

Obrigada por ver esta apresentação
Gostaríamos de recordar-lhe que esta
apresentação é propriedade do autor.

É-lhe fornecida pela Sociedade Portuguesa de
Pediatria no contexto do 17º Congresso
Nacional de Pediatria, para seu uso pessoal,
tal como submetido pelo autor

© 2016 pelo autor



Nefropatia Ig A Púrpura Henoch-Schonlein

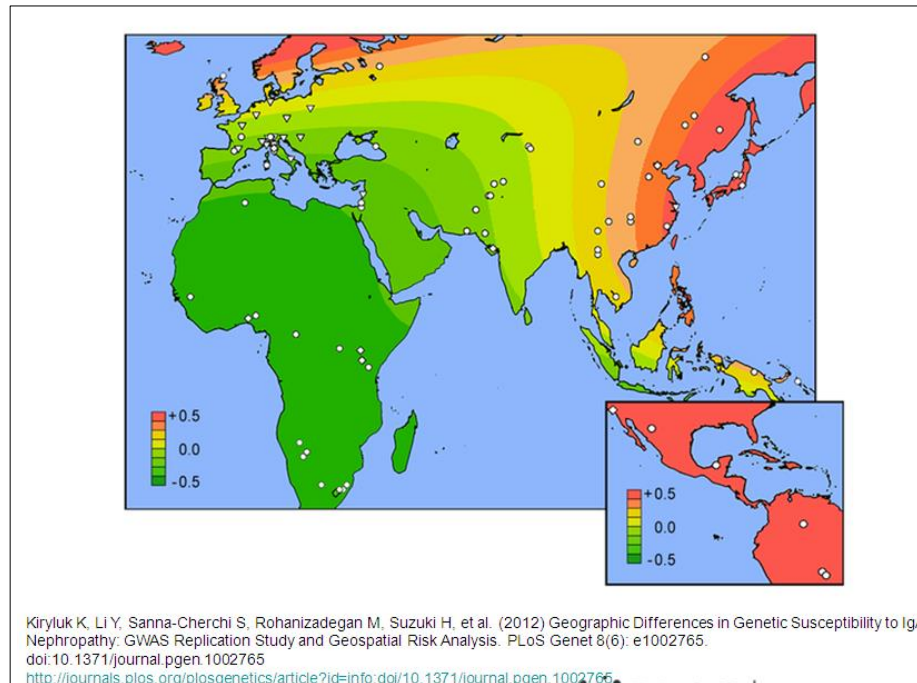


Helena Pinto
Unidade Nefrologia pediátrica
Centro Hospitalar S. João do Porto

Porto, 3 Novembro 2016

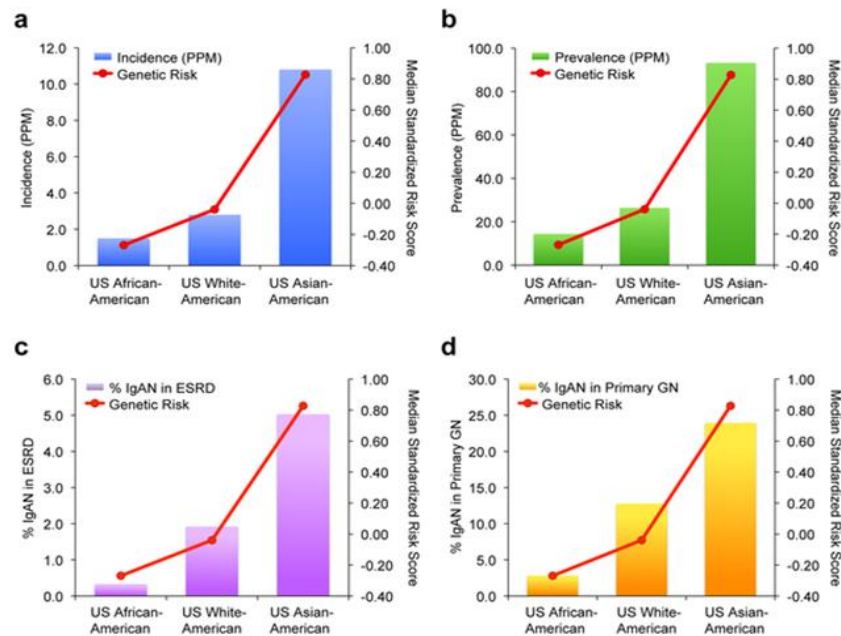
Nefropatia Ig A

- Glomerulonefrite primária mais frequente em todo o Mundo
- A prevalência varia de acordo com as diferentes áreas geográficas
Ásia: 35-45%; Europa: 30-40%



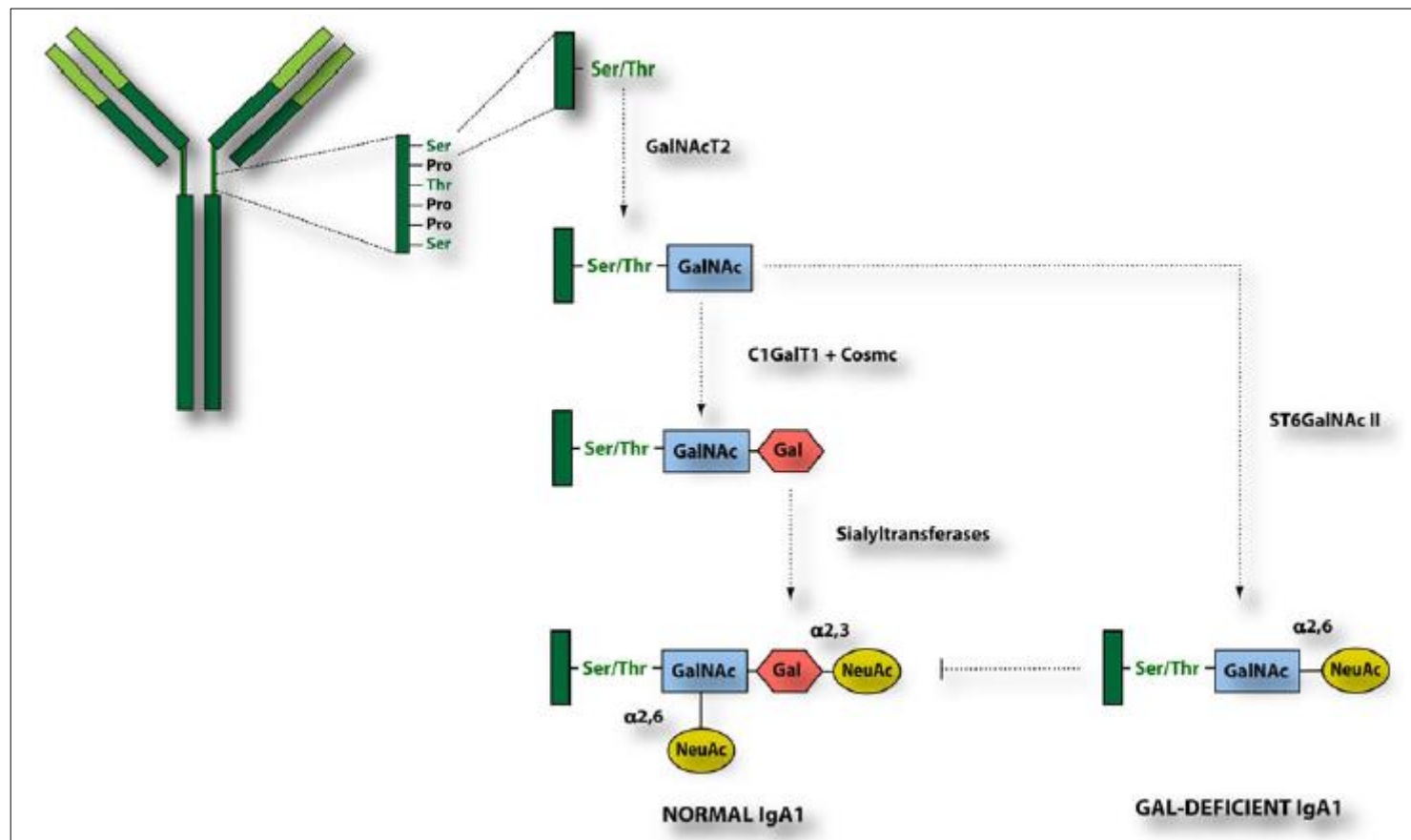
Nefropatia Ig A

► Factores genéticos

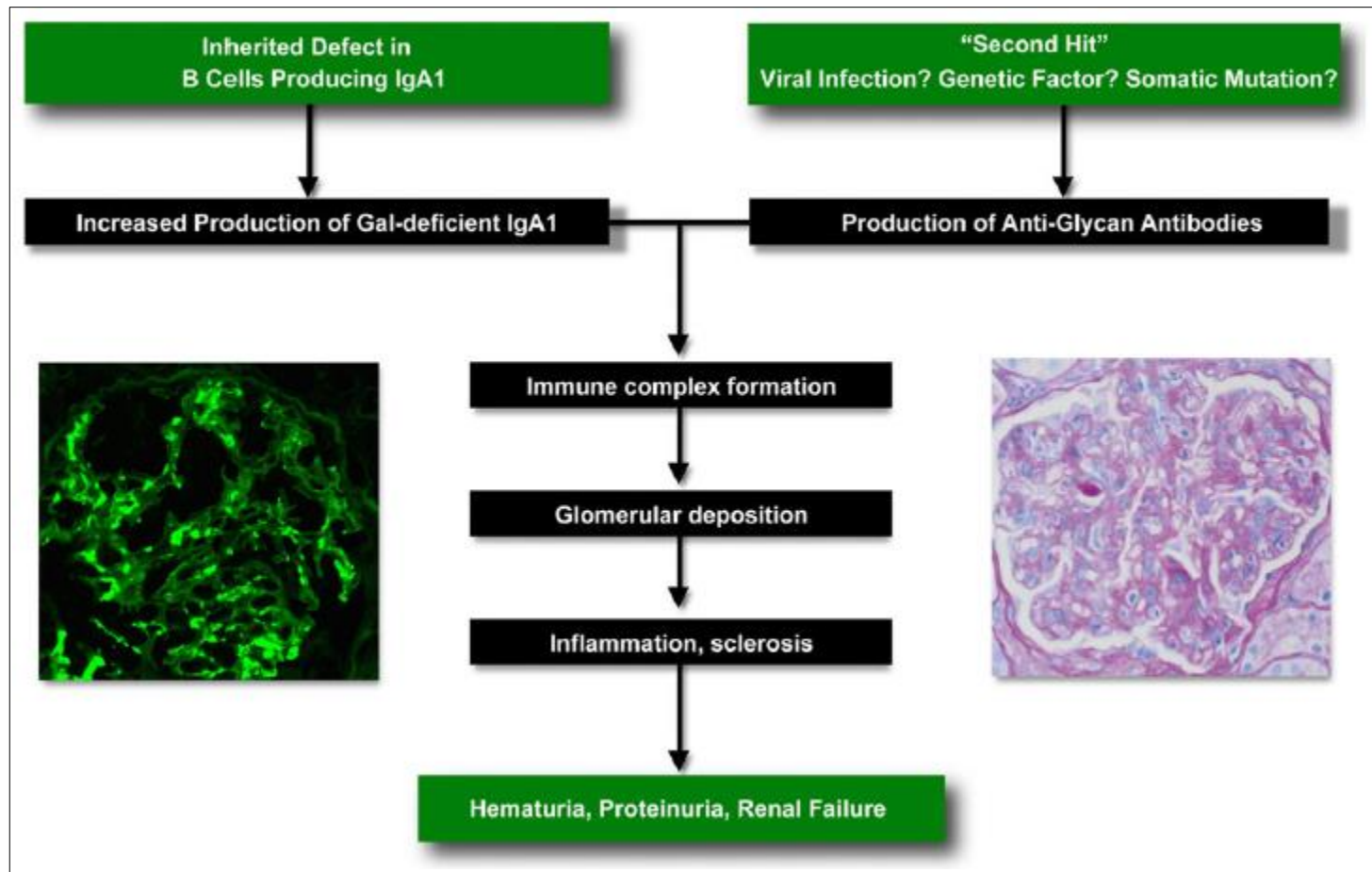


Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, et al. (2012) Geographic Differences in Genetic Susceptibility to IgA Nephropathy: GWAS Replication Study and Geospatial Risk Analysis. *PLoS Genet* 8(6): e1002765. doi:10.1371/journal.pgen.1002765

Etiopatogénese: formação de Ig A1 galactose-deficiente



Etiopatogénese



Locus (genes)

