IL PRURITO NEI PAZIENTI IN DIALISI
Dermatological Disease in Patients With CKD

• Nearly 100% of patients with ESRD are affected by at least 1 dermatological disorder

• Also common in patients with CKD

• Skin disorders have significant effects on quality of life and general appearance

• Some disorders are associated with excessive morbidity and must be treated aggressively
Il Prurito “Uremico”:
Sinossi della relazione

- Definizione
- Epidemiologia
- Patogenesi
- Diagnosi e Quadri clinici
- Significato prognostico
- Approcci terapeutici

Ospedale “Casa Sollievo della Sofferenza”, IRCCS, San Giovanni Rotondo
Il Prurito Uremico

• **Definizione**
• Epidemiologia
• Patogenesi
• Diagnosi e Quadri clinici
• Significato prognostico
• Approcci terapeutici
**Definition**

Itching (pruritus, itch) - an unpleasant sensation associated with the immediate desire to scratch.

Itching is a distinct type of sensation.
Chronic Pruritus

Chronic Pruritus: pruritus lasting longer than 6 weeks

- Most frequent symptom in dermatology
- Highly prevalent
- Women are more affected than men
- Significant associations between pruritus and depression
  and pruritus and QoL
- High burden of chronic pruritus in society
Pruritus – Epidemiology in the general population

**Chronic pruritus:**

Prurigo and allied conditions: 8,2 % (Rea et al. 1976)

General population France: 2 year period: 12,4 % (Wolkenstein et al. 2003)

Working population: point prevalence: 16,8 % (Ständer et al. 2010)

**First population-based study on Chronic Pruritus in Germany** (Matterne et al. 2011):

point prevalence (CP): 13,5 %

12-month prevalence (CP): 16,4 %
Uraemic pruritus
definition

Itch related to chronic renal failure, not associated with acute renal insufficiency. All other causes of pruritus must be excluded to diagnose uraemic pruritus.
Il Prurito Uremico

• Definizione
• Epidemiologia
• Patogenesi
• Diagnosi e Quadri clinici
• Significato prognostico
• Approcci terapeutici
Degree of Pruritus Among Prevalent Patients in DOPPS I and II

Degree of Being bothered by Itchiness


Pisoni RL et al. NDT, 21;3495-3505 (2006)
## Itchiness Among Prevalent Patients, by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>% of patients with moderate to extreme itching (pruritus)</th>
<th>p-value (DOPPS I vs II)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DOPPS I</td>
<td>DOPPS II</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>-</td>
<td>48 (430)</td>
</tr>
<tr>
<td>Belgium</td>
<td>-</td>
<td>38 (443)</td>
</tr>
<tr>
<td>Canada</td>
<td>-</td>
<td>43 (464)</td>
</tr>
<tr>
<td>France</td>
<td>38 (503)</td>
<td>36 (472)</td>
</tr>
<tr>
<td>Germany</td>
<td>48 (426)</td>
<td>42 (488)</td>
</tr>
<tr>
<td>Italy</td>
<td>-</td>
<td>40 (514)</td>
</tr>
<tr>
<td>Japan</td>
<td>46 (1973)</td>
<td>43 (1555)</td>
</tr>
<tr>
<td>Spain</td>
<td>46 (445)</td>
<td>40 (553)</td>
</tr>
<tr>
<td>Sweden</td>
<td>-</td>
<td>40 (446)</td>
</tr>
<tr>
<td>UK</td>
<td>48 (414)</td>
<td>50 (462)</td>
</tr>
<tr>
<td>US</td>
<td>44 (2268)</td>
<td>40 (1444)</td>
</tr>
</tbody>
</table>

*Source: Pisoni RL et al. NDT, 21;3495-3505 (2006)*
Prevalence of uremic pruritus in children on dialysis (18 years or younger) and in adult dialysis patients (older than 18 years).
Il Prurito Uremico

- Definizione
- Epidemiologia
- **Patogenesi**
- Diagnosi e Quadri clinici
- Significato prognostico
- Approcci terapeutici
Cause di prurito nell’ESRD

**Cause uremiche**

- Prurito uremico
- Xerosi cutanea
- Anemia
- SHPT

**Altre cause**

- Senescenza
- Farmaci
- Epatopatie
- Diabete mellito
- Ipotiroidismo
- Carenza di ferro
- M. linfoproliferative
- Ipercalcemia

