMODULIN, 
URINARY TRACT INFECTIONS AND RENAL SCARS

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INTRODUCTION

Urinary Tract Infections (UTI) are among the most common bacterial infections in childhood. Febrile UTI (FUTI) have been proved to produce renal scars (RS) in patients with VUR, but in some cases could be documented RS in children without UTI. The renal damage is correlated with the grade of reflux and the number of UTI, but other factors may have a role.

Chemoprophylaxis has been widely used to reduce occurrence of UTI in children with recurrent UTI and or VUR with limited results.

The identification of biomarkers that could noninvasively identify children at risk for FUTI has been claimed as a research priority.
Uromodulin (UMOD) represents the most common urinary protein and is produced in the thick ascending limb cells of Henle’s loop. Recent studies have shown the role of UMOD in protecting from UTI, by a binding with type I-fimbriated Escherichia coli. A defect of UMOD production may increase the susceptibility of UTI.

Measuring urine UMOD concentration and studying UMOD genotype in children with FUTI may reveal if there is a group at increased risk of recurrent UTI and/or SCARS.

UMOD concentration and genotype could identify children predisposed to SCARS independently from UTI (Study A- B, personal data).
STUDY A

We studied 42 patients with VUR, A group of 17 controls (no VUR, UTI).

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Renal scars were detected in 22 patients (Group A).
No scar was detected in 20 patients (Group B).

U was lower in Group A (21.7 ± 12 μg/ml) compared to Group B (28.4 ± 11.9 μg/ml).
31 patients with VUR were enrolled.

Renal scars were detected in 16 children:

Genotype rs4293393
Genetic variant present in UMOD promoter
(single nucleotide polymorphism
Guanosine residue vs adenosine rs)
was present in 10 pts

1/15 pt (no scars) 6%
9/15 (scars) 60%
OBJECTIVES:

The primary end point of the study is the evaluation of urine UMOD concentration in children with FUTI and in a control group comparable for age and sex with no history of UTI. Aim of our study is to evaluate if low concentration of UMOD in the urine is associated with UTI and/or scars in children with VUR.

The secondary purpose of the study is the identification of a specific mutation of the gene that encodes UROMOD, rs4293393 TC, in the two groups of patients, which has been associated with a higher risk of nephropathy.
STUDY DESIGN

Multi-center, prospective study. Children with a new diagnosis of FUTI * will enter the study. A control group of children of similar age and gender distribution, without any history of UTI or renal disease, will also be enrolled.

UMOD concentration (U) measured (µg/ml) in first morning urine using an ELISA method.

A cystography will detect the presence and grade of VUR*. A DMSA scan will detect the presence of a renal scar *.

(according to the Italian guidelines)

For the analysis of the primary endpoint, the test group will be compared to the control group, for secondary outcomes we are planning to divide our patients in four groups:

<table>
<thead>
<tr>
<th>VUR</th>
<th>VUR + RS</th>
<th>NO VUR</th>
<th>NO VUR RS</th>
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</thead>
</table>

* FUTI: Failed Ultrasound Transient Infection
* UTI: Urinary Tract Infection
* VUR: Vesicoureteral Reflux
* RS: Renal Scar
STUDY POPULATION

Children with FUTI will be recruited by all participating Centers.

All patients will fill in a questionnaire in order to obtain information regarding: family history of urinary tract malformations, urinary disorders, previous episodes of UTI and assumption of antibiotic tx.
Age, weight, height, SBP and DBP with oscillometric method.

Blood samples: serum sodium, creatinine and DNA for UMOD genotyping.
Urine samples for uromodulin (second morning urine samples) collected (mid-stream) in a sterile container and frozen within 2 h at -80°C. UMOD concentration (U) will be measured (µg/ml) along with creatinine and sodium > 1 month after resolution.

Imaging: Renal ultrasonography, cystography and DMSA renal scintigraphy (according to the Italian guidelines)

Control Group will be constituted by children of same age and sex
INCLUSION CRITERIA

Age between 0 and 18 years
Febrile (>38° C) UTI
Glomerular filtration rate (Schwartz f.) > 60 ml/min/1.73 m²
Agree statement

EXCLUSION CRITERIA

Age > 18 years
Glomerular filtration rate (Schwartz f.) ≤ 60 ml/min/1.73 m²
Patients with neurogenic bladder, myelomeningocele, uretero-pelvic junction and/or uretero-vescico junction obstruction, or other malformations leading to potential voiding disturbances, urethral valves
Patients with ongoing urinary tract infection.
<table>
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<tr>
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<td>Informed Consent</td>
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<td>US</td>
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<td>DMSA scan</td>
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<td>Cystography</td>
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<td>Urine Culture</td>
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<td>Renal function (BUN, serum creatinine)</td>
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<tr>
<td>Weight, height</td>
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<td>Blood sample for DNA</td>
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<tr>
<td>Urinary sample for uromodulin (frozen at -80°C)</td>
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<td>X</td>
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Data Management
Data will be recorded on excel.

Statistical Analysis
Data will be recorded and analyzed by SPSS Program.

Sample size
According to unpublished data in a limited number of pediatric patients, the mean value of UROMOD in urines is about 36 µg/g of creatinine, and the standard deviation is about 16. We are interested to detect a difference in UROMOD urinary concentration between the test group and the control group of at least 9 µg/g of creatinine (25%). For a two sided test for inequality, with a power of 0.8 and an alpha level of 0.05, and assuming equal variance, about 51 patients per group will be needed.