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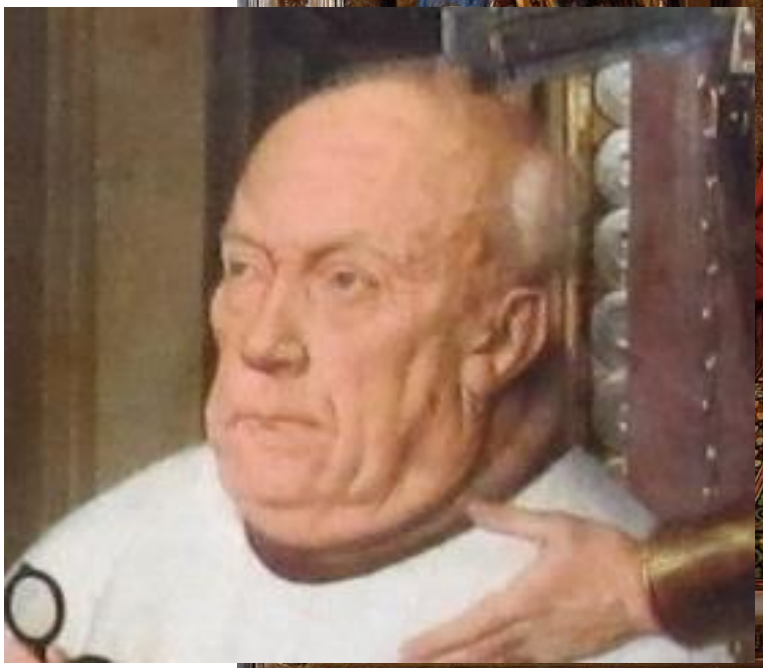
Les biomarqueurs sériques de l'inflammation en 2017: dans la pratique ?

Dr Eric Dayer, PD
Institut Central des Hôpitaux
Hôpital du Valais, Sion

Berne, le 22 aout 2017

From rubor, calor dolor to (VIERGE AU CHANOINE, J. VAN EYCK, 1435) GIGANTOCELLULAR ARTERITIS - GCA



Large scope of inflammation
Exemples of what is to me significant

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1. **Systemic Inflammatory Response, fevers and Acute phase response**
2. **CRP versus ESR: non-sense debate?**
3. **Use combined with clinical score**
    1. Examples: Gigantocellular Arteritis (GCA, Horton) and rheumatoid arthritis
4. **Procalcitonin (PCT) and bacteremia in emergency and intensive care units:**
    1. What is missing for personalized targeted therapy?
5. **Auto-inflammatory diseases and Inflammasomes:**
    1. More frequent than expected by the rare genetic diseases, Gout,
    2. Consequences: AA amyloidosis, but therapeutic options
6. **Unregulated cytokine storm:**
    1. Ferritin and macrophage activation syndrome (MAS)
7. **Low-grade inflammation (hsCR) and CV risk**
8. **Time to redefine inflammation:**
    - As innate immune response to insults to restablish homeostasis

SIRS (Systemic Inflammatory Response Syndrome)

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- **The systemic response to a wide range of stresses.**
  - Temperature >38°C
  - Heart rate >90 beats/min.
  - Respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg.
  - White blood cells > 12,000 cells/ml or < 4,000 cells/ml or >10% immature (band) forms.
- **Note**
  - Two or more of the following must be present.
  - These changes should be represent acute alterations from baseline in the absence of other known cause for the abnormalities.

American College of Chest Physicians/Society of Critical Care Medicine Consensus.
Crit Care Med. 1992;20:864-874.

Disease groups causing recurrent fevers

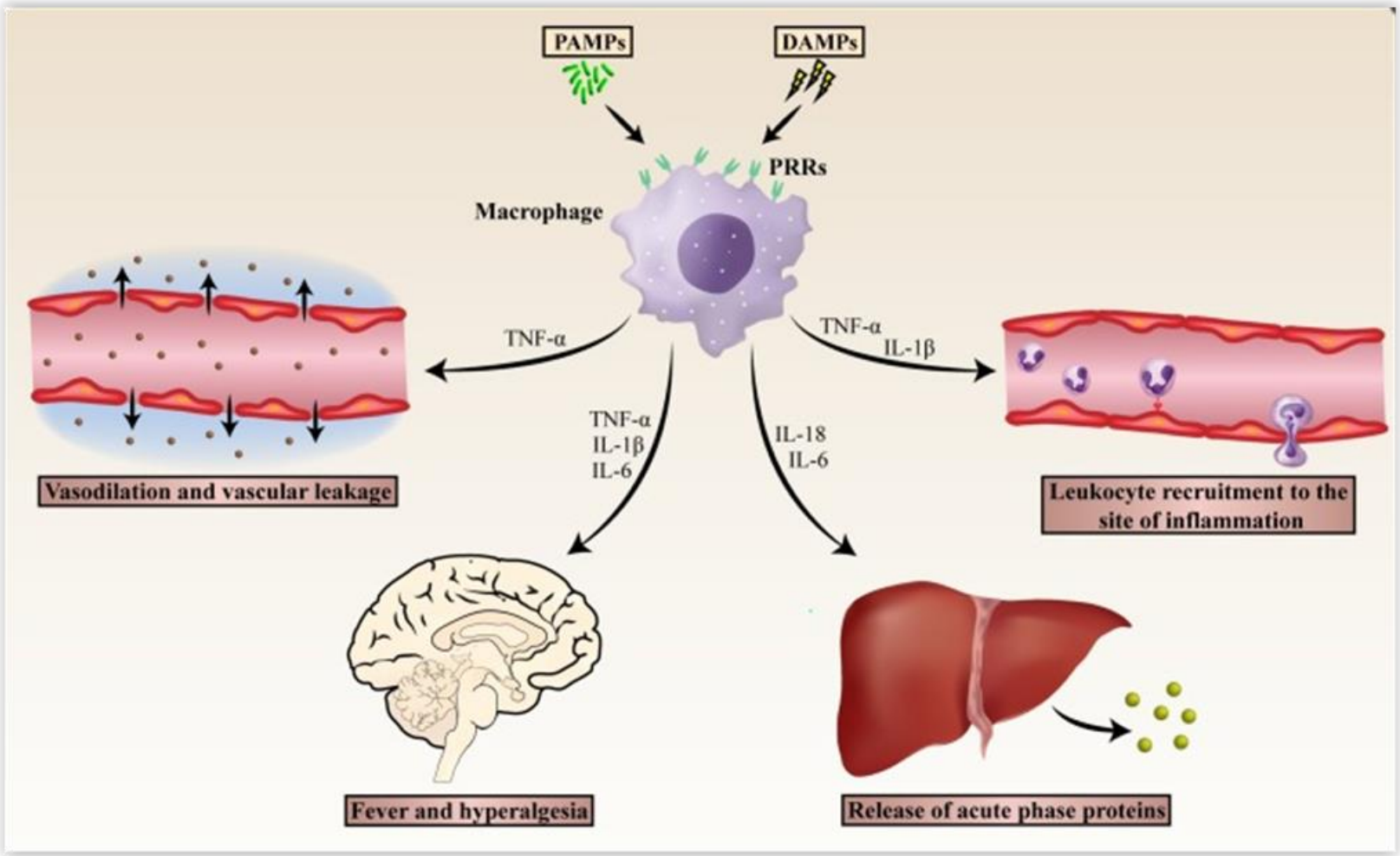
- **The big three**
  - Inflammatory, infectious:
    - persistent,
    - undertreated,
    - increased susceptibility
  - Inflammatory, non-infectious
    - Autoimmune
    - Autoinflammatory
  - Mostly inflammatory
    - Malignancies

- **The little three**
  - Mostly non inflammatory:
    - Munchausen,
    - Drug fever,
    - Benign hyperthermia

- **Miscellaneous**
  - Varous mechanisms
    - Central fever
    - Dehydratation…

Kallinich T., Allergy 2013, EAACI Position paper

Systemic inflammatory response



Pathophysiological changes in systemic inflammatory response

- Neuroendocrine changes
  - Fever, somnolence, fatigue and anorexia
  - Increased adrenal secretion of cortisol, adrenaline and glucagon
- Haematopoietic changes
  - Anaemia
  - Leucocytosis
  - Thrombocytosis
- Metabolic changes
  - Loss of muscle and negative nitrogen balance
  - Increased Lipolysis
  - Trace metal sequestration
  - Diuresis
- Hepatic changes
  - Increased blood flow
  - Increased acute phase protein production

Gabay and Kushner, NEJM, 1999

Acute phase response from hepatocytes

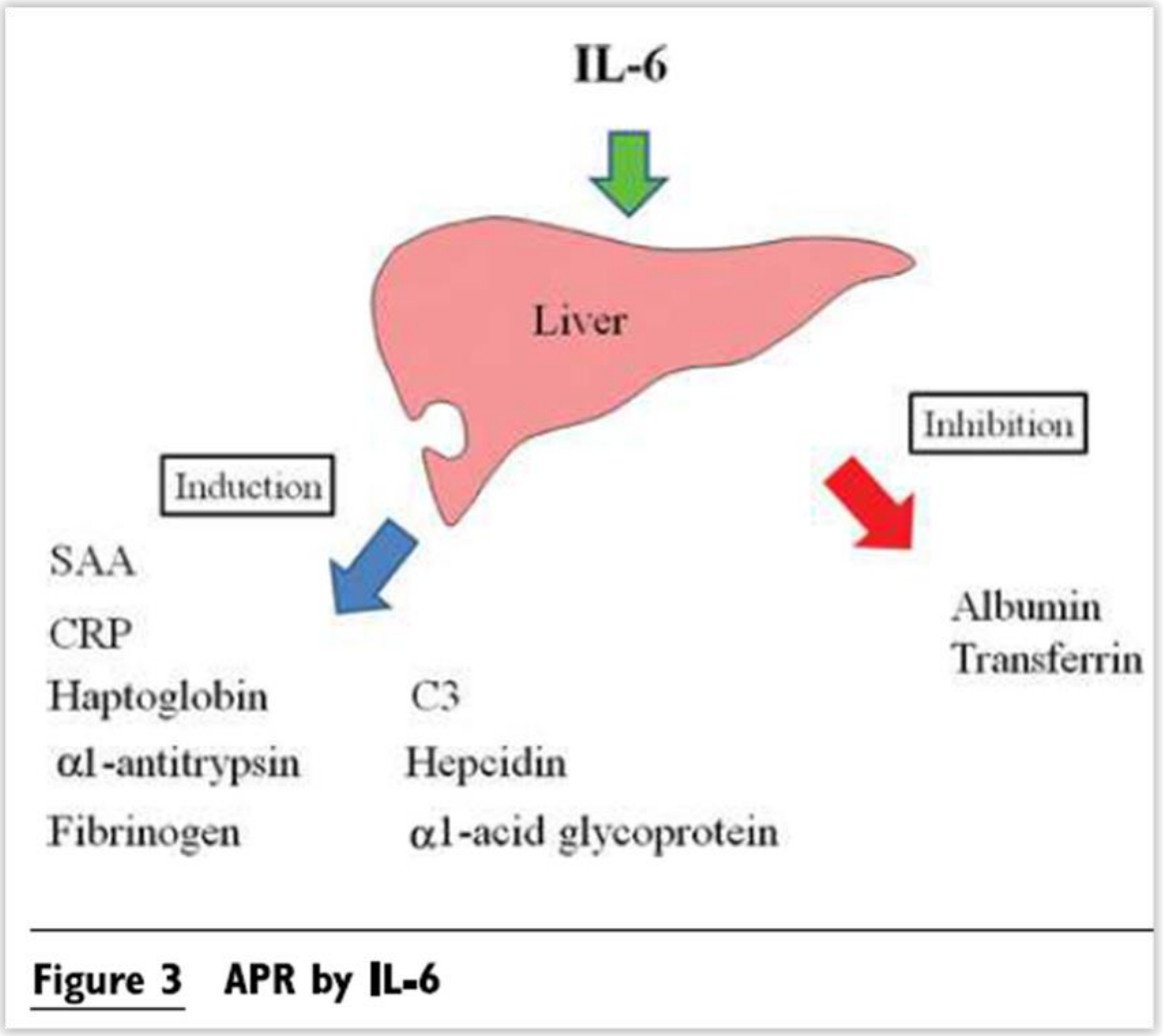
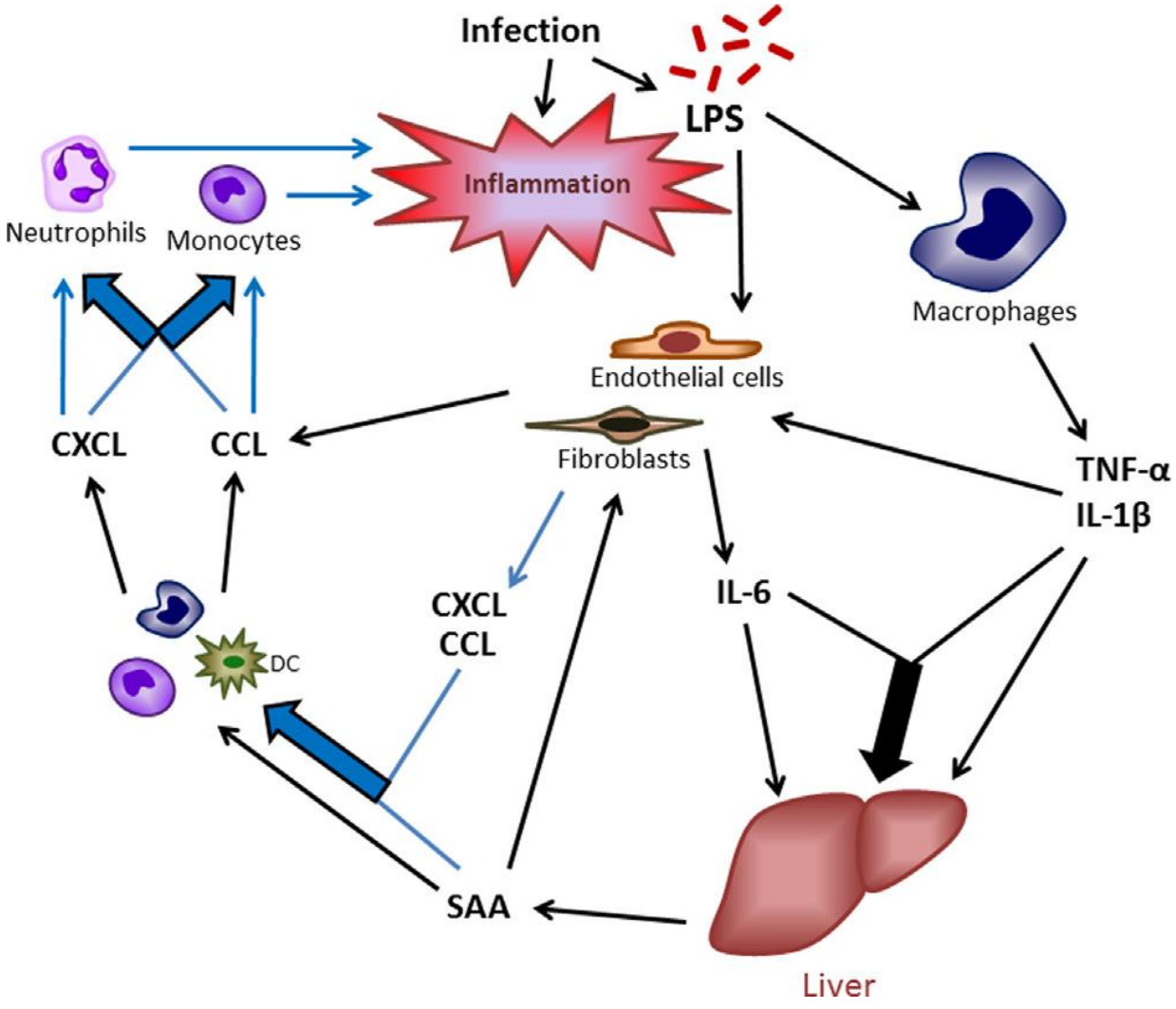


Figure 3 APR by IL-6

Complex interplay of cells and stimuli



CRP versus ESR: non-sense debate?