ITGAM, ITGAX

CARD9

VAV3

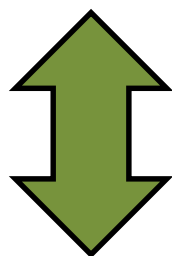
DEFA1, DEFA3, DEFA4, DEFA5, DEFA6

TNFSF13

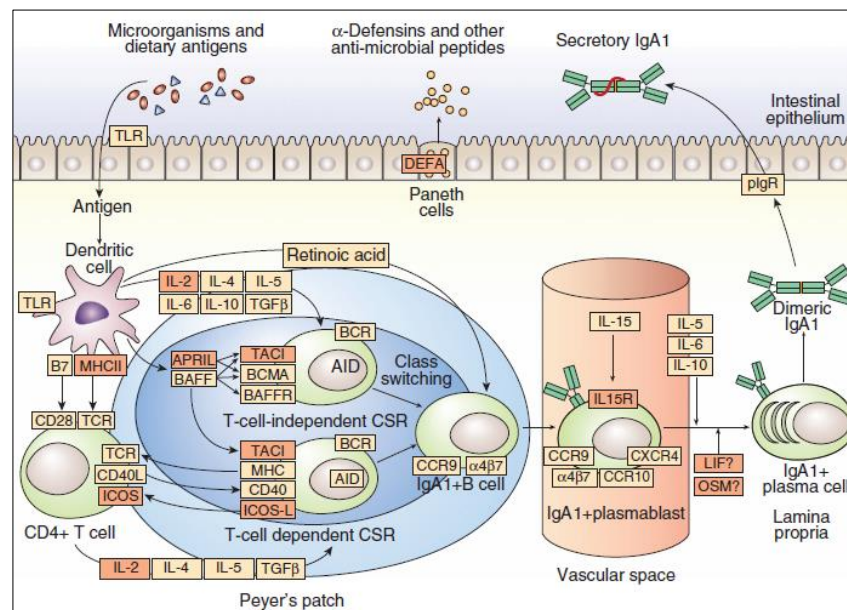
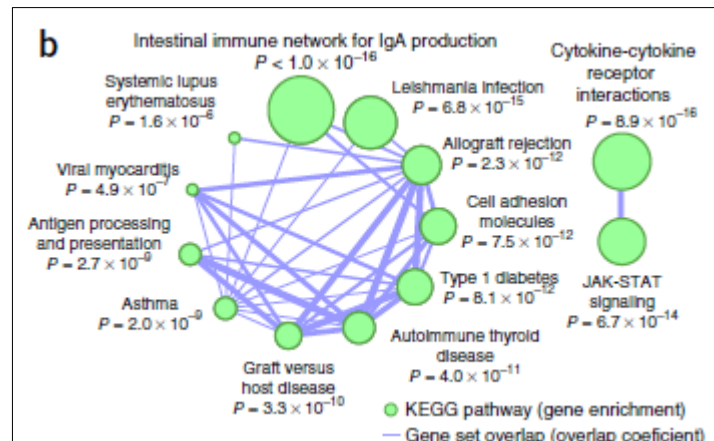
LIF, OSM, HORMAD2, MTMR3

PSMB8, PSMB9, TAP1, TAP2

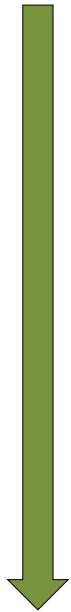
HLA-DQA1, HLA-DQB1, HLA-DRB1



*Imunidade Intestinal
Inflamação*



Apresentação clínica muito variável



- Hematúria microscópica isolada (60-92%)
- Hematúria macroscópica coincidente com infecção respiratória superior (13-26%)
- Hematúria microscópica e proteinúria (62-75%)
- Síndrome nefrótica (12-21%)
- Síndrome nefrítico (12%)
- Formas raras

Diagnóstico: necessita sempre realização de **biópsia renal**

A prevalência e história natural da **nefropatia Ig A** dependem da indicação para realização de biópsia renal :

- Europa e EUA: atitude expectante, limitando a biópsia renal aos casos que desenvolvem proteinúria
- Japão, China, Coreia: realização de biópsia renal após rastreio (universal) positivo para hematúria/proteinúria em idade escolar

Evolução natural: muito variável

- Assintomáticos/ remissão espontânea
- Estabilidade clínica
- Perda progressiva de função renal (5-15%)
IRCT: 25-55 anos
TSR: 91-93% 10 anos; 82-87% 20 anos após diagnóstico

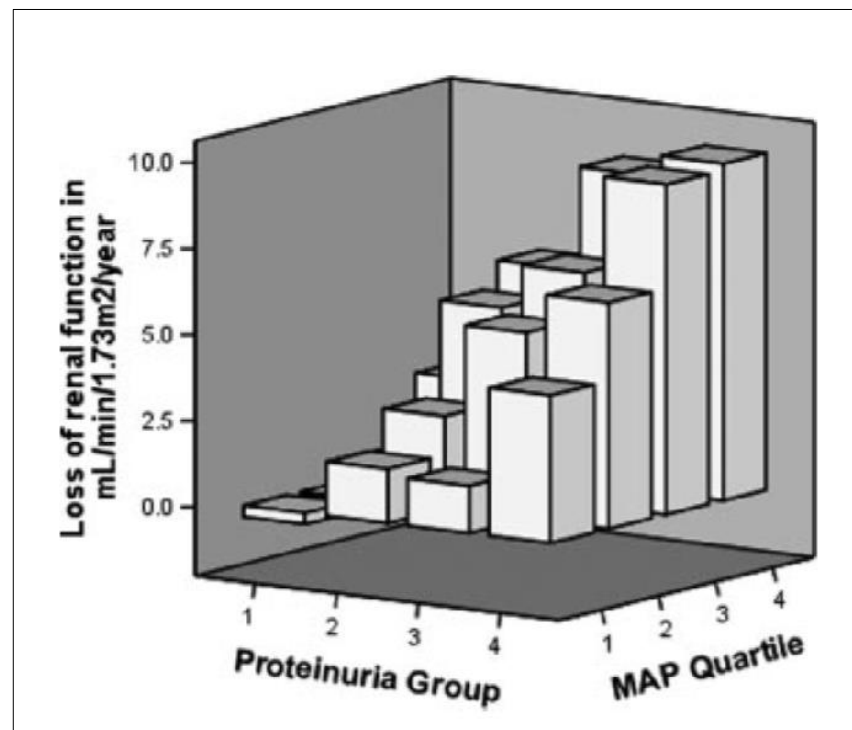
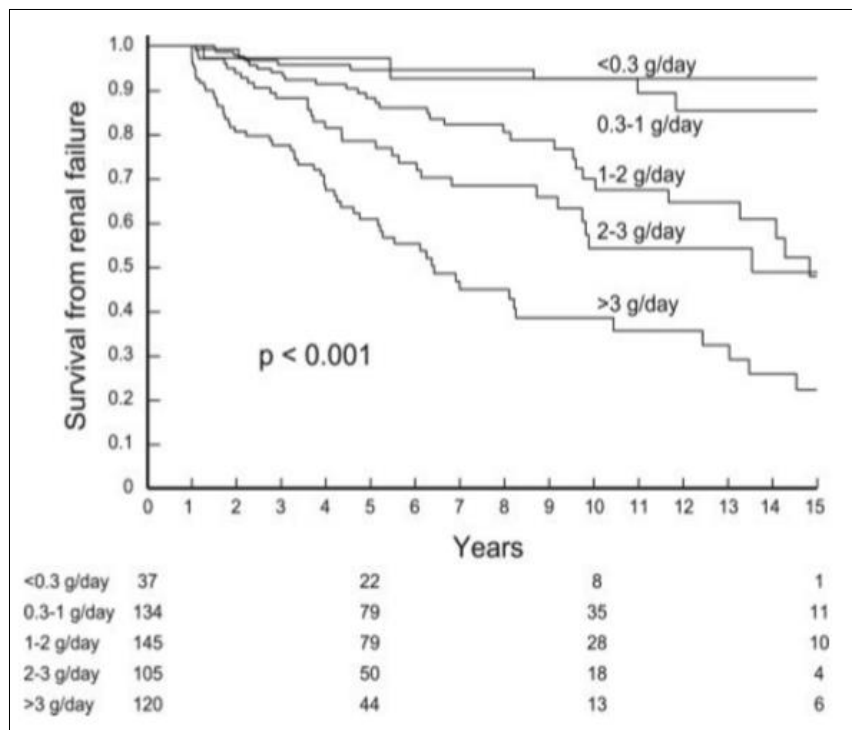
Factores clínicos de risco para progressão DRC

- **Proteinúria**
- **Hipertensão arterial**
- **Função renal no diagnóstico**
- **Hematúria?**

Factores clínicos de risco para progressão DRC

Remission of Proteinuria Improves Prognosis in IgA Nephropathy

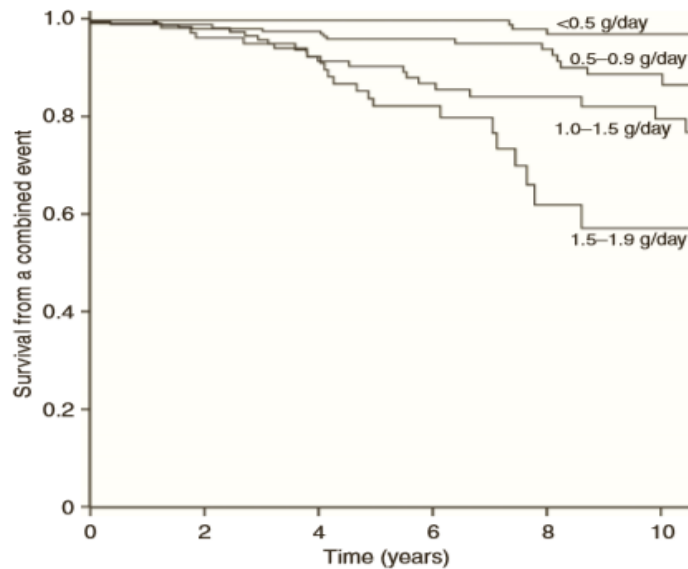
Heather N. Reich,* Stéphan Troyanov,[†] James W. Scholey,* and Daniel C. Catran,* for the Toronto Glomerulonephritis Registry



Factores clínicos de risco para progressão DRC

Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments

Rosanna Coppo^{1,7}, Stéphan Troyanov^{2,7}, Shubha Bellur^{3,8}, Daniel Cattran^{4,7}, H. Terence Cook^{5,7}, John Feehally^{6,7}, Ian S.D. Roberts^{3,7}, Laura Morando⁸, Roberta Camilla⁸, Vladimir Tesar⁸, Sigrid Lunberg⁸, Loreto Gesualdo⁸, Francesco Emma⁸, Cristiana Rollino⁸, Alessandro Amore⁸, Manuel Praga⁸, Sandro Feriozzi⁸, Giuseppe Segoloni⁸, Antonello Pani⁸, Giovanni Cancarini⁸, Magalena Durlík⁸, Elisabetta Moggia⁸, Gianna Mazzucco⁸, Costantino Giannakakis⁸, Eva Honsova⁸, B. Brigitta Sundelin⁸, Anna Maria Di Palma⁸, Franco Ferrario⁸, Eduardo Gutierrez⁸, Anna Maria Asunis⁸, Jonathan Barratt⁸, Regina Tardanico⁸ and Agnieszka Perkowska-Ptasinska⁸, on behalf of the VALIGA study of the ERA-EDTA Immunonephrology Working Group⁸



Number at risk			
<0.5 g/day	338	198 (59%)	97 (29%)
0.5–0.9 g/day	315	185 (59%)	77 (24%)
1.0–1.5 g/day	167	97 (58%)	46 (28%)
1.5–1.9 g/day	108	68 (63%)	14 (13%)

Necessidade de biópsia renal em crianças com hematúria microscópica e proteinúria > 500 mg/dia/1.73m²

