NEW SCIENTIFIC COMPANY España, S.r.l.
Valencia, 558 - 08026 Barcelona
Teléfono: (+34) 93 244 82 94
Facsimil: (+34) 93 244 82 95
e-mail: nsce@newscientific.com
Inscrita R.M. Barcelona, Tomo 20089, Folio 83, Hoja 1008, Inscripción 1ª
N.I.F.: ES - B 59 305 474

BIOMEDICINA - PATOLOGIA CLINICA - INFORMATICA

Proteinúria de Bence Jones

Protocolo Operacional para a determinação da presença de Proteínas de Bence Jones em Urina:

Proposta e Relação Bibliográfica

New Scientific Company España, S.r.l.

Valencia, 558, 4º 1ª
08026 - Barcelona

Tel.: (+ 34) - 93 244 82 94
Fax: (+ 34) - 93 244 82 95
E-mail: nsce@newscientific.com
Web: www.newscientific.com

Introdução :

As ***Proteínas de Bence Jones (BJP)*** são, por definição, ***Cadeias Leves LIVRES MONOCLONAIS (CLLM)*** [1, 5, 9, 11, 24, 35, 37]. Quando na bibliografia se empregam indistintamente, de modo inexacto e gerando confusão, os termos Proteínas de Bence Jones, Cadeias Leves (Light Chains), Cadeias Leves Livres (Free Light Chains), Cadeias Kappa e Lambda, etc., está-se na realidade a fazer estritamente referência às Proteínas de Bence Jones.

As ***BJP*** são indicadoras de um processo maligno [1, 2, 3, 4, 5, 6, 8, 9, 11, 15, 37, 38, 39]. ***A sua presença está demostrada em 60-87% de casos de Mieloma Múltiplo (MM)*** [2, 4, 9, 22, 38] e, ***em 15-20% dos MM são o único produto biológico excretado pelo clone maligno*** (Mieloma Micromolecular, de Bence Jones ou de Cadeias Leves) [2, 4, 9, 21, 23, 38].

Dada a sua fisiopatologia, ***a sua presença é demonstrável na urina antes e com maior facilidade do que no soro*** [21, 35, 36, 38], excepto em caso de redução da Filtração Glomerular. Por isso, ***no caso de suspeita de Gamapatía Monoclonal, é imprescíndivel estudar a urina do doente*** pois pode revelar-se um componente monoclonal nela, constituído por BJP, sem que se observe qualquer anomalia no soro do mesmo doente.

As ***BJP*** são, por elas mesmas, uma "entidade maligna" que produz efeitos patológicos principalmente no ***rim*** [2, 4, 6, 8, 9, 13, 16, 17, 22, 25, 27, 28, 29, 30, 31, 32, 33, 34, 38]. As BJP são nefrotóxicas e estão estreitamente ligadas às complicações renais do MM, nel quai a 2.ª causa de morte é a falha renal [38, 40]. A lesão renal é frequentemente o primeiro sintoma que leva ao diagnóstico final da MM [17, 26, 27, 38] e é, além disso, um factor prognóstico importante que influencia a sobrevivência do doente [5, 14, 16, 20, 22, 27, 40].

A determinação periódica [2, 3, 4, 8, 38] da ***presença e quantidade de BJP*** presente na urina é um elemento indispensável para o diagnóstico [1, 5, 7, 9, 10, 11, 15, 24, 26, 36] (estabelecimento do seu grau, etc.), o prognóstico [2, 4, 7, 8, 9, 10, 11, 16, 17, 18, 20, 22, 26] e o controlo da evolução e resposta ao tratamento [1, 2, 4, 5, 7, 8, 9, 11, 12, 15, 19, 22, 23, 37, 38] do ***MM***.

A procura das BJP deve prever, para confirmar a sua composição, ***o uso de um método imunológico e***, para confirmar a sua distribução monoclonal, ***o uso de um método electroforético***, além de ter presente os seguintes factos:

1.- Ao estudar a urina, podemos encontrar qualquer uma das seguintes proteínas, ou uma mistura delas:
   - ***BJP*** (= CLLM)
   - Cadeias Leves Livres Policlonais (CLLP)
   - Cadeias Leves Livres Oligoclonais ou "Ladders"
   - ***Imunoglobulinas Completas*** (monoclonais e/ou policlonais) (***IG's***)

2.- A presença na urina de ***IG's completas*** (acompanhando as BJP ou sozinhas) é bastante mais ***frequente*** do que geralmente se considera, em especial em doentes com a função glomerular afectada.