Teorie: Neuropatica, Immunitaria, Oppiode, Dermatologica.
### Selected Factors and Odds of Pruritus (I)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AOR of having moderate to extreme itching (pruritus)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 yrs)</td>
<td>1.04</td>
<td>0.002</td>
</tr>
<tr>
<td>Male (vs female)</td>
<td>1.10</td>
<td>0.005</td>
</tr>
<tr>
<td>Time with ESRD (vs 1-5 yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-12 months</td>
<td>0.91</td>
<td>0.06</td>
</tr>
<tr>
<td>5-10 yrs</td>
<td>1.00</td>
<td>0.92</td>
</tr>
<tr>
<td>&gt;10 yrs</td>
<td>0.80</td>
<td>0.0002</td>
</tr>
<tr>
<td>Smoking status (yes vs no)</td>
<td>1.15</td>
<td>0.0009</td>
</tr>
<tr>
<td>Belgium (vs US)</td>
<td>0.75</td>
<td>0.007</td>
</tr>
<tr>
<td>Japan (vs US)</td>
<td>1.18</td>
<td>0.01</td>
</tr>
<tr>
<td>UK (vs US)</td>
<td>1.47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ascites (vs no)</td>
<td>1.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hepatitis C (vs no)</td>
<td>1.29</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Also adjusted for race, spKt/V, hemoglobin, 13 comorbid classes, hepatitis B, serum albumin, serum calcium, serum ferritin, serum phosphorus, WBC count, country and accounted for facility clustering effects. n=18,801

Pisoni RL et al. NDT, 21;3495-3505 (2006)
## Selected Factors and Odds of Pruritus (II)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AOR of having moderate to extreme itching (pruritus)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum Calcium</strong>&lt;sup&gt;a&lt;/sup&gt;&lt;sup&gt;b&lt;/sup&gt; (vs 8.4-9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8.4 mg/dl</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td>9.51-10.2 mg/dl</td>
<td>1.04</td>
<td>0.41</td>
</tr>
<tr>
<td>&gt;10.2 mg/dl</td>
<td>1.22</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td><strong>Serum Phosphorus</strong> (vs 3.5-5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5 mg/dl</td>
<td>1.00</td>
<td>0.97</td>
</tr>
<tr>
<td>5.5-6.7 mg/dl</td>
<td>1.21</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>&gt;6.7 mg/dl</td>
<td>1.37</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td><strong>WBC count</strong> (vs &lt;5400)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5400-6700 WBC/ml</td>
<td>1.03</td>
<td>0.55</td>
</tr>
<tr>
<td>6701-8400 WBC/ml</td>
<td>1.12</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt;8400 WBC/ml</td>
<td>1.20</td>
<td>0.00002</td>
</tr>
</tbody>
</table>

*Also adjusted for age, sex, race, time with ESRD, spKt/V, hemoglobin, albumin, phosphorus, 13 comorbid classes, ascites, hepatitis B and C, smoking, country and accounted for facility clustering effects; n=18,801.*

*Pisoni RL et al. NDT, 21:3495-3505 (2006)*
## Selected Factors and Odds of Pruritus (III)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AOR of having moderate to extreme itching (pruritus)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ferritin (vs 100-399)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 ng/ml</td>
<td>1.03</td>
<td>0.48</td>
</tr>
<tr>
<td>400-800 ng/ml</td>
<td>0.89</td>
<td>0.007</td>
</tr>
<tr>
<td>&gt;800 ng/ml</td>
<td>0.83</td>
<td>0.0007</td>
</tr>
<tr>
<td>Serum Albumin (vs 3.5-4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5 g/dl</td>
<td>1.17</td>
<td>0.03</td>
</tr>
<tr>
<td>3.5-3.5 g/dl</td>
<td>1.13</td>
<td>0.004</td>
</tr>
<tr>
<td>&gt;4.0 g/dl</td>
<td>1.00</td>
<td>0.95</td>
</tr>
<tr>
<td>Lung disease</td>
<td>1.15</td>
<td>0.01</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>1.13</td>
<td>0.04</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td>0.03</td>
</tr>
</tbody>
</table>

Also adjusted for age, sex, race, years with ESRD, spKt/V, hemoglobin, 10 comorbid classes, ascites, hepatitis B and C, calcium, ferritin, WBC count, smoking, country and accounted for facility clustering effects; n=18,801
Pisoni RL et al. NDT, 21;3495-3505 (2006)
Hypothetical Mechanism of Pruritus/Itch
Aucella et al. NDT 2007

Peripheral
Inflammation
Skin hypersensation

- Anti-histamines
- Histamine
- Mast Cell
- IgE
- Cytokines
- Complements
- Histamine-releasing factors
- Neuropeptides (Substance P)
- Scratch