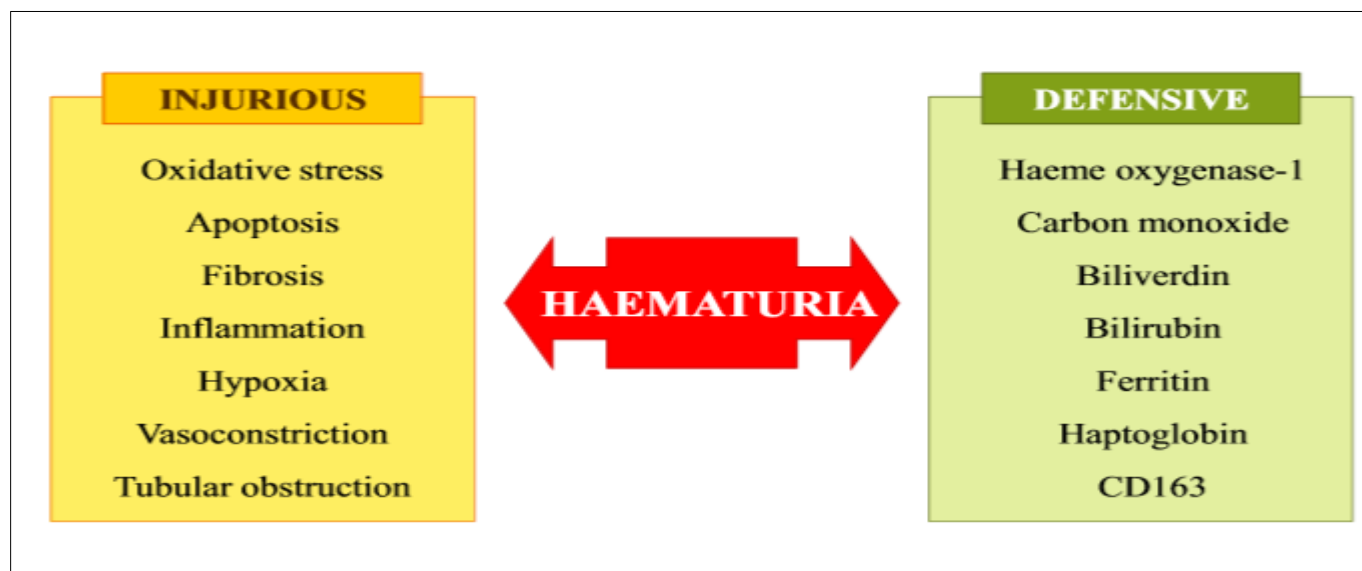
Factores clínicos de risco para progressão DRC

Pediatr Nephrol (2016) 31:523–533
DOI 10.1007/s00467-015-3119-1

REVIEW

Haematuria as a risk factor for chronic kidney disease progression in glomerular diseases: A review

Juan Antonio Moreno¹ · Claudia Yuste² · Eduardo Gutiérrez³ · Ángel M. Sevillano³ · Alfonso Rubio-Navarro¹ · Juan Manuel Amaro-Villalobos¹ · Manuel Praga³ · Jesús Egido^{1,4}

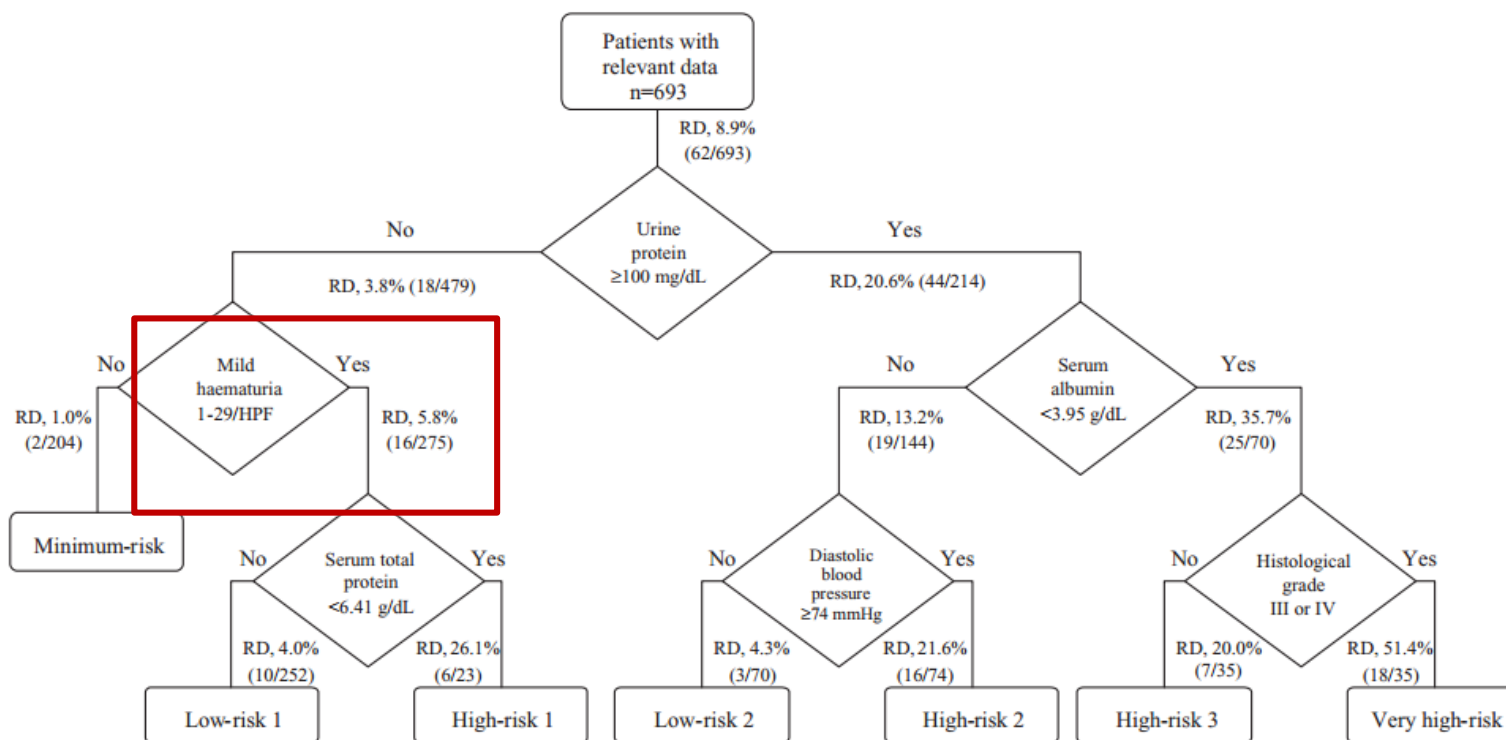


Factores clínicos de riesgo para progressão DRC

Nephrol Dial Transplant (2009) 24: 1242–1247
doi: 10.1093/ndt/gfn610
Advance Access publication 17 November 2008

Risk stratification for progression of IgA nephropathy using a decision tree induction algorithm

Masashi Goto¹, Takashi Kawamura¹, Kenji Wakai², Masahiko Ando¹, Masayuki Endoh³ and Yasuhiko Tomino⁴



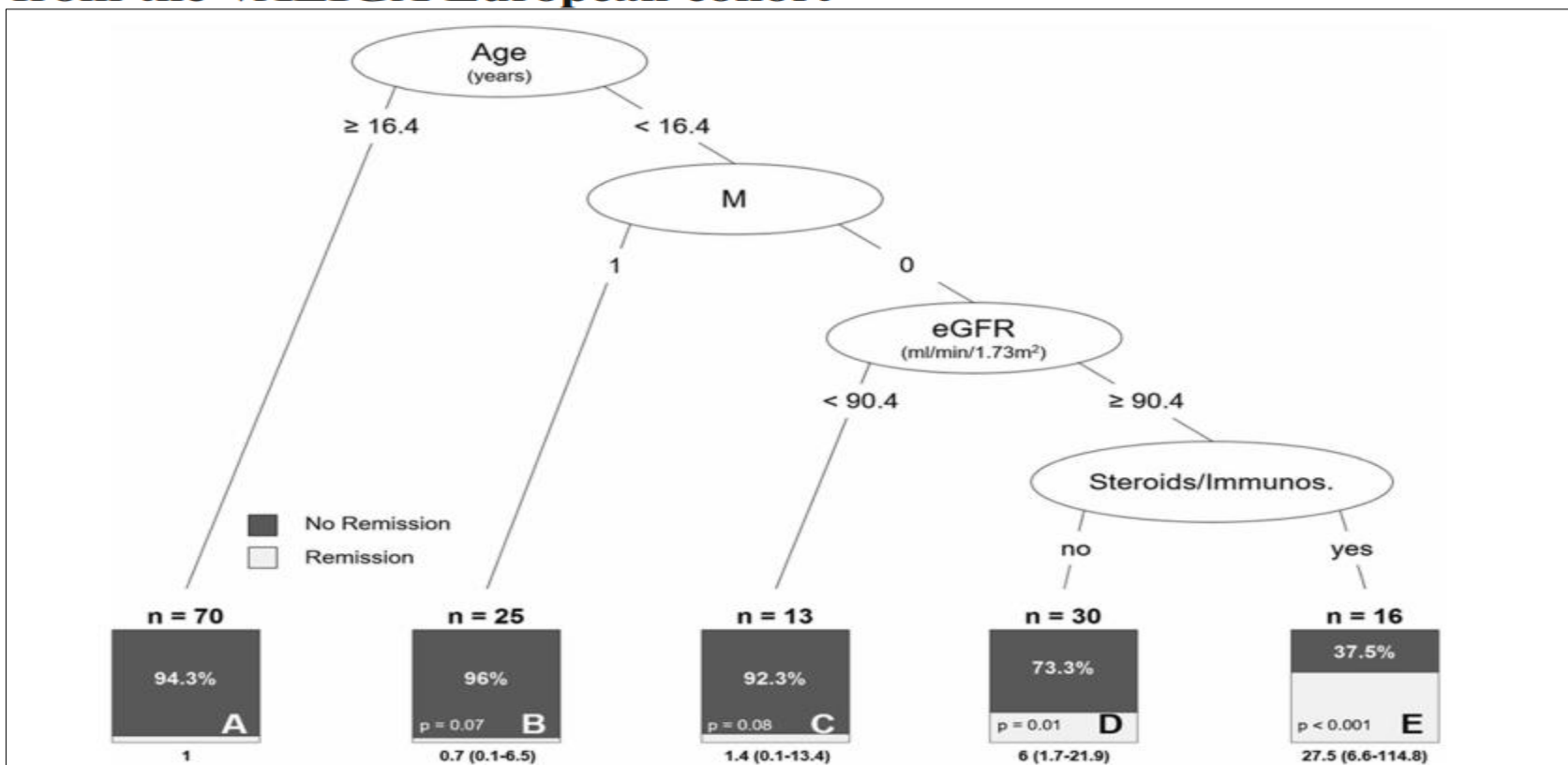
Factores clínicos de risco para progressão DRC

Pediatr Nephrol
DOI 10.1007/s00467-016-3469-3



ORIGINAL ARTICLE

Risk factors for progression in children and young adults with IgA nephropathy: an analysis of 261 cases from the VALIGA European cohort



Ratio Ig A/C3

IgA elevado: 16% crianças e adolescents (50–70 % adultos)

C3: habitualmente normal ou ligeiramente elevado

Ratio IgA/C3 elevado é um indicador de pior prognóstico em adultos com nefropatia Ig A (Kamatsu H, 2004).

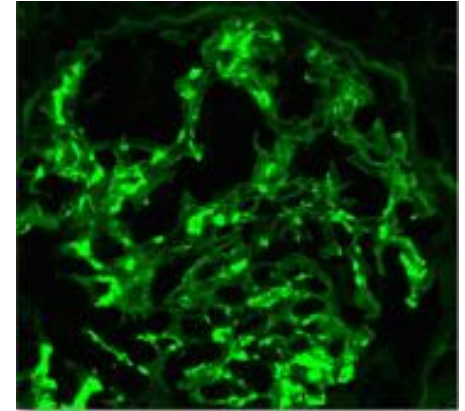
Quanto mais elevado é o MEST score, mais elevado é o ratio IgA/C3

1.55 for MEST < 1 vs. MEST $\geq$ 1 (AUC 0.78, specificity 0.74, sensitivity 0.6)

2.26 for MEST < 3 vs. MEST $\geq$ 3 (AUC 0.67, specificity 0.54, sensitivity 0.54)