3.- Os anti-soros específicos ***anti CLL*** reagem com as Cadeias Leves quando estas não formam parte das IG's completas, é dizer, quando se encontram "***livres***" (daí precisamente o seu nome).

4.- Os anti-soros ***anti Cadeias Leves Totais*** (livres + ligadas) (CLT) reagem com as Cadeias Leves tanto quando estão livres, como quando estão ligadas fazendo parte das IG's, isto é, ***reagem*** indistintamente com as CLL e ***com as IG's completas***.

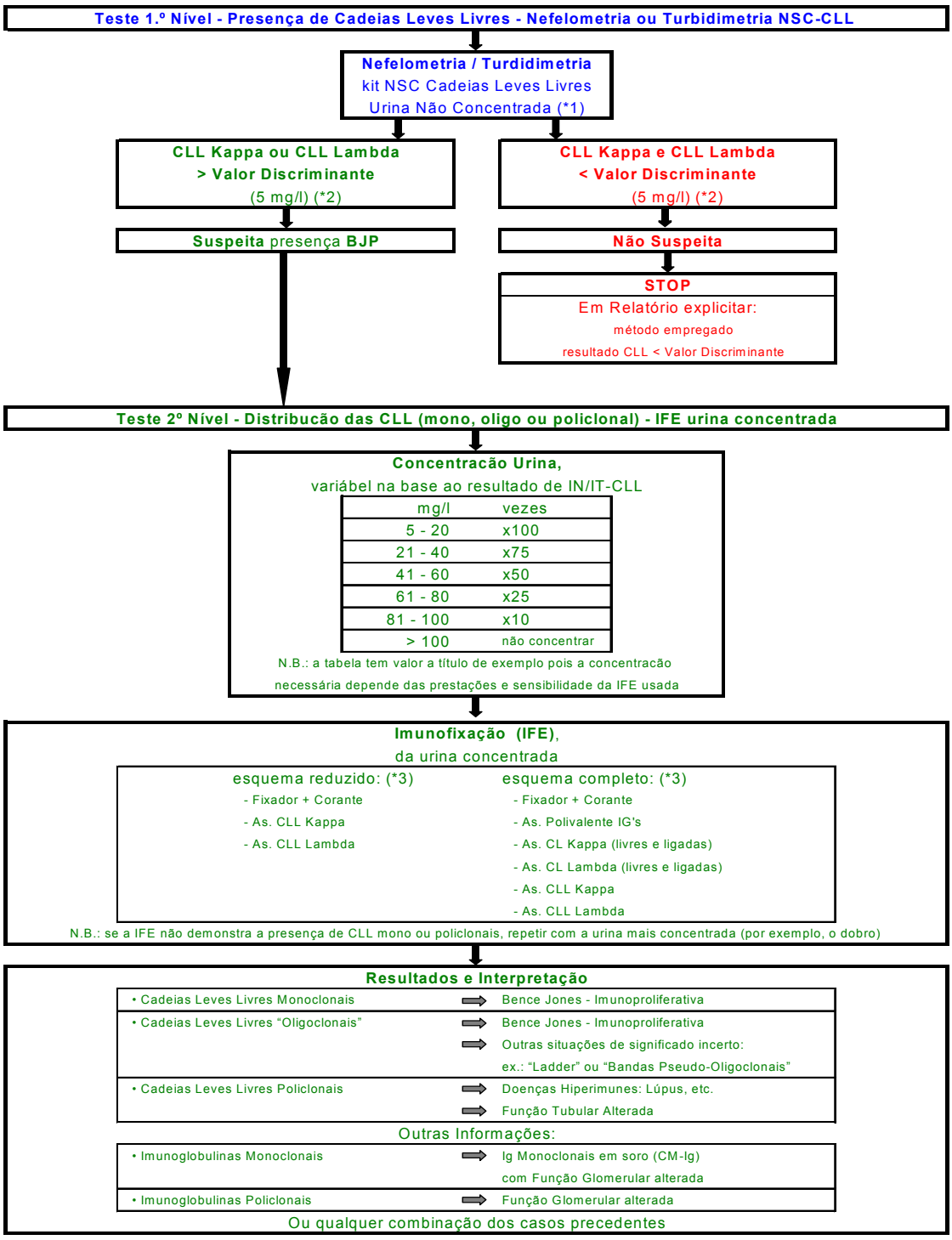
5.- Os factores anteriores têm incidência tanto na determinação qualitativa da presença na urina de BJP (=CLLM), como na sua dosificação.

