O LABORATÓRIO EM REUMATOLOGIA PEDIÁTRICA

III CURSO DE REUMATOLOGIA PEDIÁTRICA PARA MÉDICOS INTERNOS

10 DE SETEMBRO DE 2020

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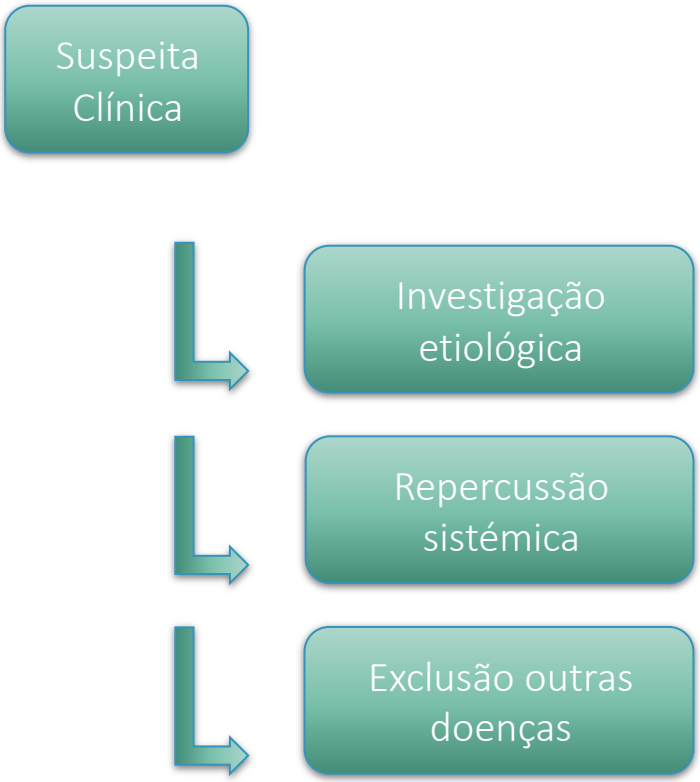
CENTRO HOSPITALAR UNIVERSITÁRIO DE LISBOA CENTRAL

EXAMES COMPLEMENTARES DE DIAGNÓSTICO



Best Prac Res Clin Rheum;28 (2014):831-843

EXAMES COMPLEMENTARES DE DIAGNÓSTICO

Best Prac Res Clin Rheum;28 (2014):831-843

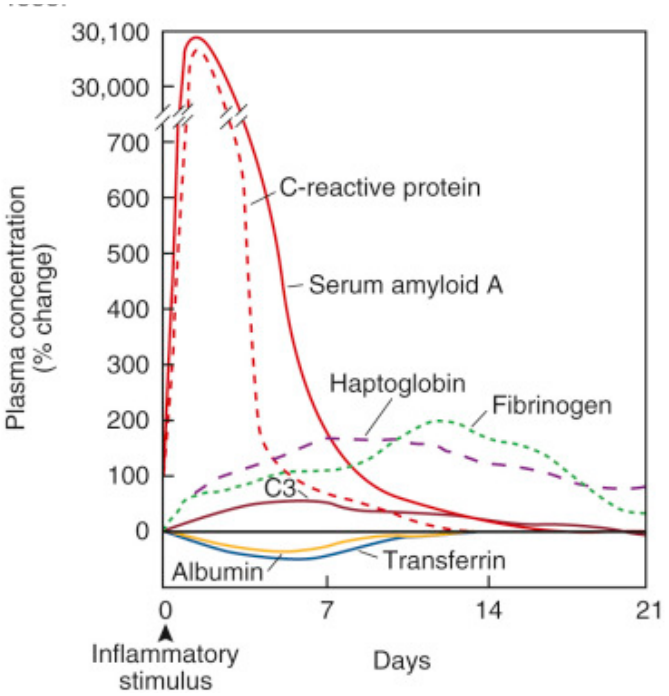
Biomarcadores - Avaliação geral

MARCADORES DE INFLAMAÇÃO

Proteínas de fase aguda

- proteína C-reactiva, amilóide A sérica
- fibrinogénio, haptoglobina
- C3

- ferritina
- procalcitonina
- calprotectina sérica (S100A8/S100A9)

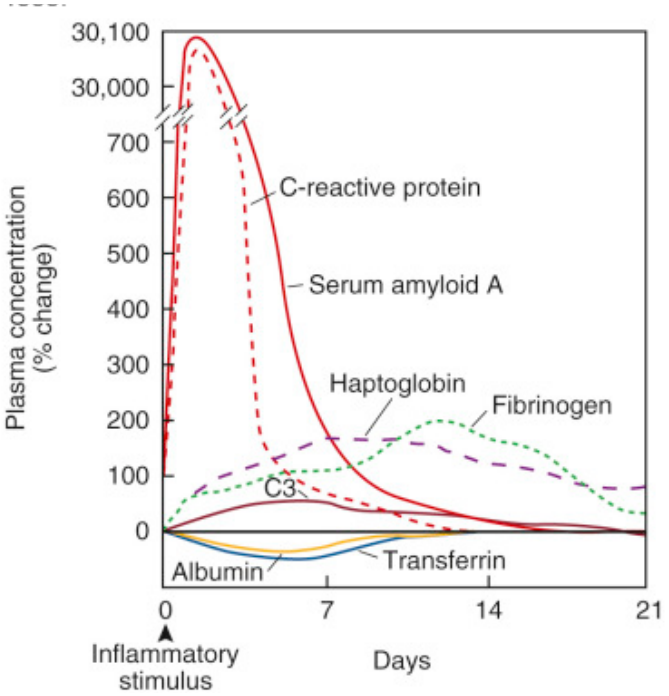


NEJM. 1999 Feb; 448–454.