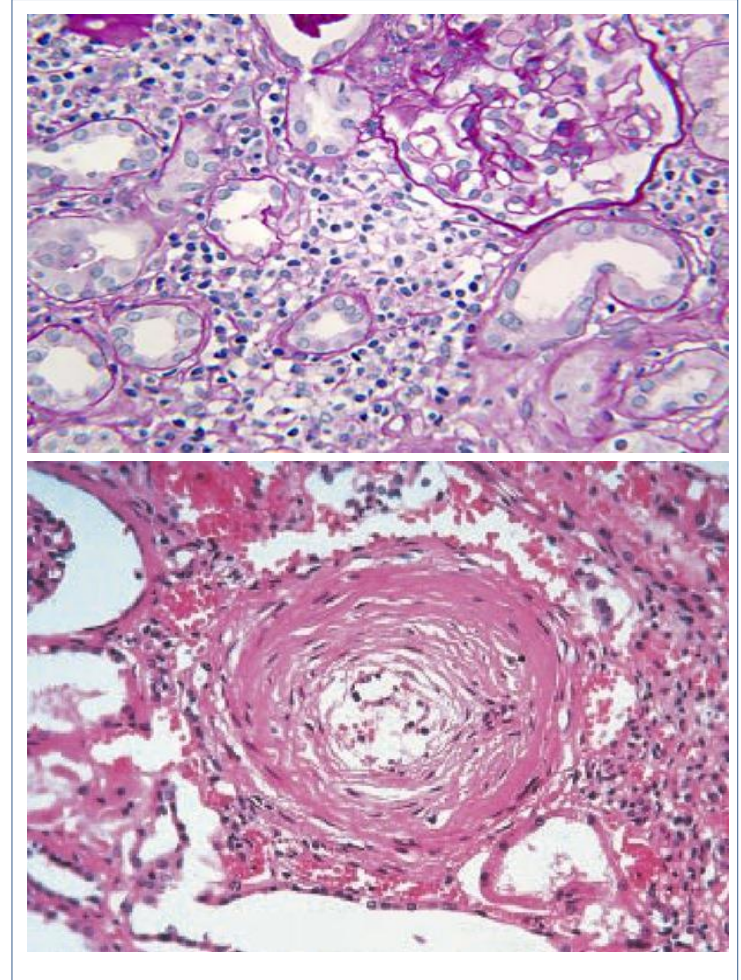
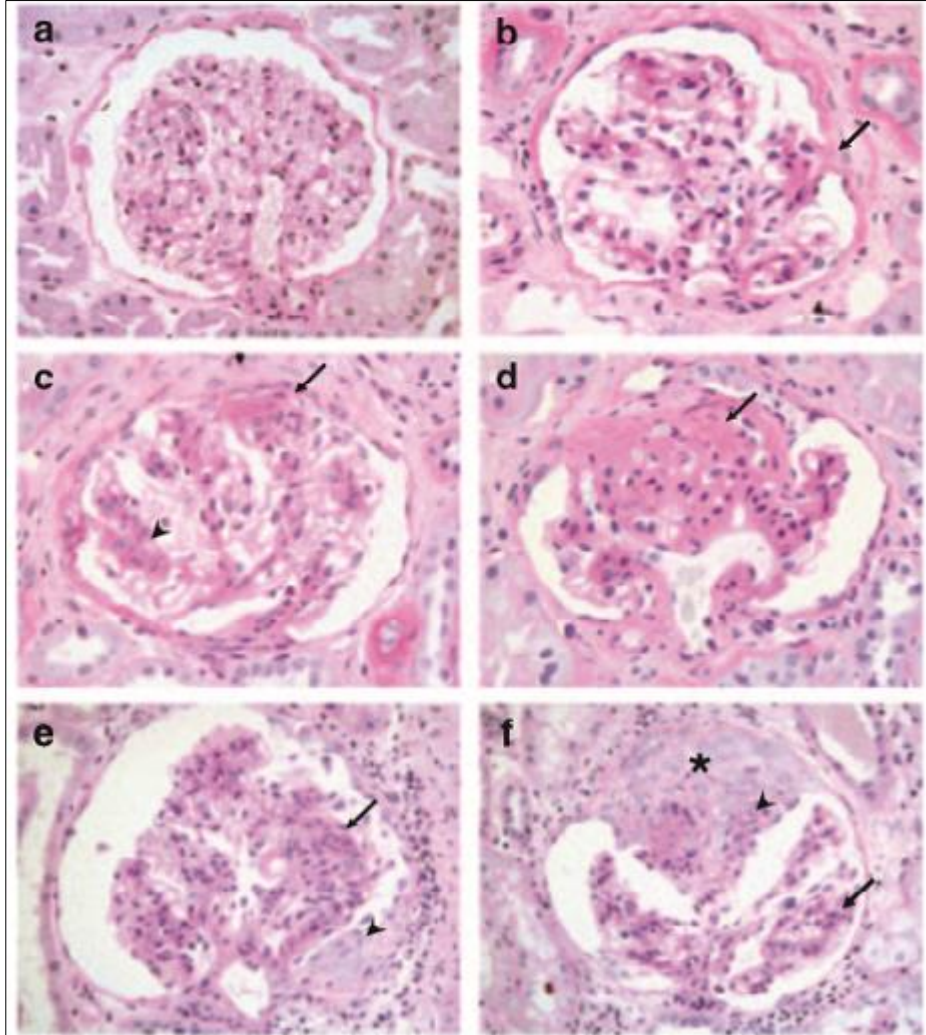
Exame histopatológico

- MO imunofluorescência/imunohistoquímica: presença dominante ou co-dominante de depósitos de Ig A (podem tb ser Ig G, Ig M e C3 +)
- Grande diversidade de lesões histológicas



Lesões ativas	Lesões crônicas/ escleróticas
Proliferação mesangial	Glomerulosclerose segmentar e focal
Hipercelularidade endocapilar	Atrofia tubular/ fibrose intersticial
Crescentes epiteliais	Esclerose arteriolar
Necrose glomerular	

Exame histopatológico



The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility

A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society: Ian S.D. Roberts¹, H. Terence Cook², Stéphan Troyanov³, Charles E. Alpers⁴, Alessandro Amore⁵, Jonathan Barratt⁶, Francois Berthoux⁷, Stephen Bonsib⁸, Jan A. Bruijn⁹, Daniel C. Cattran¹⁰, Rosanna Coppo⁵, Vivette D'Agati¹¹, Giuseppe D'Amico¹², Steven Emancipator¹³, Francesco Emma¹⁴, John Feehally⁶, Franco Ferrario¹⁵, Fernando C. Fervenza¹⁶, Sandrine Florquin¹⁷, Agnes Fogo¹⁸, Colin C. Geddes¹⁹, Hermann-Josef Groene²⁰, Mark Haas²¹, Andrew M. Herzenberg²², Prue A. Hill²³, Ronald J. Hogg²⁴, Stephen I. Hsu²⁵, J. Charles Jennette²⁶, Kensuke Joh²⁷, Bruce A. Julian²⁸, Tetsuya Kawamura²⁹, Fernand M. Lai³⁰, Lei-Shi Li³¹, Philip K.T. Li³², Zhi-Hong Liu³¹, Bruce Mackinnon¹⁹, Sergio Mezzano³³, F. Paolo Schena³⁴, Yasuhiko Tomino³⁵, Patrick D. Walker³⁶, Haiyan Wang³⁷, Jan J. Weening³⁸, Nori Yoshikawa³⁹ and Hong Zhang^{37,*}

The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification

A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society: Daniel C. Cattran^{1,†}, Rosanna Coppo^{2,†}, H. Terence Cook^{3,†}, John Feehally^{4,†}, Ian S.D. Roberts^{5,†}, Stéphan Troyanov^{6,†}, Charles E. Alpers⁷, Alessandro Amore², Jonathan Barratt⁴, Francois Berthoux⁸, Stephen Bonsib⁹, Jan A. Bruijn¹⁰, Vivette D'Agati¹¹, Giuseppe D'Amico¹², Steven Emancipator¹³, Francesco Emma¹⁴, Franco Ferrario¹⁵, Fernando C. Fervenza¹⁶, Sandrine Florquin¹⁷, Agnes Fogo¹⁸, Colin C. Geddes¹⁹, Hermann-Josef Groene²⁰, Mark Haas²¹, Andrew M. Herzenberg²², Prue A. Hill²³, Ronald J. Hogg²⁴, Stephen I. Hsu²⁵, J. Charles Jennette²⁶, Kensuke Joh²⁷, Bruce A. Julian²⁸, Tetsuya Kawamura²⁹, Fernand M. Lai³⁰, Chi Bon Leung³¹, Lei-Shi Li³², Philip K.T. Li³¹, Zhi-Hong Liu³², Bruce Mackinnon¹⁹, Sergio Mezzano³³, F. Paolo Schena³⁴, Yasuhiko Tomino³⁵, Patrick D. Walker³⁶, Haiyan Wang³⁷, Jan J. Weening³⁸, Nori Yoshikawa³⁹ and Hong Zhang^{37,*}

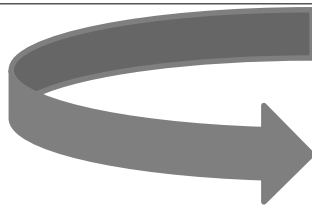
The Oxford IgA nephropathy clinicopathological classification is valid for children as well as adults

A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society: Rosanna Coppo¹, Stéphan Troyanov², Roberta Camilla¹, Ronald J. Hogg³, Daniel C. Cattran⁴, H. Terence Cook⁵, John Feehally⁶, Ian S.D. Roberts⁷, Alessandro Amore¹, Charles E. Alpers⁸, Jonathan Barratt⁶, Francois Berthoux⁹, Stephen Bonsib¹⁰, Jan A. Bruijn¹¹, Vivette D'Agati¹², Giuseppe D'Amico¹³, Steven N. Emancipator¹⁴, Francesco Emma¹⁵, Franco Ferrario¹⁶, Fernando C. Fervenza¹⁷, Sandrine Florquin¹⁸, Agnes B. Fogo¹⁹, Colin C. Geddes²⁰, Hermann J. Groene²¹, Mark Haas²², Andrew M. Herzenberg²³, Prue A. Hill²⁴, Stephen I. Hsu²⁵, J. Charles Jennette²⁶, Kensuke Joh²⁷, Bruce A. Julian²⁸, Tetsuya Kawamura²⁹, Fernand M. Lai³⁰, Lei S. Li³¹, Philip K. Li³², Zhi H. Liu³¹, Sergio Mezzano³³, F. Paolo Schena³⁴, Yasuhiko Tomino³⁵, Patrick D. Walker³⁶, Haiyan Wang³⁷, Jan J. Weening³⁸, Norishige Yoshikawa³⁹ and Hong Zhang^{37,*}

Classificação de Oxford da nefropatia Ig A

Variable	Definition	Score
Mesangial hypercellularity	<4 Mesangial cells/mesangial area=0 4-5 Mesangial cells/mesangial area=1 6-7 Mesangial cells/mesangial area=2 >8 Mesangial cells/mesangial area=3 The mesangial hypercellularity score is the mean score for all glomeruli	M0 ≤ 0.5 M1 > 0.5^a
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion	S0 – absent S1 – present
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina	E0 – absent E1 – present
Tubular atrophy/interstitial fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	0-25% – T0 26-50% – T1 > 50% – T2

^aMesangial score should be assessed in periodic acid-Schiff-stained sections. If more than half the glomeruli have more than three cells in a mesangial area, this is categorized as M1. Therefore, a formal mesangial cell count is not always necessary to derive the mesangial score.



MEST score

Classificação de Oxford da nefropatia Ig A: correlação clínico-patológica

	MAP mm Hg	P-value	GFR ml/min per 1.73 m ²	P-value	Proteinúria g/day	P-value
Mesangial hypercellularity score ≤ 0.5	100 $\pm$ 18	>0.1	84 $\pm$ 28	>0.1	1.4 (0.6–9.2)	<u>0.001</u>
Mesangial hypercellularity score > 0.5	98 $\pm$ 17		82 $\pm$ 38		2.0 (0.5–18.5)	
No endocapillary hypercellularity	101 $\pm$ 19	<u>0.008</u>	76 $\pm$ 31	<u>0.001</u>	1.5 (0.5–11.3)	<u>0.01</u>
Any endocapillary hypercellularity	95 $\pm$ 15		92 $\pm$ 40		2.0 (0.5–18.5)	
No extracapillary proliferation	98 $\pm$ 17	>0.1	84 $\pm$ 37	>0.1	1.5 (0.5–18.5)	<u>0.002</u>
Any extracapillary proliferation	98 $\pm$ 18		80 $\pm$ 35		2.2 (0.5–12.0)	
No segmental glomerulosclerosis	94 $\pm$ 16	<u>0.04</u>	95 $\pm$ 40	<u>0.003</u>	1.5 (0.5–7.2)	<u>0.004</u>
Any segmental glomerulosclerosis	100 $\pm$ 18		79 $\pm$ 34		1.9 (0.6–18.5)	
<i>Tubular atrophy and interstitial fibrosis</i>						
None (0%)	91 $\pm$ 17	<u>0.03</u>	109 $\pm$ 35	<u><0.001</u>	1.5 (0.5–7.2)	<u>0.03</u>
Mild (1–25%)	99 $\pm$ 18		86 $\pm$ 35		1.7 (0.5–18.5)	
Moderate (26–50%)	100 $\pm$ 12		59 $\pm$ 17		1.8 (0.6–7.5)	
Severe ($\geq 51\%$)	105 $\pm$ 24		46 $\pm$ 27		3.0 (1.1–9.0)	
<i>Artery score</i>						
Absent	96 $\pm$ 17	<u>0.02</u>	92 $\pm$ 40	<u><0.001</u>	1.8 (0.5–18.5)	>0.1
Mild	104 $\pm$ 15		67 $\pm$ 19		1.5 (0.6–4.6)	
Moderate	101 $\pm$ 20		70 $\pm$ 25		1.6 (0.8–7.3)	
Severe	102 $\pm$ 7		72 $\pm$ 33		1.7 (1.1–2.2)	

GFR, glomerular filtration rate; MAP, mean arterial pressure.