Systemic

- Renal failure
- Cholestasis
- Biliary cirrhosis

- μ Opioid peptide
- μ Opioid antagonist
- κ Opioid Agonist
- κ Opioid peptide
- κ Opioid receptor (Neural tissues)
- Induce
- Suppress
- Morphine
- Recognition of itch / pruritus
Il Prurito uremico, una sfida non risolta
Aucella F, Gesuete A. GIN 2009
Schematic synopsis of potential pathogenic factors in chronic kidney disease-associated pruritus

CNS
- Opioid disbalance
- Psychological factors

Supplemental influences
- Scaly skin, dry skin
- Serological factors

Stimuli
- Parathormone
- Histamine
- Tryptase
- Xenobiotica
- Uremic toxins
- Cytokines
- Inflammation

Neuropathy

Nerve-proliferation
Every dog and cat knows that scratching relieves an itch. But for ages, not even neuroscientists knew why.


Now, a University of Minnesota study shows that scratching turns off activity in spinal cord nerves that transmit the itching sensation to the brain. The researchers hope eventually to learn just how the inhibition works.
Il Prurito Uremico

• Definizione
• Epidemiologia
• Patogenesi
• **Diagnosi e Quadri clinici**
• Significato prognostico
• Approcci terapeutici
European Guideline on Chronic Pruritus

In cooperation with the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV)

Fig. 1. Diagnostic algorithm.
Diagnosis & differential diagnosis

CKD Patient with Chronic Pruritus

Psychiatric Diseases

Thyroid Abnormalities

Iron Deficiency Anemia

Lymphoma

Inflammation

Liver Disease
Hepatitis C

Uremic Pruritus

Neurologic Diseases

Allergic Reactions
Criteri per la diagnosi di prurito

• Esclusione di tutte le altre possibili cause;
• 3 o più episodi in meno di 2 settimane col sintomo che dura almeno alcuni minuti e si ripete più volte al giorno;
• Episodi di prurito meno frequenti, ma presenti da almeno 6 mesi.
Frequency and Parts of the body affected

Frequency

- Once in several weeks
- Once in several days
- Once a day
- Several times a day
- Always

Parts of the body

- Head
- Face
- Back
- Chest & abdomen
- Arm
- Hand
- Thigh & leg
- Foot
- Others

N=1631
Skin affected in patients with uraemic pruritus.

(a) Scratches on the arm hosting the fistula.

(b) Deep scars on the shoulders and the back of female patient on haemodialysis.

(c) Prurigo nodularis with excoreations and superinfection on the forearm of a patient on peritoneal dialysis.

(d) Kyrles disease on the back of a patient on haemodialysis.

NDT 2002
Mettang
(a) Scratch marks with excoriations at the lower leg.

(b) Typical hyperkeratotic partly excoriated nodules (prurigo nodularis) located on the forearm.

(c) Deep scars and prurigo nodules at the shoulders and back of a female patient.

Mettang T, Kidney Int 2014
Esempio di scala analogica visuale per l’autovalutazione del sintomo prurito

Scala A: intensità del prurito

0% 25% 50% 75% 100%

Scala B: durata del prurito

0% 25% 50% 75% 100%
Il Prurito Uremico

- Definizione
- Epidemiologia
- Patogenesi
- Diagnosi e Quadri clinici
- **Significato clinico e prognostico**
- Approcci terapeutici
Relationship of QoL mental composite summary (MCS) score with the degree of patient-reported pruritus, with and without adjustments for sleep quality.

DOPPS, Pisoni, NDT 2006
Relationship of QoL physical composite summary (PCS) score with the degree of patient-reported pruritus, with and without adjustments for sleep quality.  

DOPPS, Pisoni, NDT 2006
Relationship of degree of pruritus with adjusted odds of HD patients being awake at night, sleepy during the day or not having enough sleep (yes vs no).
Relative risk (RR) of mortality for HD patients with moderate to extreme pruritus vs no/mild pruritus with or without adjustments for sleep quality and feeling drained (DOPPS I).
Figure 3 | Kaplan–Meier analysis for the survival of patients. The prognosis of patients with severe uremic pruritus was significantly worse than those of the others (log rank test, $\chi^2 = 14.426; P = 0.0001$).

Narita I et al. KI 2006
Pruritus and survival

Figure 2. Hemodialysis patients with moderate/severe uremic pruritus had a worse overall survival than those with no/mild uremic pruritus.