MARCADORES DE INFLAMAÇÃO

Amilóide A sérica

- Indicação na avaliação de doenças auto-inflamatórias
  - ++ seguimento / monitorização da resposta à terapêutica
  - suspeita diagnóstica
- ++ na Febre Mediterrânea Familiar
  - detecção de inflamação sub-clínica
- Risco de amiloidose secundária



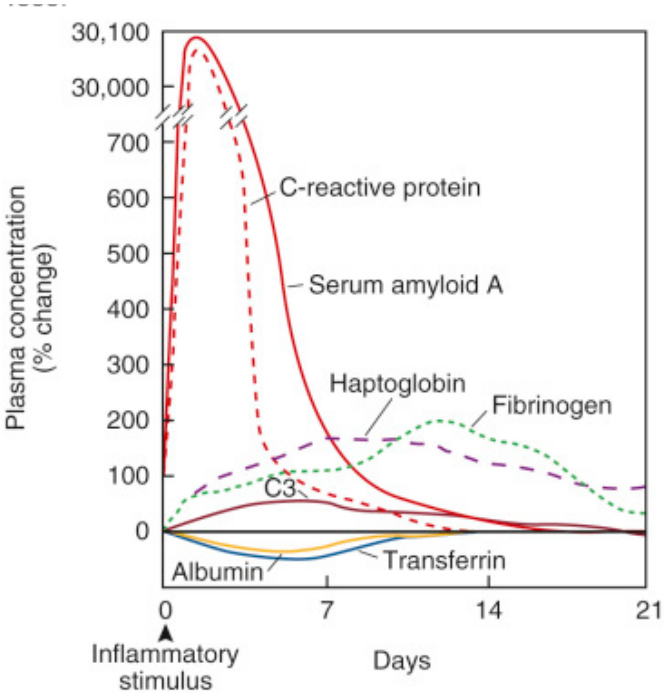
World J Nephrol 2016;5(1): 66-75. Clin Exp Rheumatol 2018; 36 (Suppl. 110): S54-S60.

MARCADORES DE INFLAMAÇÃO

Complemento (C3, C4 e CH100 ou CH50)

- maioria são proteínas de fase aguda

- valores diminuídos
  - causa hereditária *vs* por consumo
- C3 e C4 frequentemente ↓↓ no LES com doença activa
  - sobretudo na nefrite lúpica (↓↓ C3)
  - úteis na monitorização da doença

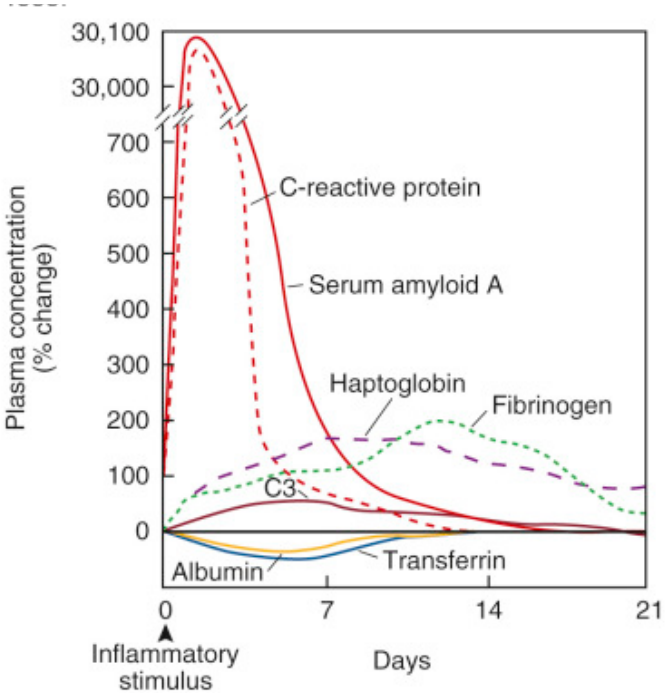


J Allergy Clin Immunol. 2017 December; 140(6):1473–1483.

MARCADORES DE INFLAMAÇÃO

Ferritina

- marcador inespecífico de inflamação
  - activação macrofágica
- elevação marcada (freq >1000ng/mL)
  - AIJ sistémica ↑↑
  - Síndrome de Activação Macrofágica ↑↑↑
- outras causas não-inflamatórias



International Immunology, Vol. 29, No. 9, pp. 401–409.