- **ESR: global evaluation with many pitfalls**
  - Used for its negative predictive value (*no inflammatory syndrome*)
  - Depend of viscosity, cells ,Ig and fibrinogen mostly
  - Most often concordant with CRP as screening
  - ESR >100 mm/Hour : infection 40%, endocarditis…
    - Malignant and renal 30%
    - Inflammatory systemic dis. 20%, Thyroid and Horton…
- **CRP: convenient, reactive acute phase protein marker**
  - Mostly produced by hepatocytes in response to IL-6
  - Highest increase in infections,
  - Very dynamic changes >1000 folds increase
  - Monitoring of the inflammatory state (resolution or treatment response)
  - hsCRP: useful to assess baseline CRP; associated with increased vascular risk
  - Low grade inflammation: 3-10 mg/L usually without clinical symptoms

ESR

Increased ESR	Decreased ESR
Acute Heavy Metal Poisoning	Congestive heart failure
Collagen Vascular Disease	Polycythemia
Carcinomas	Sickle Cell Anemia
Cell or tissue injury	
Gout arthritis	
Infections	
Inflammatory disorders	
Leukemia	
Myocardial infarction	
Nephritis	
Syphilis	

Factors causing false increases	Factors causing false decreases
Increased fibrinogen, globulin, cholesterol levels	Cachexia
High room temperature	Coagulation of the blood sample
Macrocytic anemia	Increase in bile salts
Menstruation	Increase in phospholipids
Pregnancy	Making the sedimentation sample wait more than two hours
Tilting or lying down of the ESR tube	Increase in adrenal steroids
Drugs: Dextrane, methyldopa, methysergide, penicillamine, procainamide, teophylline, trifluoperidole, vitamin A	Hypofibrinogenemia
	Hyperglycemia
	Hyperalbuminemia
	Leukocytosis
	Microcytic anemia
	Drugs: ACTH, cortisone, ethambutol, quinine, salicylates

(Adapted from A Textbook of Natural Medicine, Pizzorno and Murray, 1992)

Acute phase proteins and the systemic inflammatory response

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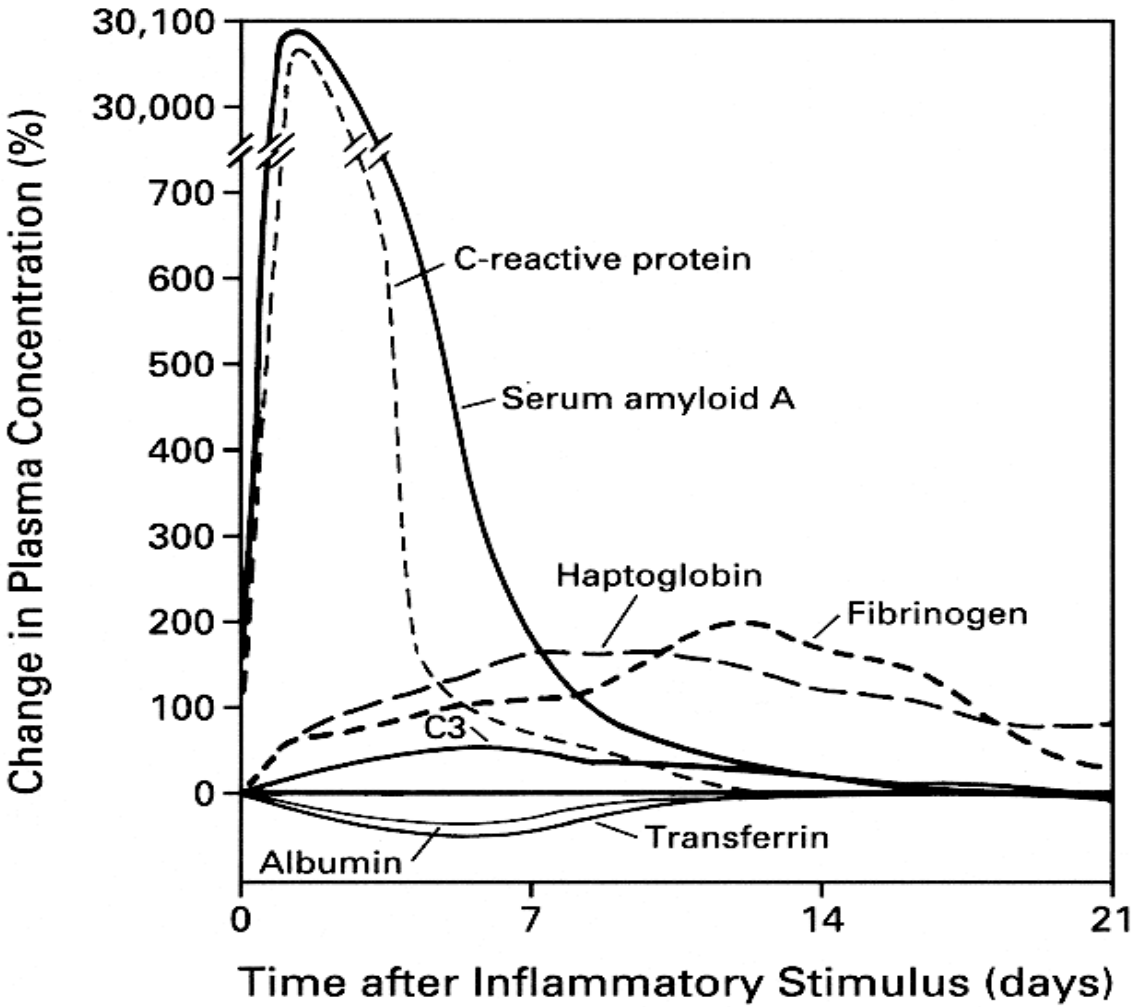

4 general stimuli:

1. Injury, trauma
2. Infection (Procalcitonin)
3. Inflammatory diseases (autoimmunity and autoinflammatory)
4. Many cancer

Gabay and Kushner, 1999

C-reactive protein in patients undergoing curative surgery for colorectal cancer

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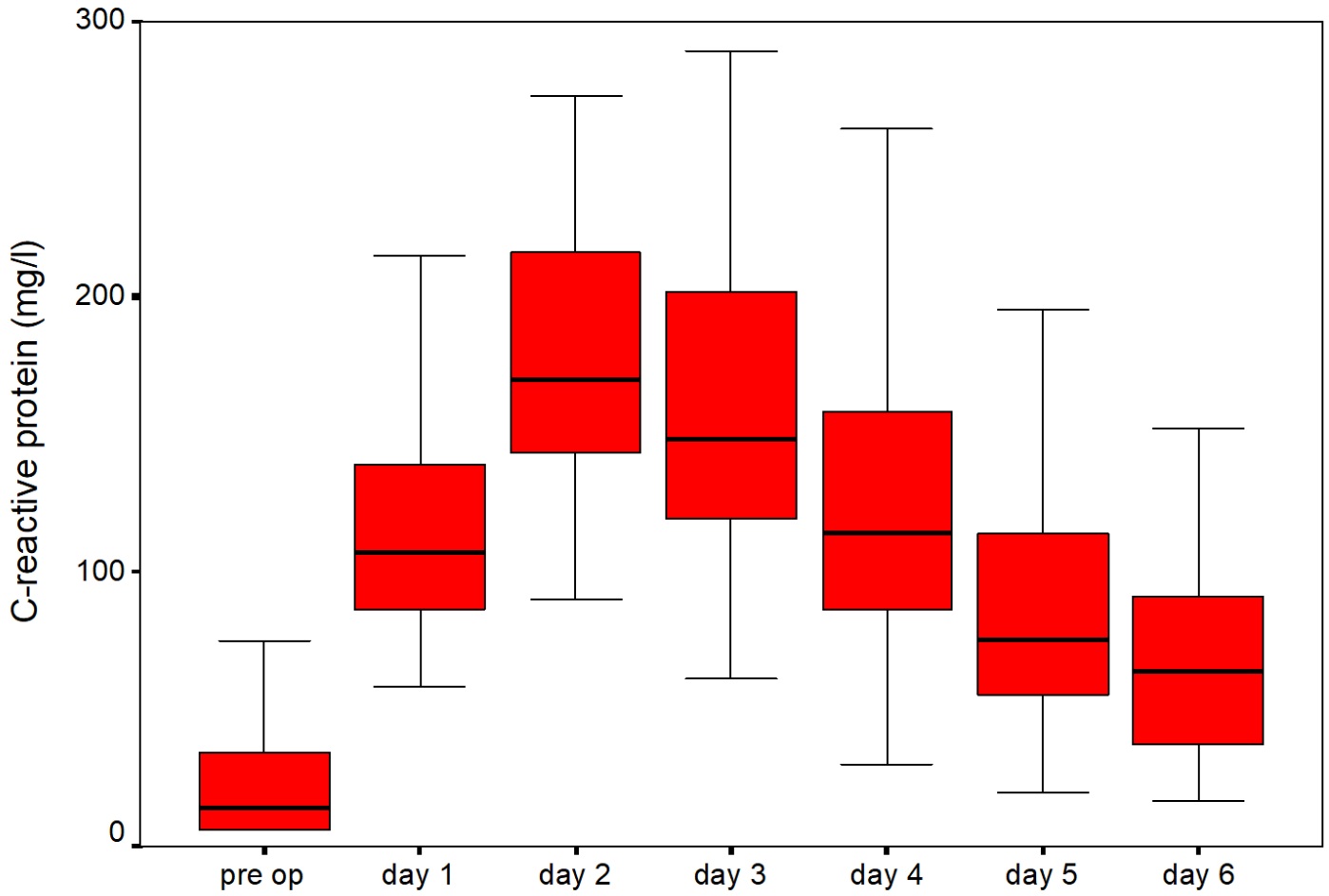


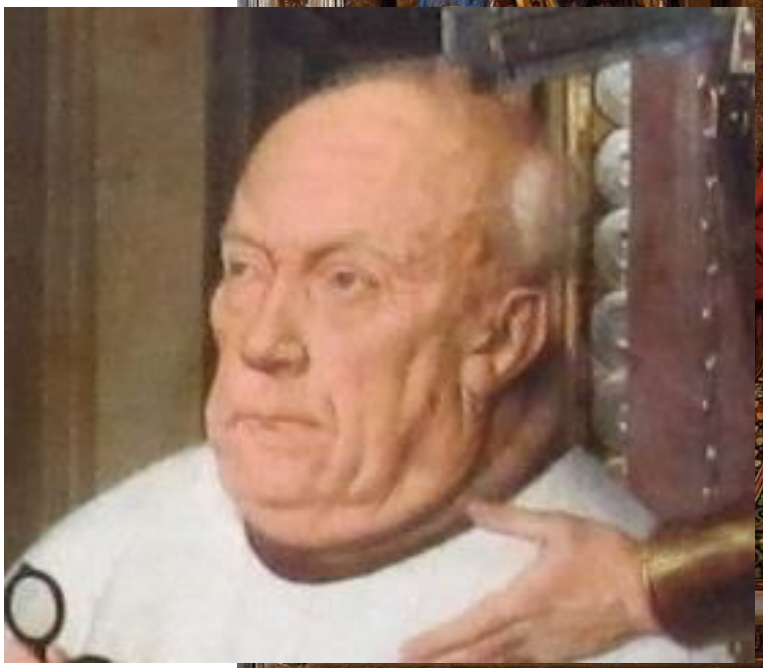
Crozier et al., 2004

Assays of inflammatory markers and clinical use

Marker	Stability	Assay availability	Standard available	Interassay variability	Cost
ESR	Unstable	everywhere	yes	10%-15%	low
hsCRP	Stable	everywhere	yes	<10%	low
Procalcitonin	Stable	everywhere	yes	<15%	high
Fibrinogen	Stable	everywhere	yes	<10%	low
Ferritin	Stable	everywhere	yes	<10%	medium
Serum amyloïd A	Stable	few	yes	<10%	medium
Cytokines (IL-6, IL1RA, TNF)	Unstable unless frozen	few	yes	<20%	high

Dayer, Nature clinical rheumatology practice, 2007

Investigation of inflammatory syndrom
A daily clinical question for physician



K.E. (12.07.1952, F,)
Scanner Total Body du 22.07.2016

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Indication

- **Female 65 y, Febrile with inflammatory syndrom, CRP:122 mg/L without clear clinical localisation.**
- **Nuccal headache irradiating in the temporal regions of the head**
- **Left carotid artery examination normal. Painful cervical spine mobilisation**
- **Differential diagnosis : GCA (Horton), spondylodiscitis ?**