O protocolo operacional proposto na página seguinte prevê o uso da Nefelometria (ou Turbidimetria), com anti-soros específicos anti CLL, como método imunológico de primeiro nível cujo objectivo é evidenciar a presença de CLL na urina, e o uso da Imunofixação, também com anti-soros específicos anti CLL, como método electroforético de confirmação cujo objectivo é demonstrar ou descartar a monoclonalidade das CLL antes evidenciadas. No teste de confirmação, Imunofixação, se submeterão aquelas amostras que tenham tido resultados positivos no teste de primeiro nível, Nefelometria.

Proposta Protocolo Operacional :

Esquema Protocolo

O protocolo operacional esquematizado a seguir é um exemplo de como empregar o método de Imunoprecipitação em fase líquida (Nefelometria ou Turbidimetria) para a procura das Proteínas de Bence Jones na urina, numa primeira abordagem diagnóstica:



Nota (*2): ou otro valor definido pelo utilizador

Notas

Nota (*1) - Tipo de Amostra :

Para o estudo das CLL em geral, e das Proteínas de Bence Jones (BJP) em particular, empregam-se diferentes tipos de amostra sem que haja acordo sobre qual é a mais conveniente; as mais commumente empregadas são:

- urina de 24 horas
- primeira urina da manhã
- urina extemporânea; geralmente a segunda urina da manhã

A amostra tradicional é a urina de 24 horas que, além da avaliação da diúrese, permite fazer a média da presença das CLL de um período de tempo razoável.

Alguns propõem o uso de uma urina extemporânea, geralmente a segunda da manhã, pela sua facilidade de obtenção e porque é mais difícil sua contaminação, estimando a diúrese através da determinação da Creatinina urinária com o objectivo de descartar amostras demasiado diluídas que poderiam dar Falsos Negativos. Esta proposta apresenta uma maior comodidade na obtenção e manuseio da amostra, mas não tem em conta a muito provável produção cíclica das CLL (apontada por alguns autores, ainda que não demonstrada para as CLL, mas sim para outras proteínas) que, dada a sua curtíssima hemivida, determinaria também variações na sua excreção urinária que poderiam levar a que amostras próximas do limite de sensibilidade do metódo empregado pudessem dar resultados falsamente negativos, além de dificultar a medida quantitativa neste tipo de amostra, avaliando inclusive a Creatinina como estimação da diúrese.

O uso da primeira urina da manhã tão pouco traz algo de novo em relação à outra urina extemporânea e além é mais susceptível de contaminação.

A nossa opinião é que, até que se demonstre o contrário, e sobretudo se houver interesse na determinação quantitativa, o melhor é empregar a urina de 24 horas com Azida Sódica como conservante para prevenir uma eventual contaminação bacteriana.

Nota (*2) - Valor Discriminante :

O valor discriminante proposto no protocolo, 5 mg/l (0,5 mg/dl), deve ser considerado como uma proposta de orientação pois é o utilizador quem deve determinar, de acordo com os clínicos e coerentemente com a sensibilidade do método de confirmação empregado (usualmente IFE), o valor discriminante a empregar.

De qualquer modo, o valor proposto (5 mg/l) é inferior aos valores relatados na bibliografia (pelos poucos autores que se atrevem a dar valores concretos) que coincidem em que resulta suficiente uma sensibilidade ao redor de 10 mg/l; mais, *Beetham* chega a afirmar nas conclusões do seu artigo que "*todos os laboratórios deveríam ser capazes de detectar BJP ao redor de 10 mg/l*", depois de ter constatado que 35% dos laboratórios participantes num estudo na Grã-Bretanha não eram capazes de detectar uma BJP de 60 mg/l (6 mg/dl) (*Detection of Bence Jones Protein in Practice. R. Beetham - Ann Clin Biochem 2000; 37: 563-570*).