SÍNDROME DE ACTIVAÇÃO MACROFÁGICA

Classification of macrophage activation syndrome in systemic juvenile idiopathic arthritis

A febrile patient with known or suspected systemic juvenile idiopathic arthritis is classified as having macrophage activation syndrome if the following criteria are met:

Ferritin >684 ng/ml

and any 2 of the following:

Platelet count ≤181 x 10^9/liter

Aspartate aminotransferase >48 units/liter

Triglycerides >156 mg/dl

Fibrinogen ≤360 mg/dl

Importância da ferritina

- AIJ-S ↑↑ vs AIJ-S com SAM ↑↑↑

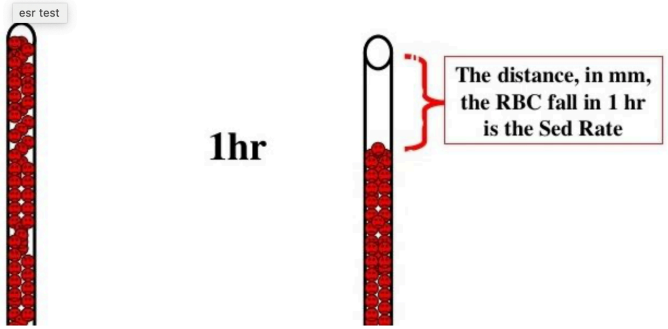
Descida (“paradoxal”) do fibrinogénio

Ann Rheum Dis 2016 Mar;75(3):481-9

MARCADORES DE INFLAMAÇÃO

Velocidade de sedimentação

- avaliação indirecta das proteínas de fase aguda



- resposta lenta
- inespecífica: utilidade diagnóstica?
- útil no seguimento e monitorização do tratamento de doenças conhecidas

Eur. J. Immunol. 2016. 46: 2068–2077

MARCADORES DE INFLAMAÇÃO

Proteína C-reactiva e velocidade de sedimentação

- LES
- Dermatomiosite / polimiosite juvenil
- Esclerodermia
- Síndrome de Sjogren

Valor ↑↑ da vs

Valor ↓ / normal da PCR

Aumento da PCR
- infecção
- serosite
- artrite

Lupus. 2011 May;20(6):588-97; Clin Rheumatol. 2018 Jul;37(7):1835-1844

MARCADORES DE INFLAMAÇÃO

Calprotectina sérica (S100A8/S100A9)

- correlação positiva com a actividade de várias doenças reumáticas / inflamatórias
- marcador de actividade subclínica nas AIJ
  - potencial preditor de recaída após suspensão de terapêutica?
- valores ↑↑↑ em determinados síndromes autoinflamatórios
  - potencial utilidade diagnóstica (FMF, associados ao PSTPIP1, AIJ-S)

Front. Immunol. 2019;10:182. Clin Immunol. 2013 Jun;147(3):229-241. Arthritis Rheum 2019;71(3):451-459. Arth Res Ther 2015;17:200 Reumatologia 2017;55(1):10

MARCADORES DE INFLAMAÇÃO

Calprotectina sérica (S100A8/S100A9)

TABLE 1 | Serum concentration of phagocyte-specific S100 proteins in inflammatory diseases [adapted and updated from Kessel et al. (73)].

	S100A8/A9 levels (ng/ml)	N†	References	S100A12 levels (ng/ml)	N†	References
POLYGENIC AUTOINFLAMMATORY DISEASES						
Systemic-onset JIA	14,920 ± 4,030	60	(76)	7,190 ± 2,690	60	(75)
	24,750 ± 11,410	20	(77)	3,700 (1,080)**	33	(78)
Polyarthritis JIA	2,380 ± 530	89	(52, 63)	395 (45)**	89	(78)
PFAPA	3846 ± 1197	15	(79)	685 ± 210	15	(79)
MONOGENIC AUTOINFLAMMATORY DISEASES						
FMF	110,000 ± 82,000	20	(71)	6,720 ± 4,960	17	(75)
				33,500 (22,200)**	7	(56)
PAPA	116,000 ± 74,000	11	(71)	–		
PAMI	2,045,000 ± 1,300,000	13	(71)	–		
NOMID	2,830 ± 580	18	(76)	720 ± 450	18	(75)
MWS	4,390 (2535)*	12	(61)	150 ± 60	17	(75)
FCAS	3,600 (4610)*	5	(61)	–	–	–
INFECTIONS						
Severe febrile infections	3,720 ± 870	66	(76)	470 ± 160	83	(75)
Healthy controls	340 ± 70	50	(76)	50 ± 10	45	(75)
				50 (5)**	74	(50)

FCAS, Familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; JIA, juvenile idiopathic arthritis; MWS, Muckle Wells syndrome; NOMID, Neonatal onset multisystem inflammatory disorder; PAMI, PSTPIP1-associated myeloid-related proteinemia inflammatory; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis syndrome (mean (standard deviation), ** mean (standard error of the mean), all other data are mean ± 95% confidence interval, †N, number of patients studied).*

Front. Immunol. 2019;10:182.

MARCADORES DE INFLAMAÇÃO

Calprotectina sérica (S100A8/S100A9)

- correlação positiva com a actividade de várias doenças reumáticas / inflamatórias
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  - potencial utilidade diagnóstica (FMF, associados ao PSTPIP1, AIJ-S)

Ensaios laboratoriais a aguardar validação e estandardização…

Front. Immunol. 2019;10:182. Clin Immunol. 2013 Jun;147(3):229-241. Arthritis Rheum 2019;71(3):451-459. Arth Res Ther 2015;17:200 Reumatologia 2017;55(1):10

MARCADORES DE INFLAMAÇÃO

Procalcitonina

- elevação ↑↑↑ em infecções bacterianas graves / sépsis
  - potencialmente útil na avaliação de crianças febris
- elevação ↑↑ em algumas doenças reumáticas (activas)
  - AIJ-S, vasculites ANCA+, Doença de Kawasaki
  - valores aumentam significativamente se sobreinfecção bacteriana

  → Necessidade de definir cut-off diferente para estes casos?
- valor preditivo negativo – principal interesse no momento??