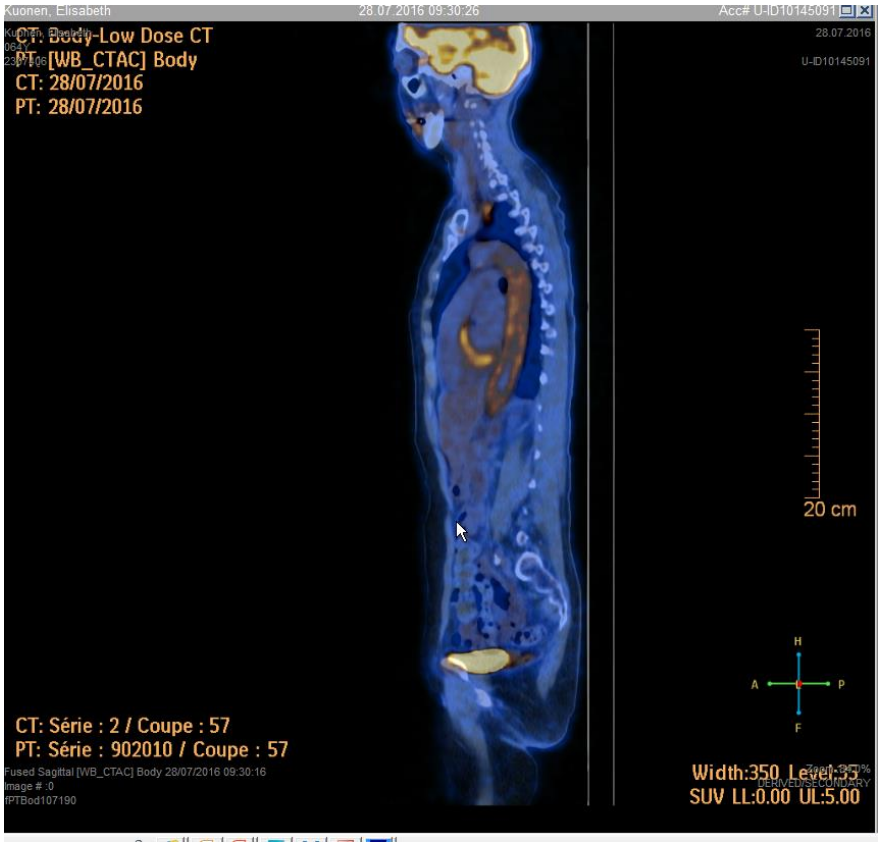
Investigations

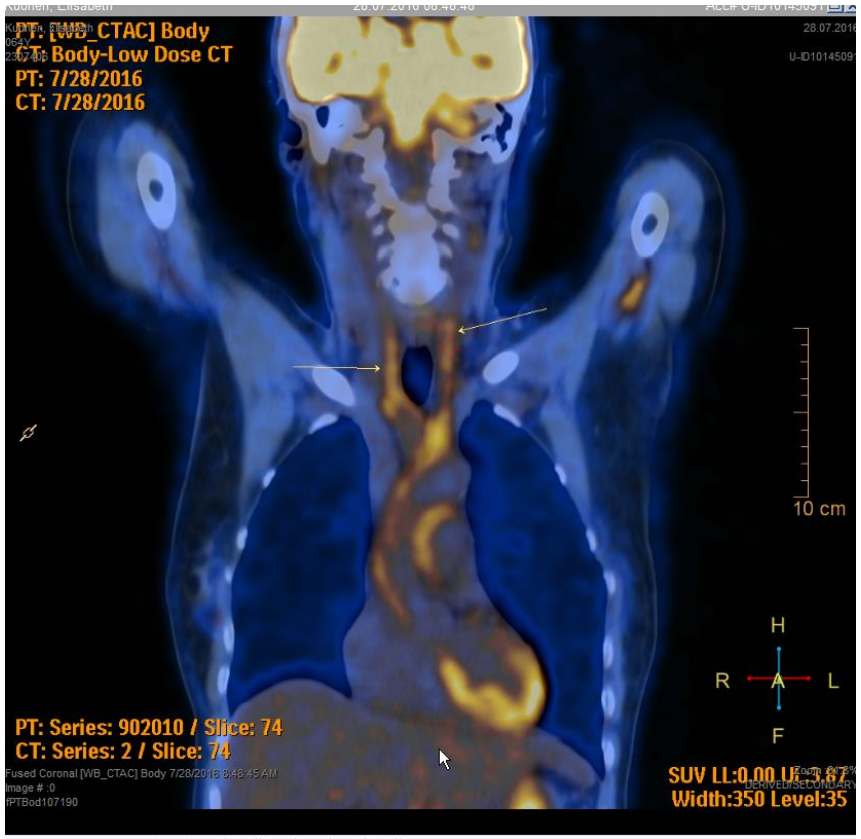
- **Carotid and Temporal Doppler was normal, NO halo sign**
- **Uniteral temporal biopsy was negative**

CT scan conclusion

- **No carotid dissection found.**
- **Circonferential peri-aortic hypodensity of the aorta ascending, as well as thoracic, abdominal aorta, suggestive of large vessel vasculitis**

PET computerized tomography was performed





GCA: Criteria American College of Rheumatology (Chapel Hill 2012)

- **CRITERIA ACR: Giganto-cellular Arteritis (GCA) Horton**

1. **Beginning of symptoms ≥50 years**
2. **New headache**
3. **Temporal arteritis anomaly (pain or no pulse)**
4. **High ESR(≥50 mm/H) or CRP > 50 mg/L**
5. **Temporal artery inflammation at the biopsy**
   - monocellular inflammation or
   - granulomatous inflammation, often with multinucleate giant cells

- **If >3 criteria = Sensitivity 93,5% and specificity 91,2%,**

Giganto-cellular arteritis:
« classical » Horton ± large vessel vasculitis

If typical symptoms : headache, temporal artery modifications, TA biopsy +

-> classical diagnosis (ACR)

BUT isolated aortic or large vessel inflammation are often expressed only by inflammatory markers and no classical signs (> 50% of GCA have aortic involvement)

-> Need of radiologic evaluation (PET-CT / angioIRM)

Biomarkers in the management of Giant-Cell Arteritis and Polymyalgia Rheumatica.

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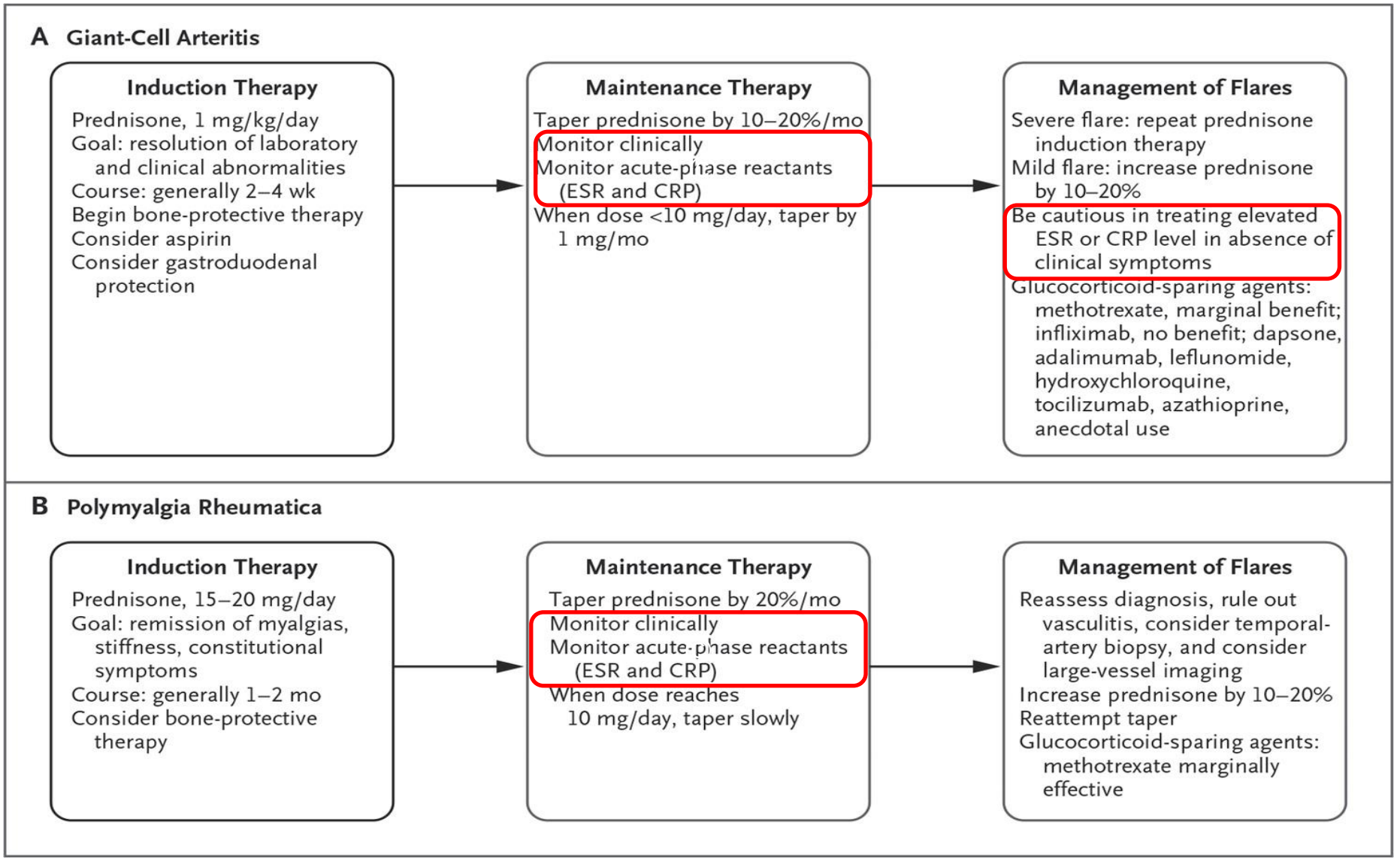

Weyand CM, Goronzy JJ. N Engl J Med 2014;371:50-57.

Disease activity score in rheumatoïd arthritis

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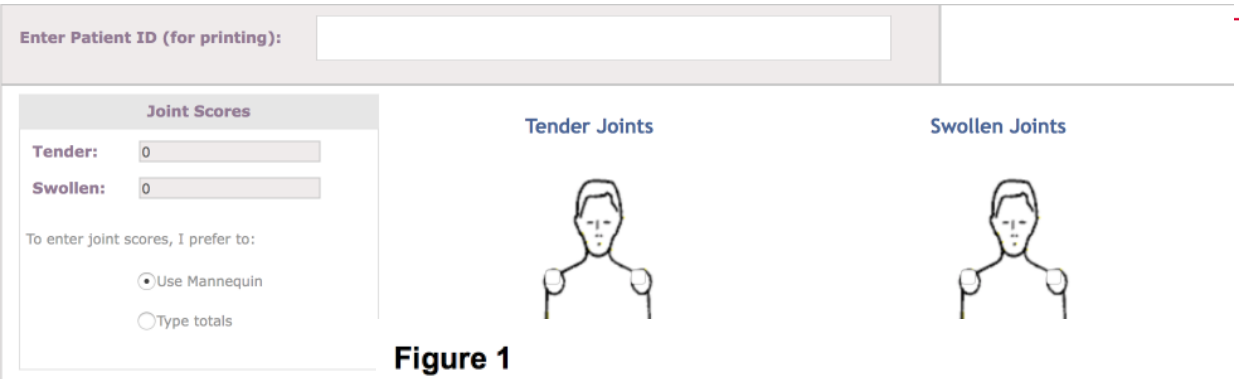


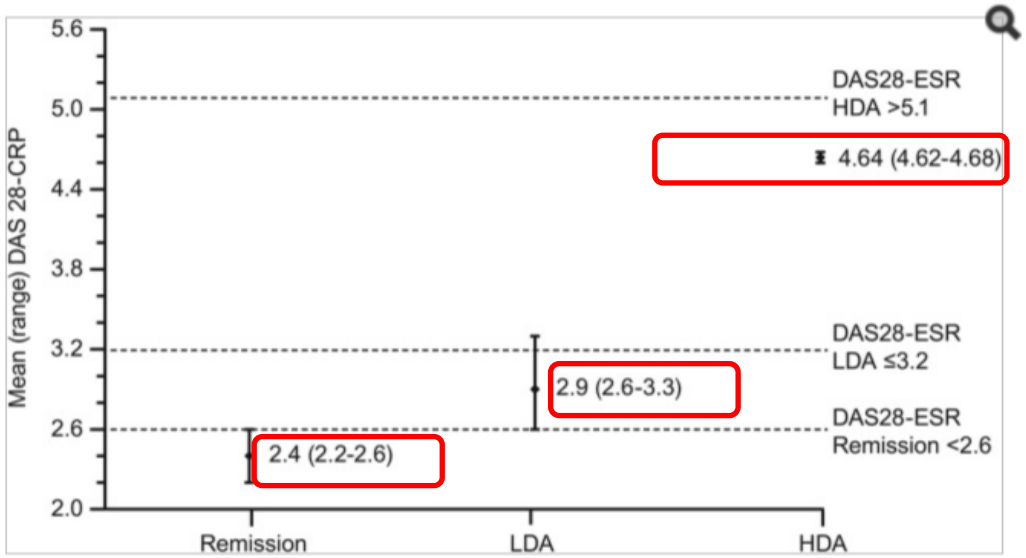
3 levels

HDA: high disease activity

LDA: low disease activity

Remission

Figure 1



DAS28-CRP cut-off values corresponding to the DAS28-ESR cut-off values for remission, LDA and HDA, average of three statistical approaches. Cut-offs for remission and LDA are from Fleischmann *et al.*[13] DAS28-CRP, Disease Activity Score in 28 joints calculated with C reactive protein; DAS28-ESR, Disease Activity Score in 28 joints calculated with erythrocyte sedimentation rate; HDA, high disease activity; LDA, low disease activity.

Essential

to define

treat to target

CRP and DAS28-ESR cut-offs for high disease activity in rheumatoid arthritis are not interchangeable.

Fleischmann RMD Open 2017

Acute phase proteins during infection

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Changes in circulating concentrations of acute phase proteins during infections.

	Viral and Bacterial Infections
CRP	Stimulated by both viral and bacterial infections, but reaches higher values during bacterial infections [44, 77, 78]
SAA	
Procalcitonin	
Ferritin	Elevated in viral infections [47, 56]
Retinol	Decreased during infections [79]
Haptogloblin	Not significantly different between neonates with and without an infection [80]
α1-antitrypsin	
LPS binding protein	Elevated in bacterial infections as compared to viral infections [68]
sTREM-1	
Neutrophil lipocalin	More elevated in bacterial infections as compared to viral infections [81]

CRP: C-reactive protein; SAA: serum amyloid A; sTREM-1: soluble triggering receptor expressed on myeloid cells-1.