Na urina de doentes normais as BJP em particular devem estar ausentes e, de um modo mais geral apenas devem ter traços da presença de CLL policlonais. Consequentemente, qualquer valor detectável de CLL deveria ser considerado potencialmente positivo e deveria confirmar-se a sua distribuição (monoclonal ou não) com uma Imunofixação, com o objectivo de descartar a presença de BJP.

De todos as maneiras, nem está estabelecido nem há acordo sobre o significado clínico de pequenas quantidades de BJP e, além disso, a sensibilidade do método nefelométrico mostrou-se em alguns estudos superior ao da Imunofixação empregada como confirmação. Assim sendo, ainda que a escolha mais purista seria a de usar como valor discriminante o limite de sensabilidade do método nefelométrico, na prática a maioria dos utilizadores usam o valor proposto de 5 mg/l (ponto mais baixo da curva de calibração) ou muitos até 10 mg/l, tal como pormenoriza a pouca bibliografía disponível, como valor discriminante para a crivagem.

Nota (*3) - Anti-soros Empregados na Imunofixação :

O esquema clássico, tipo soro, usualmente empregado prevê o uso dos seguintes anti-soros: IgA, IgG, IgM, Cadeias Kappa (livres+ligadas) e Cadeias Lambda (livres+ligadas). O emprego deste esquema na urina pode apresentar complicações interpretativas que podem dar lugar a resultados falsamente negativos em relação à presença de BJP, como por exemplo, naqueles casos em que a presença de uma Imunoglobulina completa monoclonal mascare a banda de BJP devido a uma comigração aparente (situação que se supõe pouco frequente, porque usualmente não se controla, mas que na prática se dá com uma frequência significativa).

Para a urina resulta mais seguro e por isso recomendável empregar o esquema alternativo que prevê o uso de anti-soros anti Cadeias Leves Livres: Polivalente IG's, Cadeias Kappa (livres+ligadas), Cadeias Lambda (livres+ligadas), Cadeias Kappa Livres e Cadeias Lambda Livres.

Referências Bibliográficas :