Mean $\pm$ s.d., median (range).

Classificação Oxford da nefropatia Ig A

Associação entre variáveis histopatológicas e declínio da função renal

	Odds ratio	95% confidence intervals		P-value
<i>Tubular atrophy or interstitial fibrosis</i>				
0–25%	1	(Reference)		
26–50%	3.0	1.3	7.4	0.01
51–100%	21.8	2.3	206.2	0.007
Segmental glomerulosclerosis present	2.8	1.2	6.2	0.01
Mesangial hypercellularity score > 0.5	2.1	0.9	4.7	0.08

GFR, glomerular filtration rate.
Decline defined by the worst half of the rate of renal function decline (slope > –1.6 ml/min per 1.73 m² per year). This model is adjusted for the initial GFR and the follow-up blood pressure and proteinuria.

Tratamiento

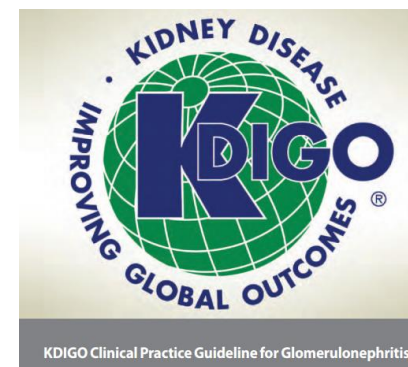
10.2: Antiproteinuric and antihypertensive therapy

10.2.1: We recommend long-term ACE-I or ARB treatment when proteinuria is >1 g/d, with up-titration of the drug depending on blood pressure. (1B)

10.2.2: We suggest ACE-I or ARB treatment if proteinuria is between 0.5 to 1 g/d (in children, between 0.5 to 1 g/d per 1.73 m^2). (2D)

10.2.3: We suggest the ACE-I or ARB be titrated upwards as far as tolerated to achieve proteinuria <1 g/d. (2C)

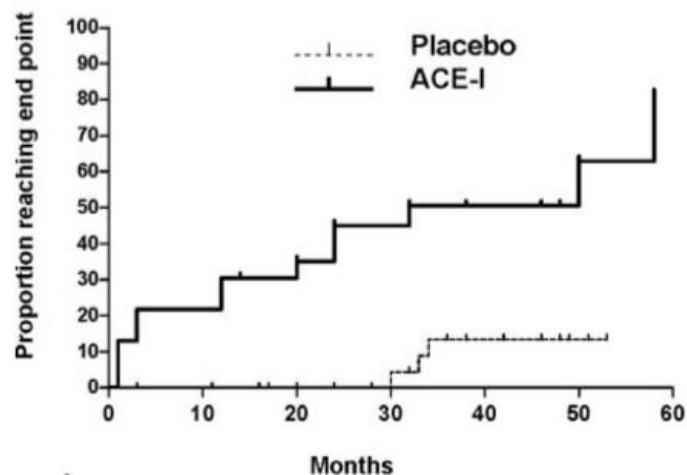
10.2.4: In IgAN, use blood pressure treatment goals of $<130/80$ mm Hg in patients with proteinuria <1 g/d, and $<125/75$ mm Hg when initial proteinuria is >1 g/d (see Chapter 2). (Not Graded)



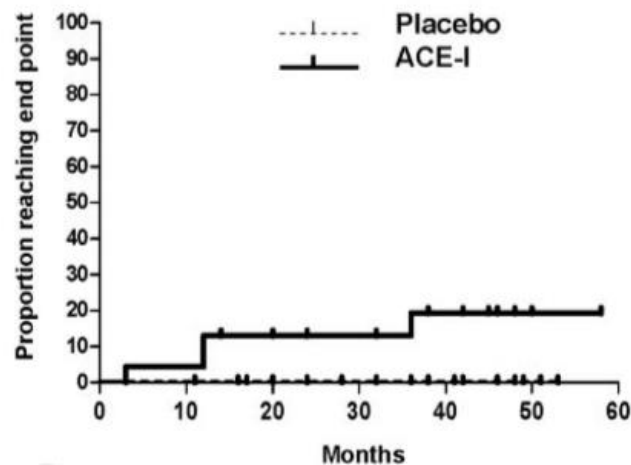
IgACE: A Placebo-Controlled, Randomized Trial of Angiotensin-Converting Enzyme Inhibitors in Children and Young People with IgA Nephropathy and Moderate Proteinuria

Rosanna Coppo,^{*} Licia Peruzzi,^{*} Alessandro Amore,^{*} Antonio Piccoli,[†] Pierre Cochat,[‡] Rosario Stone,[§] Martin Kirschstein,^{||} and Tommy Linné;[¶] on behalf of the EC Biomed Concerted Action Project BMH4-97-2487(DG 12-SSMI) and IgACE European Collaborative Group

End point proteinuria reduction < 500 mg/day/1.73 m²



End point proteinuria reduction < 160 mg/day/1.73 m²



IgACE: A Placebo-Controlled, Randomized Trial of Angiotensin-Converting Enzyme Inhibitors in Children and Young People with IgA Nephropathy and Moderate Proteinuria

Rosanna Coppo,* Licia Peruzzi,* Alessandro Amore,* Antonio Piccoli,[†] Pierre Cochat,[‡] Rosario Stone,[§] Martin Kirschstein,^{||} and Tommy Linné;[¶] on behalf of the EC Biomed Concerted Action Project BMH4-97-2487(DG 12-SSMI) and IgACE European Collaborative Group

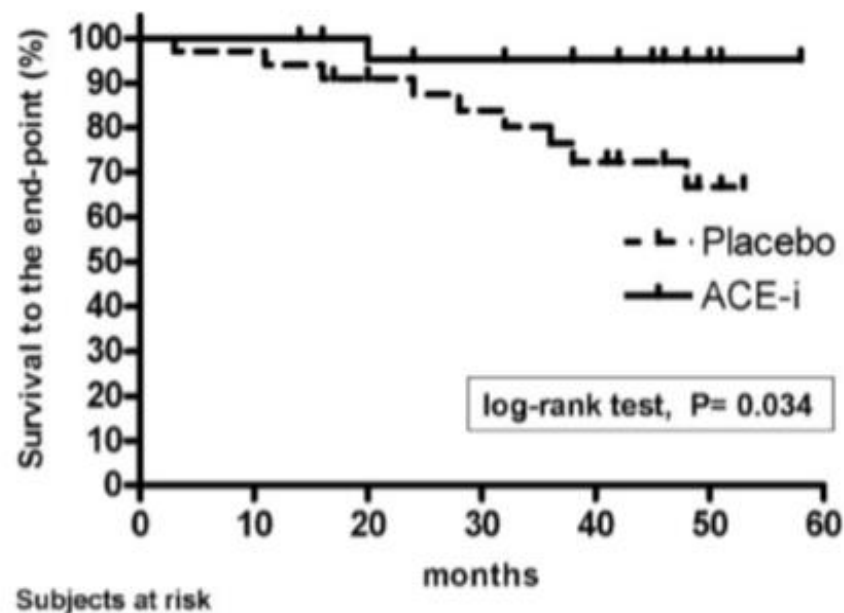


Figure 5. Survival without the combined end point of 30% reduction of baseline CrCl and/or increase in proteinuria up to >3.5 g/d/ 1.73 m² in IgAN patients receiving ACE-I or placebo (Kaplan-Meier estimates, log rank, $P = 0.034$).

Tratamento

10.3: Corticosteroids

10.3.1: We suggest that patients with persistent proteinuria ≥ 1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR > 50 ml/min per 1.73 m^2 , receive a 6-month course of corticosteroid therapy. (2C)

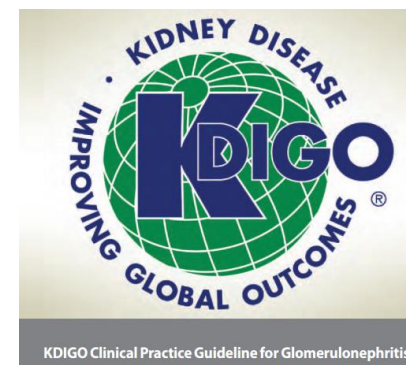


Table 26 | Corticosteroid regimens in patients with IgAN

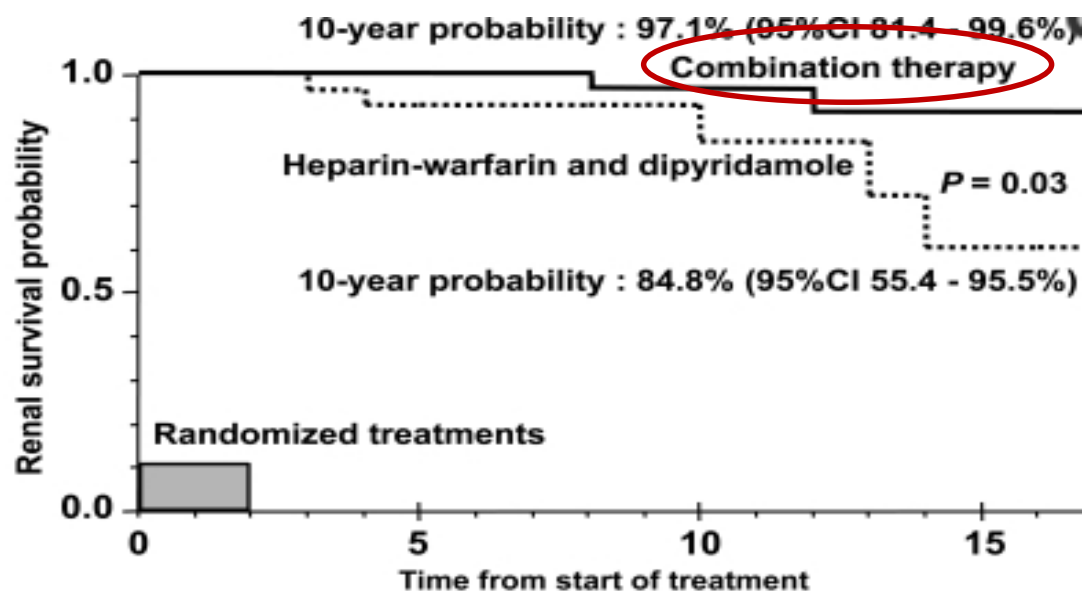
References	Pozzi C <i>et al.</i> ⁵⁰⁹	Manno C <i>et al.</i> ⁵¹⁰ ; Lv J <i>et al.</i> ⁵¹¹
Regimen	i.v. bolus injections of 1 g methylprednisolone for 3 days each at months 1, 3, and 5, followed by oral steroid 0.5 mg/kg prednisone on alternate days for 6 months	6-month regime of oral prednisone ^a starting with 0.8–1 mg/kg/d for 2 months and then reduced by 0.2 mg/kg/d per month for the next 4 months

IgAN, immunoglobulin A nephropathy.

^aPrednisone and prednisolone are equivalent and can be used interchangeably with the same dosing regimen.