Table 1. Diagnostic Criteria for Sepsis, Severe Sepsis, and Septic Shock.*

Sepsis (documented or suspected infection plus ≥1 of the following)†

General variables

- Fever (core temperature, >38.3°C)
- Hypothermia (core temperature, <36°C)
- Elevated heart rate (>90 beats per min or >2 SD above the upper limit of the normal range for age)
- Tachypnea
- Altered mental status
- Substantial edema or positive fluid balance (>20 ml/kg of body weight over a 24-hr period)
- Hyperglycemia (plasma glucose, >120 mg/dl [6.7 mmol/liter]) in the absence of diabetes

Inflammatory variables

- Leukocytosis (white-cell count, >12,000/mm^3)
- Leukopenia (white-cell count, <4000/mm^3)
- Normal white-cell count with >10% immature forms
- Elevated plasma C-reactive protein (>2 SD above the upper limit of the normal range)
- Elevated plasma procalcitonin (>2 SD above the upper limit of the normal range)

Hemodynamic variables

- Arterial hypotension (systolic pressure, <90 mm Hg; mean arterial pressure, <70 mm Hg; or decrease in systolic pressure of >40 mm Hg in adults or to >2 SD below the lower limit of the normal range for age)
- Elevated mixed venous oxygen saturation (>70%)‡
- Elevated cardiac index (>3.5 liters/min/square meter of body-surface area)§

Tissue-perfusion variables

- Hyperlactatemia (lactate, >1 mmol/liter)
- Decreased capillary refill or mottling

Severe sepsis (sepsis plus organ dysfunction)

Septic shock (sepsis plus either hypotension [refractory to intravenous fluids] or hyperlactatemia)¶

Procalcitonin and bacterial infection

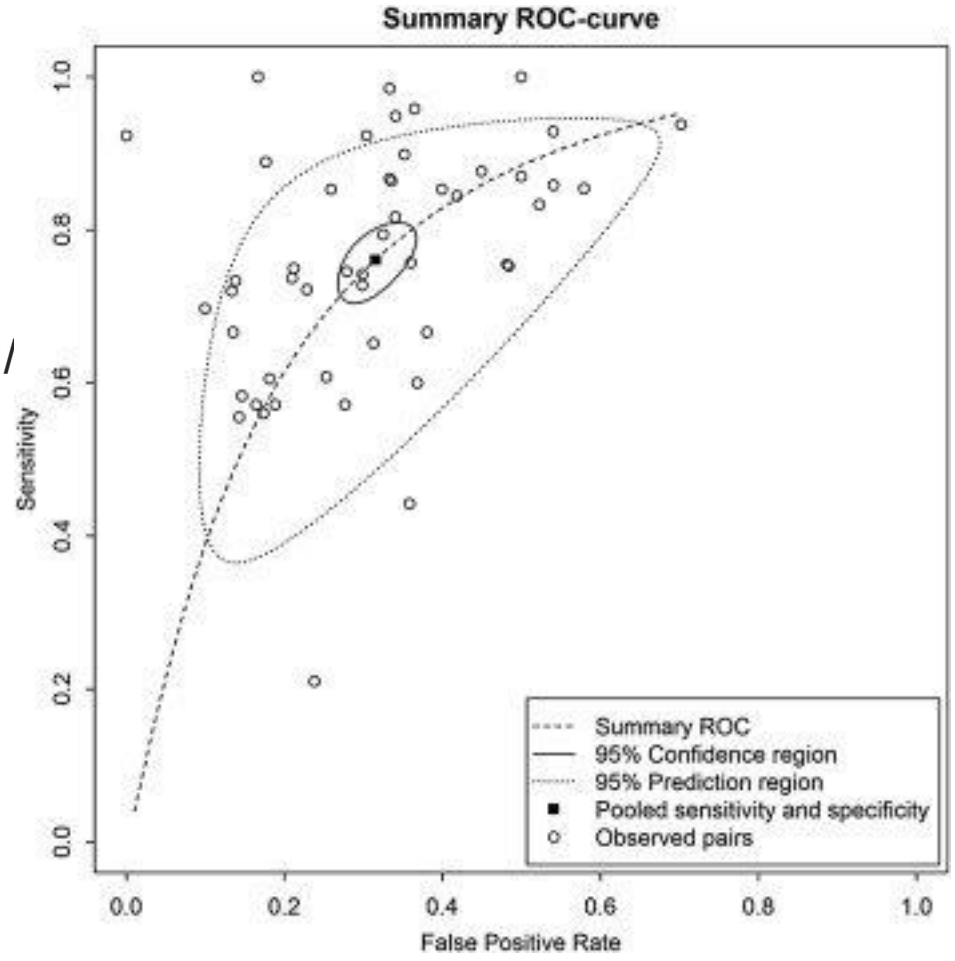
- Normally produced by parafollicular cells in thyroïd
- 100-1000 fold increase in response to endotoxin, produced by most cells.
- Appropriate to improve the diagnosis and followup of bacterial infections in specific settings
- Included in the evaluation of septic shock, **predicts mortality** in emergency and intensive care units
- Inappropriate to exclude bacterial infection in general practrice
- Appropriate to **exclude bacterial infection** in emergency settings
- Appropriate to **limit antibiotic use** and follow resolution of infection in ICU
- **Price issue to be solved** (excessive usage in ICU has to be limited) : high laboratory reagent costs)

Procalcitonin and bacterial infection

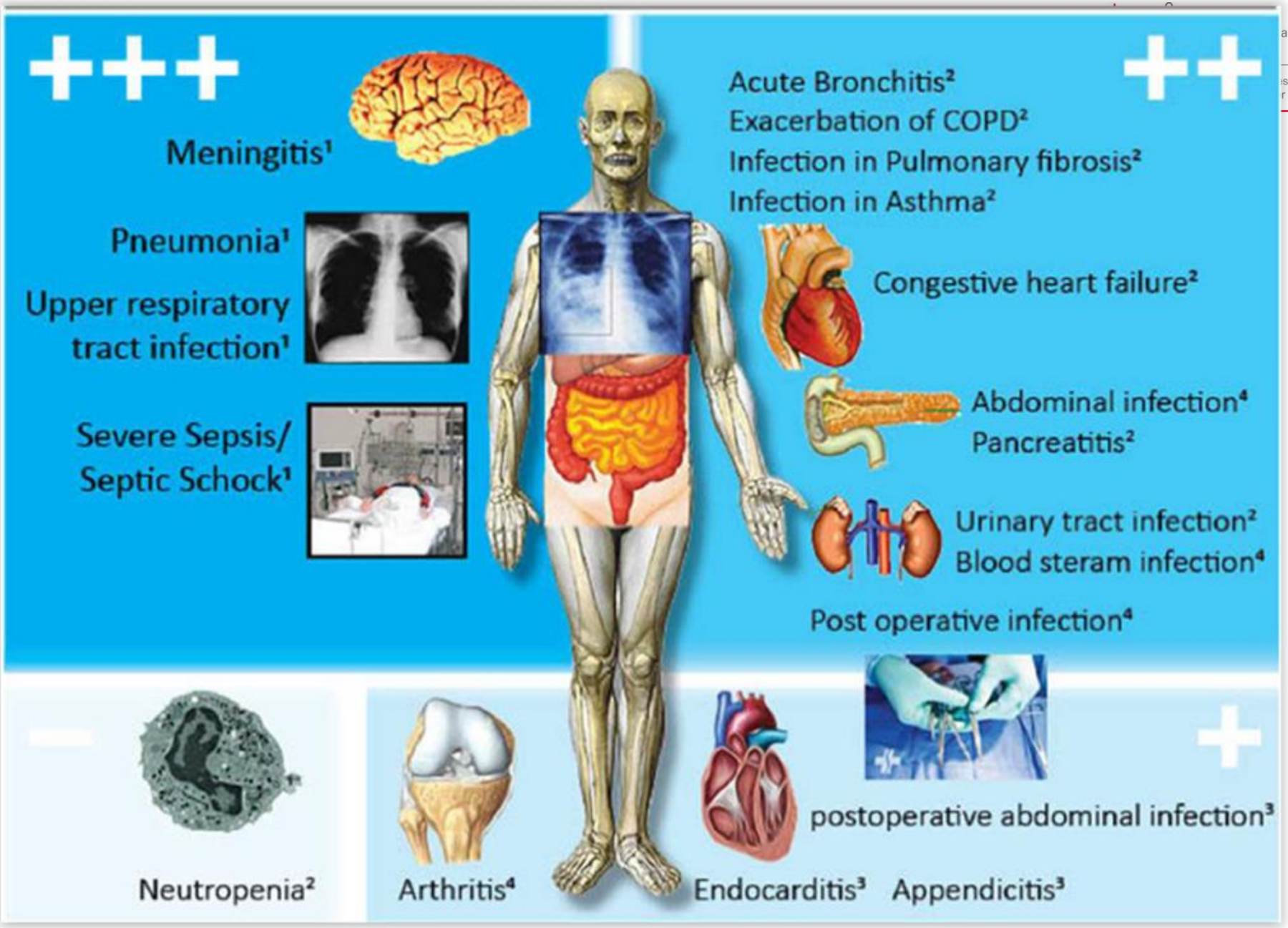
- **To rule out the presence of bacteraemia**

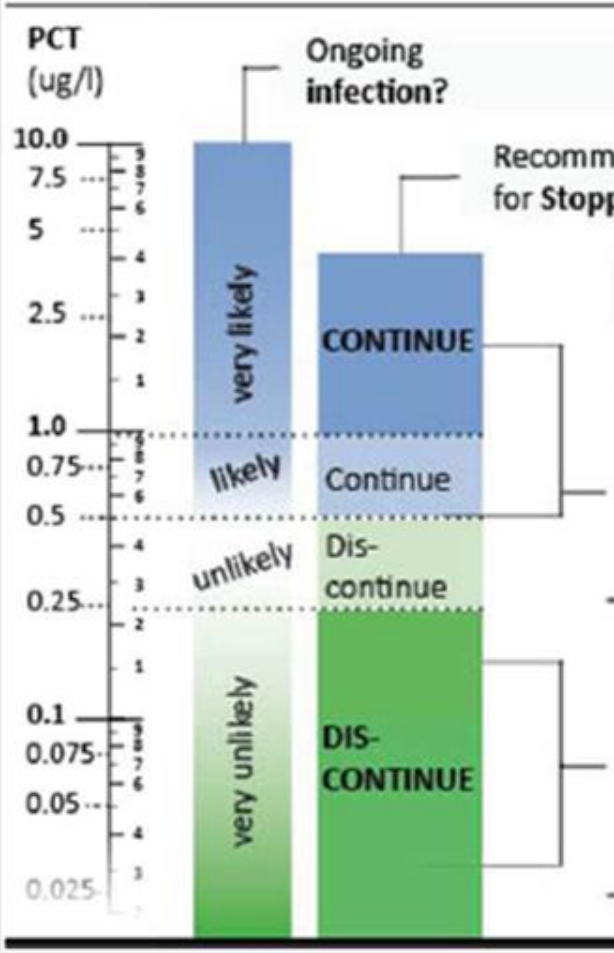
- **SUBGROUPS**
  - Sensitivity ranging
    - from 66% in immunocompromised/ neutropenic patients
    - to 89% in ICU patients
  - Specificities ranging
    - from 55% in bacteraemia versus local infections
    - to 78% in immunocompro-mised/neutropenic patients

- **Biomarker guided therapy?**



Clin Microbiol Infect 2015; 21: 474–481
The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis
S. H. Hoeboer1, P. J. van der Geest1, D. Nieboer2 and A. B. J. Groeneveld1

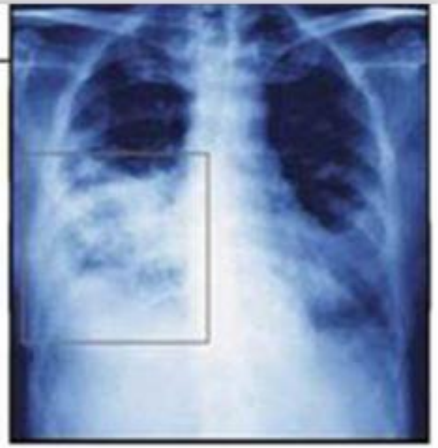

+++
Meningitis¹
Pneumonia¹
Upper respiratory tract infection¹
Severe Sepsis/ Septic Schock¹
++
Acute Bronchitis²
Exacerbation of COPD²
Infection in Pulmonary fibrosis²
Infection in Asthma²
Congestive heart failure²
Abdominal infection⁴
Pancreatitis²
Urinary tract infection²
Blood steram infection⁴
Post operative infection⁴
+
postoperative abdominal infection³
Appendicitis³
Endocarditis³
Arthritis⁴
Neutropenia²

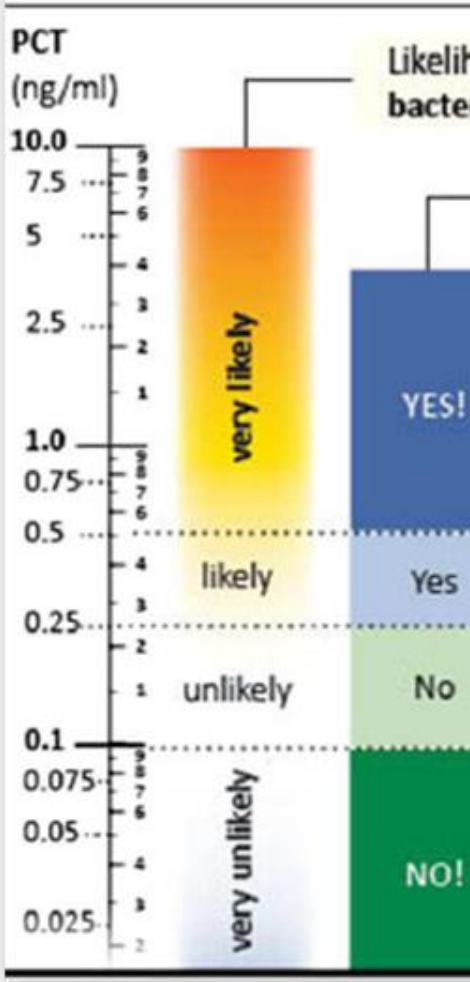


Important considerations and overruling criteria

- Consider the course of PCT
- If antibiotics are continued:
  - Daily measurement of PCT; discontinue antibiotics when PCT decreases >80% of the peak level or an absolute PCT value <0.5ng/ml is reached.
  - If PCT remains high, consider treatment failure.

- Always consider clinical course of patients in addition to PCT levels.
- If Antibiotics are discontinued, close clinical evaluation is recommended.





Likelihood of **bacterial infection**

Recommendation for **antibiotic treatment**

YES!

Yes

No

NO!

