Recumbency and treatment failures: what makes TNFα and how to get where?

1. Causes of parturient paresis
2. Differential diagnosis of "recumbency"
3. Downer cow complications
4. Therapy in downer cow complications

1. Causes of parturient paresis in cows

etiology	pathogenesis
• alkaline reaction of fodder (DCAD> 100 meq/kg DM) and the internal environment • Ca supply (> 80g / d), • PI supply (> 50 g / d) • ↑ energy supply (obesity) • ↑ age, dairy breeds • ↑ performance • **↑ radicals/**↓ trace elements	↓ Vitamin D3 receptors on gut + bone ↓ parathyroid hormone receptors on renal + bone ↓ number and activity of osteoclasts ↓ easily exchangeable Ca in the bone ↓ renal synthesis of vitamin D meta-metabolites - ↓ hydroxylations (activation) of cholesteryl kalziferols in kidney and liver ↓ easily exchangeable Ca in the bone / (mobilization **↓ osteoclasts maturation**

2. Differential diagnosis of "downer cows"

Downer cow

- two "milk fever treatments" or
- “within 24 hours with treatments."

treatment success

Hypokalcemic
Milk fever

no treatment success

Downer cow Syndrome

?

2. **Differential diagnostic „Downer cow“**

(modif. n. Dirksen 1990)

Sensorium freely	**Sensorium disturbed**	**general condition disturbed**
• serious injury: fractures, ruptures, bruises, paralysis • metabolic distur-bances/ require-ments: ↓Pi, ↓ Ca, ↓K • Psychogenic im-mobility (anxiety, insubordination)	• milk fever (↓Ca) • Tetania (↓Mg) • Ketosis • Lever coma	• Severe intra-abdo-minal diseases: ... Ileus, peritonitis, intestinal rupture • intoxications, heavy puerperal disorders • mastitis paralytika

3. Downer cow complications

. . . what complicated the parturient paresis respectively the Recumbency?

