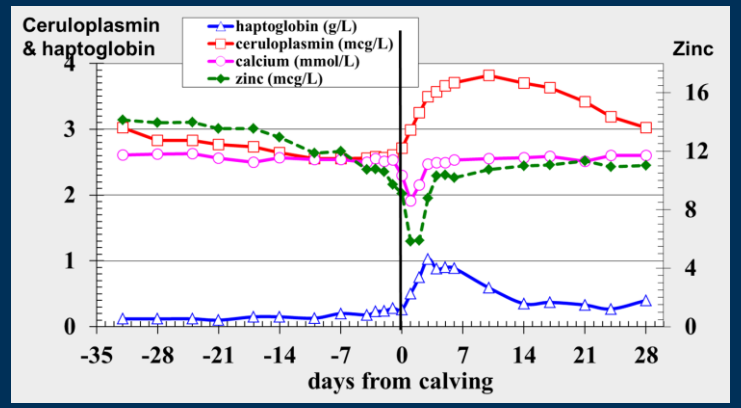
How to assess the immune response in periparturient cows?



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Summary

1. **Critical points in the periparturient cows**
   - Variations in immune parameters: adaptive and innate systems
   - Inflammation
   - Causes of altered inflammatory response
2. **How to interpreter inflammatory response around calving**
   - Implication at the Liver level
   - Physiological vs pathological
   - How to measure? presence or consequences?
   - When to measure?
3. **Indexes to classify inflammation severity in the peripartum**
   - LFI (Liver Functionality Index)
   - How to use it?
4. **Perspectives and Implications**

Overview of Critical points of TP

Trevisi & Minuti, 2018; Res Vet Sci 116: 47-54

1. **⬇ immune-competence**

   Goff & Horst, 1997, Lacetera et al., 2005)

2. **Inflammatory like status** (Cappa et al., 1989; Bionaz et al., 2007) also in apparently healthy dairy cows

3. **Marked NEB** mobilization of adipo-se & muscle tissues

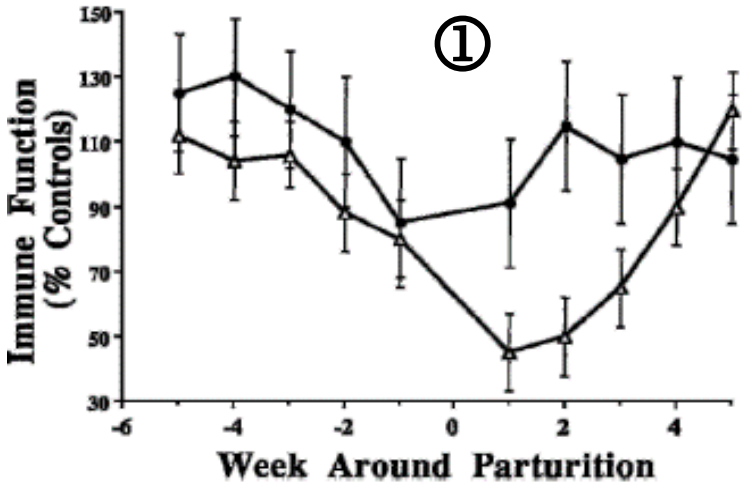
   Grummer, 1995; 2007

4. **Oxidative stress**

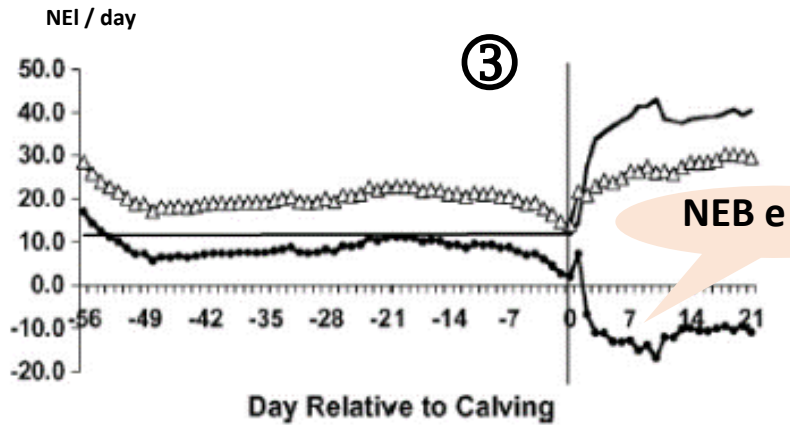
   Bernabucci et al., 2005; Bionaz et al., 2007;Sordillo & Aitken, 2009; Celi, 2011

5. **Hypocalcemia**

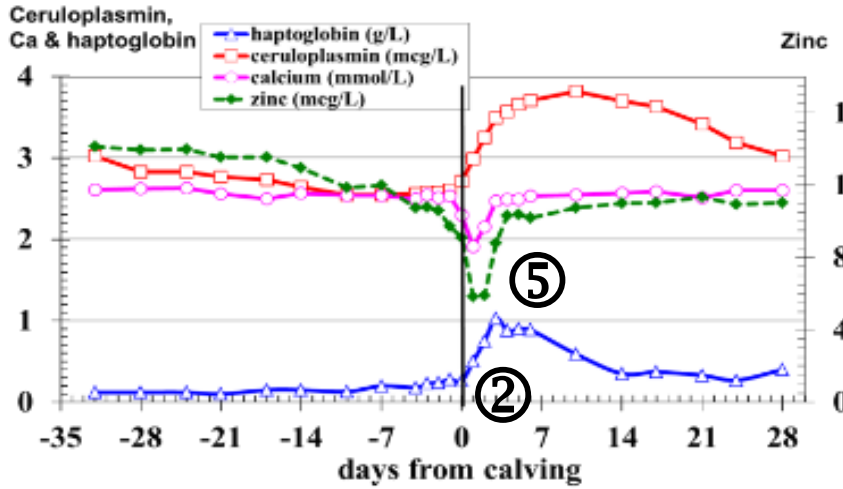
   Goff, 2007; DeGaris & Lean, 2009



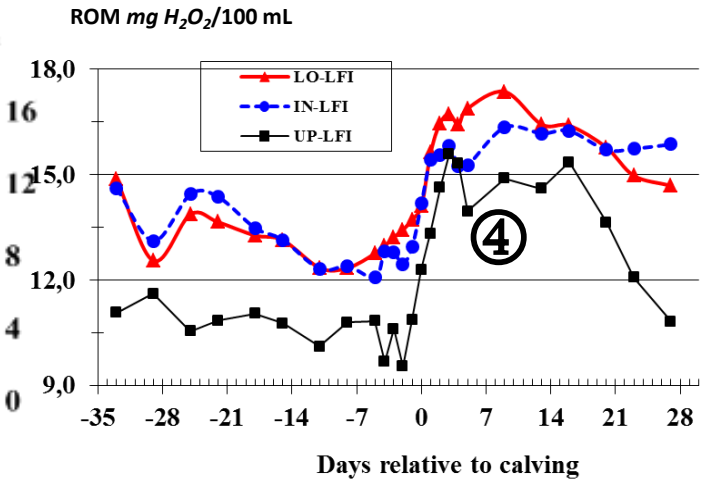
Neutrophil function (iodination; º) and lymphocyte function (blastogenesis; ÿ) are impaired in TP. (Goff & Horst 1997, JDS 80: 1260-1268)



Energy (NEl/day) required (----), consumed (Δ), and energy balance (•) for cows during TP (Grummer, 2007, Theriogenology S281–S288)



Bertoni & Trevisi, 2013 VET CLIN N AM-FOOD A 29):413–431



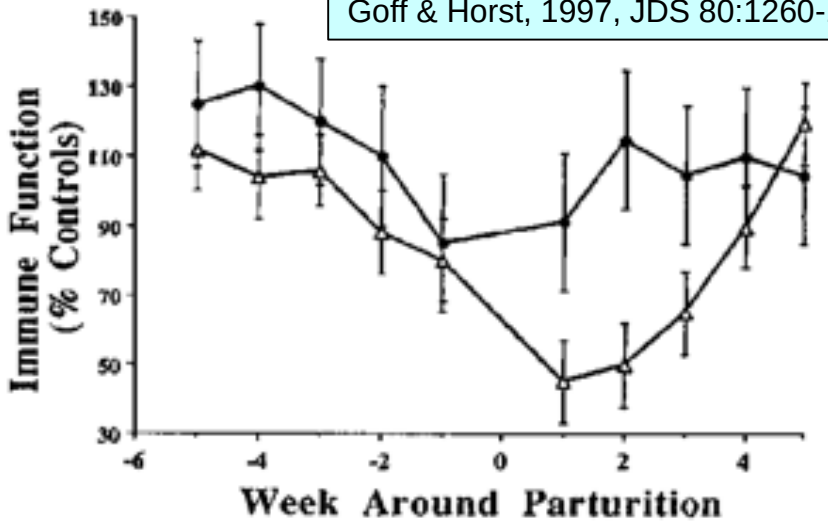
Trevisi et al., 2010 77:310–317

Are pregnant cows immunodepressed?

Some immune functions depressed before calving:

- ⬇ phagocytosis of NEU
- ⬇ proliferation of LYMPH

?



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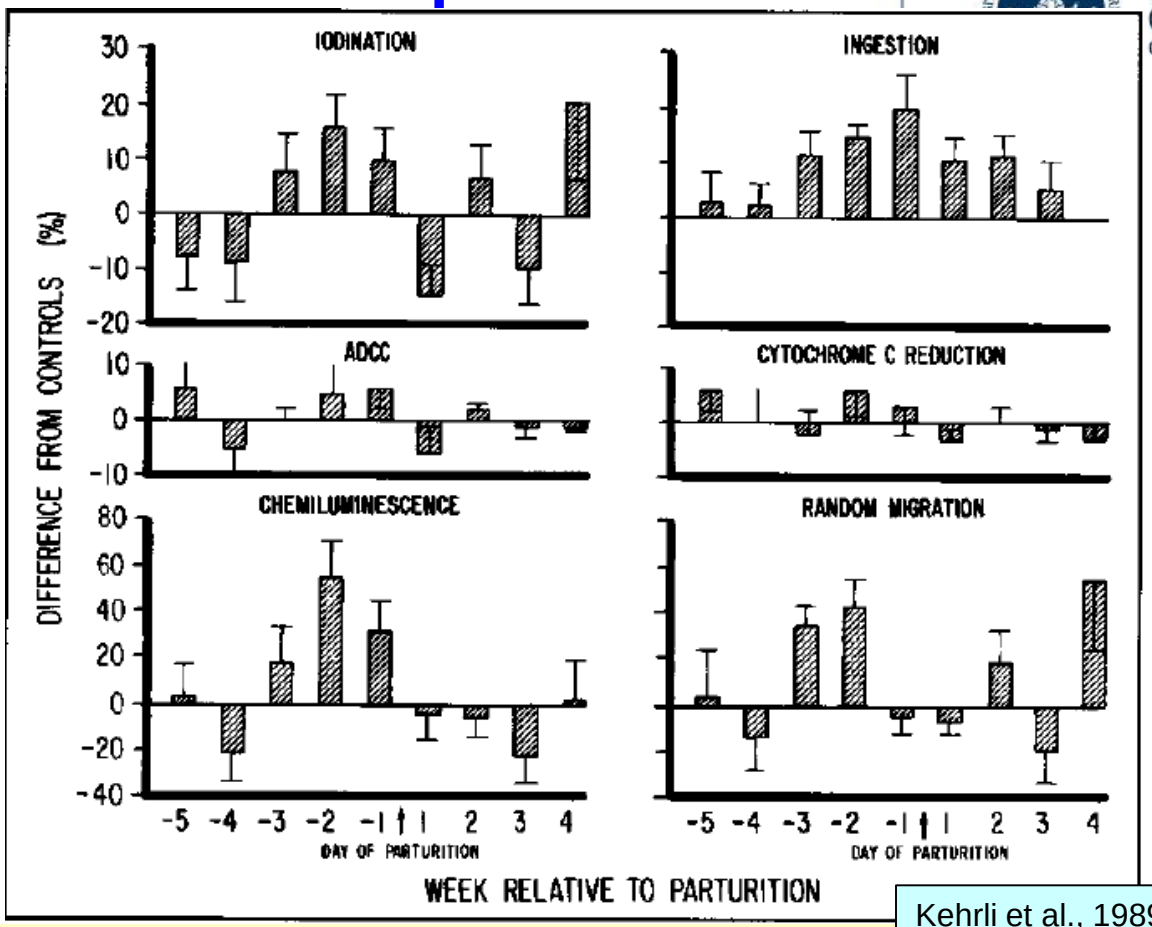
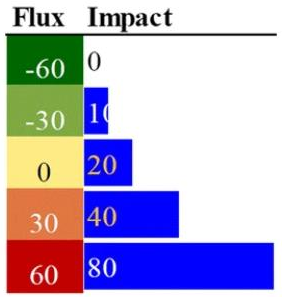


Kehrli et al., 1989 AJVR: 50:207

- Heifers (later used in literature as multiparous)
- Correction of immunological data on “steer population”
- “immunosuppression appears after calving (but occurs only for some parameters)”

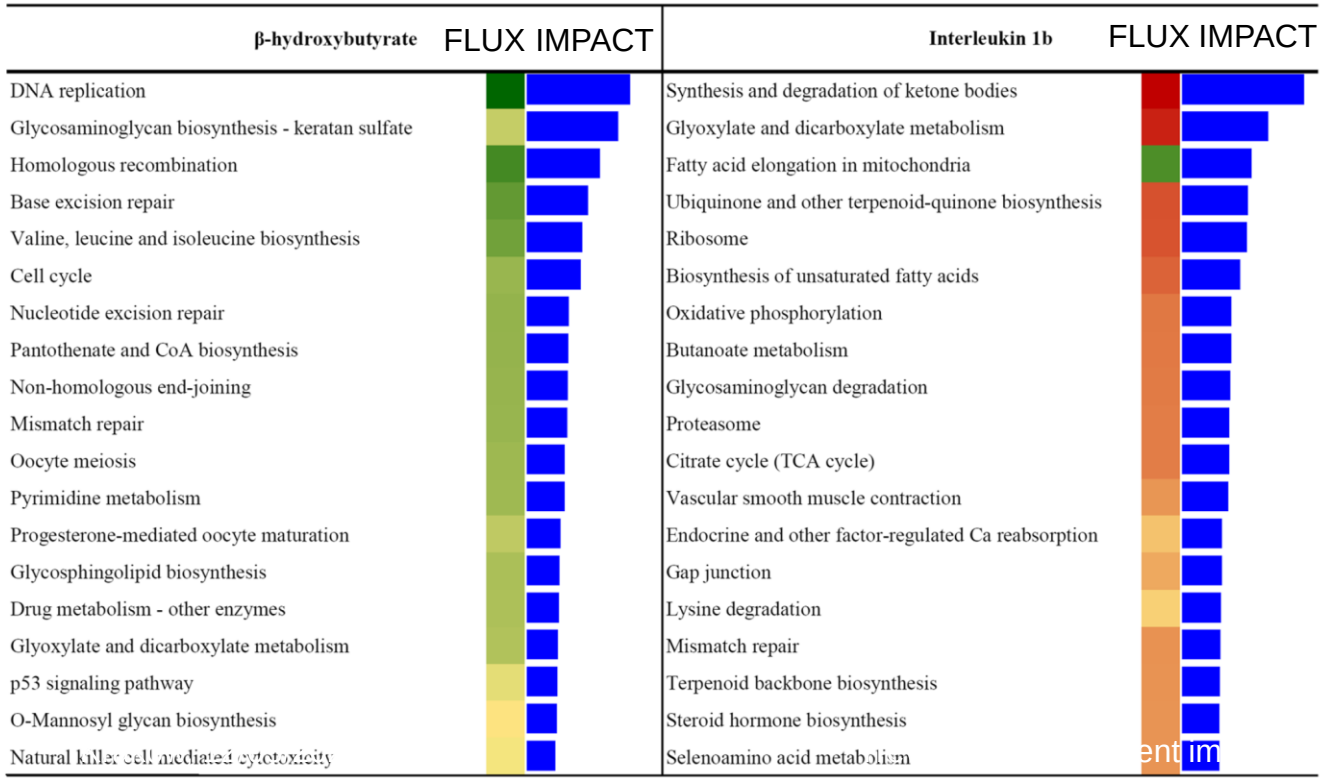
Immunodepression: oversimplification?