Long-Term Results of a Randomized Controlled Trial in Childhood IgA Nephropathy

Koichi Kamei,^{*} Koichi Nakanishi,^{✉†} Shuichi Ito,^{*} Mari Saito,[‡] Mayumi Sako,[‡] Kenji Ishikura,[§] Hiroshi Hataya,[§] Masataka Honda,[§] Kazumoto Iijima,^{||} Norishige Yoshikawa,[†] and for the Japanese Pediatric IgA Nephropathy Treatment Study Group



Combination	40	40	40	37	35	30	19	13	10
Heparin-warfarin + dipyridamole	38	34	28	23	17	11	8	6	3
	No. of patients at risk								

Prednisolona
Azatioprina
Heparina
Dipiridamol

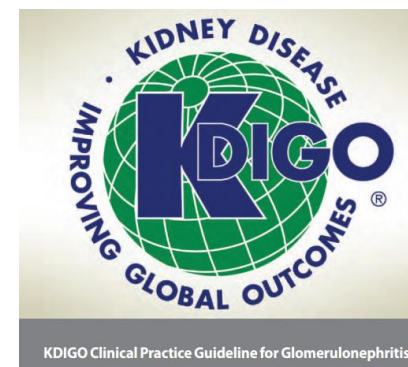
Tratamento

10.4: *Immunosuppressive agents (cyclophosphamide, azathioprine, MMF, cyclosporine)*

10.4.1: We suggest not treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients (unless there is crescentic IgAN with rapidly deteriorating kidney function; see Recommendation 10.6.3). (2D)

10.4.2: We suggest not using immunosuppressive therapy in patients with GFR <30 ml/min per 1.73 m^2 unless there is crescentic IgAN with rapidly deteriorating kidney function (see Section 10.6). (2C)

10.4.3: We suggest not using MMF in IgAN. (2C)



Tratamento: outros imunossupressores

Trial	Ballardie <i>et al.</i> , United Kingdom ⁶⁶	Yoshikawa <i>et al.</i> , Japan ⁶⁴	Yoshikawa <i>et al.</i> , Japan ⁶⁵
Combination regimen	Oral prednisolone 40 mg/d reduced to 10 mg (end of year 2) + oral cyclophosphamide 1.5 mg/kg per day for 3 months, and then oral azathioprine 1.5 mg/kg per day for minimum 2 years and up to 6 years	Oral prednisolone (2 mg/kg per day, maximum, 80 mg/d for 4 weeks tapered to alternate steroid at 1 mg/kg until end of year 2) + oral azathioprine (2 mg/kg per day for 2 years) + anticoagulants (heparin followed by warfarin and dipyridamole)	Oral prednisolone (2 mg/kg per day, maximum, 80 mg/d for 4 weeks tapered to alternate steroid at 1 mg/kg until end of year 2) + oral azathioprine (2 mg/kg per day for 2 years) + warfarin + dipyridamole
Control regimen	Supportive therapy only	Supportive therapy + anticoagulants (see above)	Above regimen without azathioprine
RAS blockade	Inconsistent	Not reported	Prohibited
Key outcome in combination group versus control	Marked improvement of renal survival at 5 years	Higher reduction in proteinuria and percentage of sclerosed glomeruli	More complete remissions of proteinuria
Comment		Study included pediatric patients only	Study included pediatric patients only

Therapeutic regimens and outcomes in controlled trials in IgAN patients. RAS, renin-angiotensin system.

Cyclosporine A combined with medium/low dose prednisone in progressive IgA nephropathy

Lin Xu ^{a,b}, Zhong-Cheng Liu ^c, Guang-Ju Guan ^{a,*}, Xue-Ai Lv ^b, Qing Luo ^a

CsA at a dose of 2–3 mg/kg/day in combination with medium/low dose prednisone was effective in inducing remission of IgAN,

Tratamento: imunossupressores, não esteróides

Mycophenolate mofetil therapy for steroid-resistant IgA nephropathy with the nephrotic syndrome in children

Zhijuan Kang • Zhihui Li • Cuirong Duan • Tianhui Wu •
Mai Xun • Yunfeng Ding • Yi Zhang • Liang Zhang •
Yan Yin

Conclusion Corticosteroid therapy showed satisfactory efficacy in IgAN children with nephrotic syndrome and slight pathological damage. The effect of MMF was good for steroid-resistant IgAN children, but poor for those with tubular atrophy/interstitial fibrosis and renal function impairment.

Eculizumab treatment for rescue of renal function in IgA nephropathy

Therese Rosenblad • Johan Rebetz • Martin Johansson •
Zivile Békássy • Lisa Sartz • Diana Karpman

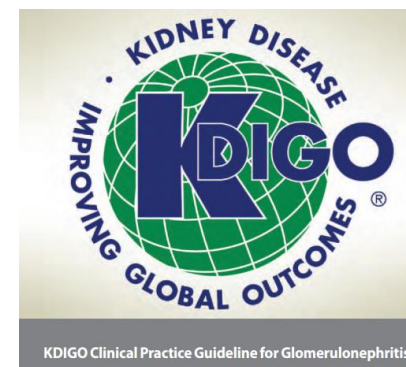
Case Diagnosis/Treatment We describe the clinical course of an adolescent with rapidly progressive disease leading to renal failure in spite of immunosuppressive treatment. Due to refractory disease the patient was treated with eculizumab (anti-C5) for 3 months in an attempt to rescue renal function. Treatment led to clinical improvement with stabilization of the glomerular filtration rate and reduced proteinuria. Discontinuation of treatment led to a rapid deterioration of renal function. This was followed by a single dose of eculizumab, which again reduced creatinine levels temporarily.

Tratamento

10.6.3: Crescentic IgAN

10.6.3.1: Define crescentic IgAN as IgAN with crescents in more than 50% of glomeruli in the renal biopsy with rapidly progressive renal deterioration. (*Not Graded*)

10.6.3.2: We suggest the use of steroids and cyclophosphamide in patients with IgAN and rapidly progressive crescentic IgAN, analogous to the treatment of ANCA vasculitis (see Chapter 13). (2D)



Tratamento

10.5.3: Tonsillectomy

10.5.3.1: We suggest that tonsillectomy not be performed for IgAN. (2C)

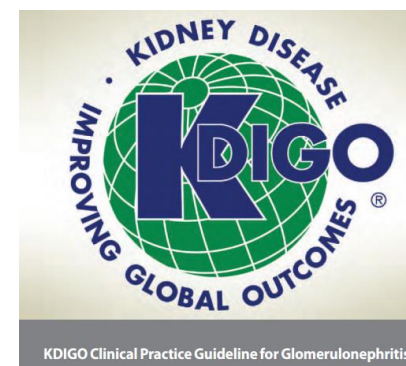


Table 1. Summary of non-randomized studies evaluating the efficacy of tonsillectomy in treatment of patients with IgAN

Source	Patient population	No.	Age (mean ± SD)	Gender (M/F)	Duration of follow-up (mean ± SD)	Tonsillectomy (Y/N)	Use of steroids	Outcome	Favors tonsillectomy
Rasche <i>et al.</i> [29]	European	55	29 ± 15	36/14	40.8 ± 48	16/39	Yes	Developing ESRD	No
Piccoli <i>et al.</i> [30]	European	61	28.3 ± 10.9 ^a	39/22	250 (12–300) ^{a,b}	15/46	No	Worsening renal function	No
Chen <i>et al.</i> [31]	Chinese	112	27.3 ± 9.5	66/46	130 ± 50.3	44/58		CR and renal survival	Yes (for CR) No (for renal survival)
Hotta <i>et al.</i> [22]	Japanese	329	36.1 ± 12.8	178/151	82.3 ± 38.2	250/79	Yes	CR or worsening renal function	Yes (for CR)—most efficacious if combined with steroids No (for worsening renal function)
Xie <i>et al.</i> [32]	Japanese	118	32 ± 11.8	64/54	192.9 ± 74.8	48/70	Yes	Renal survival	Yes
Yamamoto <i>et al.</i> [33]	Japanese	208	35.1 ± 13.7	104/104	76 (18–288) ^b	136/72	Yes	Doubling of serum creatinine	Yes—most efficacious if combined with pulse steroids
Maeda <i>et al.</i> [34]	Japanese	200	31.6 (25.2–48.5) ^b	67/133	62.4 ± 2.4	70/130	Yes	CR	Yes—even when adjusted for steroid therapy
Kawaguchi <i>et al.</i> [35]	Japanese	388	38.8 ± 13.8	177/211	24	307/81	Yes	CR	Yes—most efficacious if combined with pulse steroids
Komatsu <i>et al.</i> [21]	Japanese	55	39 ± 11.5	21/34	54 ± 21.2	35/20	Yes	CR or doubling of serum creatinine	Yes—if combined with pulse steroids

CR, complete remission.

^aThis is for the entire group of patients which included 121 patients with mesangial glomerulonephritis in addition to those with IgAN.

^bThis is median with minimum and maximum range.

Tratamento



Não Tratar
+ evolução para DRC

Tratar
+ efeitos laterais

Tratamento

BAIXO RISCO

Proteinúria $<0.2\text{g}/\text{dia}/1.73\text{m}^2$
TFG normal
MEST 0

Vigilância clínica e
analítica

RISCO MODERADO

Proteinúria $0.2\text{-}0.5\text{g}/\text{dia}/1.73\text{m}^2$
TFG normal
Qualquer MEST

Inibidor SRAA
3-6 meses

Se
Proteinúria $>0.5\text{g}/\text{dia}/1.73\text{m}^2$

Corticóides

RISCO ELEVADO

Proteinúria $>0.5\text{-}1\text{g}/\text{dia}/1.73\text{m}^2$
Qualquer MEST

Inibidor SRAA
Considerar caso-a-caso
início de corticóides

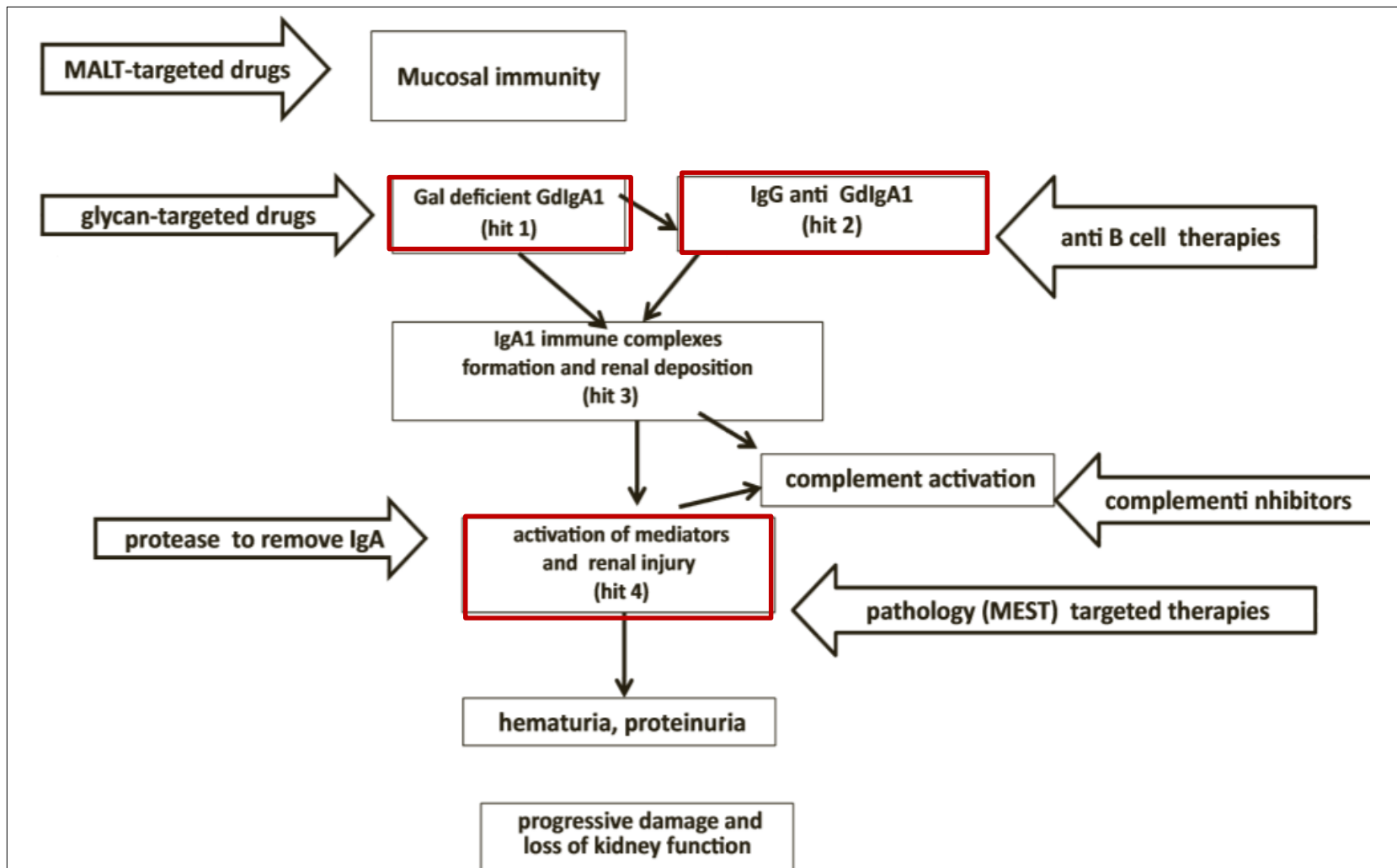
RAPIDAMENTE PROGRESSIVA

Diminuição rápida da TFG
IRA
Proteinúria nefrótica
Crescentes

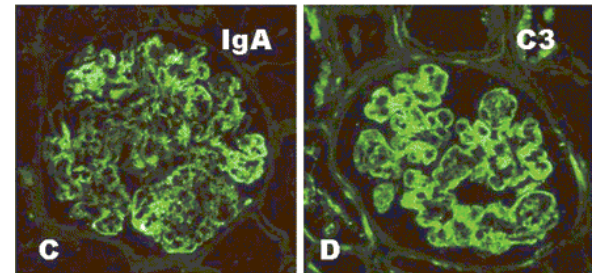
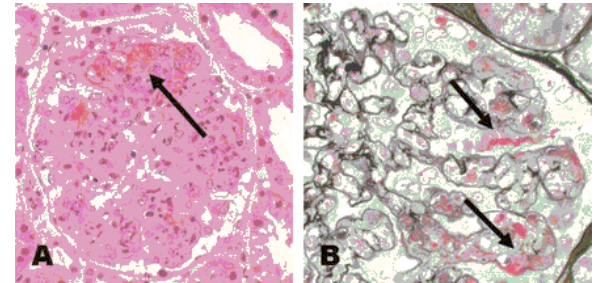
Inibidor SRAA
Corticóides
Outros
imunossupressores