- obesity
- Endotoxins
- TNFα
- ↓Pi
- ↓ Antioxidants
- Thrombosis

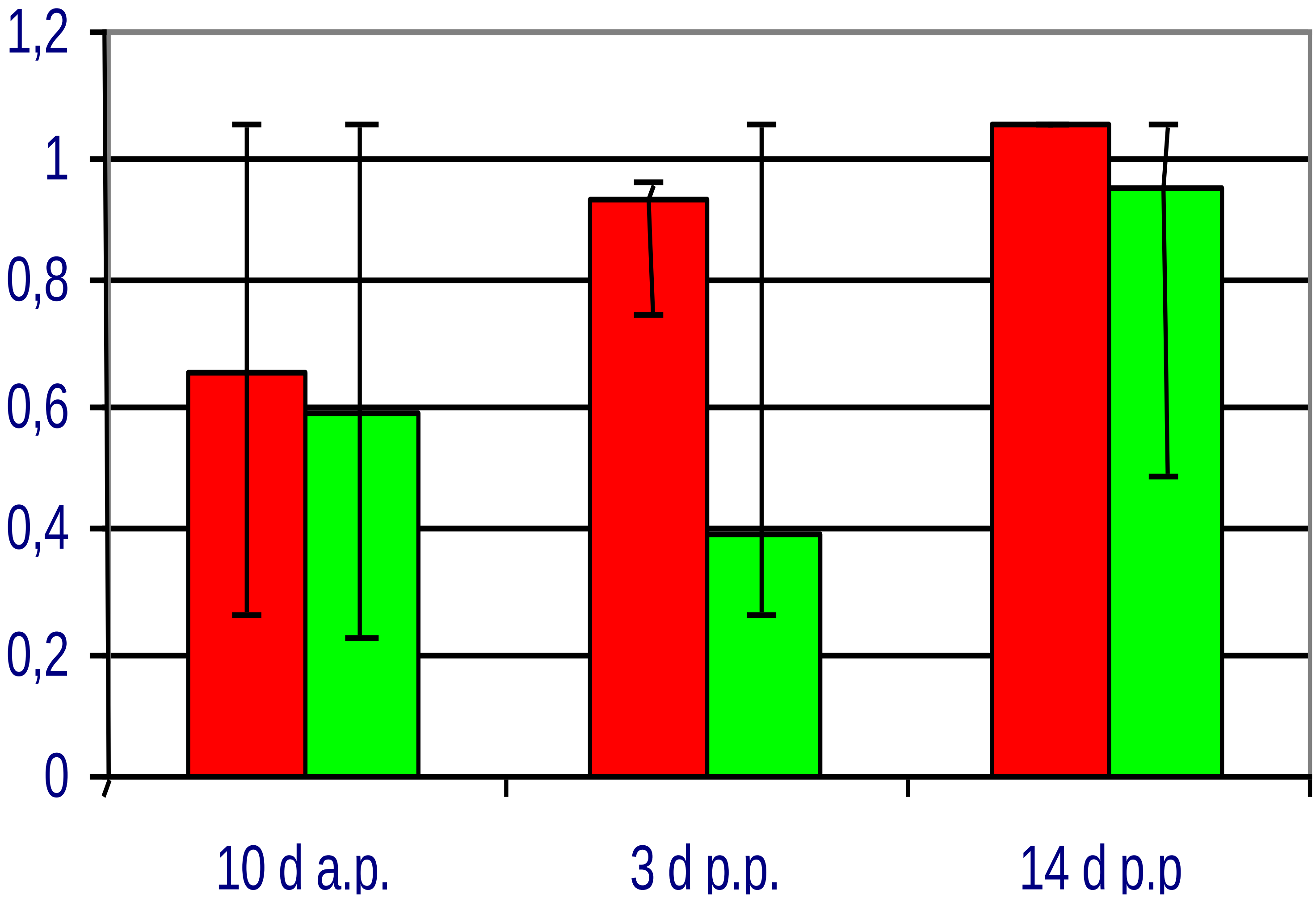
?

Significance of Endotoxins

?