Impact of leukocytes functions in TP on metabolism



red = activated;
green = inhibited

DEG in leukocytes	Correlated genes	Negatively correlated	Positively correlated
Glucose	15	1	14
β-Hydroxy butyric acid	271	243	28
Ceruloplasmin	6	4	2
Bilirubin	18	3	15
Haptoglobin	4	0	4
IL-1β	385	88	297



Changes in DEG in leukocytes (−20±2, −3±1, 3, 7 DFP):

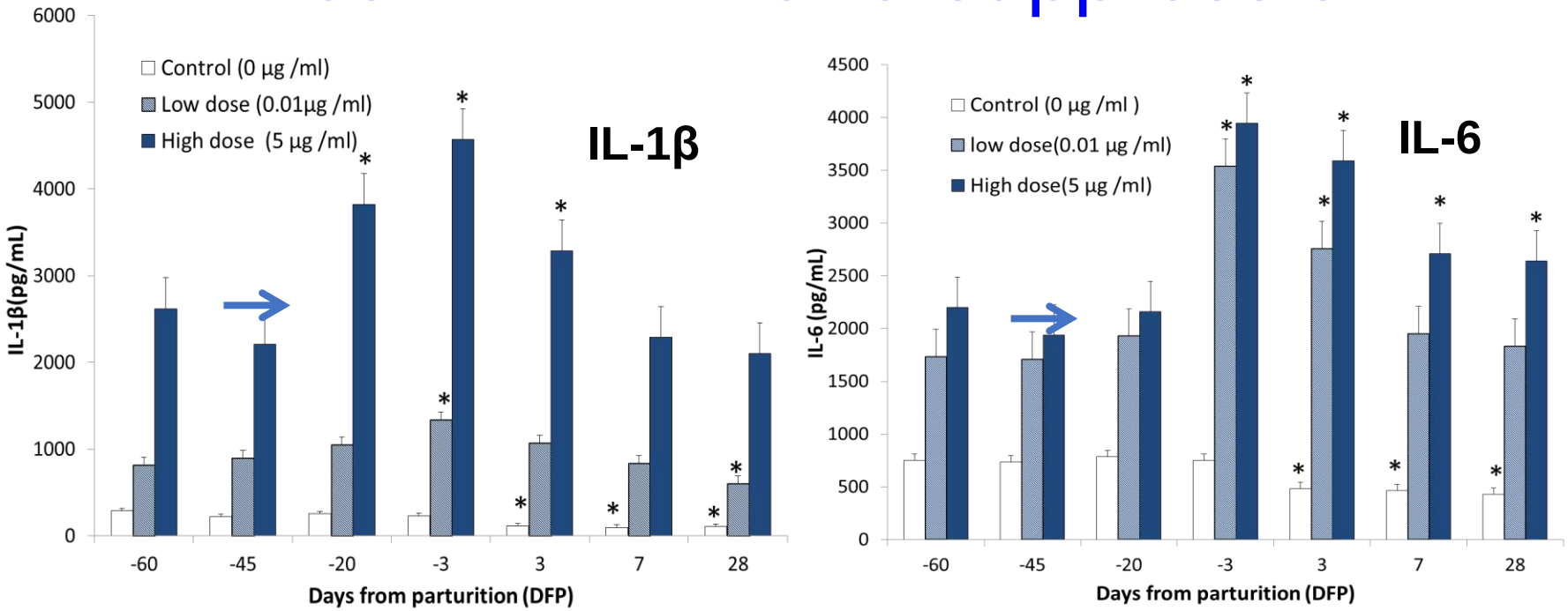
- more intense after calving
- Many genes activated: **phagocytosis, migration, adhesion, extravasation**

DEG in leukocytes correlated with:

- BHB, inhibits several genes
- IL-1β activates several pathways related to metabolism (mainly cellular energy)

Minuti et al., Functional & Integrative Genomics 2019 (20):293-305; doi:10.1007/s10142-019-00720-0

↑ of PIC release around calving does not confirm immune-suppression



Whole Blood stimulation Assay

LPS*:* 0, 0.01 and 5 µg LPS /ml of blood

Incubation (rotative oven): 38°C for 3.5 h

Jahan et al. 2015. Vet Imm & Imm 165:119-126

- **Control (no LPS). IL-1β & IL-6 levels: higher in dry period vs early lactation**
- **LPS Stimulation**
  - The greatest response of IL-1β ➡ from -20 to 3 DFP
  - The greatest response of IL-6 ➡ from -3 to 3 DFP
  - Max response of IL-6: similar for both LPS dosages

Immunocompetence in TP

- “Overall”, these data suggest an **increase of immune system activities & functions** in circulating leukocytes **during TP**
- the direct **contact between immune cells and some circulating molecules** before calving (i.e. hormones, NEFA/lipoproteins) **may influence the gene expression** of circulating leukocytes

Thus, functions of the immune system can be (more or less) dysregulated around calving, but not suppressed

In any case, an inflammatory response occurred after calving

An inflammatory like status occurs after calving (in healthy cows also)

②

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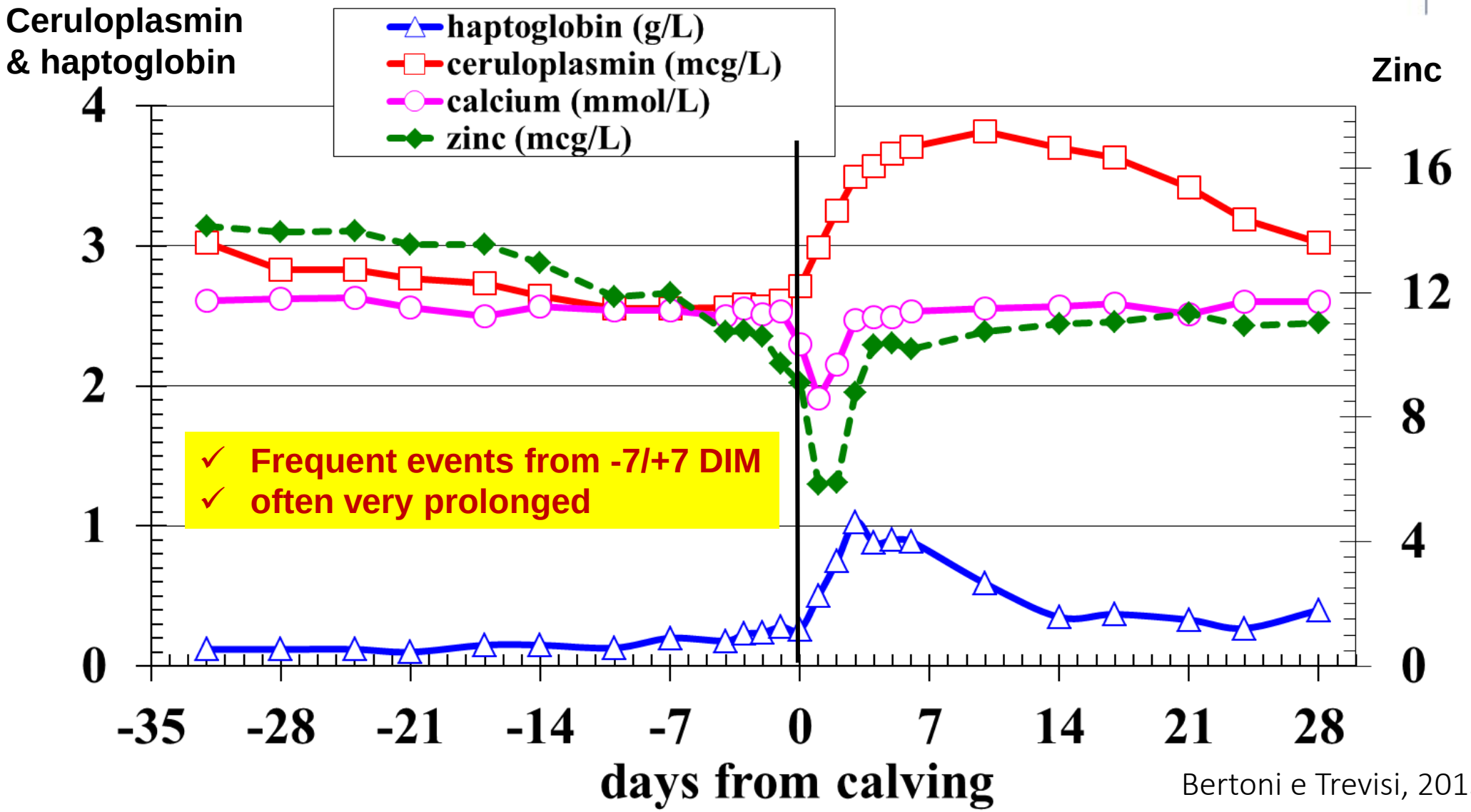

Bertoni e Trevisi, 2013
VET CLIN N AM-FOOD A 29(2):413–431

Inflammation & TP

The spark: 1989

*Cappa V., **Trevisi E.**, Bertoni G. 1989.*
Differences in blood parameters and milk production in the first month of lactation in cows with or without postpartum problems ***Zoot. Nutr. Anim., 15: 645-660***

We observed
- a **worse liver status in Herd 2** (i.e. lower lipoprotein and albumin), which suggested a possible liver lipidosis

- the **cause** was not related to an acute liver damage (as in cows affected by retained placenta), but to **"stressful" conditions around calving** that interfered with the liver metabolism (higher ceruloplasmin and globulin))

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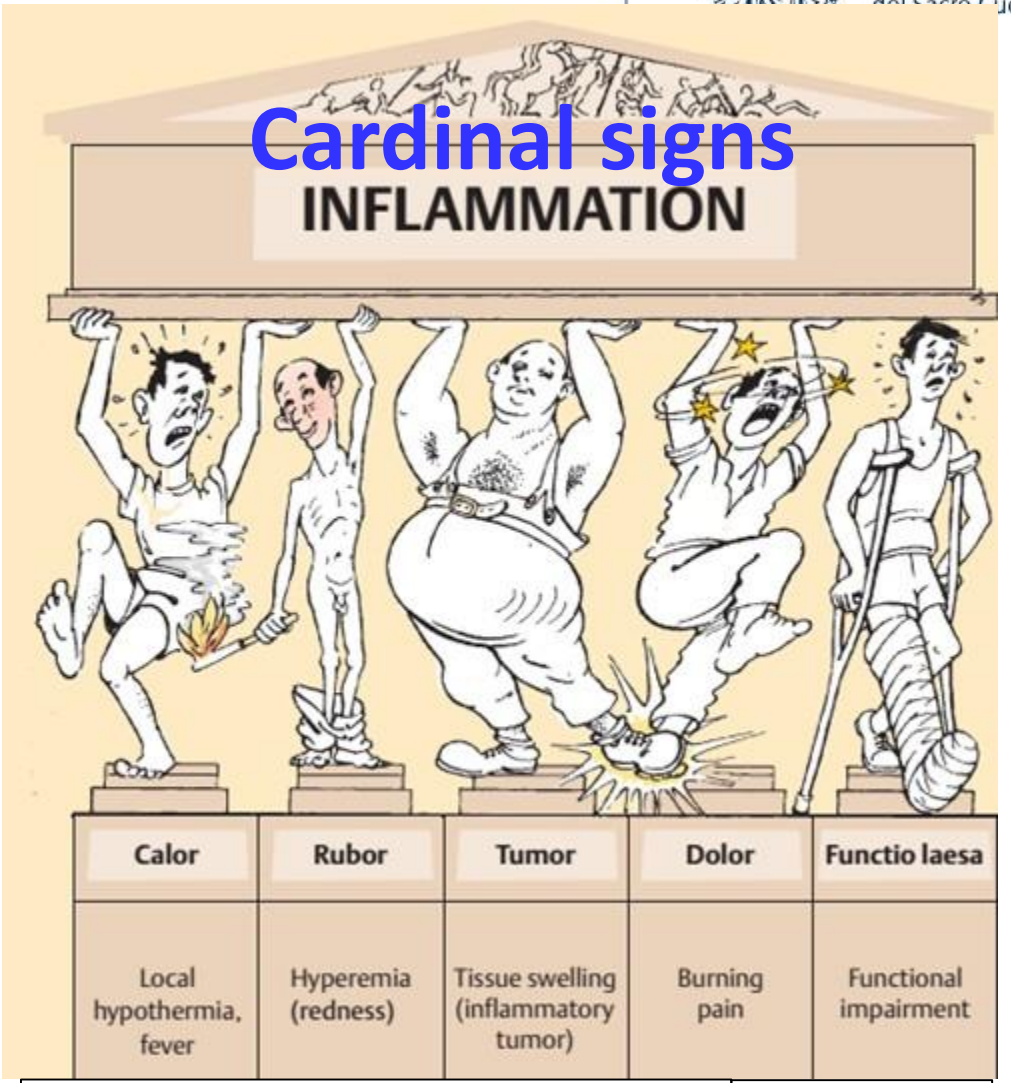
TABLE 9. - *Mean values of blood parameters found during the whole experimental period (for herd 2 animal with displaced abomasum are escluded).*

Mean values of first 30 DIM

Parametro - *Parameter*		Stalla 1 *Herd 1*		Stalla 2 *Herd 2*		Varianza dell'errore *Error mean square*		Valori di riferimento (1) *Reference values (1)*
POST PARTUM PROBLEMS		**WITHOUT**		**WITH**				
Ematocrito - *PCV*	l/l	0,33	B	0,31	A	0,0068	E-1	0,25-0,32
Glucosio - *Glucose*	mmol/l	3,90		3,75		0,2663	E-0	3,30-3,90
Urea - *Urea*	»	5,47	B	3,39	A	0,1074	E+1	4,00-5,70
Calcio - *Calcium*	»	2,38	b	2,31	a	0,3708	E-1	2,40-2,80
Fosforo inorg. - *Inorg. phosphorus*	»	1,37	A	1,54	B	0,8879	E-1	1,30-2,00
Magnesio - *Magnesium*	»	0,99	B	0,88	A	0,8200	E-2	0,80-1,10
Sodio - *Sodium*	»	142,28	B	139,11	S	0,5793	E+1	135-142
Potassio - *Potassium*	»	3,89	A	4,07	B	0,1020	E-0	3,80-5,50
Zinco - *Zinc*	µmol/l	12,83	B	10,83	A	0,9062	E+1	10,5-17,0
Ceruloplasmina - *Caeruloplasmin*	»	3,21	A	3,52	B	0,2576	E-0	1,40-2,40
Proteine totali - *Total protein*	g/l	82,68	B	77,25	A	0,3189	E+2	80-85
Globuline - *Globulin*	»	40,88	A	49,48	B	0,3819	E+2	40,0-50,0
Albumine - *Albumin*	»	36,37	B	33,16	A	0,5848	E+1	35,0-40,0
GOT/AST	U/l	99,84		99,20		0,2416	E+3	62,0-83,0
GGT	»	23,09		23,90		0,4910	E+2	18,0-27,0
Colesterolo totale - *Total cholesterol*	mmol/l	2,52	b	2,34	a	0,2011	E-0	3,4-5,2

Inflammation: definition

- ✓ **Rapid and generic response of the innate immune system**
- ✓ **Local protective response** of living mammalian tissue to injury due to **any etiologic agent (biotic & abiotic)**
- ✓ Body defense reaction to **eliminate or limit the spread** of **injurious agents**
- ✓ 2 basic processes with some overlapping:
  - **early inflammatory response**
  - **healing**



Modifed from Mosley, https://slideplayer.com/slide/11338617/

Inflammation: causes & progression

(Medzhitov et al, 2008, modified)

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INDUCERS ➡ SENSORS (i.e. TLRs) on resident immune cells(*) ➡ SIGNALS (mediators) ➡ EFFECTORS

Agents

Exogenous (PAMPs)

Microbial → PAMPs, virulence factors

Non microbial → allergens, irritants, foreign bodies, toxic compounds, psychological stressors

PAMPs *= pathogen-associated molecular pattern;*

DAMPs *= damage-associated molecular pattern*

Endogenous (DAMPs)

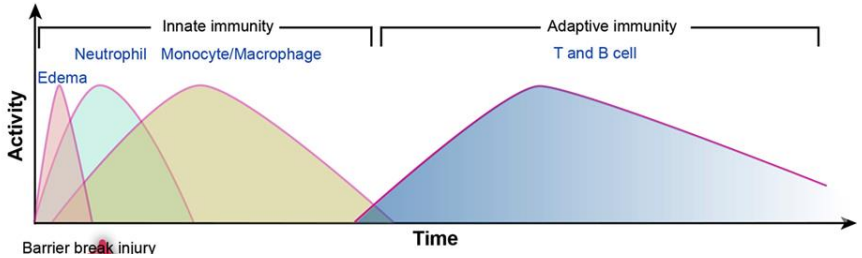
Cell

Plasma

Extracellular matrix

SENSORS ➡ Soluble systems & Cells

- Signals released from stressed, malfunctioning or dead cells and from damaged tissues
- Endogenous crystals
- Products of extracellular matrix breakdown