Indian J Rheumatol 2018;13:173-7; Rheumatology 2015;54:231-240 ; Ann Rheum Dis 2003;62:337–340

Biomarcadores – Investigação Dirigida

AUTO-ANTICORPOS

Podem ser úteis para:

- Diagnóstico
  - confirmação diagnóstica
  - diagnóstico precoce
  - formas de apresentação menos típicas
- seguimento / monitorização
- prognóstico

Autoimmunity Reviews 2012;3:207–211; Best Pract Res Clin Rh 2014; 28:907-920

ANTICORPOS ANTI-NUCLEARES

Grupo de antigénios celulares predominantemente encontrados no núcleo

Gold standard para detecção de ANA: imunofluorescência indirecta (IFI)

Resultados:

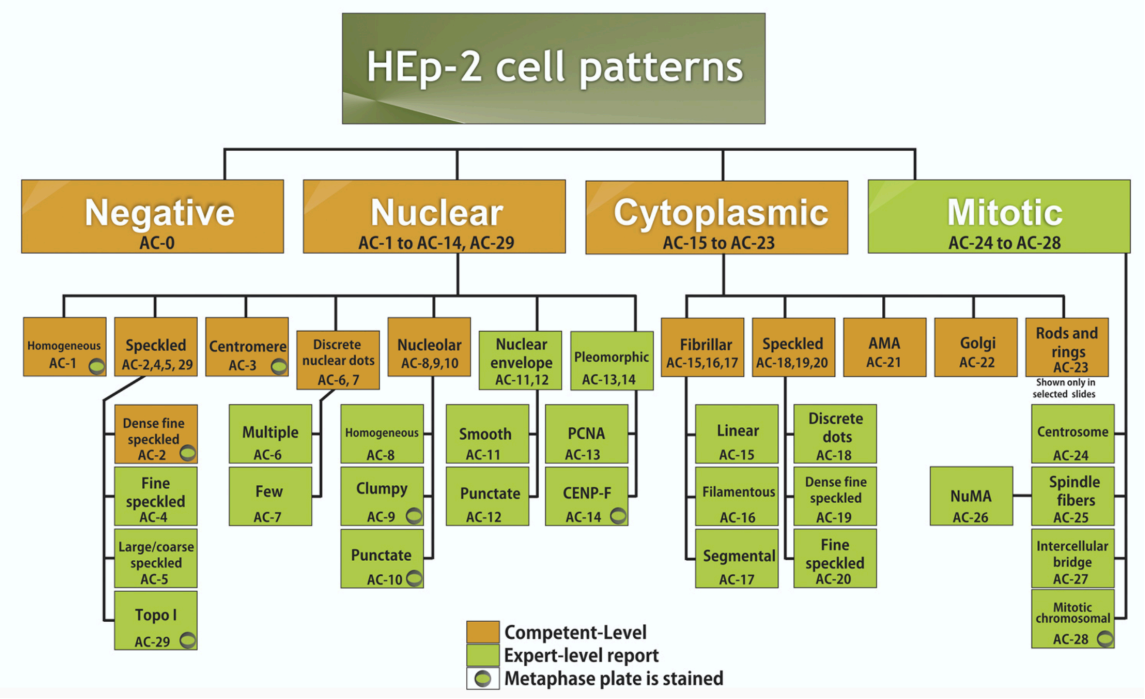
- Título (maior diluição positiva)
- Padrão de fixação

