Urine protein differentiation and *Protis*, a new expert system for its interpretation

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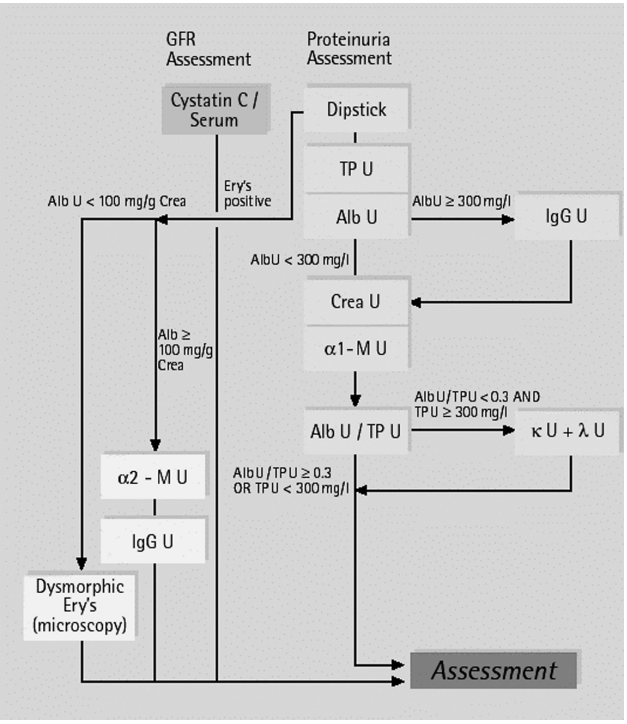
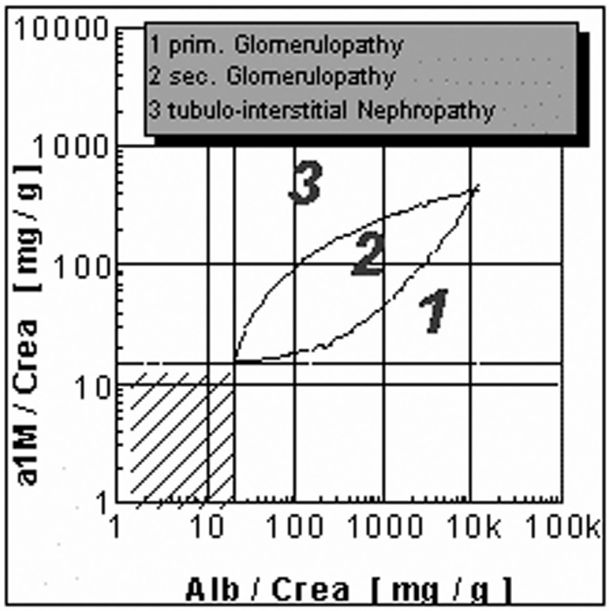
Proteinuria and hematuria are the most often found symptoms of renal disease. Recently we have learned that urine protein patterns mirror the sites and mechanisms of the events.
Renal dysfunctions are excluded with high certainty when cystatin C in serum, total protein, albumin and α_1-microglobulin, hemoglobin and leucocyte esterase excretion are normal (1,2).
Figure1 shows the strategy as workflow.

Figure 1. Proposed combination for serum and urine screening tests for the exclusion and differentiation of renal diseases.



By quantitating single proteins with different molecular weight (IgG, albumin, α_1-microglobulin, α_2-macroglobulin) in urine, prerenal forms can be separated from glomerular and tubulo-interstitial (Fig.2) and postrenal ones. Figure 2 shows the differentiation pattern from patients with a primary glomerulopathy, secundary glomerulopathy and patients with a tubulo-interstitial nephropathy.

Figure 2. Urinary α_1-microglobulin excretion rates in comparison to albuminuria in primary glomerulopathies (*1*), secundary glomerulopathies (*2*) and tubulo-interstitial diseases (*3*) separated by two hyperbolic curves. The two lines characterize the upper reference limits for albumin (20 mg/ g creatinine) and α_1-microglobulin (14 mg/ g creatinine).



Albuminuria can further be differentiated with regard to selectivity of glomerular barrier, degree of tubular involvement and postrenal contamination. Measuring urine IgG has been found to be helpful in separating primary and secondary glomerular diseases. By calculating the minimal tubular marker excretion due to overload the degree of interstitial

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involvement in tubular diseases may be calculated (4). Bence-Jones proteinuria is suspected whenever albumin excretion is below 30% of total protein and confirmed by light chain analysis (3).

In case of hematuria α_2-macroglobulin can be used to identify postrenal bleeding, whenever albuminuria exceeds 100 mg/L. A relation α_2-macroglobulin/albumin above 2.0 $x10^{-2}$ and an IgG/albumin above $20.0x10^{-2}$ is typical for a renal hematuria (Fig.3).