✓Amplification

✓Maintenance

✓Progression

✓Reiteration

✓Resolution

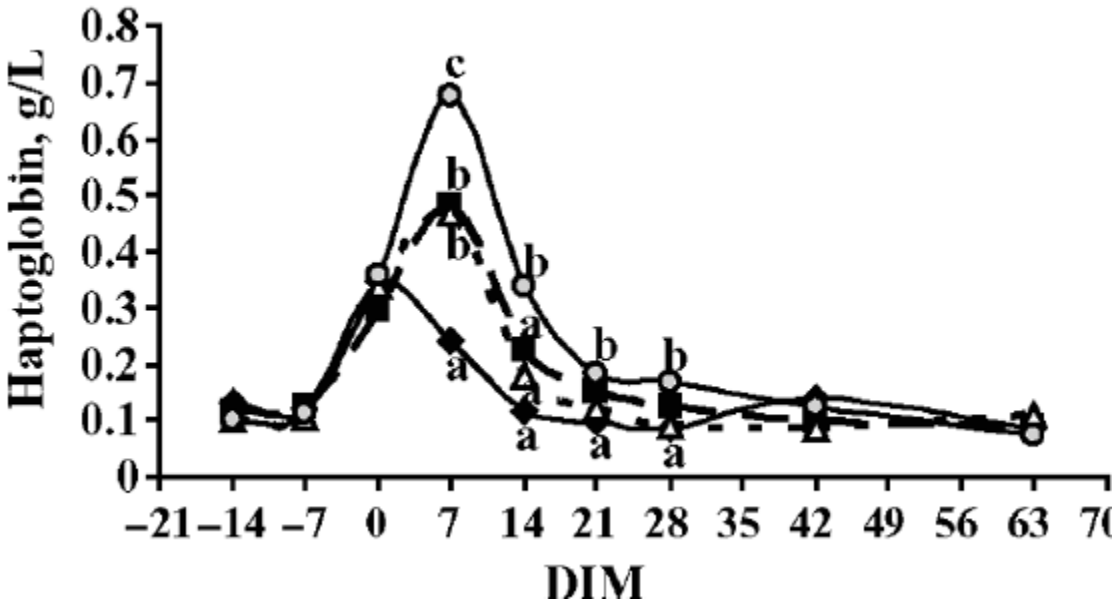
Pro- vs anti-inflammatory mediators

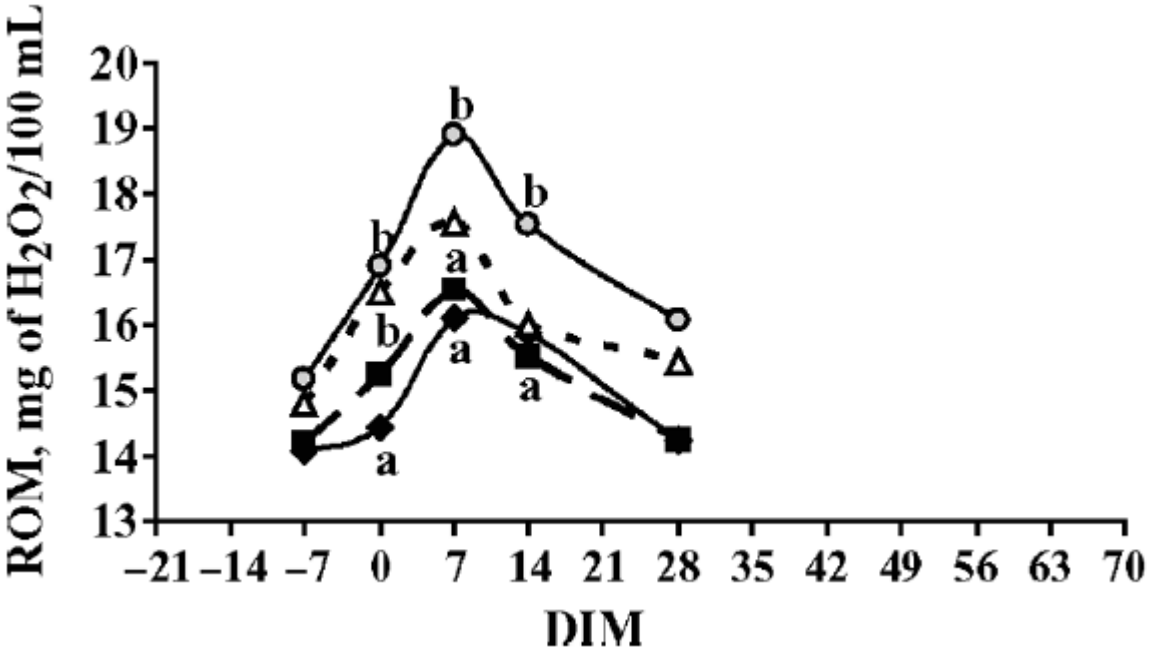
Ideally it should starts within 12 h

(*) dendritic cells, plasmacytoid dendritic cells, macrophages

Inflammation & oxidative stress at calving time

Bionaz et al. 2007 J. Dairy Sci. 90:1740–1750

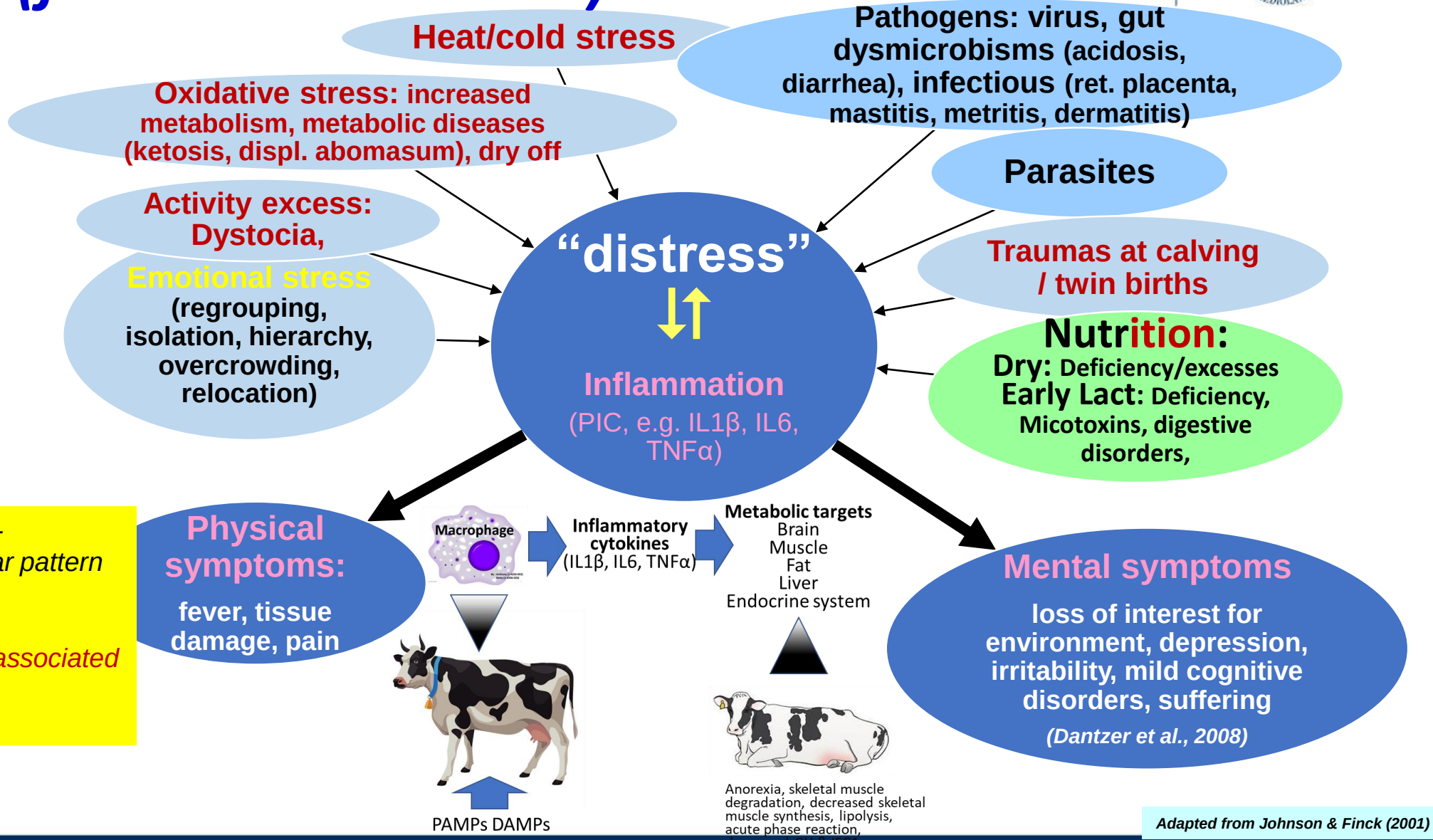




Inflammation occurs in all the cows after calving, with different level of severity

Oxidative stress also occurs at the same time (or shortly after)

Agents of inflammation in TP *(from mild to severe)*



PAMPs *= pathogen-associated molecular pattern (EXOGENOUS);*

DAMPs *= damage-associated molecular pattern (ENDOGENOUS)*

Adapted from Johnson & Finck (2001)

Inflammation: Local & Systemic response

(modified from Petersen, 2004)

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STIMULUS

PAMPs & DAMPs
(Tissue destruction, Inflammation, Infection, Neoplastic growth, Bacterial products as LPS, exotoxins, teichoic acid)

Complement system
Opsonins
Aggregation of platelets

LOCAL RESPONSE

Fibroblasts Endothelial cells Epithelia cells?

Macrophages

TH2 Lymphocytes

IL-1 type cytokines
IL-6 type cytokines

IL-4, IL-10

IL-1, IL-6, IL-8 (type) ⇒ neutrophil attraction & local activation ⇒ Local TNFα

SYSTEMIC RESPONSE

Growth factors (insulin, TGF-β, etc.)

glucocorticoids

IMMUNE SYSTEM

Activation of cells, stimulation of cytokines production

LIVER

ACUTE PHASE PROTEIN RESPONSE

- ↑ *+APP: AGP, SAA, Hp (ra), CRP (IL-1 dependent) Fib, Hp (hu), CuCp, (IL-6 dependent)*
- ↓ *-APP: alb, PON, lipoprotein, RBP, carrier Cortisol*

PGE2 ⇒ Sleep, Fever, Anorexia

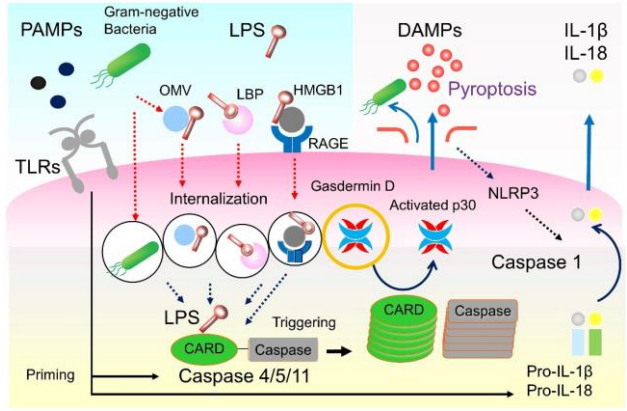
BRAIN
Hypothalamus ➡ CRH (Corticotropin Releasing hormone)

Pituitary ➡ ACTH (corticotropin) ⇒ ADRENAL GLAND

time

ACTIVATION

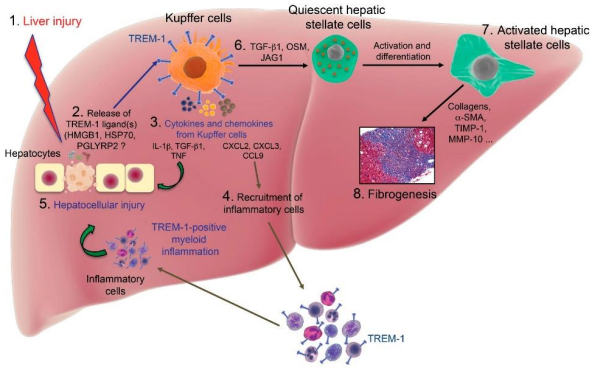
Early events (min.)



Moriyama & Nishida 2021. *Int. J. Mol. Sci.* **2021**, *22*(16), 8882; https://doi.org/10.3390/ijms22168882

RESPONSE

Later events (hours … days)



Nguyen-Lefebvre et al., 2018. J Clin Invest. 128(11):4870–4883.

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LIVER: crucial & conflicting role

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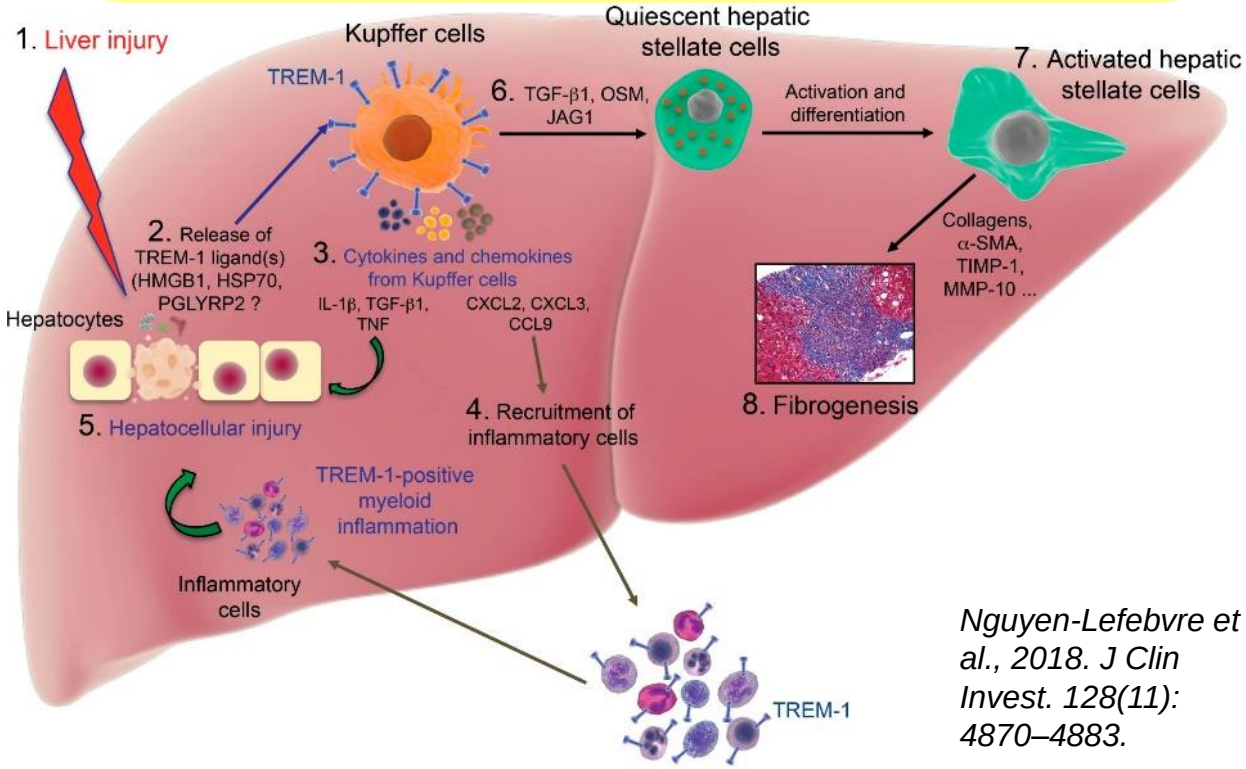
SHORT-LIVED EFFECTS of INFLAMMATION

- ✓ *Liver plays a central role for many metabolic pathways*
- ✓ *In case of inflammation, it promotes the acute phase reaction (APR) with 2 opposite consequences:*
  - ***activation*** *of the synthesis of protective proteins (**posAPP**) & "capturing" protein (e.g. of Fe, Zn)*
  - ***impairment*** of the *synthesis of the "common" proteins (less **negAPP**)*

but it is not damaged

LONG-LIVED EFFECTS OF INFLAMMATION (CHRONIC)

- Liver injury activates Triggering receptor expressed on myeloid cells 1 (TREM-1)
- Amplifies hepatic inflammation,
- Activates hepatic stellate cells
- Promotes liver disease (i.e. LIPIDOSIS) & FIBROSIS