Ann Rheum Dis 2014;73:17–23; South Med J 2012;105 (2):100-103

ANTICORPOS ANTI-NUCLEARES

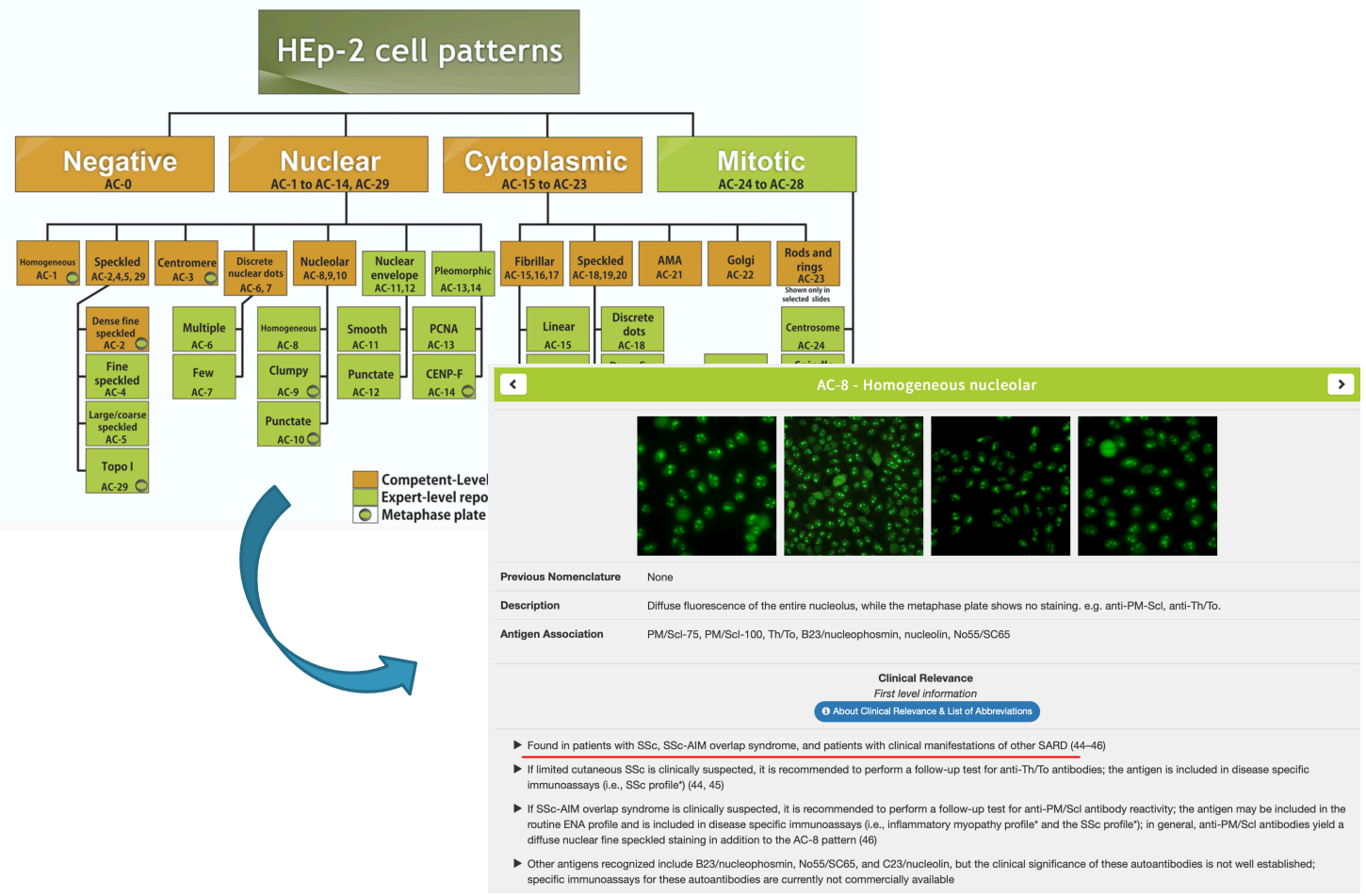
Clinical relevance of HEp-2 indirect immunofluorescent patterns: the International Consensus on ANA patterns (ICAP) perspective

www.ANApatterns.org



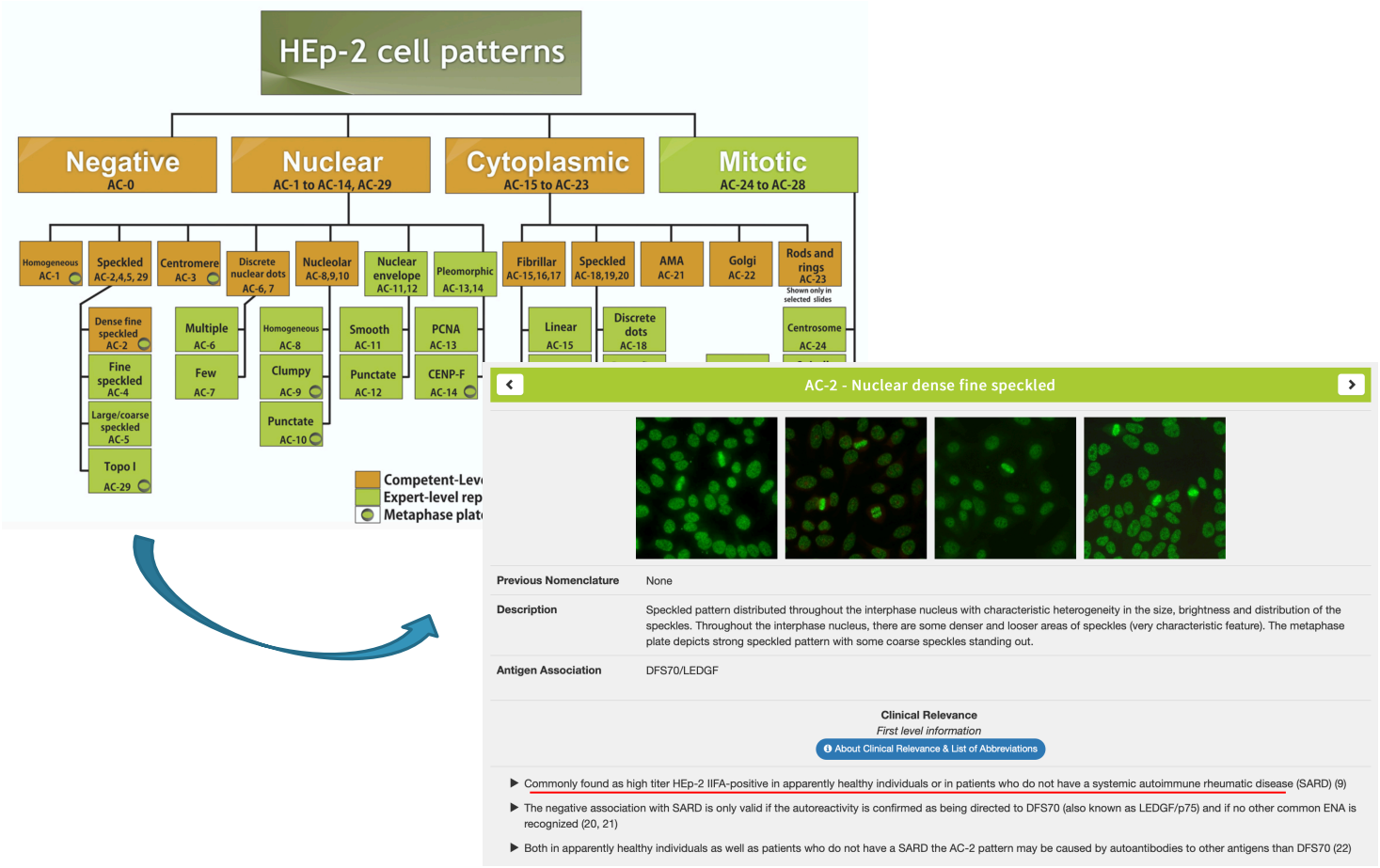
Ann Rheum Dis 2019;78:879-889.