1. **Solomon A.** Bence-Jones Proteins and Light Chains of Immunoglobulins (First of Two Parts). *N Eng J Med, Vol. 294 No. 1, Jan. 1976*
2. **Solomon A.** Bence-Jones Proteins and Light Chains of Immunoglobulins (Second of Two Parts). *N Eng J Med, Vol. 294 No. 2, Jan. 1976*
3. **Pezzoli A, Pascali E.** The Clinical Significance of Pure Bence Jones Proteinuria at Low Concentration. *A.J.C.P., Apr. 1989*
4. **Solomon A.** Bence-Jones Proteins: Malignant or Benign ?. *N Eng J Med, Vol. 306 No. 10, Mar. 1982*
5. **Whicher JT, Calvin J, Riches P, Warren C.** The Laboratory Investigation of Paraproteinemia. *Ann. Clin. Biochem, 24: 119-132, 1987*
6. **Stevens FJ, Solomon A, Schiffer M.** Bence-Jones Proteins: A powerfull Tool for the Fundamental Study of Protein Chemistry and Pathophysiology. *Biochemistry, Vol. 30 No. 28, 1991*
7. **Matsuda K, Hiratsuka N, Koyama T, ...** Sensitive Method for Detection and Semiquantitation of Bence Jones Protein by Cellulose Acetate Membrane Electrophoresis Using Colloidal Silver Staining. *Clinical Chemistry, 47, no. 4, Apr. 2001*
8. **Kyle R, Greipp P.** "Idiopathic" Bence Jones Proteinuria: Long-Term Follow-up in Seven Patients. *N Eng J Med, Vol. 306 No. 10, Mar. 1982*
9. **Tillyer CR.** Clinical Applications of Immunoglobulin Free Light Chain Estimations. *Int J Clin Lab Res, 23(1), 1993*
10. **Okada K, Oguchi N, Shinohara K, ...** BUN, Bence Jones protein, and chromosomal aberrations predict survival in multiple myeloma. *Rinsho Ketsueki, 38(12), Dec. 1997*
11. **Vegh Z, Otto S, Eckhardt S.** Monoclonal Free Light Chains in Urine and their significance in clinical diagnostics: are they really tumor markers ?. *J Clin Lab Anal, 4(6), 1990*
12. **Singhal S, Mehta J, Desikan R, et al.** Antitumor Activity of Thalidomide in Refractory Multiple Myeloma. *N Engl J Med, 341(21), 1999*
13. **Sinohara H, Matsuura K.** Does catalytic activity of Bence-Jones proteins contribute to the pathogenesis of Multiple Myeloma ?. *Appl Biochem Biotechnol, 83(1-3), Jan.-Mar. 2000*
14. **Spasov E, Goranova V.** Prognostic assessment of the Durie and Salmon staging system in patients with multiple myeloma. *Folia Med (Plovdiv), 40(3B suppl 3), 1998*
15. **Abe M, Goto T, Kosaka M, ...** Differences in kappa to lambda (kappa:lambda) ratios of serum and urinary free light chains. *Clin Exp Immunol, 111(2), Feb. 1998*
16. **Uchida M, Kamata K, Okubo M.** Renal dysfunction in multiple myeloma. *Intern Med, 34(5), May 1995*
17. **Goranova V, Spasov E.** Prognostic significance of the immunological variant in patients with multiple myeloma. *Folia Med (Plovdiv), 41(1), 1999*
18. **Weber DM, Dimopoulos MA, Moulopoulos LA, ...** Prognostic features of asymptomatic multiple myeloma. *Br J Haematol, 97(4), Jun. 1997*
19. **Kadokura M, Tanio N, Nonaka M, ...** A surgical case of solitary plasmacytoma of rib origin with biclonal gammopathy. *Jpn J Clin Oncol, 30(4), Apr. 2000*
20. **Knudsen LM, Hjorth M, Hippe E.** Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. *Eur J Haematol, 65(3), Sep. 2000*
21. **van Zaanen HC, Diderich PP, Pegels JG, ...** Renal insufficiency due to light chain multiple myeloma. *Ned Tijdschr Geneeskd, 144(45), Nov. 2000*
22. **Vivaldi P, Comotti C, Pedrazzoli M.** The kidney in multiple myeloma. The physiopathological and clinical aspects. *Recenti Prog Med, 85(2):123-33, Feb. 1994*
23. **Tillyer CR, Iqbal J, Raymond J, ...** Immunoturbidimetric assay for estimating free light chains of immunoglobulins in urine and serum. *J Clin Pathol, 44(6), Jun. 1991*
24. **Pascali E.** Clinical applications of immunoglobulin free light chain analysis. *Int J Clin Lab Res, 24(2), 1994*
25. **Ivanyi B.** Development of chronic renal failure in patients with multiple myeloma. *Arch Pathol Lab med, 117(8), Aug. 1993*
26. **Irish AB, Winearls CG, Littlewood T.** Presentation and survival of patients with severe renal failure and myeloma. *QJM, 90(12), Dec. 1997*
27. **Sakhuja V, Jha V, Varma S, ...** Renal involvement in multiple myeloma: a 10-year study. *Ren Fail, 22(4), 2000*
28. **Stevens FJ, Kisilevsky R.** Immunoglobulin light chains, glycosaminoglycans, and amyloid. *Cell Mol Life Sci, 57(3), Mar 2000*
29. **Messiaen T, Deret S, Mougenot B, ...** Adult Fanconi syndrome secondary to light chain gammopathy. Clinicopathologic heterogeneity and unusual features in 11 patients. *Medicine (Baltimore), 79(3), May 2000*
30. **Pote A, Zwizinski C, Simon EE, ...** Cytotoxicity of myeloma light chains in clutured human kidney proximal tubule cells. *Am J Kidney Dis, 36(4), Oct. 2000*
31. **Doi K, Teramoto S, Hosoi T, ...** Renal tubular acidosis type II secondary to gamma-light chain excretion in an elderly patient with multiple myeloma. *Nippon Ronen Igakkai Zasshi, 35(6), Jun. 1998*
32. **Cohen G, Haag-Weber M, Horl WH.** Immune dysfunction in uremia. *Kidney Int Suppl, 62:S79-82, Nov. 1997*
33. **Deret S, Denoroy L, Lamarine M, ...** Kappa light chain-associated Fanconi's syndrome: molecular analysis of monoclonal immunoglobulin light chains from patients with and without intracellular crystals. *Protein Eng, 12(4), Apr. 1999*
34. **Picken MM, Shen S.** Immunoglobulin light chains and the kidney: an overview. *Ultrastruct Pathol, 18(1-2), Apr 1994*
35. **Keren DF.** Procedures for the evaluation of monoclonal immunoglobulins. *Arch Pathol Lab Med, 123(2), Feb. 1999*
36. **Qiu W, Wu G.** Immunological diagnosis of light chain disease: analysis of 11 cases found in Fujian Province. *Chung Kuo I Hsueh Yuan Hsueh Pao, 15(4), Aug. 1993*
37. **Bradwell A, Carr-Smith H, Mead G, ...** Highly Sensitive, Automated Immunoassay for Immunoglobulin Free Light Chains in Serum and Urine. *Clinical Chemistry, 47:4, Apr. 2001*
38. **Fang L.** Light Chain Nephropathy. *Kidney International, vol. 27, 1985*
39. **Tillyer CR.** The estimation of free light chains of immunoglobulins in biological fluids. *Int J Clin Lab Res, 22:152-158, 1992*
40. **Molby L, Hansen HH, Jensen EL.** Development and treatment of renal insufficiency in multiple myeloma. *Ugeskr Laeger, 156(30):4343-7, Jul 1994*