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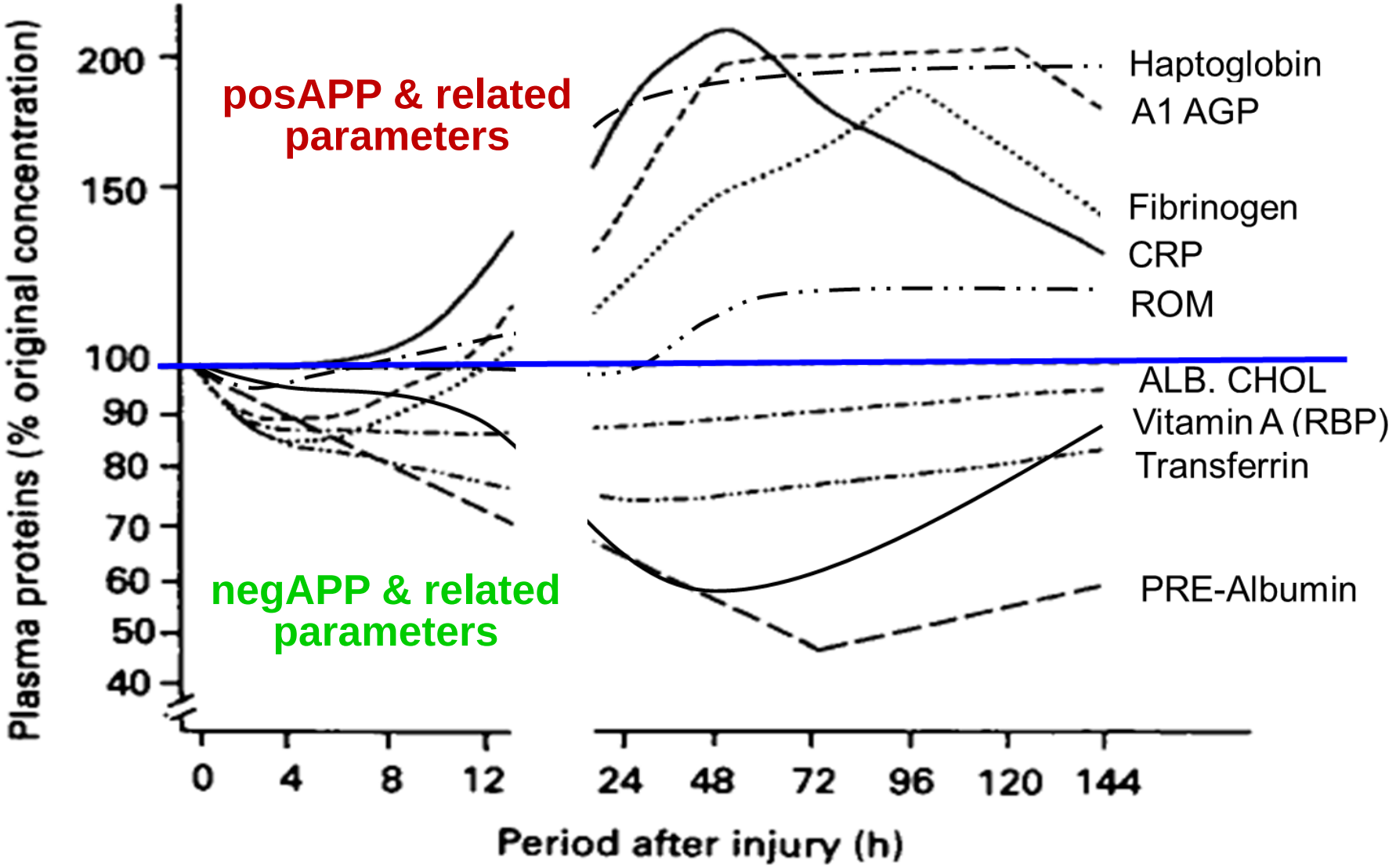
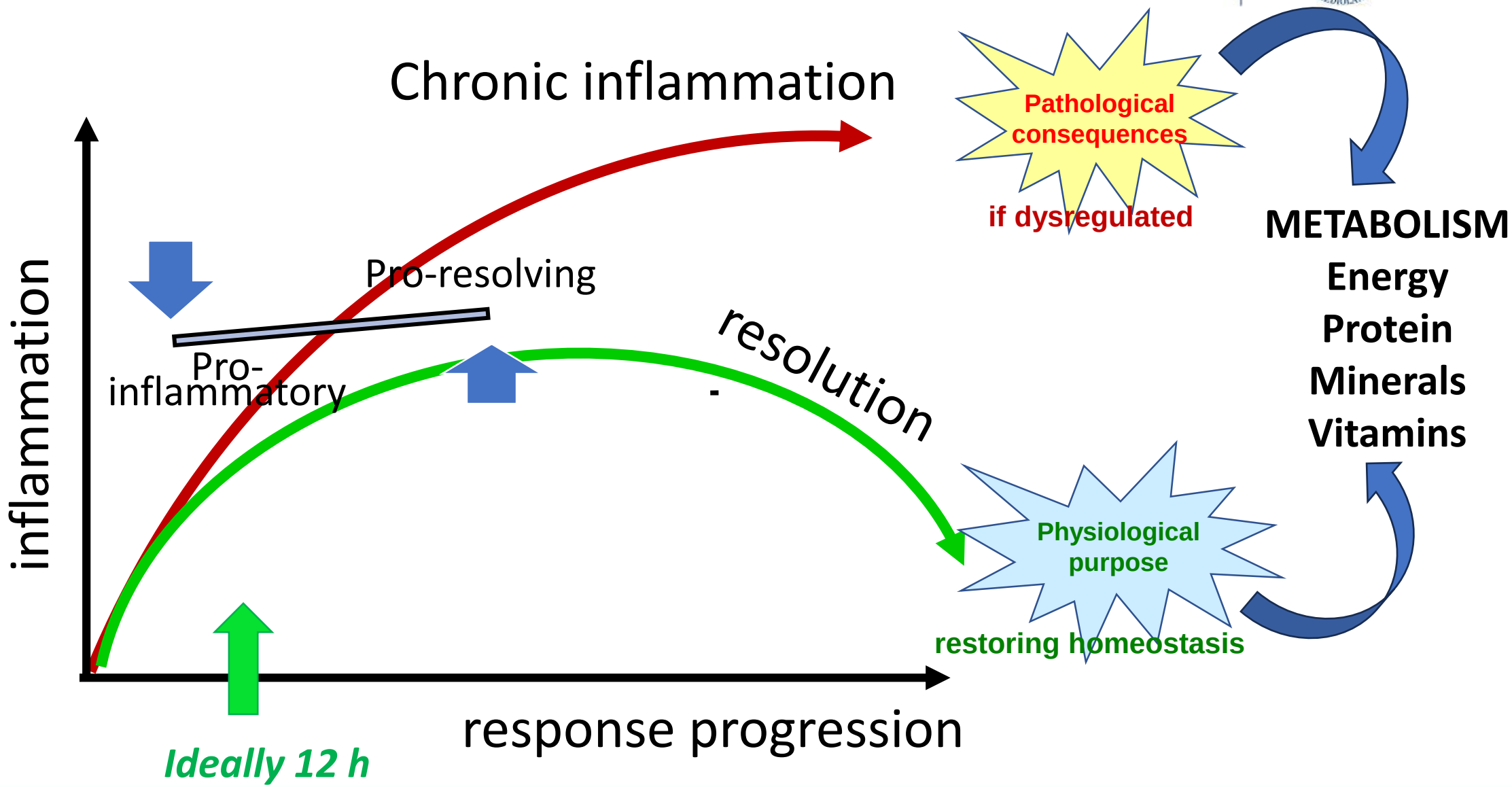
Liver: Acute Phase Response
(adult animal)



Changes in concentration of plasma proteins after injury or inflammation.

A1 AGP, alpha-acid glycoprotein; CRP, C-reactive protein; ALB, albumin; ROM, reactive oxygen metabolites; CHOL, cholesterol. Changes in CRP and haptoglobin concentrations are plotted on a logarithmic scale (*adapted from Fleck, 1989 and Bertoni & Trevisi, 2013).*

Inflammatory agents interact with metabolism



Liver response during the inflammation in the TP is crucial for many aspects

Problems are: severity and duration of these responses

Inflammation is not a negative process in se, but can cause concerns when:

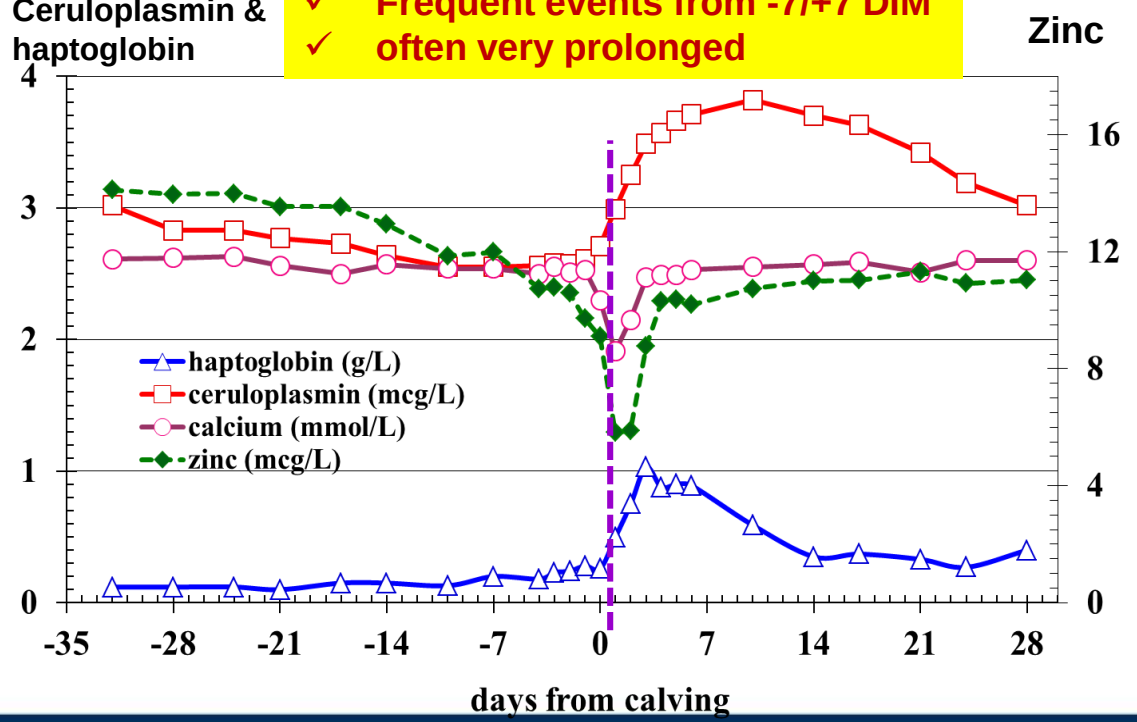
1. Excessive or uncontrolled
2. Reiterated
3. **Resolution is delayed**

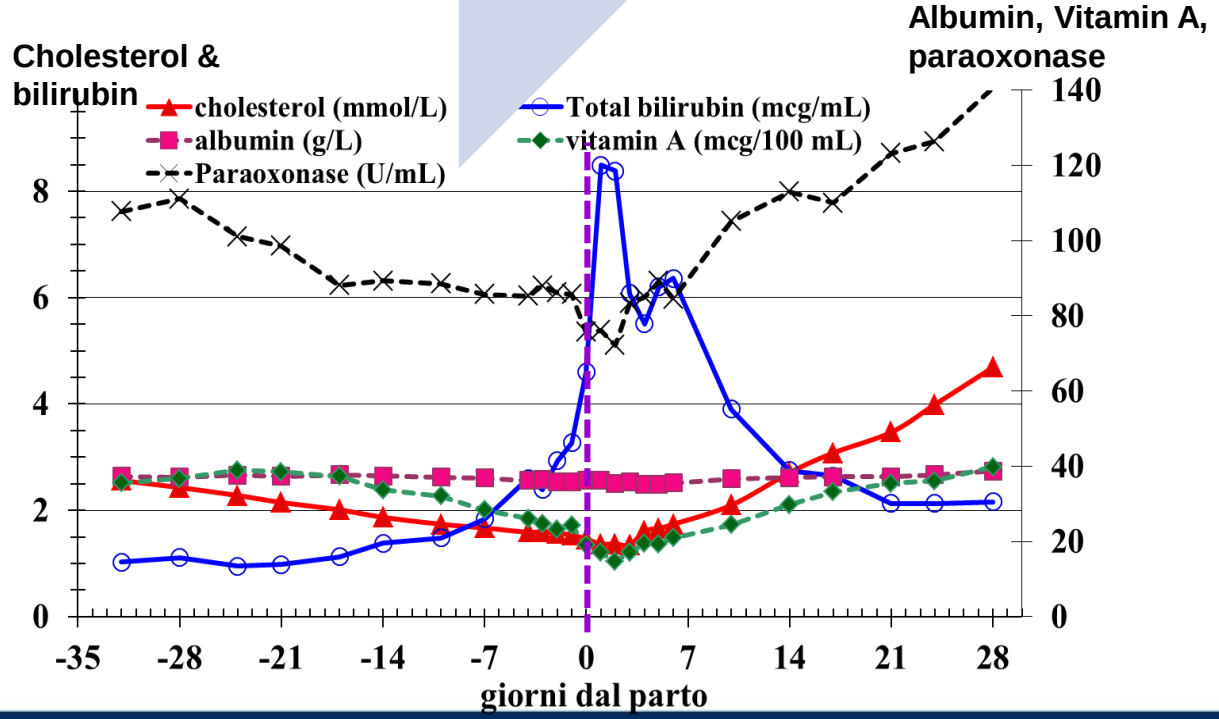
What to measure?

Inflammation presence (i.e. posAPP)?

Inflammation consequences (i.e. negAPP)?

- ✓ **Frequent events from -7/+7 DIM**
- ✓ **often very prolonged**





How to assess the severity of inflammatory events in TP?

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- **Biometric Benchmark** (es. threshold/physiological ranges of NEFA; BHB; Hp in different stages) (*Kervin et al., 2021 JDS 105:5327; Premi et al., 2021, Animals 11:1714*)
  - strength point: easy to identify cow at risk
  - weakness point: not consensus on reference ranges; time consuming, costly

- **Composite indices**:
  - **LAI** (Liver Activity Index; *Trevisi et al., 2001; Bertoni et al., 2008, JDS91:3300*)
  - **LFI (Liver Functionality Index;** *Bertoni et al., 2006; Trevisi et al., 2012 RVS 93:695*)
  - **PIRI** (Post-calving Inflammatory Response Index; *Trevisi et al., 2016 IJAS 12(s1):58*)
  - strength point: clusterize cows/herds highlighting critical (subclinical)
  - weakness point: time consuming, costly, delayed response

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LFI = Liver Functionality Index

Bertoni et al., 2006 57th EAAP Meeting, 17-20 Sept, Antalya, Turkey, pp 325
Bertoni & Trevisi 2013. Vet. Clin. North Am. Food Anim. 29(2):413–431

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parameters

3 plasma biomarkers routinely synthesized by the liver:
albumin
cholesterol (= lipoproteins)
total bilirubin (= indirect measure of enzymes needed for clearance)

calculation

- **2 measurements in the 1st month of lactation** (3 and 28 DIM)
- I step: index of each biomarker: for albumin & cholesterol= 50% VI + 50% I; for bilirubin = 67% VI + 33% R (VI = value at 3 DIM; I = increase from 3 to 28 DIM; R = reduction from 3 to 28 DIM)
- II step: Normalization of indices obtained in the I step, with reference values (X± SD) obtained from healthy cows and good performances (Bertoni et al., 2008)

$$LFI = \frac{albumins\ index - 17{,}71}{1{,}08} + \frac{cholesterol\ index - 2{,}57}{0{,}43} - \frac{bilirubin\ index - 6{,}08}{2{,}17}$$

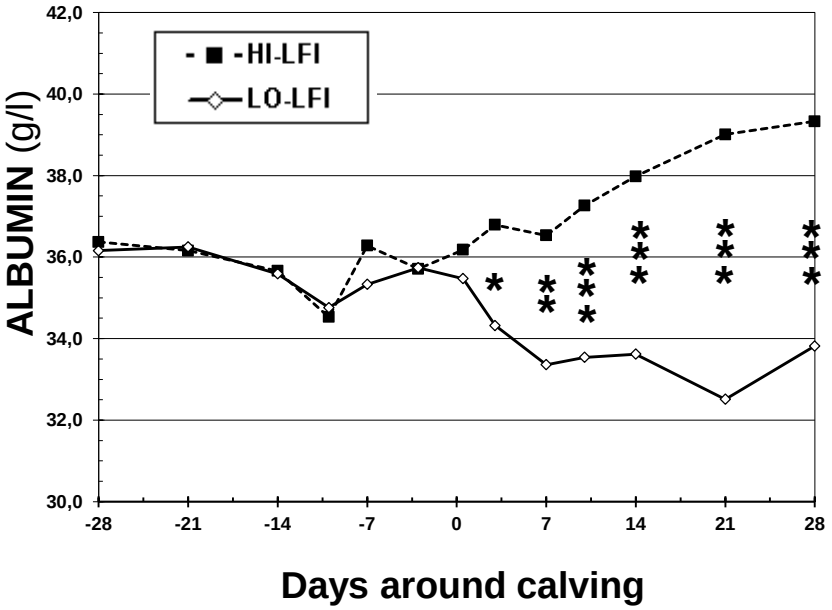
score

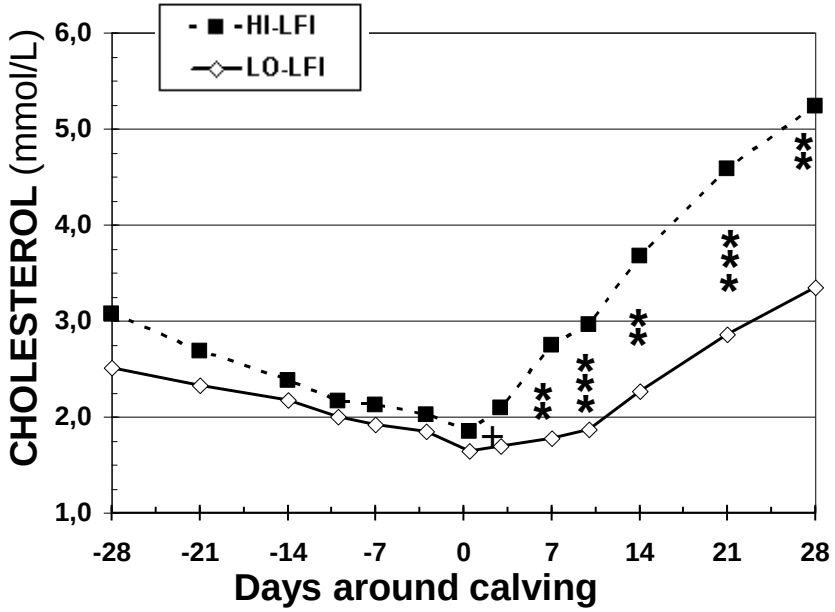
- **Final score of each cow is the sum of the normalized indices**
- The individual value can be compared within herd (clustering cows), across herds (ranking farms) …
- **More is high the LFI score and better is the adaptation** (with lower consequences due to inflammation)