ANTICORPOS ANTI-NUCLEARES



Ann Rheum Dis 2019;78:879-889.

ANTICORPOS ANTI-NUCLEARES



Ann Rheum Dis 2019;78:879-889.

ANTICORPOS ANTI-NUCLEARES

Associados a inúmeras doenças auto-imunes

- SEM relação com a actividade da doença

Patologia	Positividade ANA (%)
LES	97-100
DMTC	>99
Síndrome de Sjogren	>97
Esclerodermia juvenil	85
AIJ	81-97
Dermatomiosite juvenil	40-63

ANA positivo poderá ser seguido de pesquisa de anticorpos dirigidos

- Anticorpos anti-dsDNA - ↑ sensibilidade na monitorização do LES
- ENA (Sm, SSA, SSB, U1RNP, Jo-1, Scl-70, PM-Scl…); Ac específicos / associados miosites inflamatórias…
- Se positivos maior probabilidade de doença reumatológica

Ann Rheum Dis 2014;73:17–23; South Med J 2012;105 (2):100-103

ANTICORPOS ANTI-NUCLEARES

Crianças saudáveis

- Prevalência 5 – 18% crianças saudáveis
- Títulos habitualmente ≤ 1/320

Infecções: EBV, HIV, tuberculose

Neoplasias: doenças linfoproliferativas

Fármacos: isoniazida, clorpromazina, anti-convulsivantes, anti-TNFα

Pediatrics 1992; 89 (3):441–444; Pediatrics 95 (6) (1995) 892–895

FACTOR REUMATÓIDE

Grupo de anticorpos dirigido contra a porção Fc da IgG

- FR-IgM com alta afinidade tem maior relevância clínica

Critério de diagnóstico na AIJ poliarticular

Marcador de prognóstico na AIJ

- > risco lesão estrutural
- < probabilidade de remissão

J Rheumatol 2004;31(2):390-2; Front Immunol 2019; 9:3168. Arthritis Rheumatol 2018; 70(6):957–962

FACTOR REUMATÓIDE

Grupo de anticorpos dirigido contra a porção Fc da IgG

- FR-IgM com alta afinidade tem maior relevância clínica

Doenças Reumatológicas	AIJ poliarticular
	Crioglobulinémia mista
	Síndrome de Sjogren
	DMTC
	Granulomatose com poliangeíte
	LES
	Outras
Infecções	Crónicas ou latentes
Crianças saudáveis	3-8%

J Rheumatol 2004;31(2):390-2; Front Immunol 2019; 9:3168. Arthritis Rheumatol 2018; 70(6):957–962

ANTICORPOS ANTI-PÉPTIDO CITRULINADO CÍCLICO

Elevada especificidade para AIJ

- Muito raro em indivíduos saudáveis

Pode preceder o início da doença

Correlação com:

- Poliartrite
  - mais frequente na AIJ poliarticular FR +
- lesão estrutural articular
- actividade da doença

Pediatric Rheumatology 2012, 10:29; Clin Rheumatol 2016 Mar;35(3):601-7; Electron Physician 2016; 8(9): 2897–2903; Genet Mol Res. 2016 May 13;15(2)

ANTICORPOS ANTI-CITOPLASMA NEUTRÓFILO

Grupo de anticorpos contra grânulos existentes no citoplasma do neutrófilo

- Proteinase 3 (ANCA-PR3)
- Mieloperoxidase (ANCA-MPO)

Considerar pedir:

- Febre prolongada de origem indeterminada
- Doença com envolvimento multiorgânico
  (++ se renal, pulmonar, neurológico)
- Exantema purpúrico ou petequial
- Sinais de inflamação sistémica sem outra causa

Pediatr Clin N Am 2012;59:263–284

ANTICORPOS ANTI-FOSFOLÍPIDOS

Síndrome anti-fosfolípido:

- Fenómenos trombóticos vasculares
- Morbilidade obstétrica
- Presença de Ac anti-fosfolípidos

Síndrome Anti-fosfolípido Primário
LES
Doenças infecciosas
Doenças neoplásicas
Fármacos

Na Pediatria, mais frequentemente manifestações:

- cutâneas, hematológicas, neurológicas, cardíacas, articulares…

Pediatrics 2008;122:e1100–e1107; Pediatr Clin N Am 2012;59:263–284; Ann Rheum Dis 2017;76:1637–1641. Clin Exp Med. 2017;17(3):257-267

ANTICORPOS ANTI-FOSFOLÍPIDOS

Devem ser testado todos três:

- Anticoagulante lúpico
  - dois ensaios: APTT La e DRVVT
  - prolongamento paradoxal do APTT
- Ac anti-cardiolipina (IgG, IgM ou IgA)
- Ac anti-glicoproteína β2GP1 (IgG, IgM ou IgA)

Pesquisa de anticorpos deve ser repetida após intervalo de 2 – 3 meses

- frequentemente transitório

Valorizar títulos moderados – altos

Pediatrics 2008;122:e1100–e1107; Pediatr Clin N Am 2012;59:263–284; Ann Rheum Dis 2017;76:1637–1641. Clin Exp Med. 2017;17(3):257-267

Biomarcadores – Testes Genéticos

HLA-B27

Associação com as espondilartropatias

Presente em 5-10% da população geral → ~1% desenvolve doença

Considerar pedir:

Artrite em criança sexo masculino >6 anos de idade
Dorso-lombalgia com padrão inflamatório
Sacro-ileíte
Entesite
Artrite numa criança com história familiar de espondilartropatia, uveite ou DII
Uveíte aguda

Annu. Rev. Immunol. 2015.33:29-48 ; Pediatr Clin N Am 59 (2012) 263–284

SÍNDROMES AUTO-INFLAMATÓRIOS

TABLE I
List of the systemic hereditary autoinflammatory diseases

Syndrome	Gene	Inheritance	Age at onset	Distinctive features
FMF (MIM #249100)	*MEFV* Chr. 16	AR	Childhood	Fever episodes accompanied by abdominal pain, pleurisy, arthralgia or arthritis, serositis and synovitis
TRAPS (MIM #142680)	*TNFRSF1A* Chr. 12	AD	Childhood, but also later in life	Flares accompanied by conjunctivitis, periorbital oedema, myalgia, rash, abdominal pain, cervical lymphadenopathy
MKD/HIDS (MIM #260920)	*MVK* Chr. 12	AR	Infancy	Immunisation induced attacks of fever, GI symptoms, cervical lymphadenopathy and abdominal pain, headache, arthralgia or arthritis, aphthous ulceration
CAPS: FCAS1 (MIM #120100) MWS (MIM #191900) NOMID/CINCA (MIM #607115)	*NLRP3* Chr. 1	AD or sporadic	Neonatal/late onset in some sporadic cases	Cold induced attacks, urticarial rash, chronic meningitis, sensorineural deafness, cartilaginous/bony deformities and mental impairment in the most severe type
FCAS2 (MIM #611762)	*NALP12* Chr. 19	AD	Infancy	Cold induced attacks, urticarial rash, sensorineural deafness
DIRA (MIM #612852)	*IL1RN* Chr. 2	AR	Infancy	Diffuse pustular skin rash, sterile osteomyelitis and periostitis with articular pain
PAPA (MIM #604416)	*PSTPIP1* Ch.15	AD	Childhood	Pyogenic destructive arthritis typically involving the elbow, knee and/or ankle, pyoderma gangrenosum, severe cystic acne
Blau syndrome (MIM #186580)	*NOD2*(CARD15) Ch.6	AD	Childhood	Granulomatous inflammation of the skin, eye and joints
Majeed syndrome (MIM #609628)	*LPIN2* Ch.18	AR	Infancy	Multifocal osteomyelitis, and dermatosis
DITRA (MIM #614204)	*IL36RN* Chr. 2	AR	Childhood	Recurrent episodes of sterile pustular rash & fever
CANDLE (MIM #256040)	*PSMB8* Chr. 6	AR	Neonatal	Recurrent skin eruptions, arthralgia/arthritis and progressive lipodystrophy
SAVI (MIM #615934)	*TMEM173* Chr. 5	AD	Childhood	Systemic inflammation, cutaneous rash and pulmonary manifestations
APLAID (MIM #614878)	*PLCG2* Chr. 16	AD	Neonatal	Recurrent blistering skin lesions, ocular inflammation, enterocolitis, bronchiolitis, arthralgia
AIFEC (MIM #616050)	*NLRC4* Chr. 2	AD	Neonatal	Enterocolitis, recurrent fevers, GI symptoms, intermittent rash and macrophage activation syndrome
DADA2 (MIM #615688)	*CECR1* Chr. 22	AR	Childhood	Early onset recurrent stroke, neurologic manifestations and fever

Classification criteria for autoinflammatory recurrent fevers

Table 2 New Eurofever/PRINTO classification criteria for hereditary recurrent fevers and their performance in the 281 patients with consensus

CAPS	FMF	TRAPS	MKD
Presence of a *confirmatory NLRP3 genotype** and *at least one* among the following: ▶ Urticarial rash. ▶ Red eye (conjunctivitis, episcleritis, uveitis). ▶ Neurosensorial hearing loss. OR Presence of *not confirmatory NLRP3 genotype*† and *at least two* among the following: ▶ Urticarial rash. ▶ Red eye (conjunctivitis, episcleritis, uveitis). ▶ Neurosensorial hearing loss.	Presence of *confirmatory MEFV genotype** and *at least* one among the following: ▶ Duration of episodes 1–3 days. ▶ Arthritis. ▶ Chest pain. ▶ Abdominal pain. OR Presence of *not confirmatory MEFV genotype*‡ and *at least two* among the following: ▶ Duration of episodes 1–3 days. ▶ Arthritis. ▶ Chest pain. ▶ Abdominal pain.	Presence of confirmatory *TNFRSF1A* genotype* and at least one among the following: ▶ Duration of episodes ≥7 days. ▶ Myalgia. ▶ Migratory rash. ▶ Periorbital oedema. ▶ Relatives affected. OR Presence of a not confirmatory *TNFRSF1A* genotype† and *at least two* among the following: ▶ Duration of episodes ≥7 days. ▶ Myalgia. ▶ Migratory rash. ▶ Periorbital oedema. ▶ Relatives affected.	Presence of a *confirmatory MVK genotype** and *at least one* among the following: ▶ Gastrointestinal symptoms. ▶ Cervical lymphadenitis. ▶ Aphthous stomatitis.
Sensitivity: 1	Sensitivity: 0.94	Sensitivity: 0.95	Sensitivity: 0.98
Specificity: 1	Specificity: 0.95	Specificity: 0.99	Specificity: 1
Accuracy: 1	Accuracy: 0.98	Accuracy: 0.99	Accuracy: 1