Relação Bibliográfica - Abstracts :

9. **Clinical applications of immunoglobulin free light chain estimations**
   Int J Clin Lab Res 1993;23(1):25-9 (ISSN: 0940-5437)
   Tillyer CR
   Department of Chemical Pathology, Royal Marsden Hospital, London, UK.
   The relevance of free light chain assays to diagnosis, staging, treatment and prognosis assessment in B-cell disorders (including myeloma, chronic lymphocytic leukaemia, and lymphoma), multiple sclerosis and diabetes is discussed and their actual and potential use is examined.

10. **BUN, Bence Jones protein, and chromosomal aberrations predict survival in multiple myeloma**
    Rinsho Ketsueki 1997 Dec;38(12):1254-62 (ISSN: 0485-1439)
    Okada K; Oguchi N; Shinohara K; Tamura N; Ishii K; Noguchi Y; Hayashi S; Yamamoto H; Takeichi M; Fujimoto H; Shirota T; Hayashi T
    Third Department of Internal Medicine, Tokyo Medical College.
    The prognostic significance of some clinical features in 41 patients with multiple myeloma (including 2 patients with plasma cell leukemia) from our institution was analyzed. Out of 14 variables isolated from the univariate analysis (P < 0.05), only three (BUN, Bence Jones protein, and chromosomal aberrations) were significant in the multivariate model (P < 0.05). Derived from these three variables, three subpopulations of patients were identified. The first group included 20 patients with a low risk of death and their median survival has not been reached. In particular, no one died during the first 60 months in this group. The second group also included 14 patients with an intermediate risk of death and a median survival of 49.2 months. The third group comprised seven patients with a high risk of death during 24 months after diagnosis and a median survival of 31.6 months (P < 0.0001). Finally, Durie & Salmon's myeloma staging system was demonstrated in the present series, and it showed prognostic validity for each stage (P < 0.0222). Compared with Durie & Salmon's staging system, our prognostic model for multiple myeloma was more useful to predict prognosis when applied to the present series.

11. **Monoclonal free light chains in urine and their significance in clinical diagnostics: are they really tumor markers?**
    J Clin Lab Anal 1990;4(6):443-8 (ISSN: 0887-8013)
    Vegh Z; Otto S; Eckhardt S
    National Institute of Oncology, Budapest, Hungary.
    Bence Jones proteins (monoclonal free light chains of immunoglobulins) are the earliest known biological markers of malignant cell dyscrasia; Bence Jones proteinuria is also present in many types of B cell-related neoplasms. Sometimes, it may also occur in Hodgkin's disease. In some cases, benign monoclonal gammapathy was found to be associated nontumorous diseases as well. The type of monoclonal light chain, the degree of polymerization, and the isoelectric point of the molecule may affect the course of the disease. Urine samples from 637 patients with true or suspected lymphoproliferative diseases were investigated over a 2-yr period by different immunochemical methods. Bence Jones proteinuria was identified in 71 cases by isoelectric focusing combined with immunofixation, while the pathological protein was detected only in 63 cases by conventional methods. Bence Jones proteins can be detected by this new method at a level below the sensitivity of conventional procedures. Bence Jones proteins in the urine may signal a malignant tumor or malignant transformation of an earlier disease. The early detection of monoclonal immunoglobulin light chains in the urine may be important in clinical diagnosis, therapy, and follow-up.