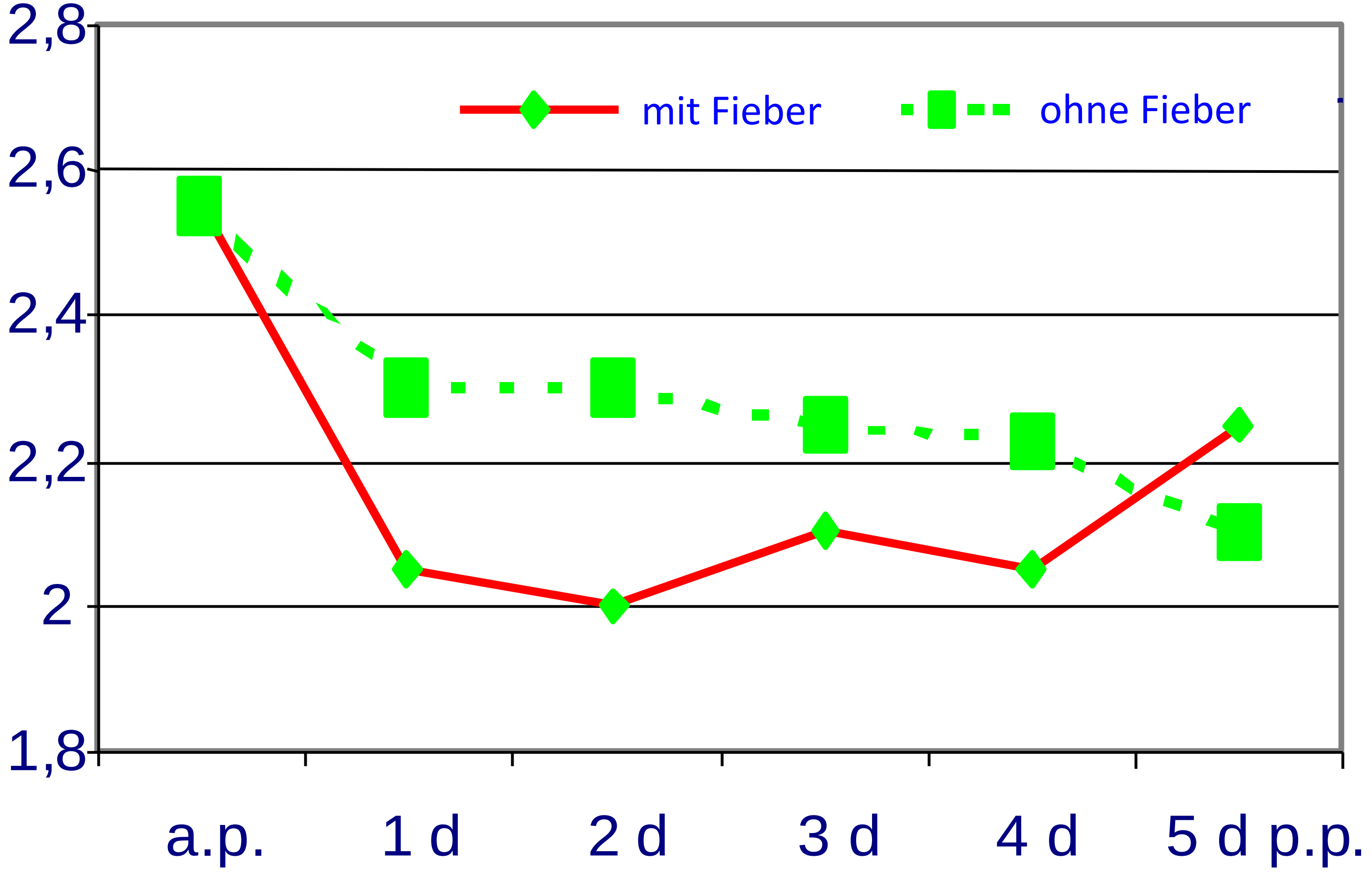
Endotoxin (EU/ml) – milk fever

Endotoxin decreases Ca

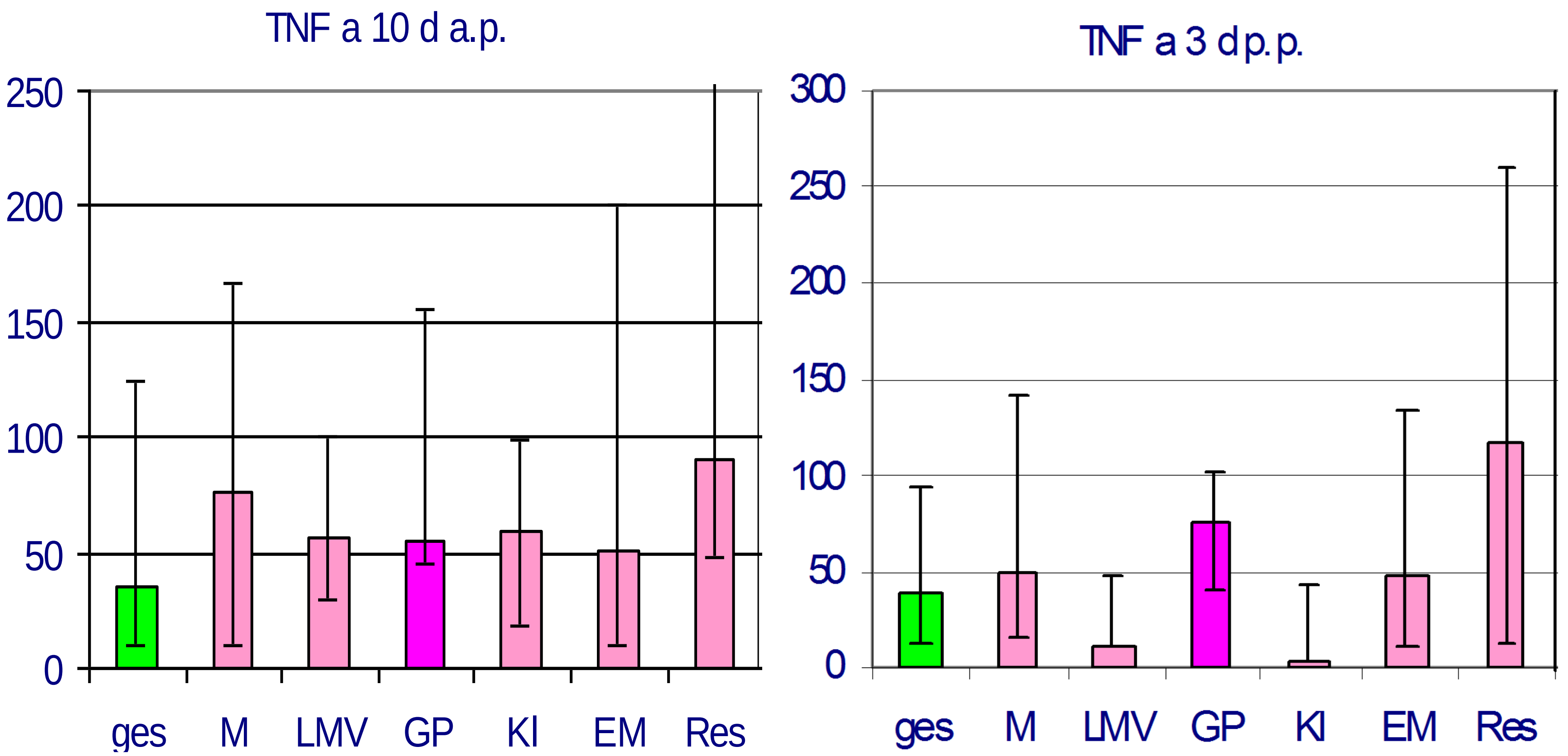


Ca (mmol/l Serum; Fritzsche 1999)

Endotoxin decreases Ca