Important considerations and **overruling criteria**

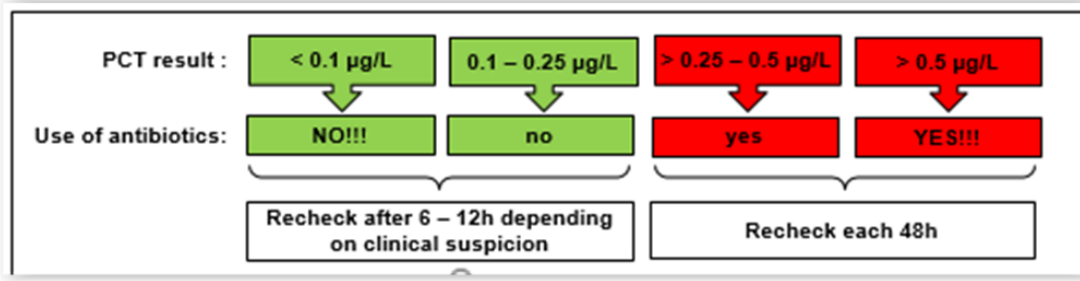
- Consider the course of PCT (dynamic monitoring)
- If antibiotics are initiated:
  - Repeat PCT on days 3, 5, 7; stop antibiotics using the same cut offs
  - if peak PCT levels are very high, then stop when 80-90% decrease of peak
  - If PCT remains high, consider treatment failure

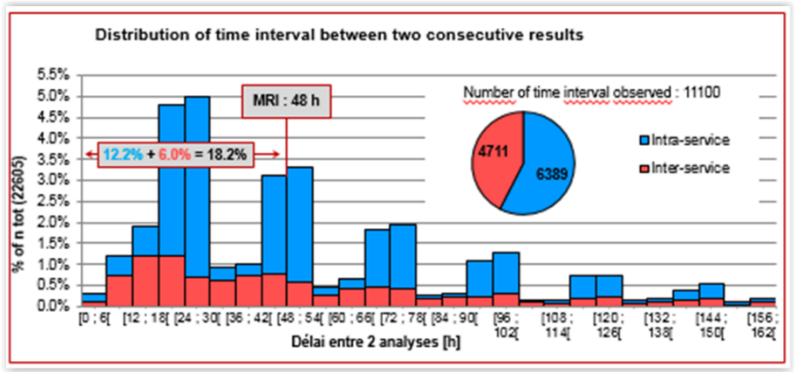
- If Antibiotics are withheld, control PCT after 6-24 hours
- Initial antibiotics can be considered in case of:
  - Respiratory or hemodynamic instability, severest comorbidities, ICU admission
  - PCT < 0.1 ug/L: CAP with PSI V or CURB >3, COPD with GOLD IV
  - PCT < 0.25 ug/L: CAP with PSI IV & V or CURB >2, COPD with GOLD III & IV

Procalcitonin retesting interval and datamining in our institution

Evaluation of the cost of early retesting of PCT

1. 18.2% under 48H set as Minimal Restesting interval (MRI)
2. 80% Due to significant biological variation

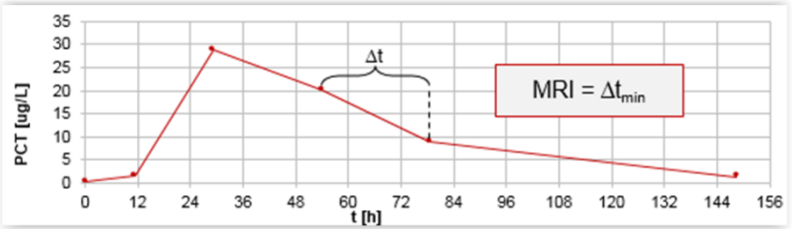


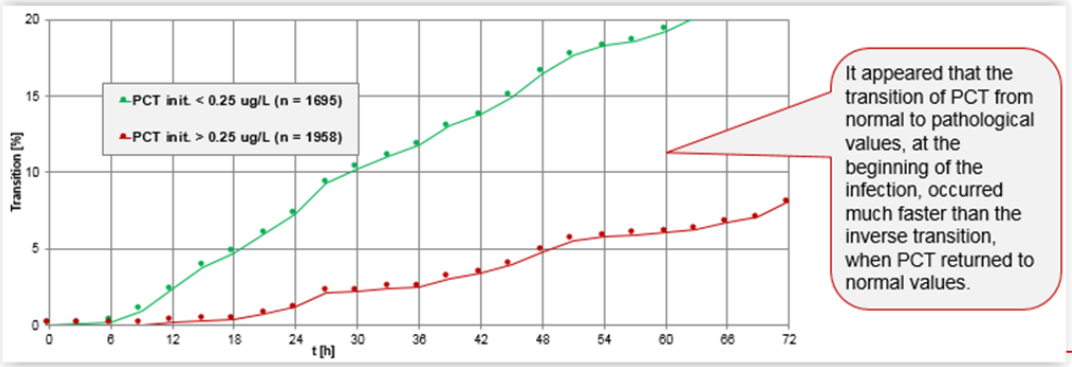


Depending of this algorithm, reevaluation of non conformity is done and the % of non conformity pass from 18.2% to 11.9% :

Initial PCT [µg/L]	MRI	% below MRI
≤ 0.25	6 h	0.1
> 0.25	48 h	11.8

Effort must be done for after initiation of antibiotics treatment when PCT is recheck





It appeared that the transition of PCT from normal to pathological values, at the beginning of the infection, occurred much faster than the inverse transition, when PCT returned to normal values.

USE different MRI in the ascending phase and in the recovery phase to lower the cost

Auto-inflammatory diseases and Inflammasomes:

1. More frequent than expected by the genetic diseases,
2. Exemple: Familial Mediterranean Fever
3. Consequences: AA amyloidosis, but therapeutic option

- **Knowledge from genetic disease such as periodic fevers**
- **Inflammation occuring without pathogens or trauma**
- **Recurrent state with spontaneous resolution in variable duration**
- **Exemple: FMF = Familial Mediterranean Fever**

Major criteria
Typical attacks
1. Peritonitis (generalized)
2. Pleuritic (unilateral) or pericarditis
3. Monoarthritis (hip, knee, ankle)
4. Fever alone
5. Favorable response to colchicine

typical acute attack =
More than 3 febriles identical episodes
And central 38°C
Duration: between12 H et 3 D

And 1 criterium associated
FMF: Se 57% Sp 99%

Arthritis Rheum 1997; 40:1879

Autoinflammation : pathology of the innate immunity

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Autoinflammation		Autoimmunity
INNATE	Immune dysregulation	ADAPTATIVE
Monocytes, macrophages, neutrophils	Predominant cells	T and B cells
IL-1,TNF, IL-12(IL-17), IL18	Cytokines target used	IFN g,IL-4 (IL-17),IL-6
Neutrophil and macrophage organ damage	Pathogenesis of organ damage	Autoantibody, Ag specific T cells
IL-1 mediated autoinflammatory dis.	Diseases examples	Thyroiditis, RA, SLE, ALPS

PAMPS et DAMPS

Pathogen? How are they recognized?

Receptors : -called : pattern recognition recepteurs = PRR

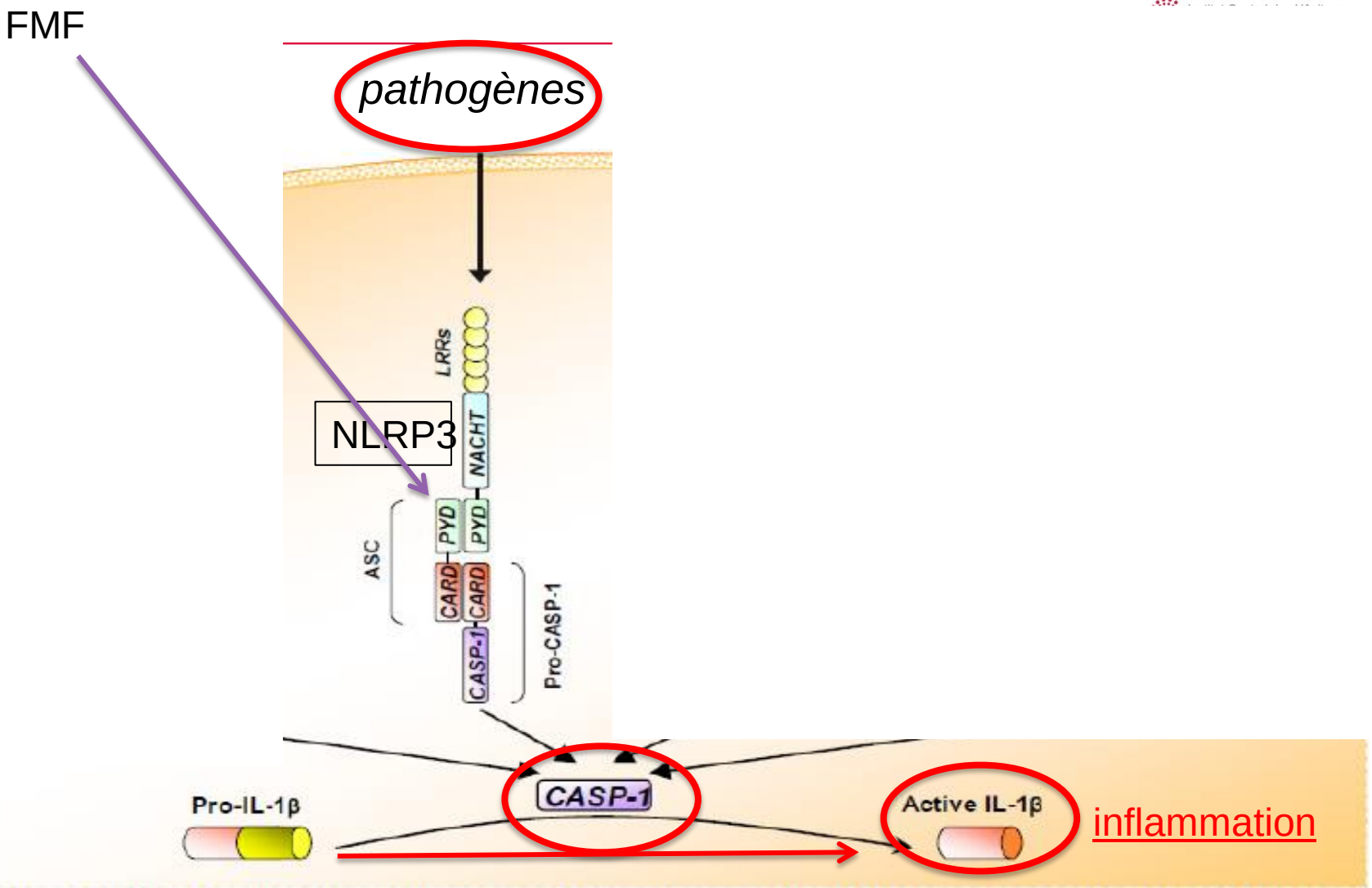
Ligands :

-**PAMPS** : pathogen associated molecular patterns

- conserved structures, essential to microbes,
- absent in mammals
- **LPS, RNA ds, flagellin, oxydative stress,**

-**DAMPS** : danger associated molecular patterns
ATP…

Physiopathology of FMF: Inflammasome



AIM: absent in melanoma; BIRs:baculovirus IAP-repeat; CARD: caspase recruitment domain; CASP: caspase; LRRs:leucin-riche repeats; NACHT:nucleotide binding/oligomerization domain; NAIP: NLR family, apoptosis inhibitory protein; NLRP: nucleotide-binding domain, leucine-rich repeat-containing receptor protein; PYD: pyrin domain

Adapté de Swiss Med Wkly. 2012;142:w13590

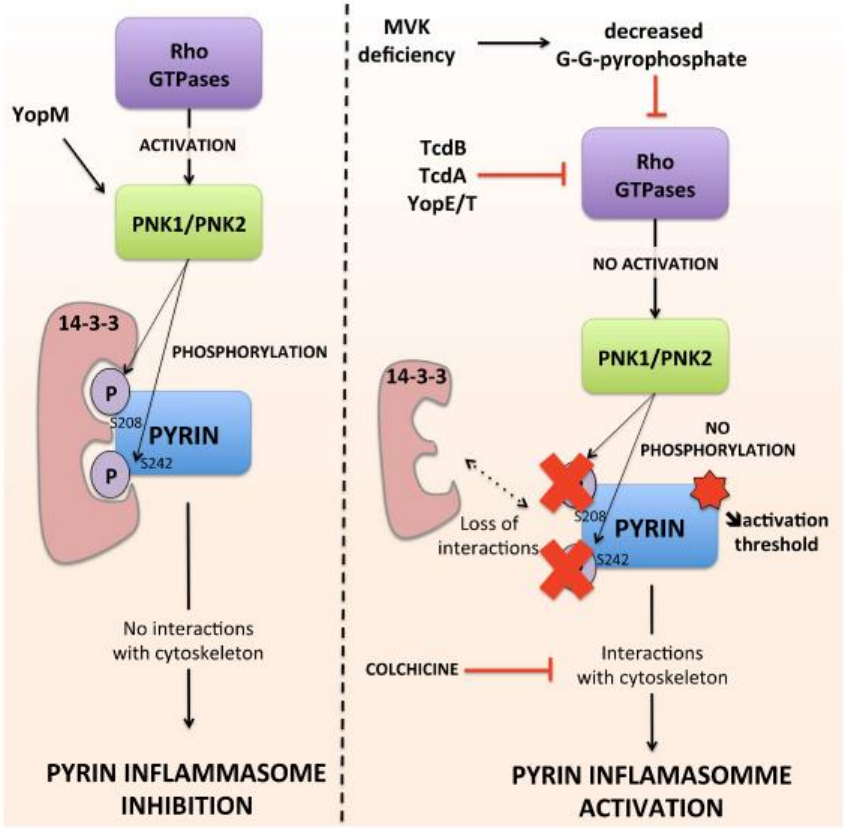
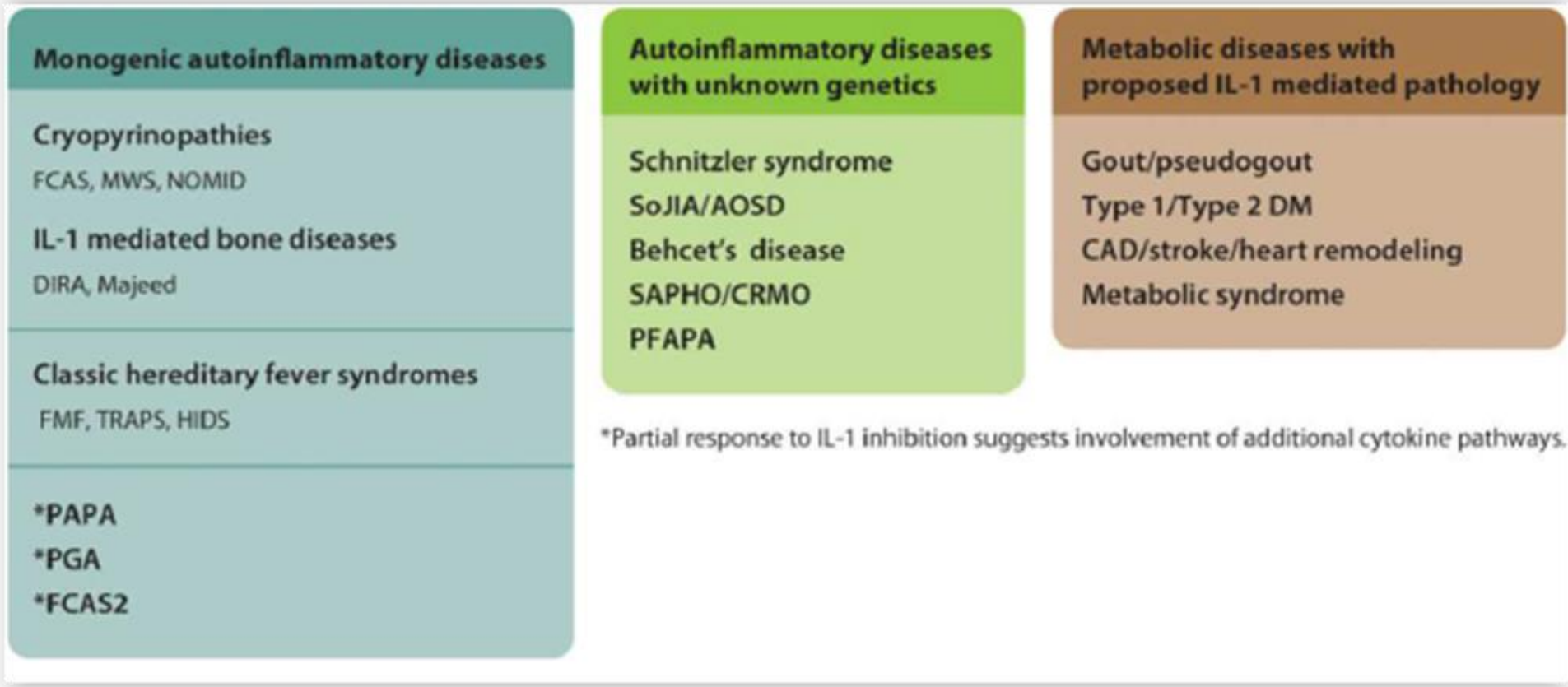