12. **Antitumor activity of thalidomide in refractory multiple myeloma**
    N Engl J Med 1999 Nov 18;341(21):1565-71 (ISSN: 0028-4793)
    Singhal S; Mehta J; Desikan R; Ayers D; Roberson P; Eddlemon P; Munshi N; Anaissie E; Wilson C; Dhodapkar M; Zeddis J; Barlogie B
    Myeloma and Lymphoma Program, South Carolina Cancer Center, University of South Carolina, Columbia, USA.
    BACKGROUND: Patients with myeloma who relapse after high-dose chemotherapy have few therapeutic options. Since increased bone marrow vascularity imparts a poor prognosis in myeloma, we evaluated the efficacy of thalidomide, which has antiangiogenic properties, in patients with refractory disease.
    METHODS: Eighty-four previously treated patients with refractory myeloma (76 with a relapse after high-dose chemotherapy) received oral thalidomide as a single agent for a median of 80 days (range, 2 to 465). The starting dose was 200 mg daily, and the dose was increased by 200 mg every two weeks until it reached 800 mg per day. Response was assessed on the basis of a reduction of the myeloma protein in serum or Bence Jones protein in urine that lasted for at least six weeks.
    RESULTS: The serum or urine levels of paraprotein were reduced by at least 90 percent in eight patients (two had a complete remission), at least 75 percent in six patients, at least 50 percent in seven patients, and at least 25 percent in six patients, for a total rate of response of 32 percent. Reductions in the paraprotein levels were apparent within two months in 78 percent of the patients with a response and were associated with decreased numbers of plasma cells in bone marrow and increased hemoglobin levels. The microvascular density of bone marrow did not change significantly in patients with a response. At least one third of the patients had mild or moderate constipation, weakness or fatigue, or somnolence. More severe adverse effects were infrequent (occurring in less than 10 percent of patients), and hematologic effects were rare. As of the most recent follow-up, 36 patients had died (30 with no response and 6 witha response). After 12 months of follow-up, Kaplan-Meier estimates of the mean (+/-SE) rates of event-free survival and overall survival for all patients were 22+/-5 percent and 58+/-5 percent, respectively.
    CONCLUSIONS: Thalidomide is active against advanced myeloma. It can induce marked and durable responses in some patients with multiple myeloma, including those who relapse after high-dose chemotherapy.

21. **Renal insufficiency due to light chain multiple myeloma**
Ned Tijdschr Geneeskd 2000 Nov 4;144(45):2133-7 (ISSN: 0028-2162)
van Zaanen HC; Diderich PP; Pegels JG; Ruizeveld de Winter JA
Sint Franciscus Gasthuis, afd. Inwendige Geneeskunde, Rotterdam.
In 3 female patients, aged 65, 83 and 76 years, with severe renal failure, light chain multiple myeloma was diagnosed, following a substantial delay on the part of the doctors concerned. Either the diagnosis had not suspected or the serum proteins had been misinterpreted. After a while, the first two patients declined further treatment with chemotherapy and haemodialysis, and subsequently died. The third patient attained a creatinine clearance of 20 ml/min and was subsequently treated for the multiple myeloma in the outpatients department. The absence of a paraprotein peak in the serum does not exclude the possibility of a multiple myeloma. In the case of light chain disease, the gammaglobulin region is, in fact, often empty. Treatment of multiple myeloma consists of a rapid rehydration and forced diuresis; the usefulness of plasmapheresis has not been demonstrated.