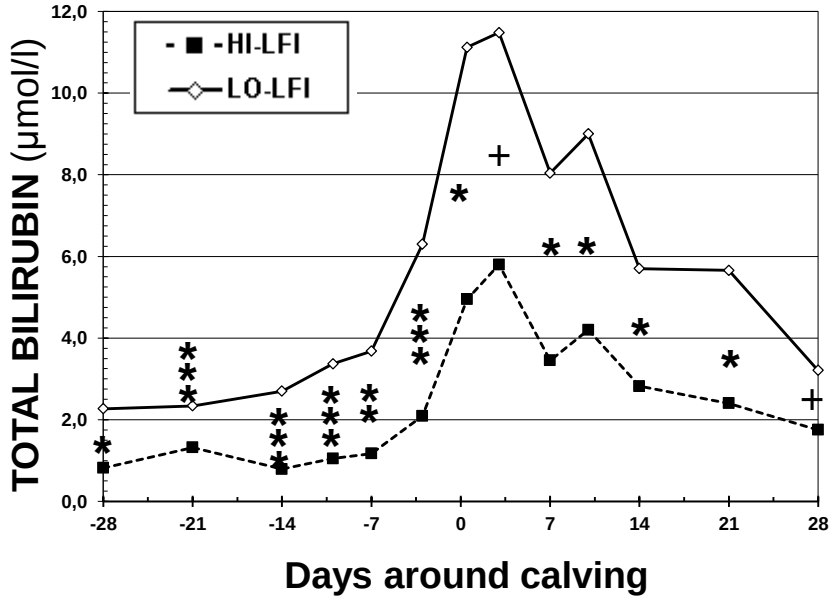
LAI e LFI: r = 0.87; P<0.001 (Trevisi et al., 2010)

LFI = Liver Functionality Index
(levels & evolution of biomarkers in TP)

Direct (albumin, cholesterol) and indirect (bilirubin) indices of negAPP response in plasma samples of periparturient cows with high (**HILFI**) and low (**LOLFI**) LFI.
(*Trevisi et al., 2012 Res Vet Sci 93:695-704*)

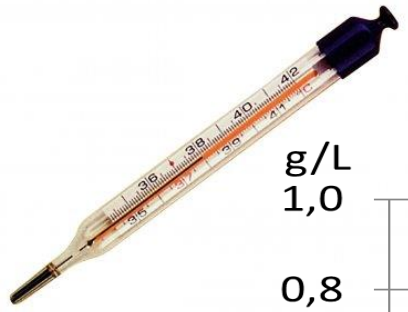






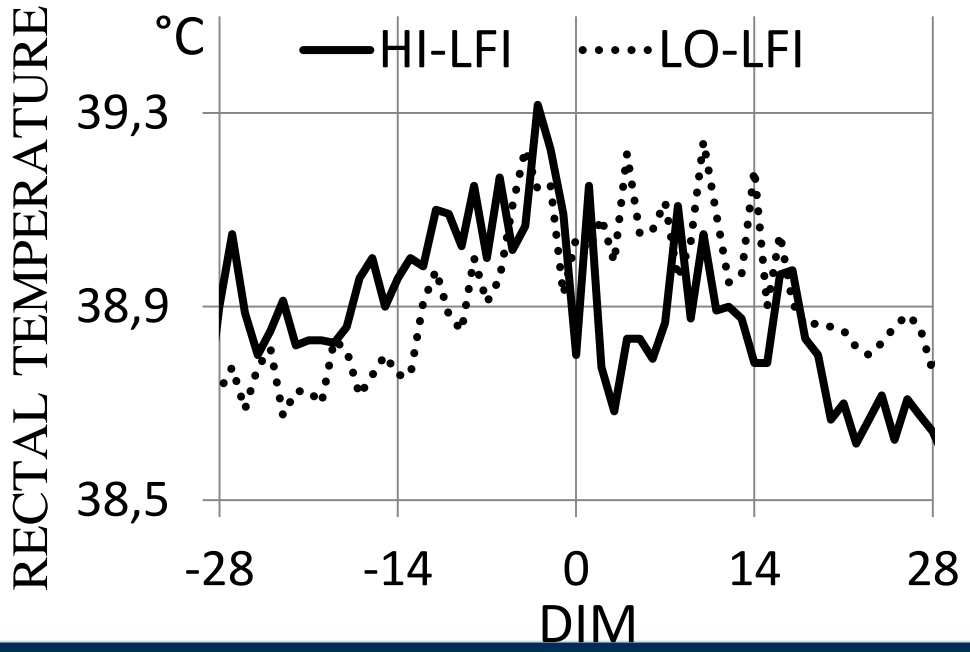
Inflammation & rectal temperature

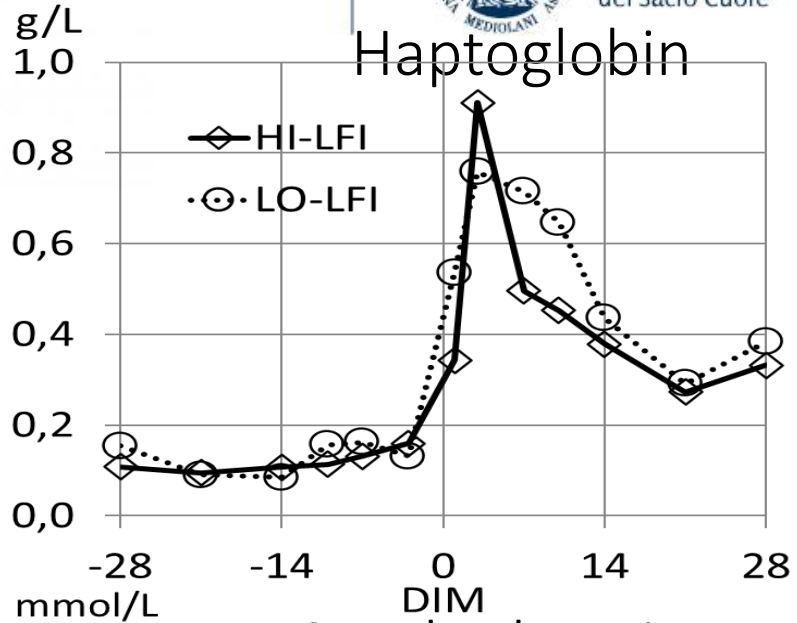
Trevisi et al., 2010 - 3rd EAAP ISEP - Parma

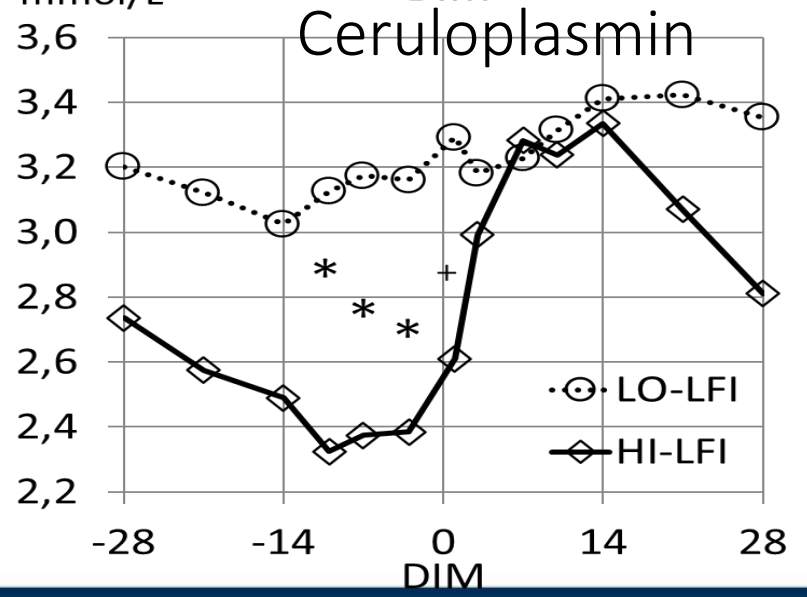


Cows with low vs high LFI:

- Higher frequency of diseases
- Higher body temperature in early lactation
- Higher CuCp before calving and slower recovery of physiological levels of +APP in the postpartum

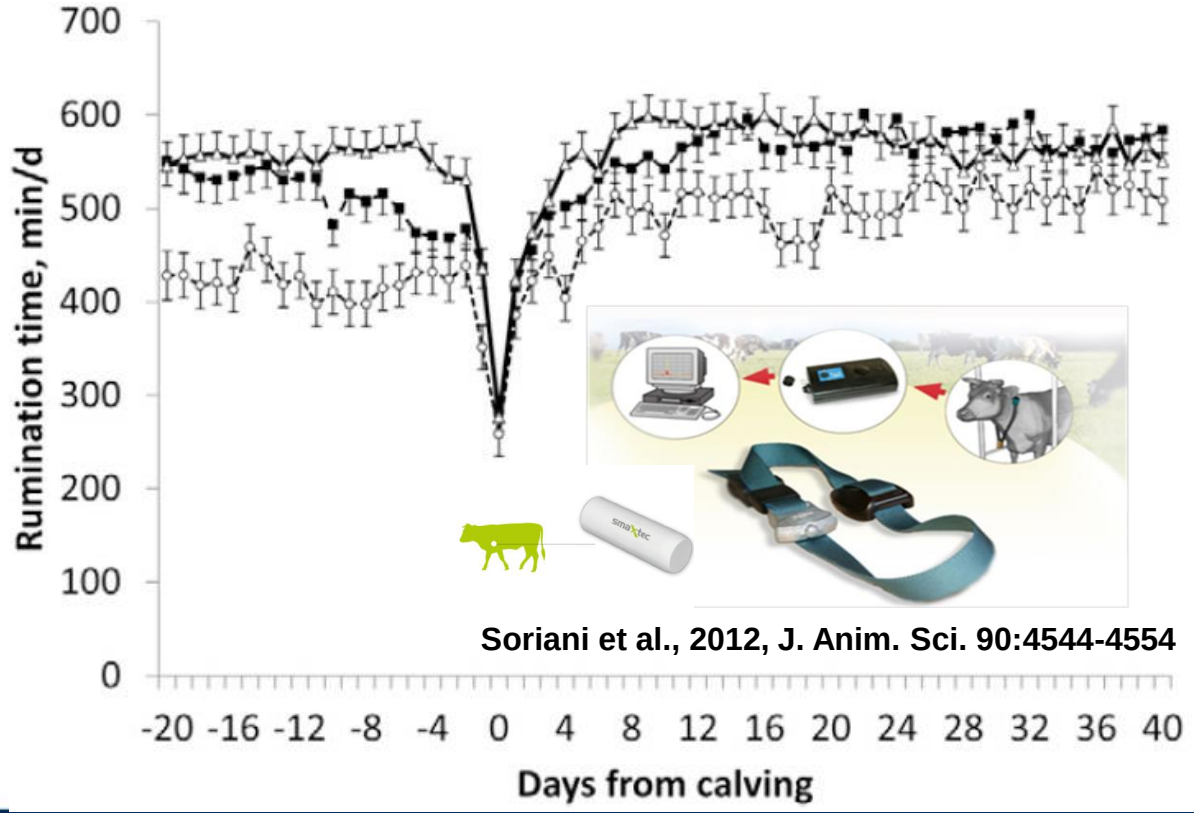






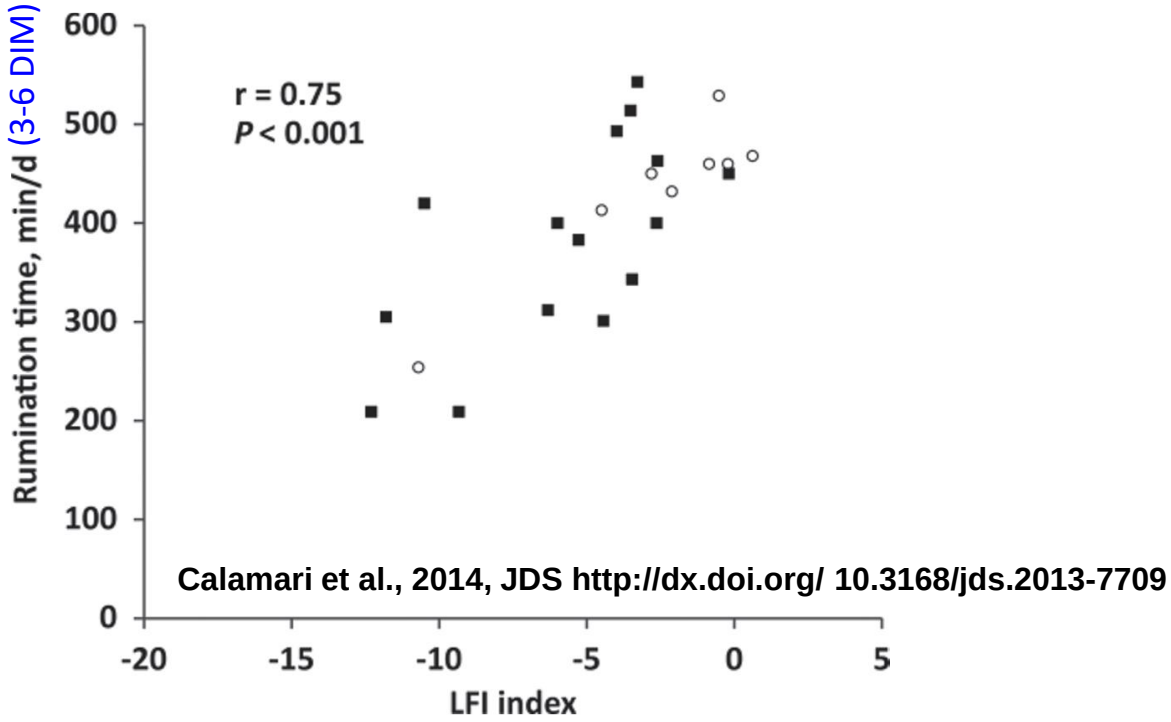
Inflammation & Rumination time

Daily behavior of rumination time (least squares means and SEM) during the transition period in **cows categorized according to the rumination time before calving** *(dotted line with open circles: short rumination time; dashed line with solid squares: middle rumination time; solid line with open triangles: long rumination time).*



Soriani et al., 2012, J. Anim. Sci. 90:4544-4554

The rumination time in the peripartum is associate negatively with LFI score



Calamari et al., 2014, JDS http://dx.doi.org/ 10.3168/jds.2013-7709

Thus: low rumination (<450 min/d) in the peripartum and/or a severe reduction are strictly related to immunometabolic conditions and predict poor performances in early lactation

Inflammation at calving & fertility

Bertoni et al., 2008 - JDS, 91:3300-3310

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UP-LAI group (the more productive) showed the best fertility

Item	UP n = 19	INUP n = 20	INLO n = 19	LO n = 19
Services per pregnancy* (n°)	1.65±1.3^{a}	2.04±1.6^{ab}	2.68±1.5^{b}	2.01±1.5^{ab}
Open Days* (DIM)	92.9±48^{a}	132.5±89^{b}	138.8±89^{b}	110.5±55^{ab}
Conception rate at 1st service (%)	52.6	45.0	21.0	36.8
Repeat breeders (at least 3 services)	21.0	45.0	57.9	31.6

*after logarithmic transformation

Inflammation (clinical or subclinical) affects fertility.

Less than 50% of cows in LO/INLO groups showed clinical signs.