Fig. 2 The pyrin inflammasome. At steady state, the phosphorylation of pyrin on serine residues S208 and S242 by the kinases PKN1/2 results in the interaction of pyrin with 14-3-3 protein, a chaperone which sequesters pyrin and blocks its ability to form an inflammasome. Decreased geranyl-geranyl pyrophosphate (secondary to deficiency in mevalonate kinase, MVK) or addition of toxins A or B from *Clostridium difficile* or YopE/T from *Yersinia pestis* inactivate the Rho GTPases, leading to inactivation of the kinases PKN1/2. This inhibition results in the dephosphorylation of pyrin, its release from the 14-3-3 protein, the activation of the pyrin inflammasome and its interaction with microtubules, and the release of IL-1β. *MEFV* mutations associated with familial Mediterranean fever (*red star*) decrease the threshold of activation of the pyrin inflammasome. Colchicine inhibits the interaction of the pyrin inflammasome with the cytoskeleton

Autoinflammatory diseases



Chronic Inflammation

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Pro-inflammatory markers

IL-1 beta
IL-6
TNF-α

Anti-inflammatory markers

TGF-β
IL-12
Inducible IL-35

IL-6, interleukin 6; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β

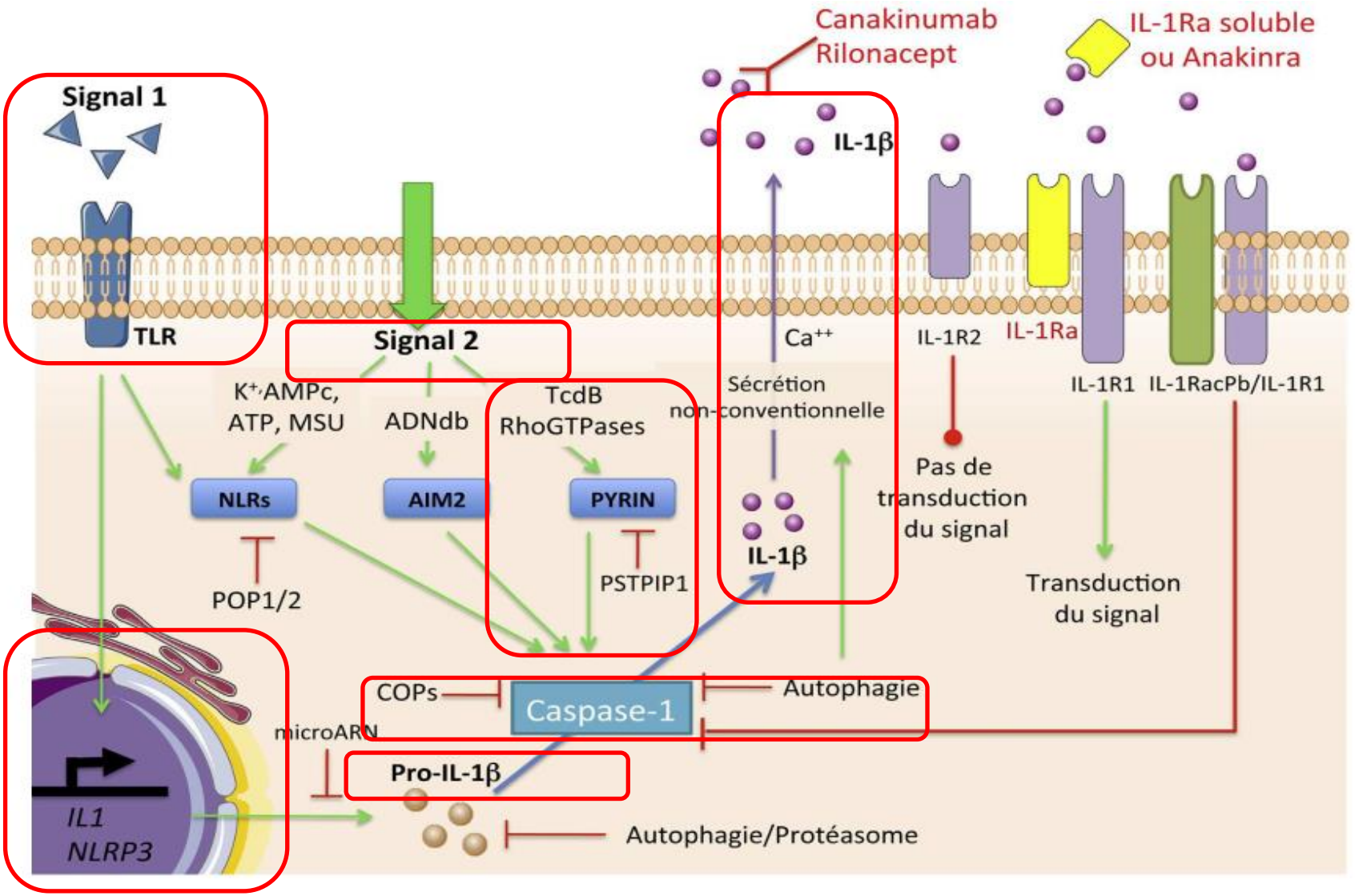
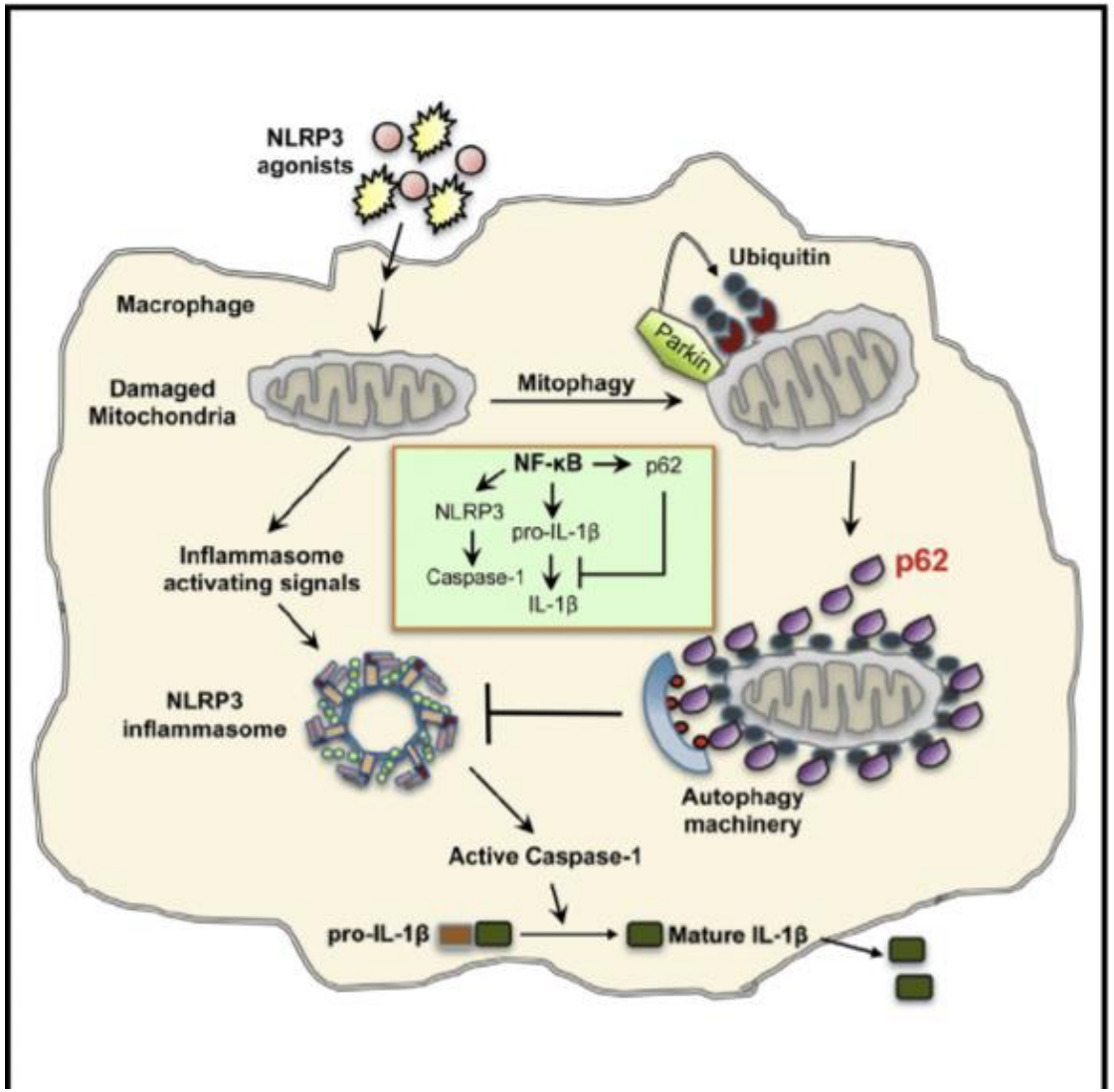


Fig. 1. Principaux mécanismes régulateurs de la voie de l'interleukine-1β. Un signal 1, ligand d'un *toll-like receptor* (TLR), est nécessaire pour pré-activer la voie de l'interleukine (IL)-1β et la transcription des gènes de l'IL-1 et du *NOD-like receptor, pyrin domain containing 3* (NLRP3). Des micro-ARN peuvent inhiber par compétition les ARN de ces protéines. Un signal 2, spécifique, est ensuite requis pour activer chacun des récepteurs de l'inflammasome : efflux de potassium (K+), modification de l'AMP cyclique, ATP ou cristaux d'urate monosodique (MSU) pour le récepteur NLRP3 ; ADN double brin (ADNdb) pour le récepteur *absent in melanoma 2* (AIM2) ; ou toxine B du *C. difficile* (TcdB) pour le récepteur pyrine. Diverses protéines peuvent inhiber ces récepteurs : les *pyrin-only proteins* (POP)1/2 pour les NLR et *proline-serine-threonine phosphatase-interacting protein 1* (PSTPIP1) pour la pyrine. L'inflammasome activé entraîne l'activation de la caspase-1 et le clivage de la pro-forme de l'IL-1β. La caspase-1 peut être inhibée par les COP (*CARD-only proteins*). L'autophagie joue un rôle régulateur à différent niveau : diminution de la quantité de pro-IL-1β disponible, dégradation de la caspase-1 et du complexe inflammasome, sécrétion de l'IL-1β activée via l'auto-phagosome. Une fois sécrétée, l'IL-1β exerce son effet via divers récepteurs, qui peuvent transduire ou inhiber le signal. Enfin, certains récepteurs solubles ou anticorps, endogènes ou synthétiques, ont un rôle inhibiteur sur la voie de l'IL-1β (comme l'IL-1Ra, le récepteur antagoniste du récepteur de l'IL-1).

Spontaneous recovery linked to autophagy..



Zhenyu Zhong, Atsushi Umemura, Elsa Sanchez-Lopez, ..., Maria T. Diaz-Meco, Jorge Moscat, Michael Karin

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In Brief

NF-κB restrains its own inflammation-promoting activity in macrophages by promoting p62-mediated removal of mitochondria that have been damaged after macrophages encounter various NLRP3-inflammasome activators.

Schematic drawing depicting SAA synthesis and interaction with its receptors.

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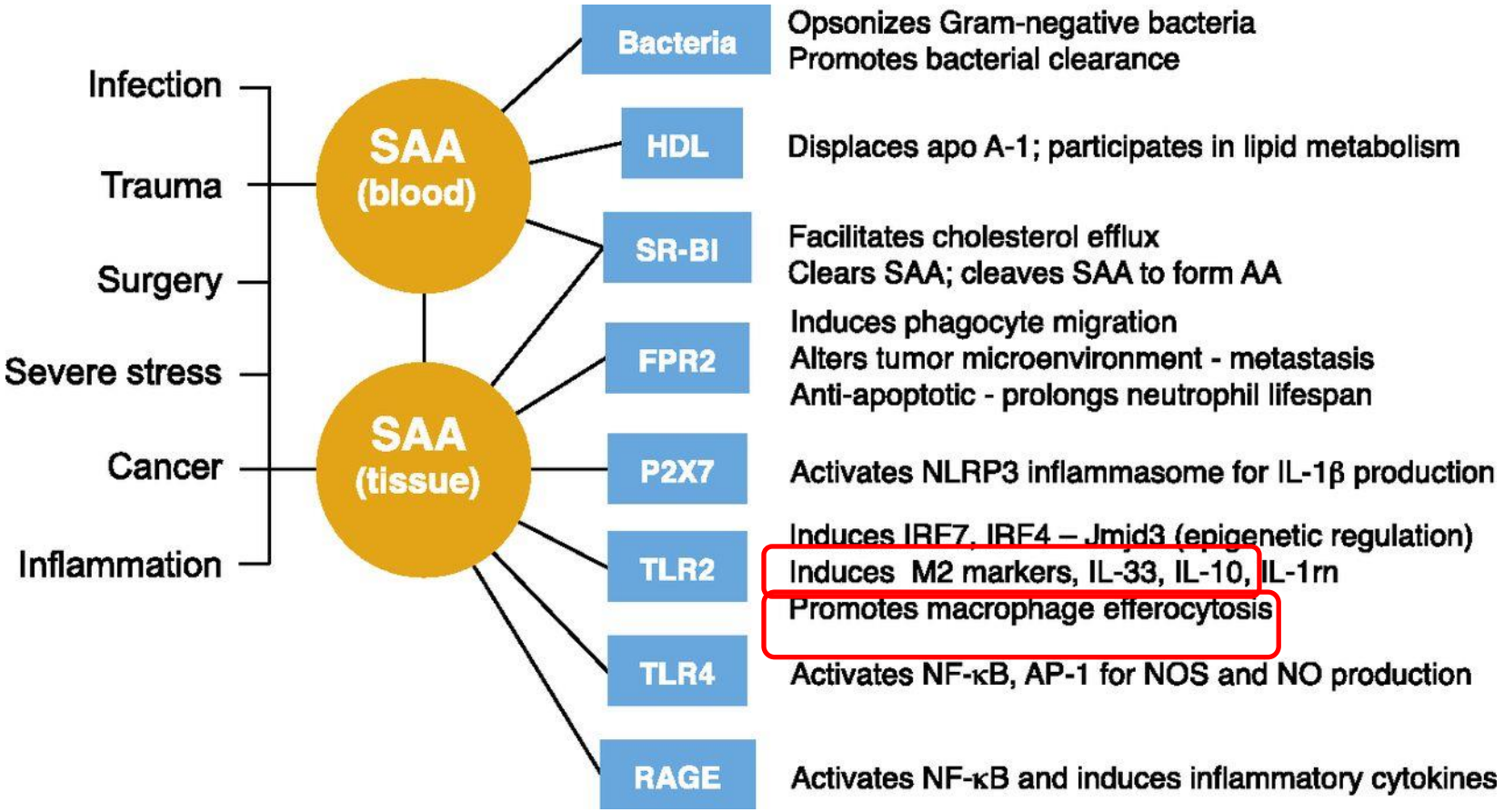