VIGILÂNCIA CLÍNICA DURANTE DÉCADAS

O FUTURO... biomarcadores específicos e novas terapêuticas



Púrpura Henoch-Schönlein



Púrpura de Henoch-Schönlein

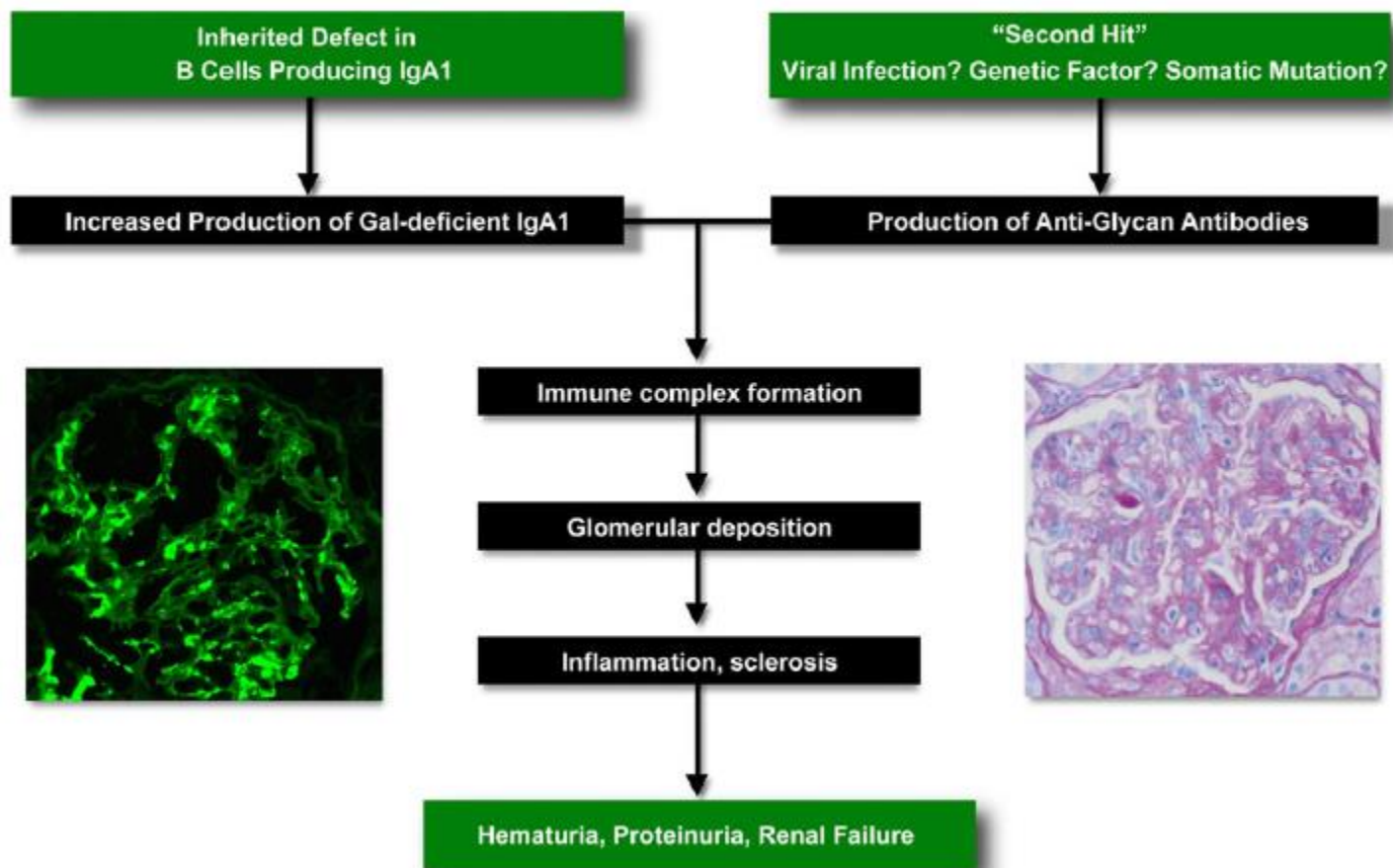
- Vasculite de pequenos vasos, sistêmica, mais frequente em idade pediátrica
- Atingimento preferencial da pele, trato GI, rim, (SNC, pulmão, gónadas)
- Incidência: 6 a 24: 100 000 crianças < 17 anos (Gardner-Medwin *et al*, 2002)
- Mais frequente no sexo masculino
- Mais prevalente: 3- 10 anos
- Habitualmente precedida de intercorrência vírica ou bacteriana
- Frequentemente autolimitada nas crianças, mas pode recorrer (1/3 dos casos), habitualmente nos primeiros 4 meses após resolução inicial

EULAR/PRINTO/PRES criteria for Henoch–Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria

Criterion	Glossary	Sensitivity (%)	Specificity (%)
Purpura (mandatory criterion)	Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, * not related to thrombocytopenia	89	86
1. Abdominal pain	Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding	61	64
2. Histopathology	Typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit	93	89
3. Arthritis or arthralgias	Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion	78	42
4. Renal involvement	Proteinuria >0.3 g/24 h or >30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample Haematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or $\geq 2+$ on dipstick	33	70
HSP EULAR/PRINTO/PRES Ankara 2008 classification definition: κ 0.90 (95% CI 0.84 to 0.96)	Purpura or petechiae (mandatory) with lower limb predominance* and at least one of the four following criteria: Abdominal pain Histopathology Arthritis or arthralgia Renal involvement	100	87

*For purpura with atypical distribution a demonstration of an IgA deposit in a biopsy is required.

Nefrite púrpura de Henoch-Schönlein: etiopatogénesis



Púrpura de Henoch-Schönlein

- 20-60% desenvolvem nefrite PHS (Pohl, 2015)
- Quando? (Narchi H, 2005)
 - 85% nas primeiras 4 semanas após início dos sintomas
 - 91% nas primeiras 6 semanas
 - 97% nos primeiros 6 meses
- Manifestações:
 - Hematúria microscópica isolada
 - Proteinúria e hematúria microscópica ou macroscópica
 - Síndrome nefrítico
 - Síndrome nefrótico
 - Síndrome nefrítico-nefrótico

Nefrite púrpura de Henoch-Schönlein

- 5-7% desenvolvem síndrome nefrítico ou nefrótico
- 20% evoluem para Doença renal crónica
- Lesões graves e ativas podem ocorrer após um período longo de estabilização com alterações urinárias mínimas ou remissão completa (➡ follow-up longo)

Nefrite púrpura de Henoch-Schönlein: Diagnóstico

- Diagnóstico clínico, na maioria dos casos
- Biópsia: lesões cutâneas atípicas ou envolvimento renal grave
- Indicações para biópsia renal:

Síndrome nefrítico/nefrótico

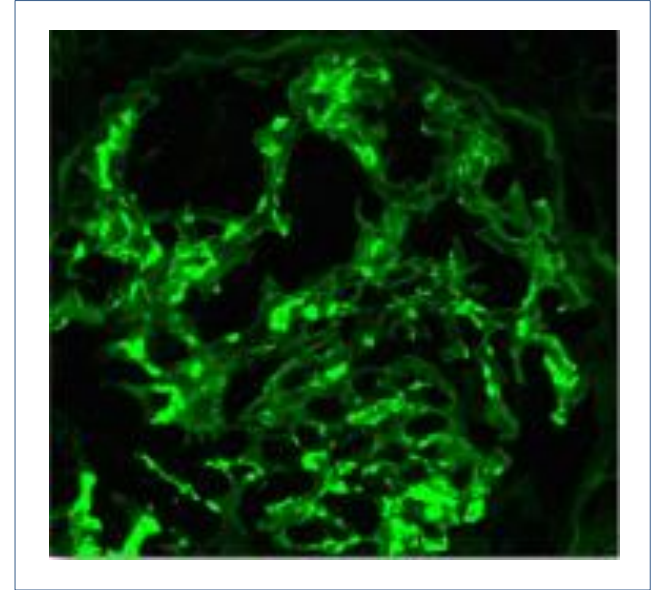
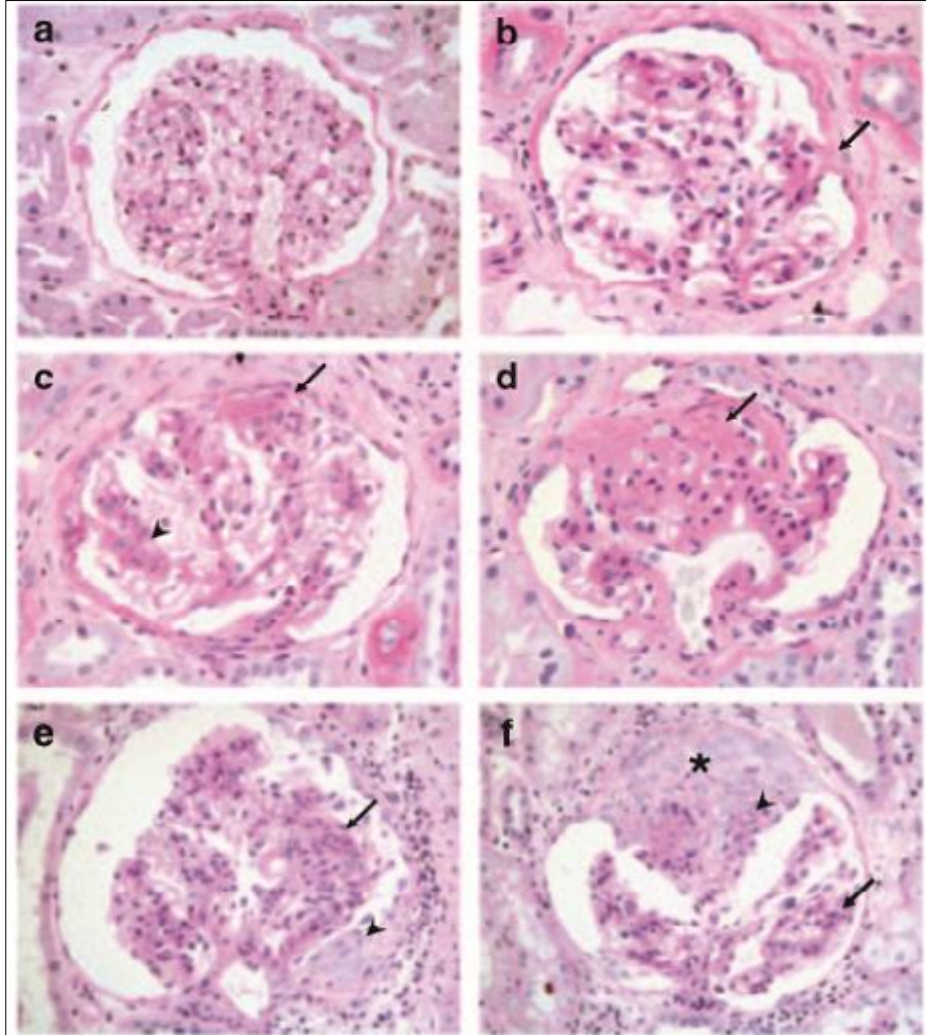
Lesão renal aguda, hipertensão e oligúria

Proteinúria nefrótica

Proteinúria persistente após 4 semanas

TFG < 80 ml/min/1.73m² persistente

Exame histopatológico



Nefrite púrpura de Henoch-Schönlein: Diagnóstico

Box 2 | ISKDC histologic classification of HSP nephritis³⁰

- I: Minimal histologic alterations
- II: Pure mesangial proliferation
- III: Focal (IIIa) or diffuse (IIIb) mesangial proliferation with <50% crescentic glomeruli
- IV: Focal (IVa) or diffuse (IVb) mesangial proliferation with 50–75% crescentic glomeruli
- V: Focal (Va) or diffuse (Vb) mesangial proliferation with >75% crescentic glomeruli
- VI: Membranoproliferative-like glomerulonephritis

Abbreviations: HSP, Henoch–Schönlein purpura; ISKDC, International Study of Kidney Disease in Children.