Concentrations of –APP are more suitable to identify the metabolic distress in early lactation

Inflammation delays the resumption of cyclicity in cows

(30.0±2.5 vs 18.4±0.8 DIM in LO & HI-LAI)

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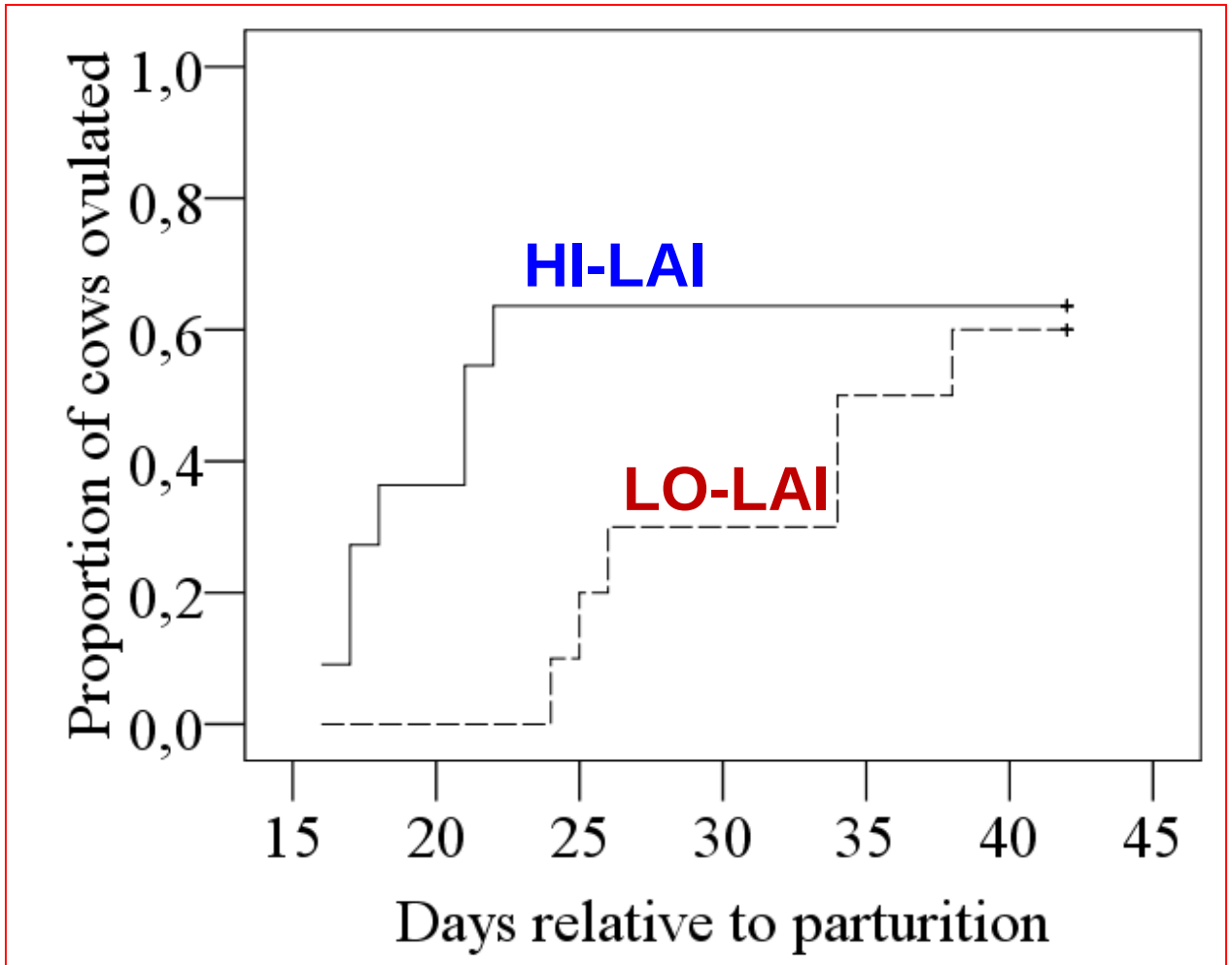
Cumulative survival chart representing the proportion of 21 high-yielding dairy cows that have ovulated during the first 42 DIM.

Cows were classified according to their LAI:
group 1 (LO-LAI, dashed line; N = 10) had a lower index value, suggestive of more pronounced inflammation, compared to
group 2 (HI-LAI, solid line; N = 11).

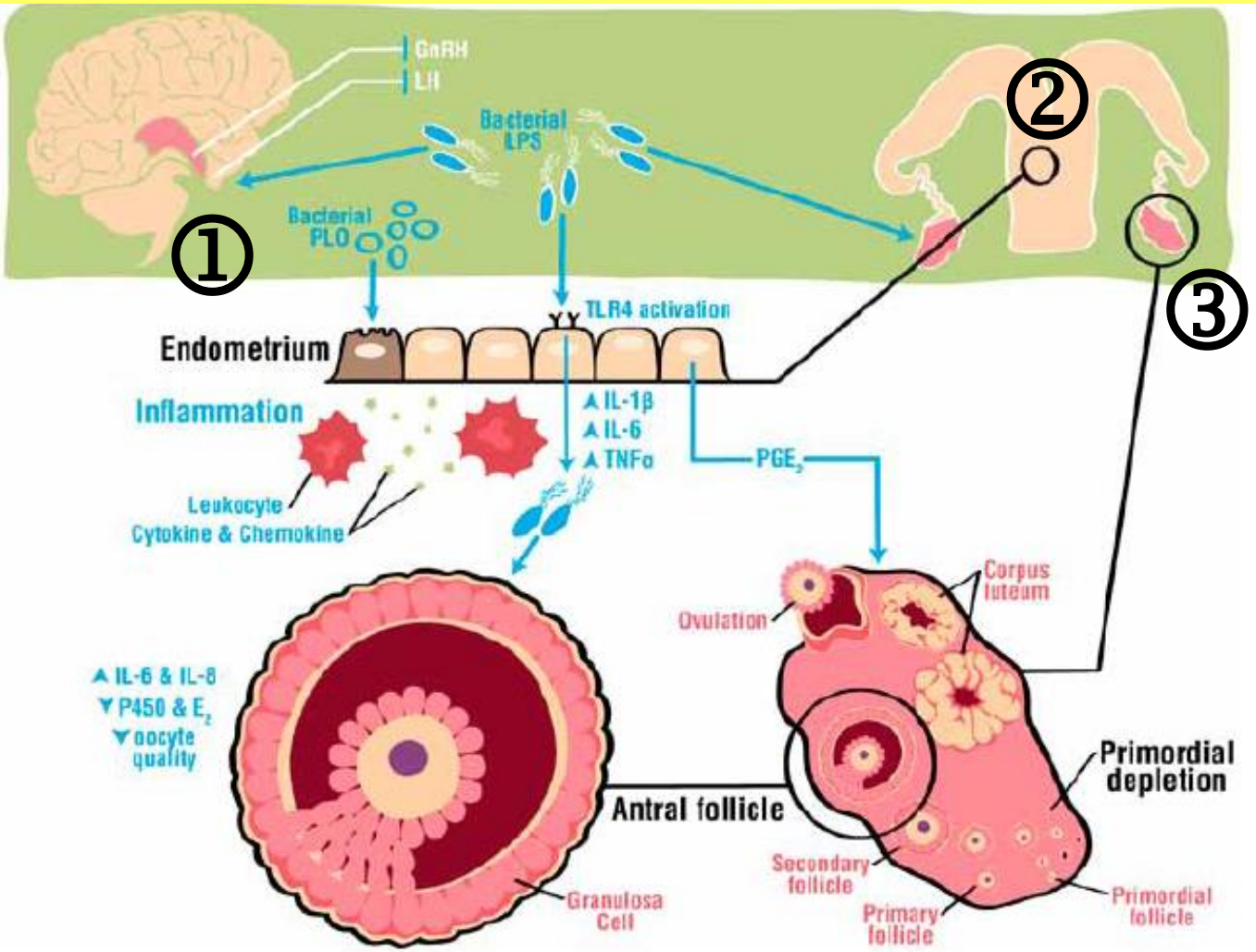


Observations on cows of Bossaert et al.,
Vet. J. 2011, 192(2):222-225

Link: inflammation (LPS), uterus & ovary

Bromfield et al., *J. Anim. Sci. 2015.93:2021–2033*

Schematic representation of uterine infection and impact on reproductive tract. (by Stacey Jones, Univ. Florida)

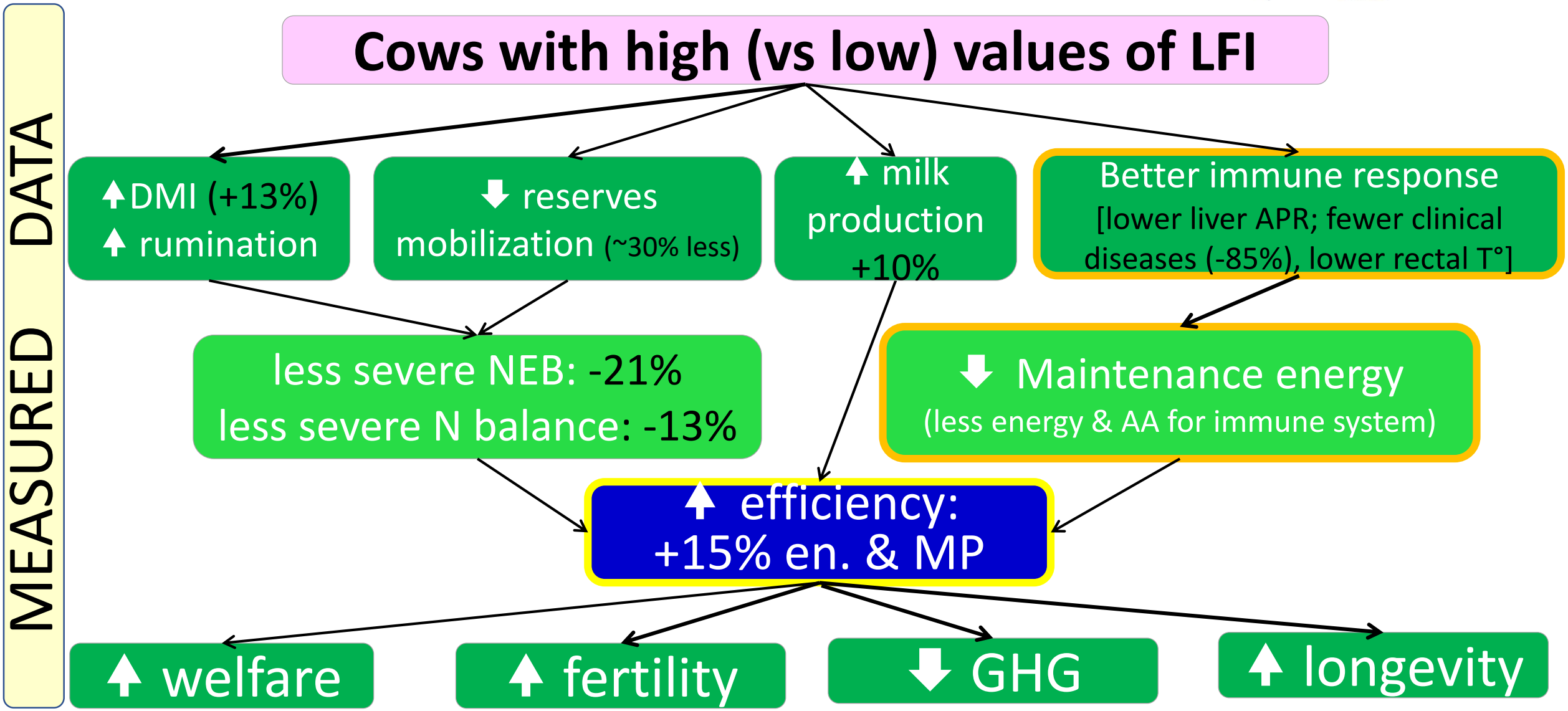


- **Uterine bacterial infection** cause the **absorption of LPS**
- LPS initiate an inflammatory response: TLR-4 activation, ↑ cytokine, chemokine, & PGE2 production. With effects on:

1. **neuroendocrine signaling**. In the **Brain**: ↓ GnRH and LH
2. **uterine health**. In **Endometrium** bacterial pyolysin disrupts cells by osmotic lysis.
3. **ovarian function**. In **Ovary** primordial follicle reserve is depleted, follicle growth is retarded, luteal phase is prolonged. *Ovarian granulosa cells respond to bacterial LPS in a TLR4-dependent manner, increasing inflammatory mediators, reducing aromatase and estradiol, and reducing oocyte competence.*

LFI can predict the success of TP

Trevisi et al., 2011 (ISBN 979-953-307-033-8)



Practical use of the LFI

- **Index of adaptation** of cows during the TP: **identifies subtle breeding problems** *(for inadequate conditions from dry off to 30 DIM)*
- **Within herd:**
  - **Identifies subjects with subclinical problems** (at 30 DIM) which:
    - ✓ still need attention and care
    - ✓ are at greater risk of infertility
  - ranks cows in different lactations
- **Between herds:**
  - **ranks farms from "good" to "poor" TP success**
  - Monitoring the health status & well-being during the TP

Summary

1. **Critical points in the periparturient cows**
   - Variations in immune parameters: adaptive and innate systems
   - Inflammation
   - Causes of altered inflammatory response
2. **How to interpreter inflammatory response around calving**
   - Implication at the Liver level
   - Physiological vs pathological
   - How to measure? presence or consequences?
   - When to measure?
3. **Indexes to classify inflammation severity in the peripartum**
   - LFI (Liver Functionality Index)
   - How to use it?
4. **Perspectives and Implications**

Perspectives

1. Are other indexes better than LFI?
2. Main causes of inflammation at calving time
3. Is it useful to contrast the inflammation at calving?

1a: Albumin-to-globulin ratio (AG) before dry-off as a possible index of inflammatory status & performance in the subsequent lactation in dairy cows

(Cattaneo et al, 2021 JDS 104(7): 8228-8242)

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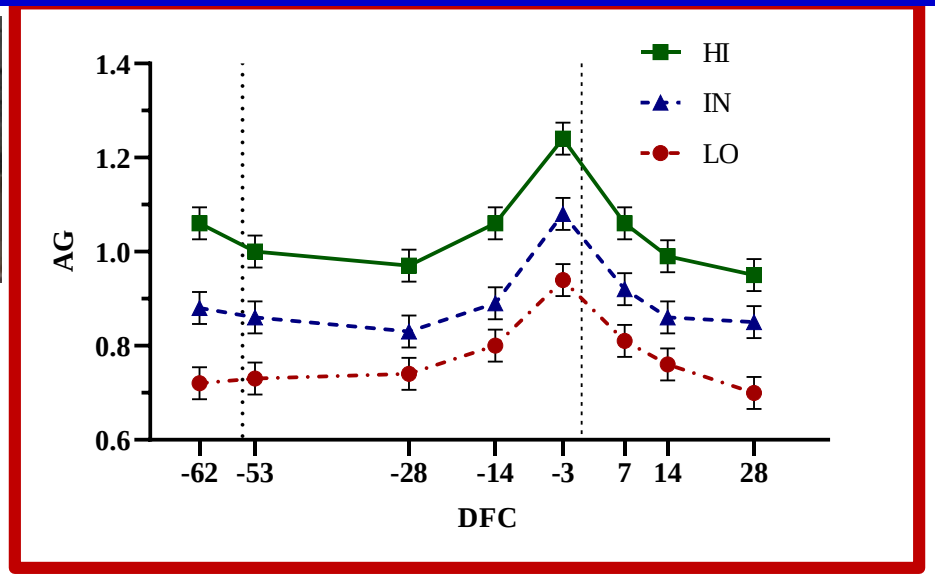
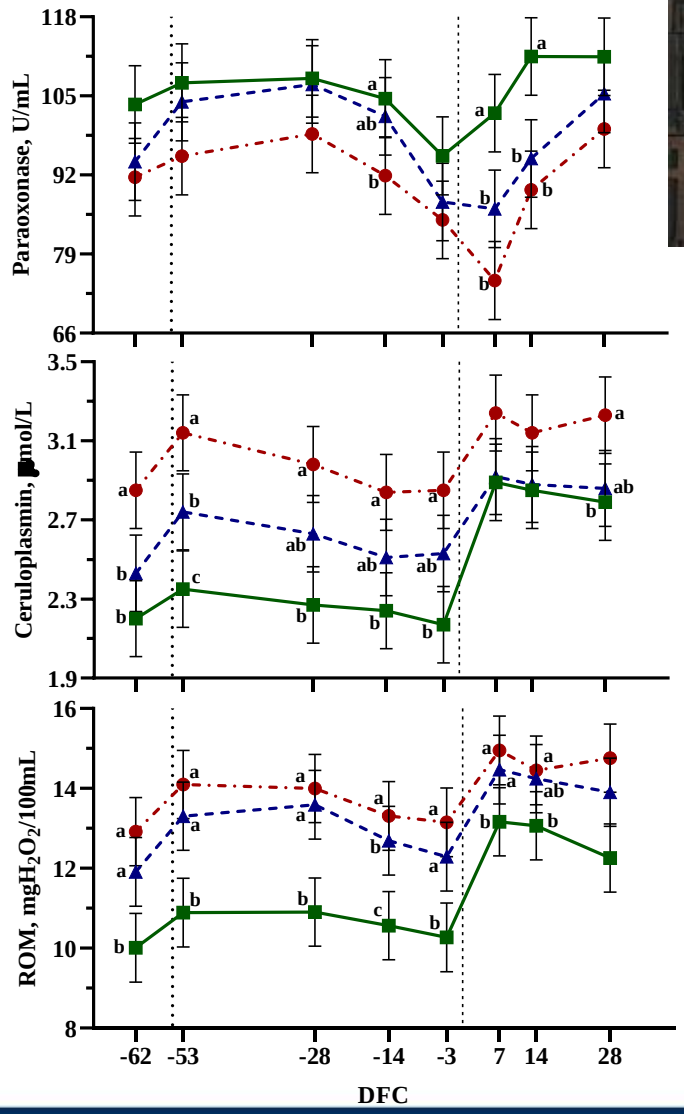
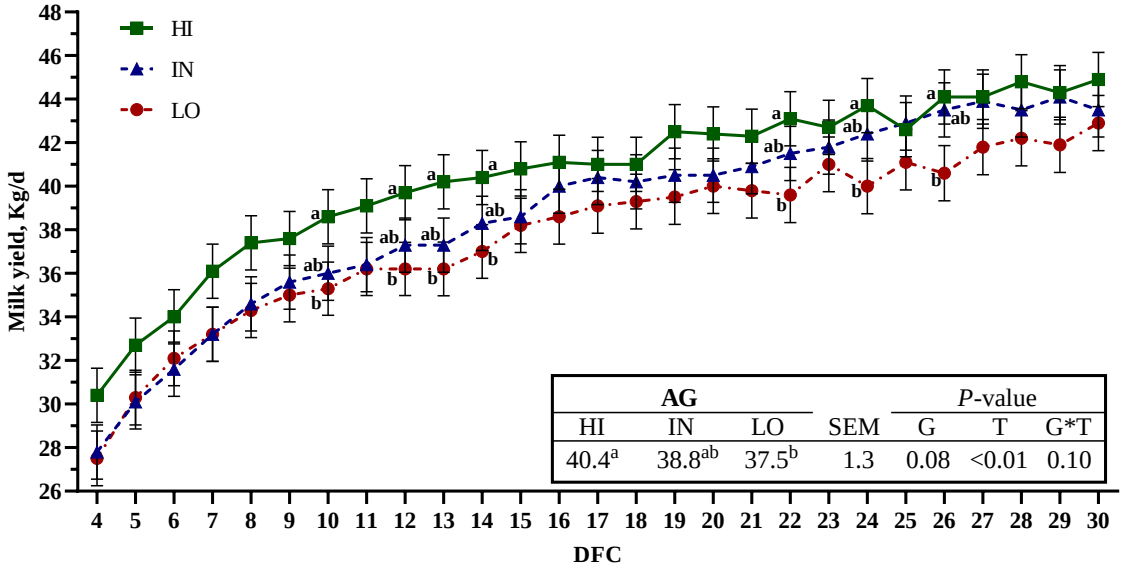






AG				*P*-value		
HI	IN	LO	SEM	G	T	G*T
40.4^{a}	38.8^{ab}	37.5^{b}	1.3	0.08	<0.01	0.10

The events that occur during the lactation/life modify the immuno-metabolic asset of cows.