… >30 síndromes auto-inflamatórios identificados à data

(monogénicos e poligénicos)

Ann Rheum Dis 2019;78:1025–1032. Presse Med 2019;48:e49-e59

SÍNDROMES AUTO-INFLAMATÓRIOS

Next-generation sequencing (NGS) - + frequentemente utilizado

- paineis alargados para genes potencialmente implicados

Whole exome sequencing (WES)

Elevado número de variantes genéticas

interpetação considerando a clínica

apoio de geneticista

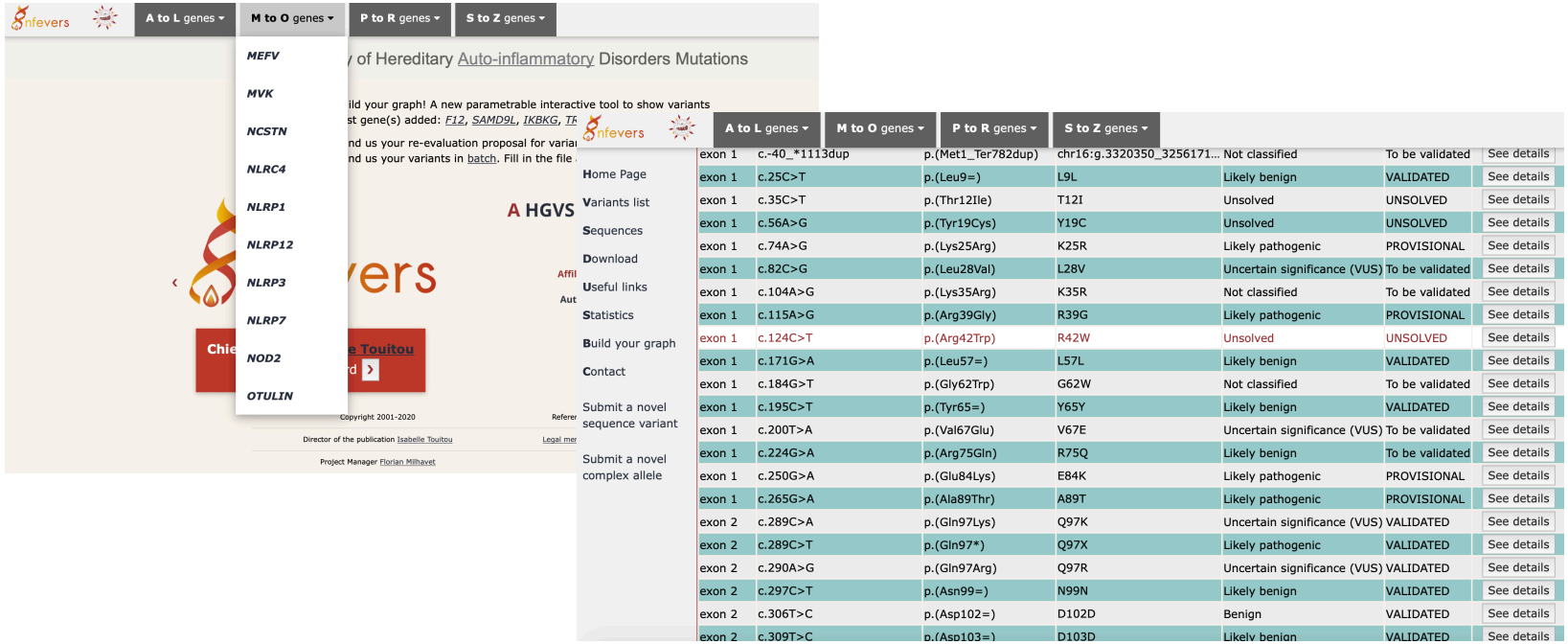
bases de dados online (ex: Infevers)

Ann Rheum Dis 2019;78:1025–1032. Presse Med 2019;48:e49-e59

SÍNDROMES AUTO-INFLAMATÓRIOS

Infevers database

https://infevers.umai-montpellier.fr/web/



O LABORATÓRIO EM REUMATOLOGIA PEDIÁTRICA

Obrigada!

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Anti-cyclic citrullinated peptide antibodies in children with Juvenile Idiopathic Arthritis. Mohamed Hamooda, Hala Fouad, Nermeen Galal, Nadia Sewelam, Dina Megahed. Electron Physician 2016 Sep 20;8(9):2897-2903

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Can procalcitonin measurement help in differentiating between bacterial infection and other kinds of inflammatory processes? I Delèvaux, M André, M Colombier, et al. Ann Rheum Dis 2003;62:337–340

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