Richard D. Ye, and Lei Sun J Leukoc Biol 2015;98:923-929

SAA for auto-inflammatory diseases

- **Linked to inflammasome associated disease with persistent elevated levels**
- **Up to 40% of recurrent fevers develop secondary AA amyloïdosis**
- **Potent inducer of IL1 via TL2 and 4….**
- **But also an inducer of recovery mechanism like M2 macrophage, Il-10…**
- **Can be used as a marker of response to treatment**

Serum Amyloïd A (SAA)

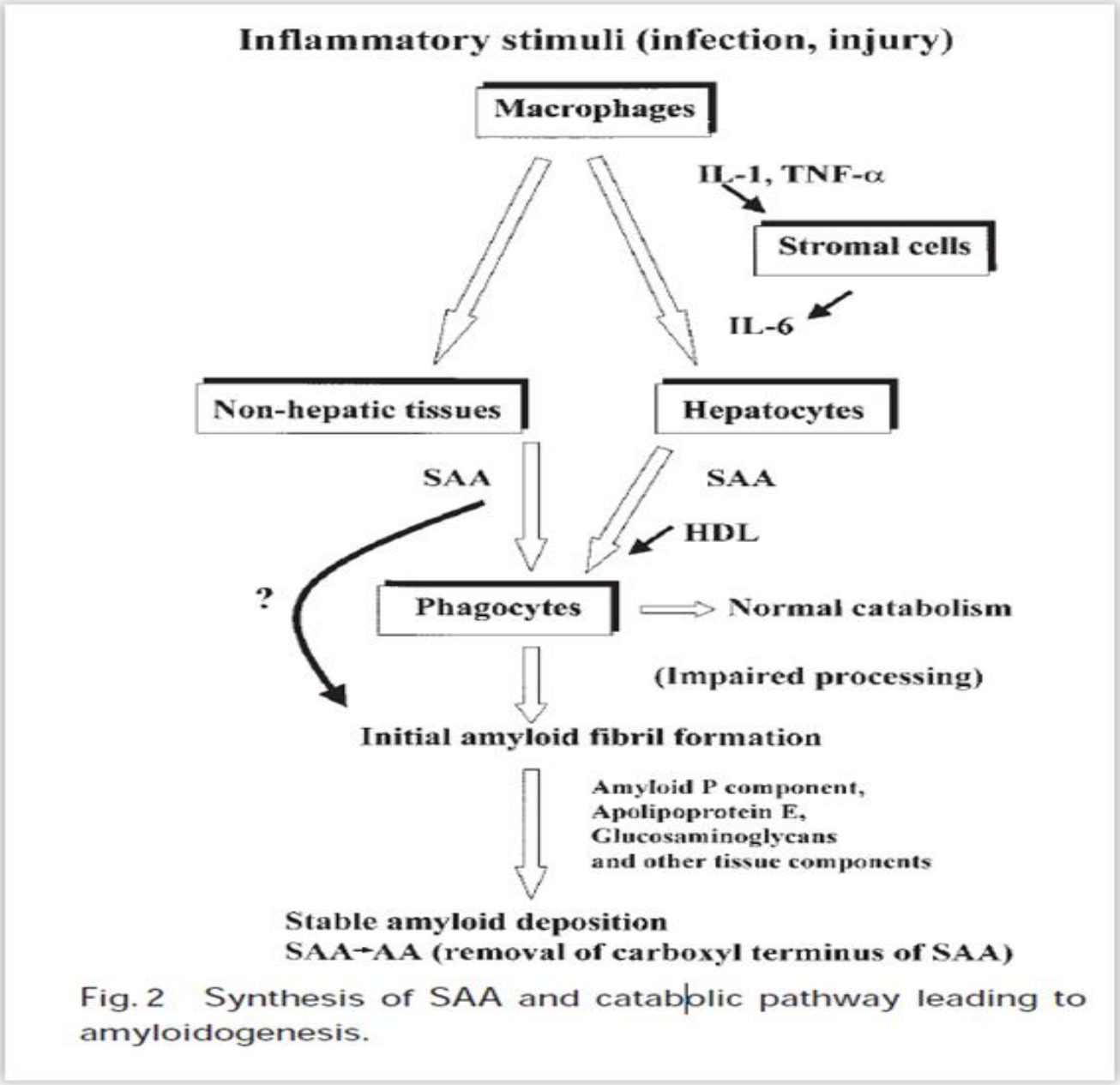


Fig. 2 Synthesis of SAA and catabolic pathway leading to amyloidogenesis.

Predictors of mortality in AA amyloïdosis

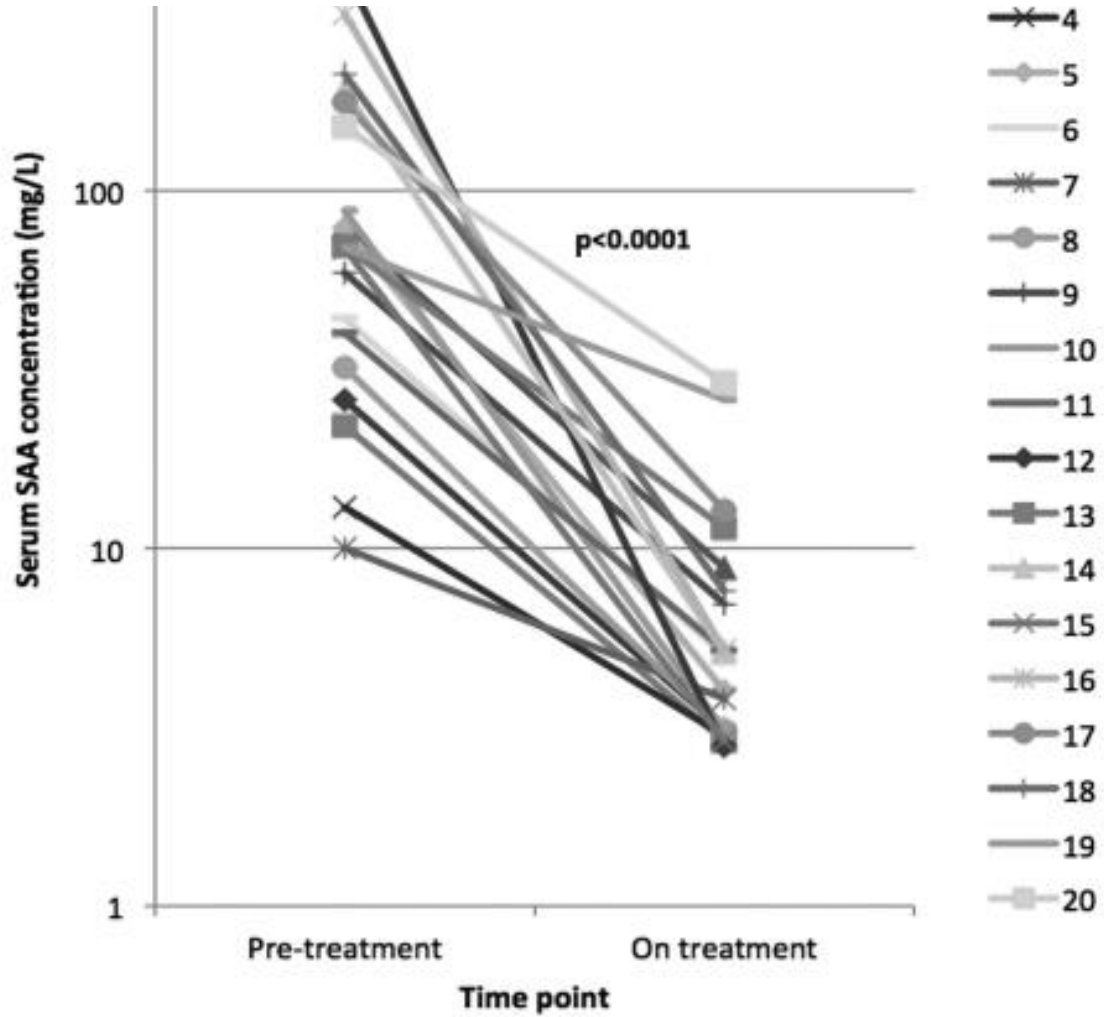
	P value	RR	95% CI
Age at dx	<0.001	1.53	1.34-1.74
Periodic fever syndroms	0.03	0.36	0.14-0.88
Median SAA (per doubling)	<0.001	1.27	1.16-1.40
Onset of ESRF	<0.001	2.97	2.10-4.21
Amyloid regression	0.04	0.13	0.02-0.94
Median survival under 13 years			

Lachmann HJ, NEJM 2007

Therapeutic blockade of interleukin-6 by tocilizumab in the management of AA amyloidosis and chronic inflammatory disorders: a case series and review of the literature

T. Lane, J.D. Gillmore, A.D. Wechalekar, P.N. Hawkins, H.J. Lachmann

- Response to anti-IL-6 lead to suppression of the inflammatory stimulus
- Decrease of amyloid deposition



CER, 2015

Macrophage activation syndrome/ferritin

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

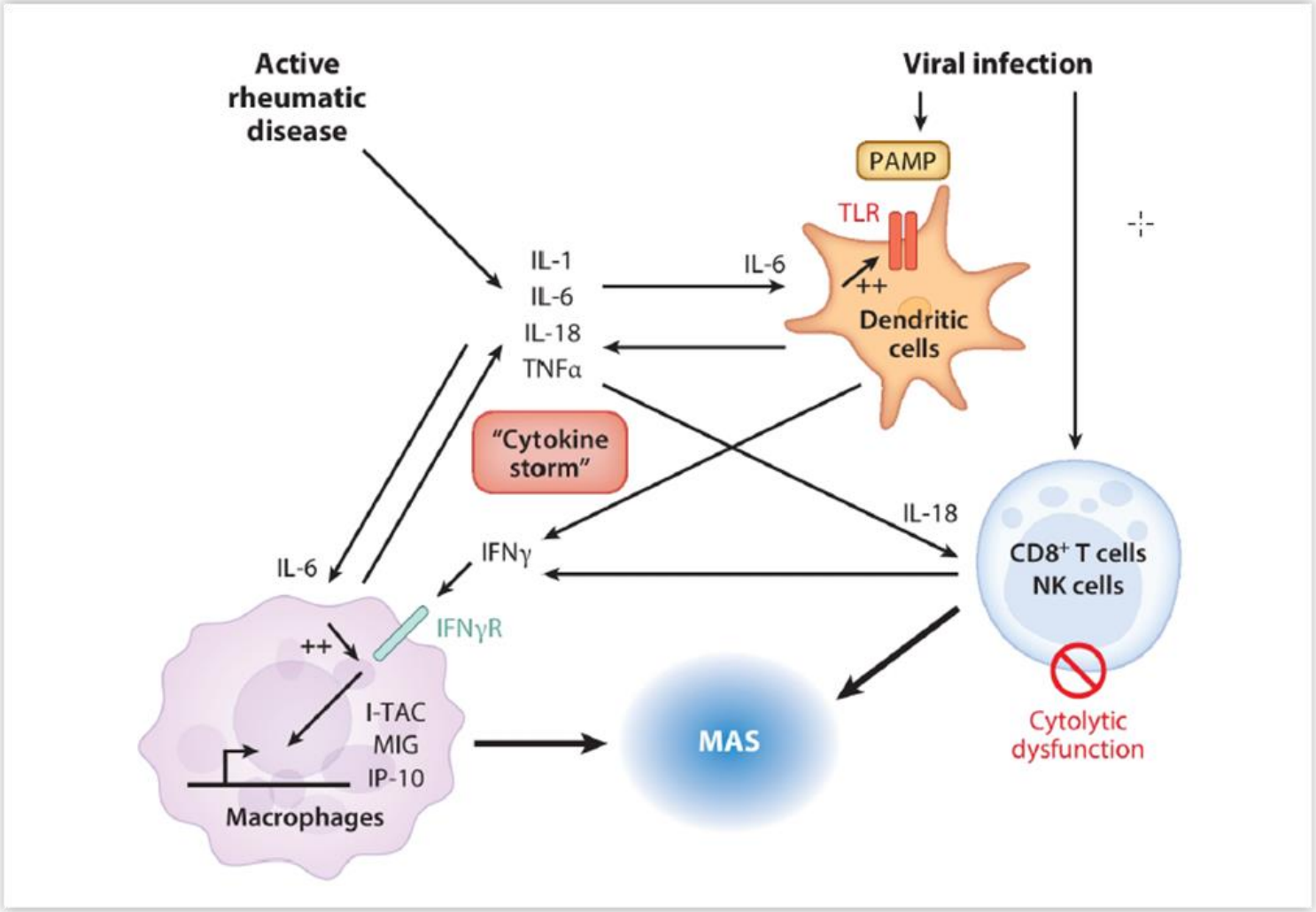
Aspartate aminotransferase >48 units/liter