Some conditions can favorize the trigger of more severe inflammatory response during new challenges….

1b –Inflammation... Prediction from milk spectra

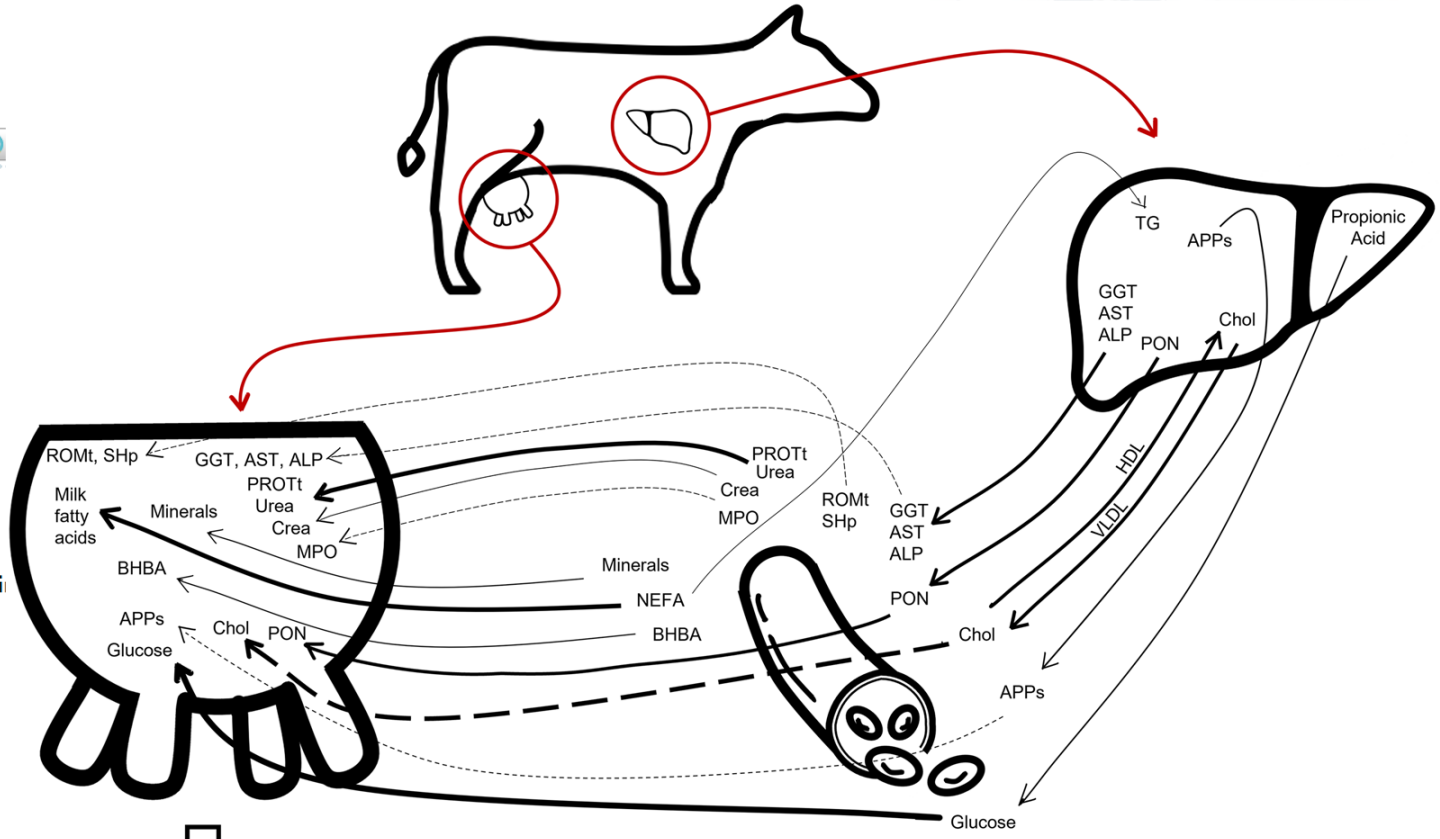
scientific reports

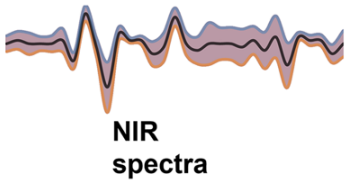
(2022) 12:8058 | https://doi.org/10.1038/s41598-022-11799-0

OPEN

In-line near-infrared analysis of milk coupled with machine learning methods for the daily prediction of blood metabolic profile in dairy cattle

Diana Giannuzzi[1]✉, Lucio Flavio Macedo Mota[1], Sara Pegolo[1], Luigi Gallo[1], Stefano Schiavon[1], Franco Tagliapietra[1], Gil Katz[2], David Fainboym[2], Andrea Mi Erminio Trevisi[3] & Alessio Cecchinato[1]





Aim: **to predict blood metabolites from milk samples**. This might allow a continuous monitoring of animal health and welfare parameters in order to optimize nutrition and productivity in the whole lactation.

PLF Tool: Milk near-infrared spectra collected by the **AfiLab instrument**

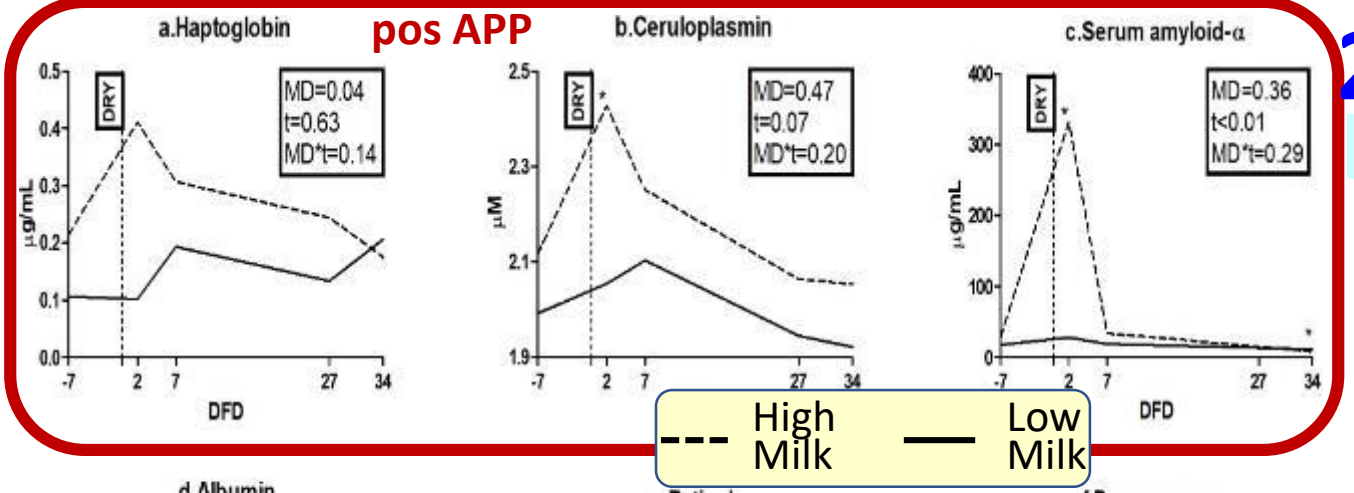
Results: **1st prediction equations for a set of blood metabolites** using diverse machine learning (385 Holstein Friesian dairy cows).

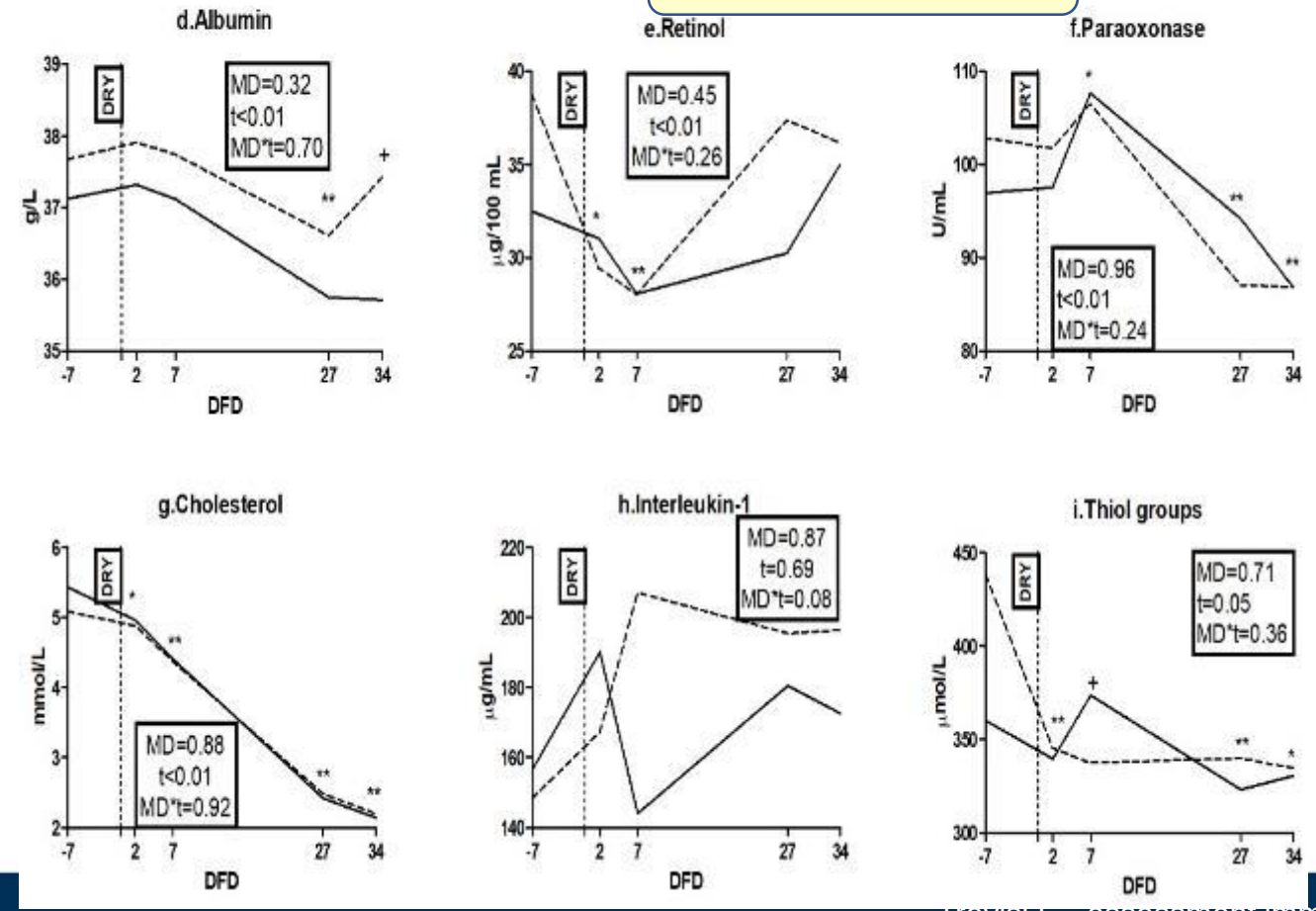
Many moderate correlations (*r*) between plasma parameters and peaks of milk spectra.

Promising tool

2a. Pre vs dry off

Mezzetti et al 2020 Ital. J. Anim. Sci. 19(1):51–65





Pre vs post dry off:

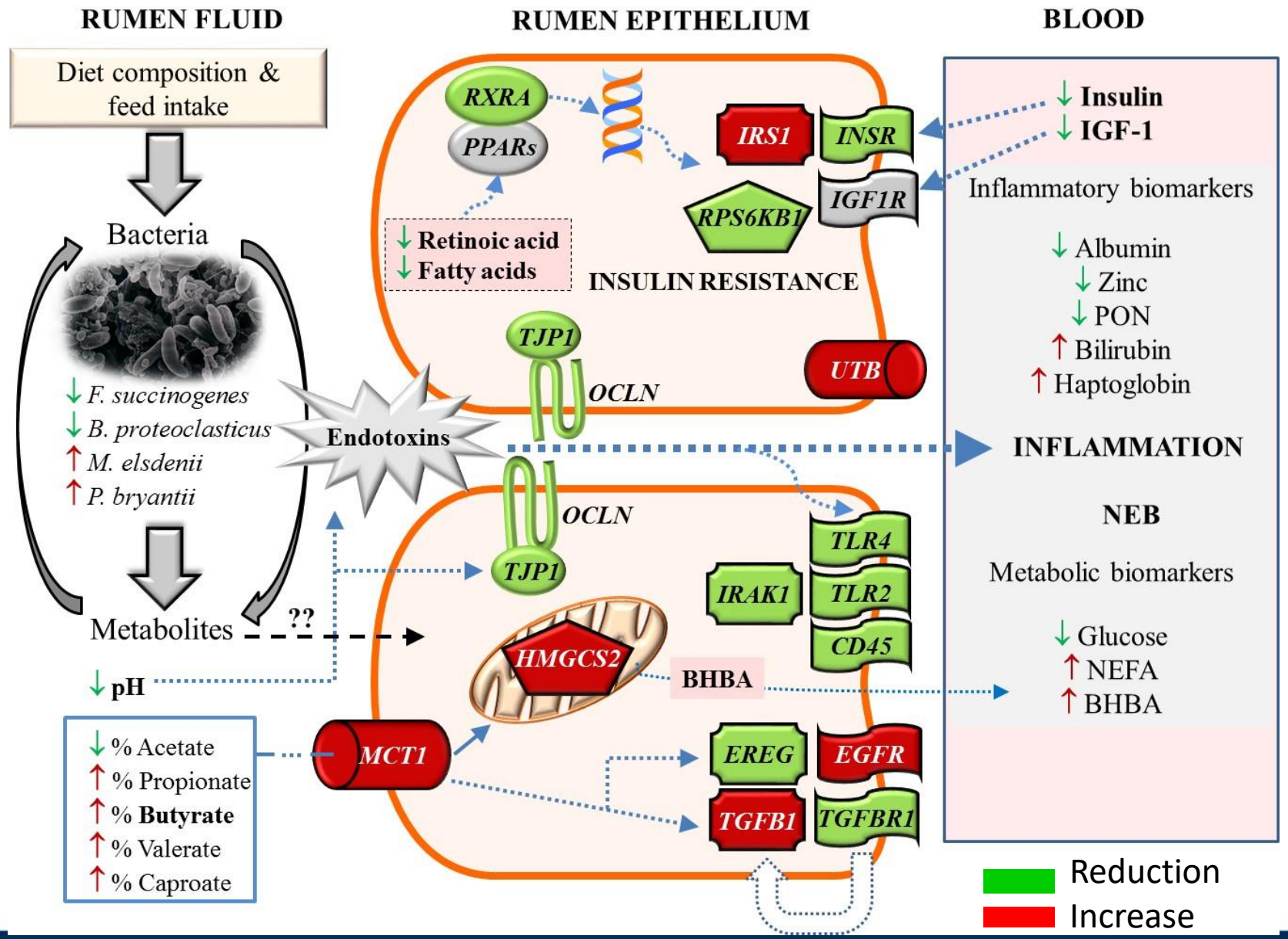
- ⬆ **CuCp & SAA** (2 DFD)
- Progressive ⬇ **Albumin** till 27 DFD
- ⬇ **Retinol** 2-7 DFD & **PON** ($P < 0.05$)
- ⬇ **Cholesterol & SHp**