Uremic Pruritus is Associated with Two-Year Cardiovascular Mortality in Long Term Hemodialysis Patients

Kidney Blood Press Res 2018;43:1000-1009

All cause mortality
cardiovascular mortality
Il Prurito Uremico

- Definizione
- Epidemiologia
- Patogenesi
- Diagnosi e Quadri clinici
- Significato prognostico
- **Approcci terapeutici**
Therapeutic options in uremic patients

**Dialysis related**
- (a) Renal transplantation
- (b) Efficient dialysis
- (c) Biocompatibility
- (d) Erythropoietin

**Topical treatment**
- (a) Skin emollients
- (b) Capsaicin
- (c) Steroids/Tacrolimus
- (d) \(\gamma\)-linolenic Acid

**Physical treatment**
- (a) Phototherapy
- (b) Acupuncture
- (c) Sauna

**Systemic treatment**
- (a) Low-protein diet
- (b) Gapapentin
- (c) Lidocaine and mexilitine
- (d) Opioid antagonists
- (e) Activated charcoal
- (f) Cholestyramine
- (g) Serotonin antagonists
- (h) Parathyroidectomy
- (i) Thalidomide
- (j) Nicergoline
- (k) Nalfurafine

Kidney Int 2007 - SR Keithi-Reddy (modified)
An Update on Pruritus Associated With CKD

Tejesh S. Patel, MD, Barry I. Freedman, MD, and Gil Yosipovitch, MD

Efficacy and Safety of Gabapentin for Uremic Pruritus and Restless Legs Syndrome in Conservatively Managed Patients With Chronic Kidney Disease

Journal of Pain and Symptom Management

Vol. 49 No. 4 April 2015

![Graph showing data on pruritus scores across visits.](image-url)
Efficacy and Safety of Gabapentin for Uremic Pruritus and Restless Legs Syndrome in Conservatively Managed Patients With Chronic Kidney Disease

Journal of Pain and Symptom Management
Vol. 49 No. 4 April 2015

Table 2
Gabapentin Side Effects

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Conservative Group (n = 34)</th>
<th>Hemodialysis Group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 side effect</td>
<td>16 (47.0)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>8 (50)</td>
<td>—</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (19)</td>
<td>—</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (19)</td>
<td>—</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>2 (12.5)</td>
<td>1 (6.66)</td>
</tr>
<tr>
<td>Unsteadiness</td>
<td>2 (12.5)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Confusion</td>
<td>1 (6.25)</td>
<td>—</td>
</tr>
</tbody>
</table>

Data expressed as number of patients (%). Patients may have had more than one side effect.
Effect of Acupressure on Patients in Turkey Receiving Hemodialysis Treatment for Uremic Pruritus


**Figure 2. Acupuncture Points**

- Large Intestine 11 (LI 11)
- Spleen 10 (SP 10)
- Stomach 36 (ST 36)
- Spleen 6 (SP 6)

**Table 4. Use of Medication for Pruritus During the Trial by Individuals in the Intervention and Control Groups**

<table>
<thead>
<tr>
<th>Use of Medication for Pruritus During the Trial</th>
<th>Groups</th>
<th>Intervention (n = 38)</th>
<th>Control (n = 40)</th>
<th>Test*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamine used</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Antihistamine not used</td>
<td>32</td>
<td>84.2%</td>
<td>15</td>
<td>37.2</td>
</tr>
</tbody>
</table>

*Test*
CONTRO IL PRURITO IN DIALISI

Terme di Comano

Fanno rinfiorire la pelle irritata
Uraemic itching: do polymethylmethacrylate dialysis membranes play a role?

Aucella F et al. NDT 2007
Review: the effect of polymethylmethacrylate dialysis membranes on UP

Aucella F et al

NDT Plus (2010) 3 [Suppl 1]: i8-i11
Protein adsorption characteristics, (a) Amounts of adsorbed total proteins, (b) Profile of adsorbed proteins (electrophoresis pattern).

Aoike I, NDT 2007
Step-up therapeutic approach for uremic pruritus in CKD.

Skin problems in chronic kidney disease
Dirk RJ Kuypers
Nat Clin Practice Nephrol 2009
Exclusion of other causes for pruritus

Assessment of severity of pruritus
  Weak → Moistening ointment oil bath
  Severe
    Quality of dialysis (Kt/V)
      Kt/V < 1.2 → Increase dose of dialysis
      Kt/V > 1.2
        Persisting
          Moistening ointment / oil bath
            and
            Gabapentin 100-300 mg or UVB phototherapy or Charcoal (6g/die) or Nalfurafine 2.5-5.0 mg p.o.

Persisting
  Naltrexone or Tacrolimus ointment or (Electro-) acupuncture

Persisting
  Consider kidney transplantation

Take home messages

• UP is a common feature of CKD: all other causes of itch need to be excluded;
• UP is underdiagnosed and undertreated;
• Nephrologists need to be aware that UP is related to lower QoL, sleep quality and mortality;
• In a step-up therapeutic approach firstly look at the dialysis quality.