Triglycerides >156 mg/dl

Fibrinogen ≤360 mg/dl

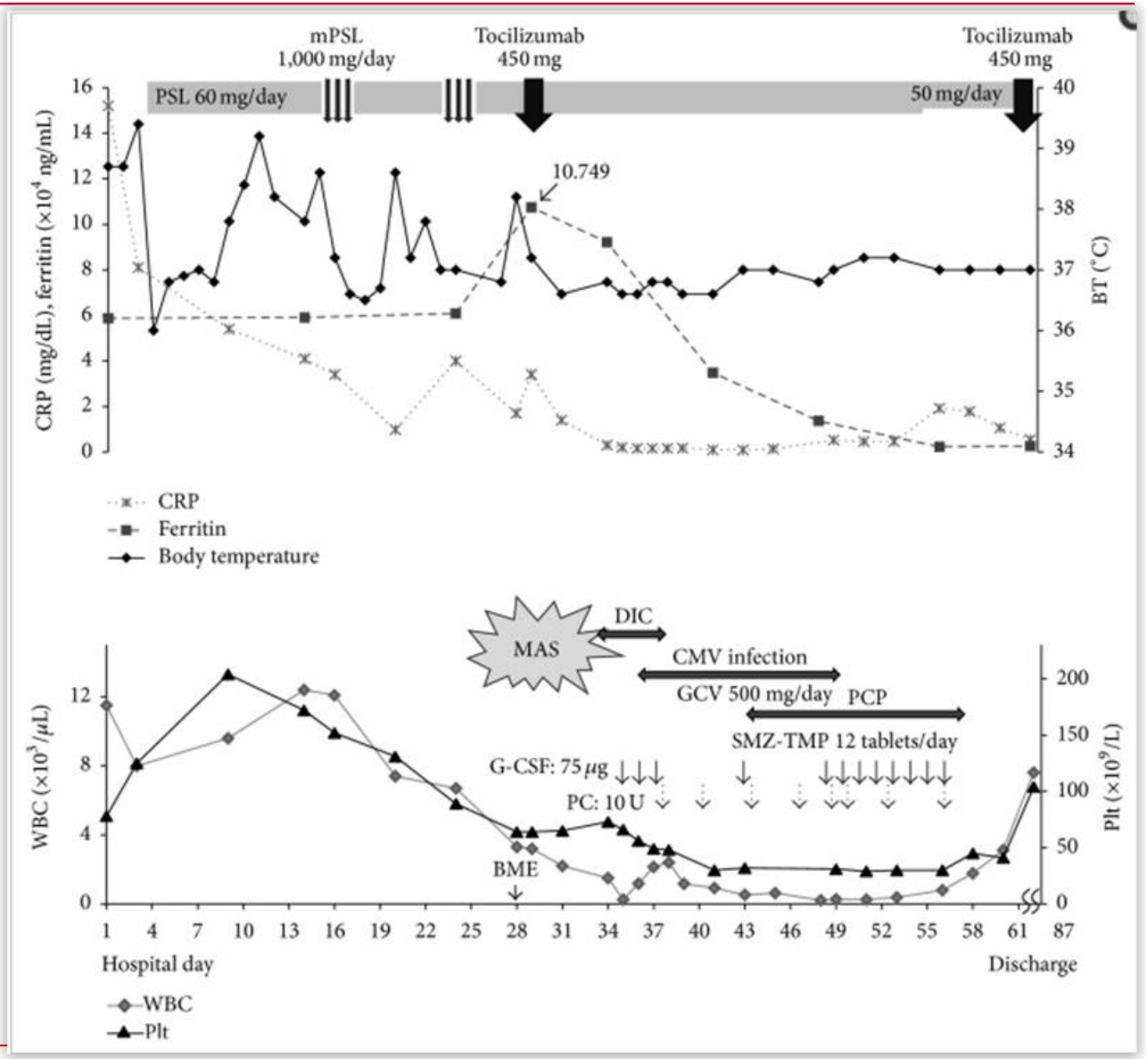
Macrophage activation syndrome

Cytokines storm leading to extracellular ferritin release

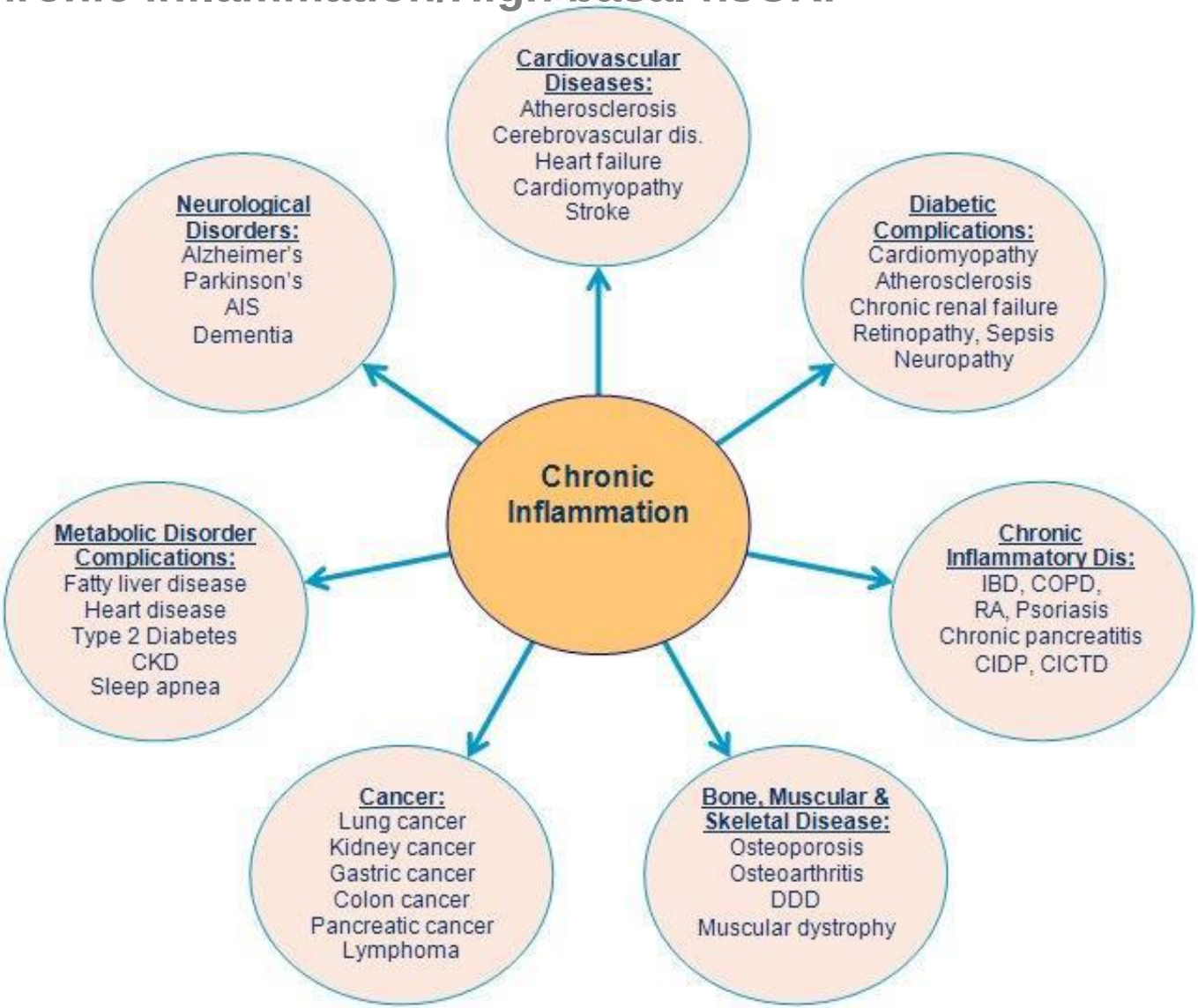


Schulert G. Ann Rev Med 2015

Follow up and treatment of a macrophage activation syndrom



Chronic inflammation/High basal hsCRP



hsCRP and cardiovascular risk

Etude	Design	Sexe	Risque relatif cardiovasculaire selon le taux de hsCRP (4e vs 1er quartiles)	AUC des facteurs de risque traditionnels seuls	AUC pour la hsCRP combinée aux facteurs de risque traditionnels
Woman's health study (Ridker et coll., 2002)	Prospective	Femmes	2,3	0,81	0,81
Rotterdam Study (van der Meer et coll., 2003)	Nested case-control	Hommes et femmes	1,2	0,746	0,748
MONICA Augsburg Study (König et coll., 2004)	Prospective	Hommes	2,2	0,735	0,75
Reykjavik Cohort Study (Danesh et coll., 2004)	Nested Case-Control	Hommes et femmes	1,4	0,64	0,65
Framingham Offspring Study (Rutter et coll., 2004)	Prospective	Hommes et femmes	1,9	0,74	0,74
Framingham Heart Study (Wilson et coll., 2005)	Prospective	Hommes et femmes	1,6	0,80	0,80
Cardiovascular Heart Study (Shlipak et coll., 2005)	Prospective	Hommes et femmes	Non disponible	0,73	0,72*

Practical implications:

1. **Classical risk factors predict more than 90% of futur myocardial infarcts**
2. **Patients with intermediate risk may benefit from hsCRP to start treatment**
3. **These biomarkers should not be used for population screening**
4. **Same for new biomarkers, so far as we know now**

ARTHRITIS & RHEUMATISM
Vol. 48, No. 7, July 2003, pp 1833–1840
DOI 10.1002/art.11078

Association Between Carotid Atherosclerosis and Markers of Inflammation in Rheumatoid Arthritis Patients and Healthy Subjects

Inmaculada del Rincón,[1] Ken Williams,[1] Michael P. Stern,[1] Gregory L. Freeman,[1] Daniel H. O'Leary,[2] and Agustín Escalante[1]

Table 6. Relationship between C-reactive protein (CRP) level and carotid artery plaque*

CRP, mg/liter	No. of carotid vessels imaged	Carotid vessels with plaque, no. (%)†	Odds ratio	95% CI
0–1.0	77	8 (10)	1.0	Referent
1.1–2.3	89	28 (31)	6.61	1.79–24.39
2.4–4.8	118	33 (28)	5.59	1.52–20.54
4.9–30	279	89 (32)	6.75	1.94–23.41
>30	41	15 (37)	8.31	1.98–34.94

* See Table 2 for other definitions.
† P for trend = 0.001 unadjusted, ≤0.001 age- and sex-adjusted, ≤0.001 age-, sex-, and cardiovascular risk factor–adjusted.

Low grade « inflammation » : CRP 3-10 mg/L

Usually assymptomatic leading to latter consequences

Leading to a new definition of inflammation:

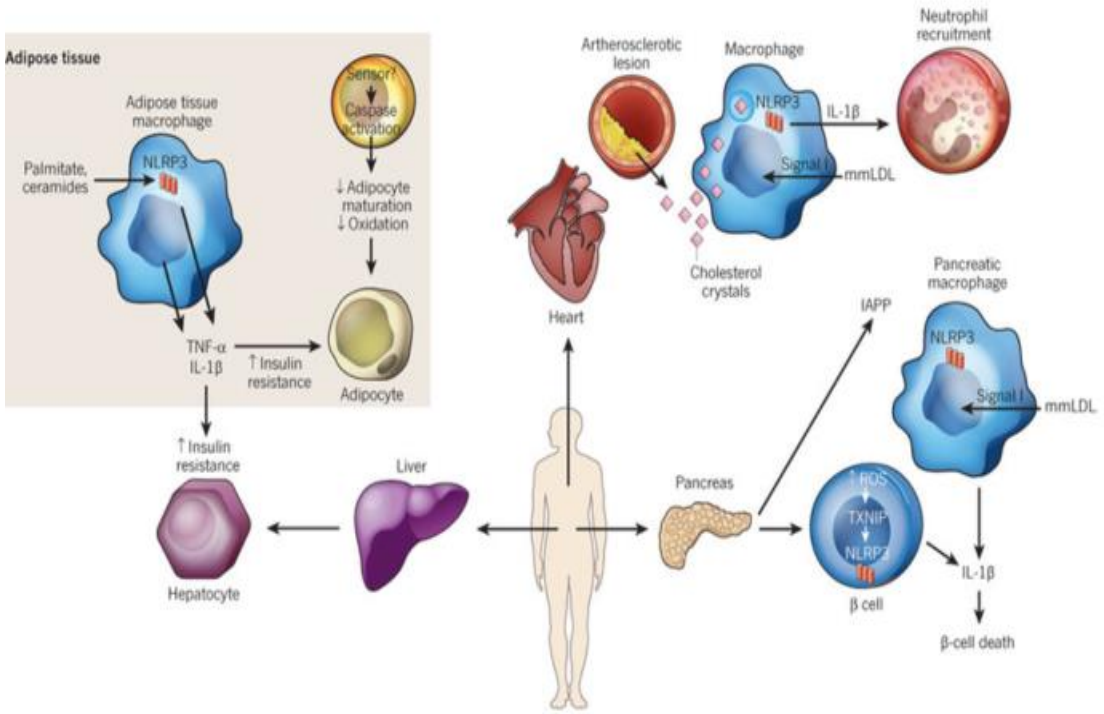


Figure 3: The role of inflammasomes in metabolic syndrome.During obesity, the NLRP3 inflammasome is activated by obesity-associated DAMPs in multiple tissues and cell types; the resultant pro-inflammatory-induced state often leads to a deterioration in metabolic functions. In adipose tissue, palmitate and ceramides activate the NLRP3 inflammasome in infiltrating macrophages, which leads to an enhancement of insulin resistance. In addition,... ⊞

0 Recommendations

Inflammasomes in health and disease

Nature 481(7381):278-86 · January 2012

Redefining INFLAMMATION

INNATE immune response to potentially harmful stimuli such as pathogens,injury and metabolic stress To restore optimal homeostatic state

TABLE 1. *Comparison of acute, low-grade, and autoinflammatory inflammation*

Parameter	Infection	Tissue injury	Low-grade inflammation	Autoinflammatory diseases
Cause	Pathogens	Trauma, tissue infarction	Metabolic malfunction	Usually spontaneous
Mediators	Molecules and cells of the innate immune response	Molecules and cells of the innate immune response	Molecules and cells of the innate immune response	Molecules and cells of the innate immune response
Classic signs of inflammation	+++	+++	None	+++
CRP response	+++	+++	+	+++
Purpose	Defense healing and repair	Healing and repair	Restoration of homeostasis	None apparent
Triggering mechanism	Pattern recognition molecules, notably for PAMPs and DAMPs	Pattern recognition molecules, notably for DAMPs	Sentinel cells that monitor for tissue stress, notably the UPR	Genetically based dysregulation

DAMP, damage-associated molecular patterns; PAMP, pathogen-associated molecular pattern. Plus symbols indicate magnitude.

In conclusion

1. **ESR as Inflammation biomarker to rule out infllammatory syndrome**
2. **Use of biomarkers in follow up alone or in clinical score of disease activity (GCA; DAS - RA)**
3. **PROCALCITONIN included in ICU septic shock evaluation and exclusion of bacteremia: not yet directing AB treatment**
4. **Chronic residual inflammation or recurrent fevers with long term consequence as AA amyloïdosis: Treatment options: anti-IL6 (monitoring with SAA)**
5. **Macrophage activation syndrome: FERRITIN as an essential marker of macrophage**
6. **Basal hs CRP levels and risk evaluation: screening limited**
7. **Time to redefine inflammation**

Thank you for your attention

Any question ?