⬆ +APP & ⬇ -APP

Post dry off: systemic INFLAMMATION (i.e. activation of immune response)

HM (MY <15 kg/d) vs LM: more severe infl. response

2b. Rumen changes during TP & inflammation



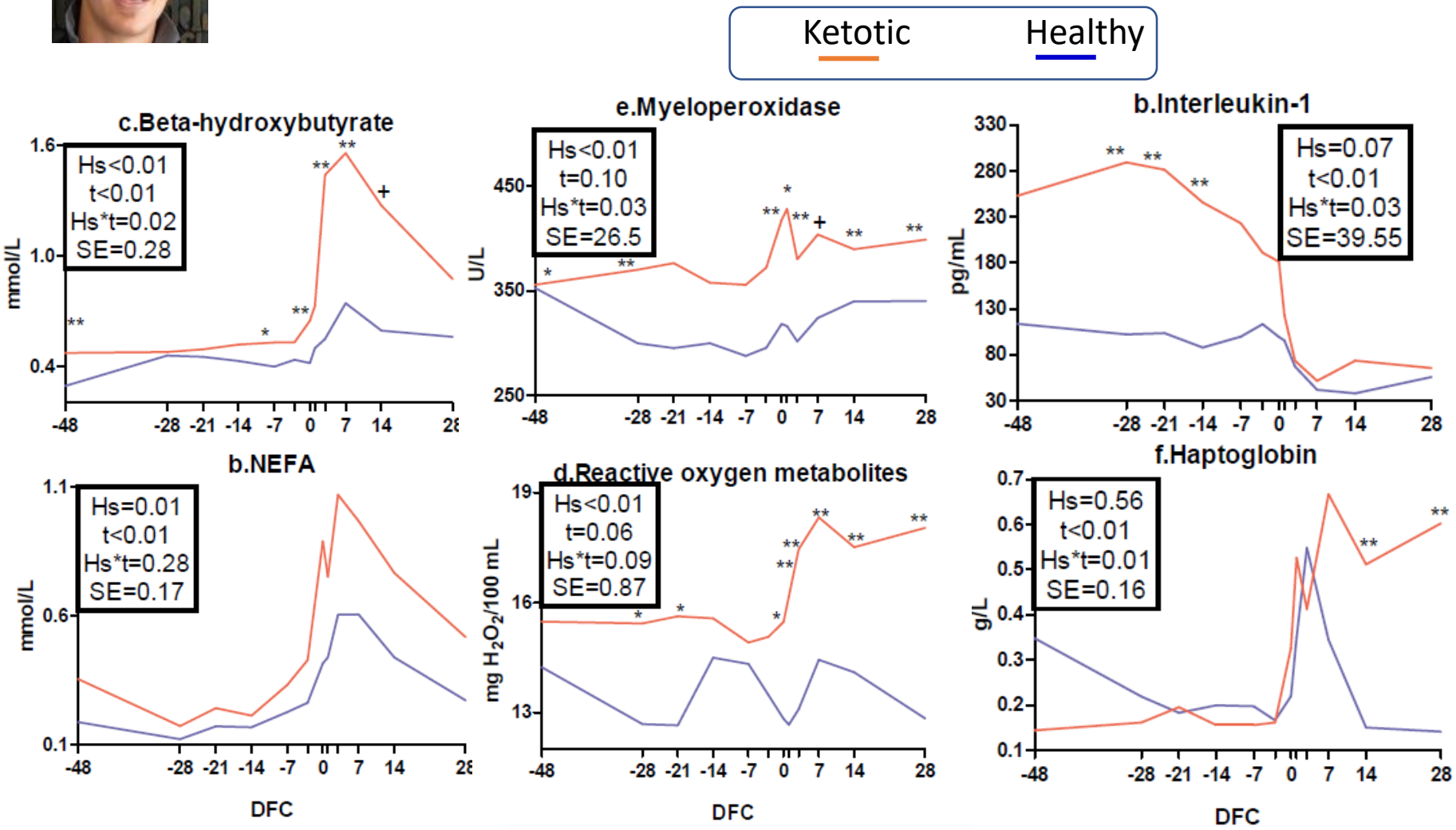
Minuti et al., *JDS* 2015, 98:8940-8951

Gene expression (GE) in rumen epithelium (Post vs Pre – partum):

- ↓ GE of tight junction
  - ↑ Permeability
- ↓ GE of many immune functions
  - ↓ Epithelium protection
- ↓ GE of glucose uptake
  - Insulin resistance

2c. Precalving dysregulation. Is ketosis preceded by a IS activation?

Mezzetti et al. (2019), JDS 102:9241-9258



Ketotic cows showed dysregulated IS in late pregnancy: high PIC, MPO, ROM (& IFNγ)

This status supports:

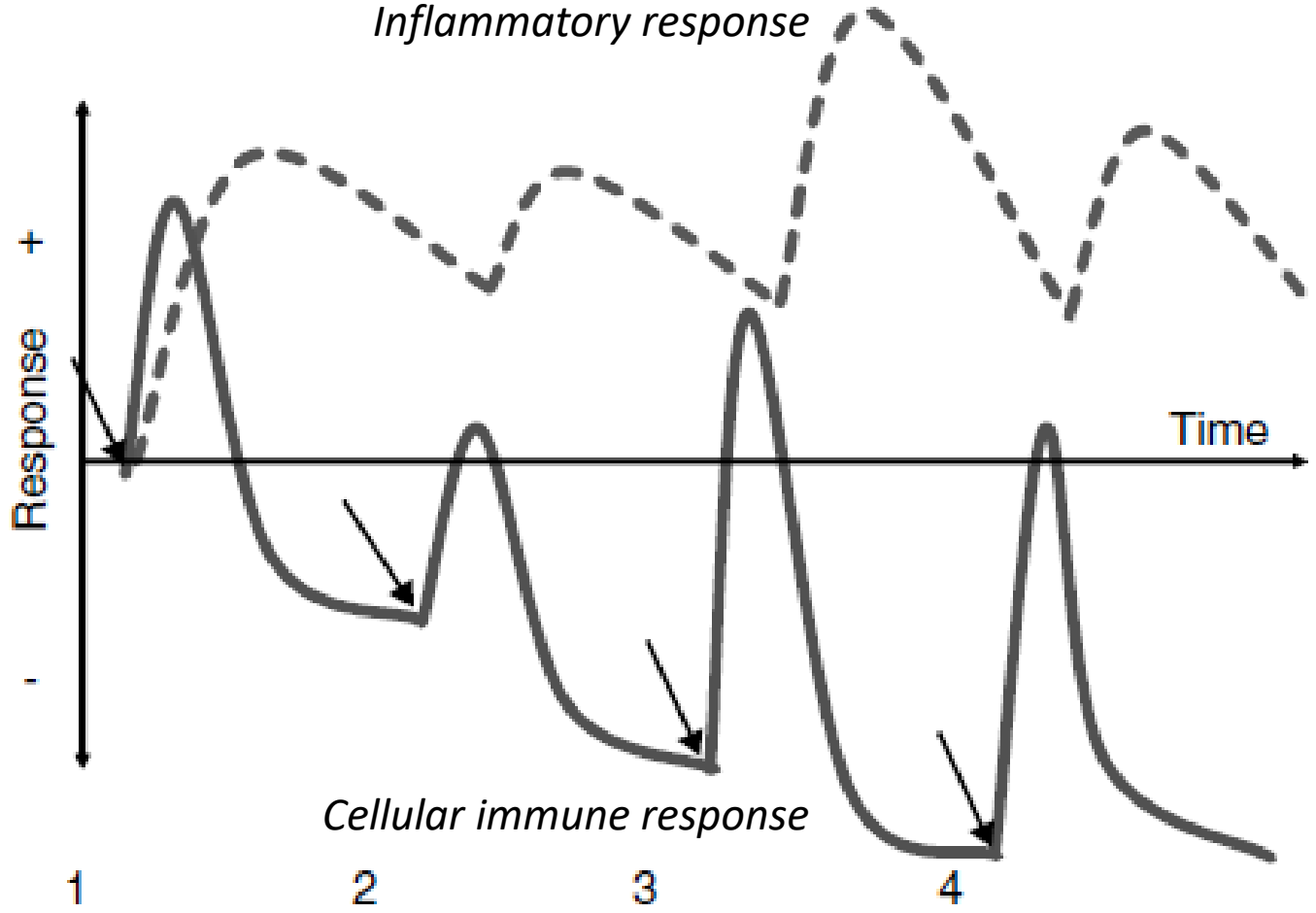
- a lower feed intake
- a higher inflammation around calving

Both conditions promote the onset of clinical ketosis

Effect of reiterated challenges on Immune System on inflammatory response and Immune cells response (NEU)

The **relationship** between the **cellular immune response** (——) and the **systemic inflammatory response** (– – –) **to multiple insults**.
+ , Positive
– , Negative

Heyland et al., Proc Nutr Soc. 2006



…the triggered response of the cellular defence function is a biphasic phenomenon:

i) with an initial hyperactive phase, which may overshoot the requisite response,
ii) followed by depression of cellular defence function.

Result: some properties are reduced, as phagocytosis, migration
Unbalancing pro- vs anti-inflammatory mediators?

3. To contrast the inflammation

When **inflammation is exaggerated** (posAPP & negAPP) the cow's metabolism is affected and metabolic diseases are promoted and infectious favorized

For this reason, we did the **first experiment to attenuate inflammation** (also subclinical) immediately after calving ...

Model “NSAIDs”: able to attenuate the inflammation in TP

Trevisi et al., 2003. 54 EAAP Meeting 8:258; Bertoni et al 2004 Vet. Res. Comm. 28(S1):217-219; Trevisi et al., 2008 J. It. Ass. Buiatrics 3:61-6; Trevisi et al., 2010 14 ICPD Meeting:165-166

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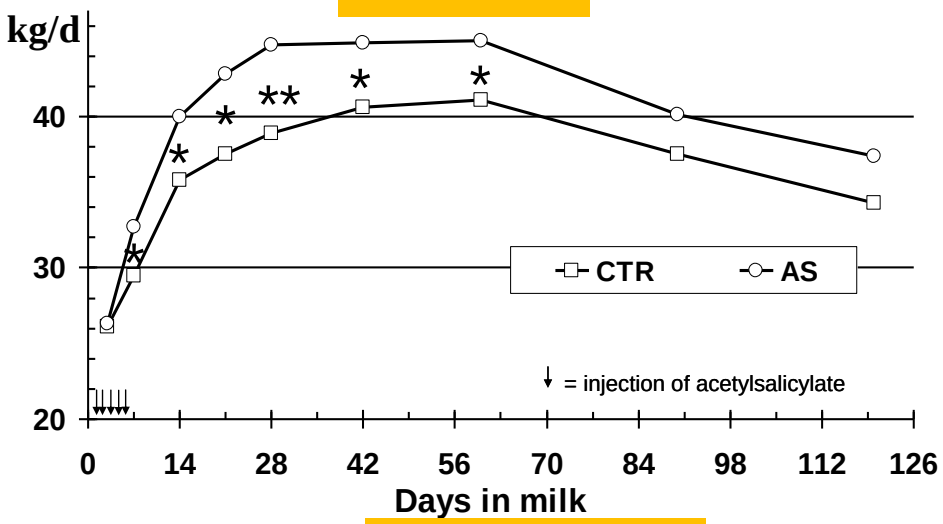
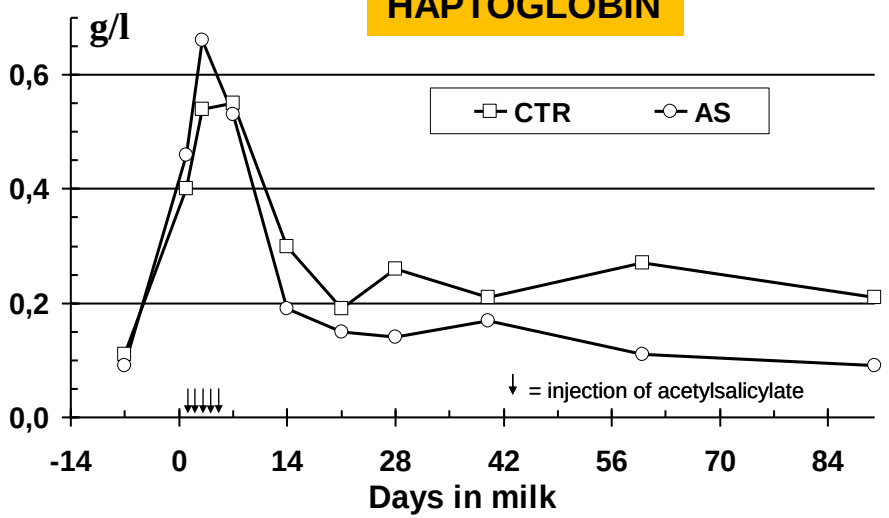
MILK YIELD



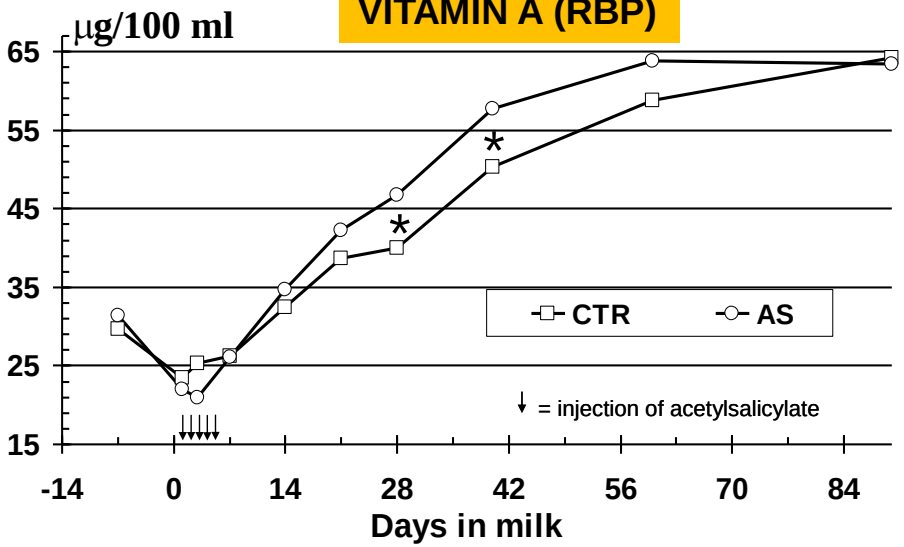
HAPTOGLOBIN



AS = daily i.m. treatments with **lysine acetylsalicylate** (15 g/d 1,2,3 DIM & 7.5 g/d 4,5 DIM)

CTR = control

VITAMIN A (RBP)



Trevisi e Bertoni (2008) In “Aspirin and health research progress”, Nova Science Publishers. pp 23-37

FERTILITY

group		CTR	AS
cows	*n°*	22,0	23,0
culled cows	*% of total*	15,8	9,5
pregnant cows	*% of total*	86,4	91,3
pregnant at 1st insemination	*% of pregnant*	21,1	52,4
repeat breeders	*% of pregnant*	36,8	28,6
services per pregnancy (§)	*n°*	2,68	2,38
open days (§)	*n°*	131,8	106,3
Fertility Status Index (FSI) (@)	*n°*	12,6	61,8

LEGEND: (§) after logarithmic tranformation; (@) Esslemont and Eddy (1977).

Aspirin model: practical considerations

- **Results of "aspirin model" supports the importance to attenuate the inflammation immediately after calving** *(e.g. more health, MY, fertility & less distress)*
- Dosage and time of treatment are really important
- Aspirin acts in a special manner: **"involves the resolving mechanisms of inflammation"**, but most of NSAIDs is not able to promotes a full resolution of inflammation
- **NSAIDs have also side effects**: increase the gut permeability
- Aspirin is a drug and cannot be used systematically, but other molecules (nutraceuticals) can mimic most of its effects

State of the art and Perspectives

- IS is the only factor showing a clear change in pre-calving
- IS is dysregulated, but not suppressed
- Dysregulating factors likely start from dry off
- Inflammatory response is altered in TP and can help to distinguish resilient from subclinical cows
- negAPP are the most effective parameters to detect timely subclinical cases

- Efforts to understand causes of derailment of the immune functions & exaggerated inflammatory response
- Strategies to tune/modulate the inflammation in the peripatum
- Immunonutrition is a relevant strategy to optimize IS
- Reduction of social stressors (also essential to guarantee high welfare)

Many thanks for the attention

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QUESTIONS?

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Dr Andrea Minuti

Dr Fiorenzo Piccioli-Cappelli