Mais grave

Lesões inflamatórias
agudas mais exuberantes

Proliferação glomerular

Crescentes: > 20-30%

Lesões agudas podem desaparecer ou evoluir para lesões
escleróticas, cicatriciais

Progressão DRC ← “surto” de inflamação aguda

Nefrite púrpura de Henoch-Schönlein: EVOLUÇÃO

Predictors of long-term renal outcome in Henoch–Schönlein purpura		
Factor	Symptoms	Outcome
Initial renal symptoms ^{15,32}	Nephrotic and nephritic syndrome	CKD >50% ¹⁵
	Nephrotic syndrome	CKD 40% ¹⁵
	Nephritic syndrome	CKD 15% ¹⁵
	Heavy non-nephrotic proteinuria	CKD 15% ¹⁵
	Haematuria and/or minimal proteinuria	CKD <5% ¹⁵
	Nephrotic syndrome persisting <3 months	ESRD 0% ³²
	Nephrotic syndrome persisting >3 months	ESRD 41% ³²
Renal symptoms during follow-up	GFR <70 ml/min/1.73m ² at 3 years*	ESRD 100% ²⁶
Initial symptoms versus increasing proteinuria during follow-up	Mean follow-up proteinuria (g per day)	ESRD RR 1.78, $P<0.01$ ³¹
	Severely impaired versus normal GFR at onset	ESRD RR 3.83, $P=0.20$ ³¹
	Nephrotic versus minimal proteinuria at onset	ESRD RR 4.74, $P=0.17$ ³¹
*Univariate analysis of predictors related to renal survival that used dialysis therapy as an end point; GFR was calculated using the Schwartz formula. Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RR, relative risk. Reproduced and modified with permission from the American Society of Nephrology © Davin, J. C. <i>Clin. J. Am. Soc. Nephrol.</i> 6, 687–689 (2011). http://cjasn.asnjournals.org/ .		

Nefrite por Púrpura de Henoch-Schönlein: pode-se prevenir?

Randomised, double-blind, placebo-controlled trial
to determine whether steroids reduce the incidence
and severity of nephropathy in Henoch-Schönlein
Purpura (HSP)

Jan Dudley,¹ Graham Smith,² Anne Llewelyn-Edwards,³ Kate Bayliss,⁴ Katie Pike,⁴
Jane Tizard¹

Conclusions This is the largest trial of the role of steroids in children with HSP. We found no evidence to suggest that early treatment with prednisolone reduces the prevalence of proteinuria 12 months after disease onset in children with HSP.

Nefrite púrpura de Henoch-Schönlein: TRATAMIENTO

11.1: Treatment of HSP nephritis in children

11.1.1: We suggest that children with HSP nephritis and persistent proteinuria, $>0.5\text{-}1\text{ g/d per }1.73\text{ m}^2$, are treated with ACE-I or ARBs. (2D)

11.1.2: We suggest that children with persistent proteinuria, $>1\text{ g/d per }1.73\text{ m}^2$, after a trial of ACE-I or ARBs, and GFR $>50\text{ ml/min per }1.73\text{ m}^2$, be treated the same as for IgAN with a 6-month course of corticosteroid therapy (see Chapter 10). (2D)

11.2: Treatment of crescentic HSP nephritis in children

11.2.1: We suggest that children with crescentic HSP with nephrotic syndrome and/or deteriorating kidney function are treated the same as for crescentic IgAN (see Recommendation 10.6.3). (2D)

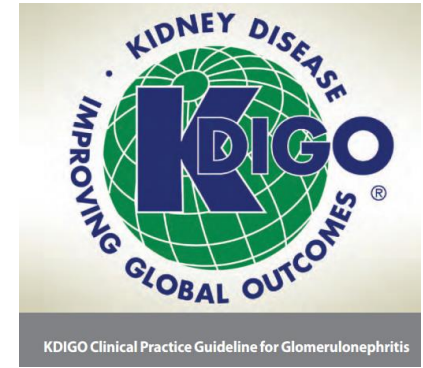


Table 2 | Comparison of primary IgA nephropathy and HSP nephritis

Clinical and histological features	Detection method	IgA nephropathy	HSP nephritis
<i>Renal histology</i>			
Crescents	Light microscopy	+/-	++
Glomerular tuft necrosis		+/-	++
Neutrophil infiltration		+/-	++
Mesangial IgA deposits	Immunofluorescence	+++	+++
IgA deposits along capillary walls		-	++
Subendothelial deposits	Electron microscopy	+/-	++
<i>Clinical presentation</i>			
Extrarenal symptoms	NA	+/-	+++
Age at onset	NA	Mostly >15 years	Mostly <15 years
Nephritic syndrome	NA	+/-	++
Nephrotic syndrome	NA	+/-	++
Disease course	NA	Continuous moderate activity with exacerbations	Repeated acute episodes
<i>Renal outcomes</i>			
Clinical remission	NA	30–50%	98%
CKD long after apparent complete remission	NA	-	+
ESRD	NA	20–40% after 20 years	1–3% in children, 30% in adults
<i>Transplantation outcomes</i>			
IgA deposit recurrence	Immunofluorescence	Frequent	Frequent
Graft loss at 5 years post-transplantation	NA	Rare	Rare
Graft loss at 10 years post-transplantation	NA	9.7%	7.5%
-, +/-, +, ++ and +++ indicate the relative likelihood of each clinical or histological feature occurring in a direct comparison of IgA nephropathy and HSP nephritis. Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; HSP, Henoch–Schönlein purpura; NA, not applicable.			

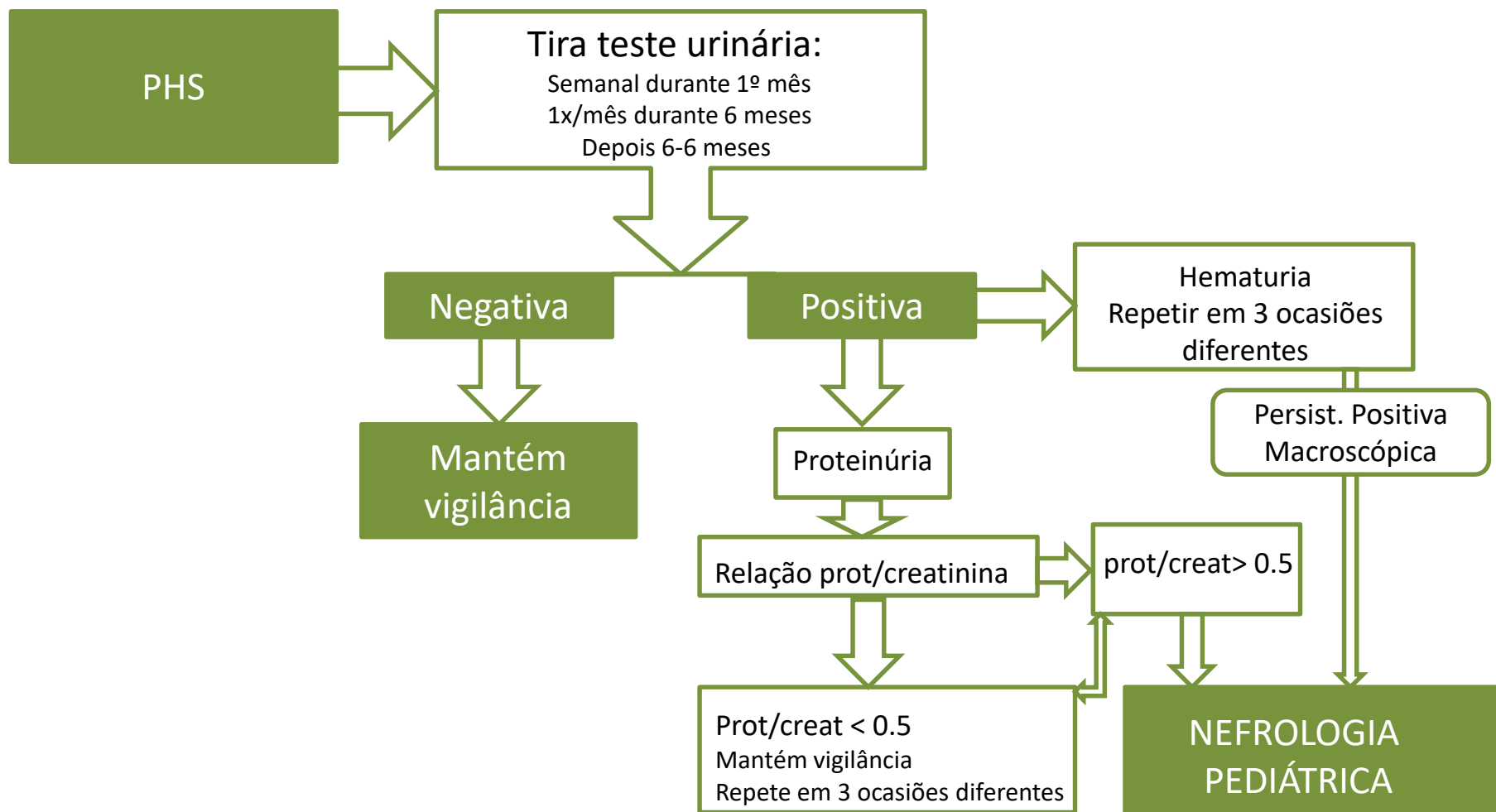
Nefrite púrpura de Henoch-Schönlein: TRATAMENTO

Pitfalls in recommending evidence-based guidelines for a protean disease like Henoch–Schönlein purpura nephritis

Jean-Claude Davin • Rosanna Coppo

“Following the KDIGO guidelines, ... may delay a potentially more effective treatment and increase the risk of CKD progression in patients”

Nefrite púrpura de Henoch-Schönlein: Seguimento



Tratamento

Hematuria microscópica
persistente
Proteínas/creat > 0.5 <1

PDS 1 mg/kg, 3-4
semanas

Hematúria macroscópica
Proteínas/creat < 1

Prednisolona
2 mg/kg/dia

Síndrome nefrítico
Síndrome nefrítico

Metilprednisolona ev
PDS oral

Proteinúria nefrótica
Histologia desfavorável

Corticóides
Outros
imunossupressores

Rapidamente progressiva
IRA

Plasmaferese

VIGILÂNCIA CLÍNICA DURANTE DÉCADAS

BIBLIOGRAFIA

- Pohj, M. Henoch-Schönlein purpura nephritis. *Pediatr Nephrol*, 2015; 30, 245-252.
- Brogan P, et al. Small vessel vasculites. *Pediatr Nephrol*, 2010; 25: 1025- 1035
- Kiryluk LiY, et al. Geographic differencs in genetic susceptibilty to Ig A nephropathy: GWAS replicacation study and Geospatial Risk Analysis. *Plos genet* 8 (6): e1002765
- Kiryluk K et al. Genetic studies of IgA nephropathy: past, presente and future. *Pediatr Nephrol*, 2010; 25: 2257-2268
- Kiryluk K et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity againts intestinal pathogens . *Nature genetics*, 2014; 46: 1187-1196
- Hogg R. Idiopathic immunoglobulin A nephropathy in children and adolescents. *Pediatr Nephrol*, 2010; 25: 823-829.
- Coppo R. The Oxford IgAnephropathy clinicopathological classiffication is valid for children as well as adults. *Kidney international*, 2010; 77: 921-927.
- Reich H, et al. Remission of proteinuria improves prognosis of IgA nephropathy. *J Am Soc Nephrol*, 2007; 18: 3177- 3183
- Miserska-Wasiak M et al. Relationship between serum IgA/C3 ratio and severity of histological lesions using the Oxford classification in children with IgA nephropathy. *Pediatr Nephrol*, 2015: 30: 113-1120.
- Kamatsu H, et al. Relationship between serum IgA/C3 ratio and progression og IgA nephropathy. *Intern Med* 43 (11): 1011.
- Roberts I et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney International*, 2009; 76: 546-556
- Cattran DC. The Oxford classification of IgA nephropathy: rationale, clincopathological correlations, and classification. *Kidney international*, 2009; 76: 534-545
- Coppo R. Biomarkers and targeted new therapies for IgA nephropathy. *Pediatr Nephrol*, june 2016; DOI: 10.1007/s00467-016-3390-9
- Ozen S et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. *Ann Rheum Dis*, 2010; 69: 798-806.
- Davin JC, Coppo R. Henoch Schonlein purpura nephritis in children. *Nature Reviews*, 2014; 10: 5-63-573.
- Brogan P, et al. Small vessel vasculites. *Pediatr Nephrol*, 2010; 25: 1025- 1035