22. **The kidney in multiple myeloma. The physiopathological and clinical aspects**
Recenti Prog Med 1994 Feb;85(2):123-33 (ISSN: 0034-1193)
Vivaldi P; Comotti C; Pedrazzoli M
UO Medicina 2o, Istituto Ospedaliero S. Chiara, Trento.
The renal concern in a multiple myeloma (MM) case has a frequency of 50% and causes a worsening of the disease with a survival average of about 12 months. The monoclonal light free chains (CLL) produced in excess by the plasmacytes are present in the urine as proteinuria of Bence Jones (PBJ) in 60-70% of patients affected by MM. They represent the major pathogenetic factor of the nephropathy in course of MM as they can deposit in shape of intratubular "casts" in the myeloma casts nephropathy (MCN). In some worse cases, dehydration or hypercalcaemia can cause an irreversible acute renal insufficiency (RI). It is therefore important in a patient affected with MM with PBJ to prevent, locate and opportunely treat these situations which worsen the nephropathy. Beside the tubular cast nephropathy, the CLL "accumulate" in the kidney even though with a lower frequency compared to MCN, in the light chains deposition disease (LCDD) and in the amyloidosis AL (AL). LCDD is characterized by a deposit of nodular amorphous materials PAS positive in the glomerulus and sometimes even in the tubulus. It usually presents itself as a chronic RI and a proteinuria causing nephrotic syndrome (NS). This quickly evolves into uraemia and its evolution can be lessened by the MM treatment. AL in course of MM also reeals with a chronic RI and NS. CLLs deposit in the typical fibrillar structure, on the vessel walls, in the glomerulus, in the mesangium and can be marked out with the Congo red colouring and the subsequent green birefringence through microscope with polarized light. Prognosis of AL is extremely severe and no benefit is given by the treatment of the hematological illness. It is therefore absolutely necessary to study the renal histology through biopsy when MM is grade B, that is, with serumal creatinine above 2 mg/dl as: MCN imposes the MM treatment programme in order to reduce the tubular excess of PBJ and to attempt to make RI reversible; MCN with tubular atrophy and interstitial fibrosis results in an unfavourable prognosis as it expresses a nephropathic irreversibility due to the loss nephrons. It will therefore necessary to start on a renal substitutional treatment programme. Renal damage in course of MM is not always tubular, rather an unexpected glomerular damage of LCDD or amyloidosis AL type can be found.(ABSTRACT TRUNCATED AT 400 WORDS).

23. **Immunoturbidimetric assay for estimating free light chains of immunoglobulins in urine and serum.**
J Clin Pathol 1991 Jun;44(6):466-71 (ISSN: 0021-9746)
Tillyer CR; Iqbal J; Raymond J; Gore M; McIlwain TJ
Department of Chemical Pathology, Royal Marsden Hospital, Sutton, Surrey.
An immunoturbidimetric assay for the assessment of free kappa and lambda light chains of immunoglobulins was developed using a commercial polyclonal antiserum with reactivity towards epitopes on the light chains, which are not expressed when they are bound to heavy chains. The assay, on a centrifugal analyser, is simple and rapid. The limit of detection is 5 mg/l of free light chain, with an assay range of 5-120 mg/l, intrabatch precisions from 1.5-6.4%, and interbatch precisions from 6.5-8.9%. The assay was only slightly less sensitive than colloidal gold staining of cellulose acetate electrophoreses for the detection of Bence-Jones protein in urine. For the serial monitoring of response to chemotherapy in patients with myeloma, the assay correlated well with serum paraprotein estimates obtained by densitometric scanning of Ponceau stained cellulose acetate electrophoreses, but not with serum beta-2 microglobulin measurements, even after correction for the effects of creatinine. These assays may prove to be of use for the monitoring of tumour response in the treatment of Bence-Jones myeloma.

24. **Clinical applications of immunoglobulin free light chain analysis**
Int J Clin Lab Res 1994;24(2):120-1 (ISSN: 0940-5437)
Pascali E
The potential of immunoglobulin-free light chain detection and measurement in biological fluids, and particularly in urine, has not yet been fully explored in clinical medicine, because of differences in sensitivity and lack of standardization of both quantitative assays and qualitative analysis. The ability to identify monoclonal free light chain, i.e., Bence-Jones protein, reliably in urine is of great clinical interest even when it occurs only in such small amounts that they frequently remain undetected by the routine methods used in many laboratories. The standardized adoption of both qualitative and quantitative procedures with comparable sensitivity is suggested to allow precise characterization of the clonal nature, and therefore the clinical role, of any free light chain excess.