This new strategy for urine proteins combined with the new GFR-parameter, Cystatin C (5) has been adapted to analytical systems. All measured parameters are listed in a medical report (Tab. I).

Table I. Medical report of urine protein differentiation from the expert system *Protis*

Urine Assessment Report protis

Submitter

DADE BEHRING

Tel.:

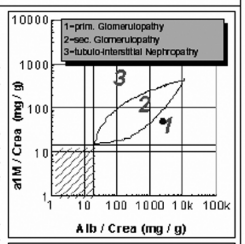
Patient Information

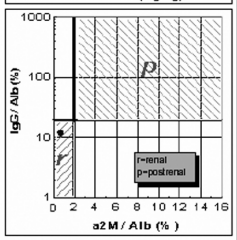
Name	Test, Test	ID	87		
Height (cm)	160	Age (Y)	22	Date of Birth	
		Weight (kg)	50	Sex	F

Sample Information

Urine	8720030408U	08.04.2003	Collection Time	24 h	Volume 1000 ml
Serum	8720030408S	08.04.2003			

Parameter	Result	Reference	Unit	Concentration
Serum				
Cystatin C	1,3	0,5 - 0,96	mg/l	
Creatinine	2,0	0,7 - 1,2	mg/dl	
Glomerular Filtration Rate				
GFR (CysC)	~53		ml/min	
Creatinine Clearance	~40	72 - 110	ml/min/1.73m²	
GFR Cockgroft	~41	72 - 110	ml/min/1.73m²	
GFR Schwartz				
Urine				
Creatinine				1,0 g/l
Total Protein	3000,0	< 100	mg/g Crea	3000 mg/l
Albumin	2500,0	< 20	mg/g Crea	2500 mg/l
IgG	300,0	< 10	mg/g Crea	300 mg/l
a1-Microglobulin	50,0	< 14	mg/g Crea	50 mg/l
a2-Macroglobulin	15,0	< 10	mg/g Crea	15 mg/l
Ig/L-chain, type kappa				
Ig/L-chain, type lambda				200 mg/l
Kappa/Lambda				





Dipstick		Cell Counts		
Erythrocytes arbit.	++	Bacteria HF	0	-
Leukocytes arbit.	0	Yeast HF	+	-
Protein arbit.	+++	Cylinder path.	0	-
Glucose arbit.	++	Ketone arbit.		
pH	7	Bacteria	0	-
spec. Weight		Yeast	0	-
Bilirubin arbit.		Small round Cells		
Urobilinogen arbit.		further Cells		
Nitrite arbit.	0	Dysmorphic Erythro	+	-

Interpretation
The glomerular filtration rate is reduced.

Nonselective glomerular proteinuria is present. This is to be classified as distinct. Additional, significant tubular proteinuria exists

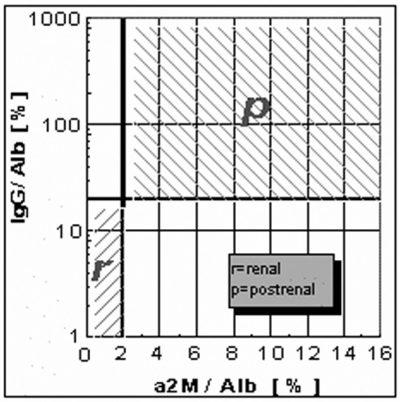
This constellation is compatible with primary or secondary glomerulopathy. (e.g. glomerulonephritis, diabetic or hypertensive nephropathy).
The presence of renal hematuria is highly likely; additional erythrocytes from postrenal sources cannot be ruled out.

08.04.2003 Signature

The result interpretation provided by protis is not intended as a substitute for a physician's diagnosis. DADE BEHRING assumes no responsibility for the result interpretation provided by the protis program.

Test, Test 87 Page 1/1

Figure 3. Comparison of IgG/albumin and α_2-macroglobulin/albumin ratios in hematuric urines from patients with renal and postrenal diseases. The two lines separate renal from postrenal bleedings.



By linking the analyser to the laboratory computer system, a test strategy can be applied which allows to quantitate the whole range of existing urine protein concentrations from undiluted urine. Serum parameters and the complex urine protein pattern is transferred to the expert system *Protis* (Dade-Behring), which compares the individual results with the knowledge base built from over 500 histological and clinically proven cases (6).
It is to be hoped, that renal diseases can be detected already in a stage where a preventive therapy is still effective. Moreover, application of this strategy can help to prevent many invasive investigations like biopsies, cystoscopies and X-ray investigation.

References

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