TNFα concentrations in cows with postpartum Diseases (unpublished)



TNFα: ↓ Pi-resorption and ↓ Ca-mobilisation by ↓ osteoclast maturation

Downer cows:

ante partum + post partum ↑ TNFα

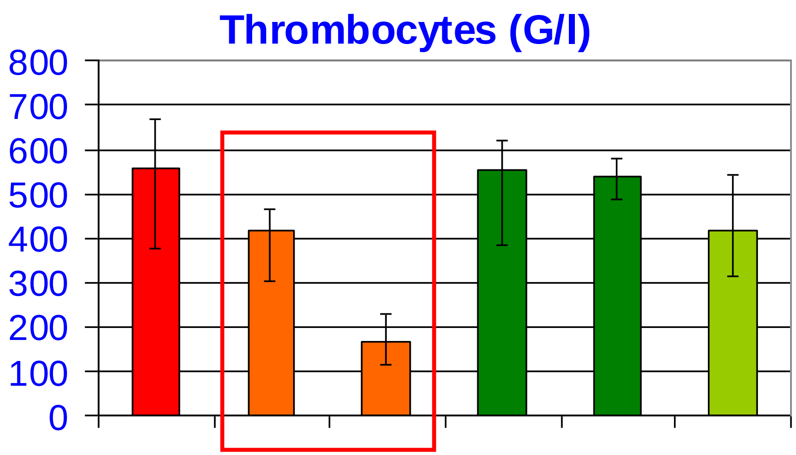
TNFa → ↓Ca^{++}

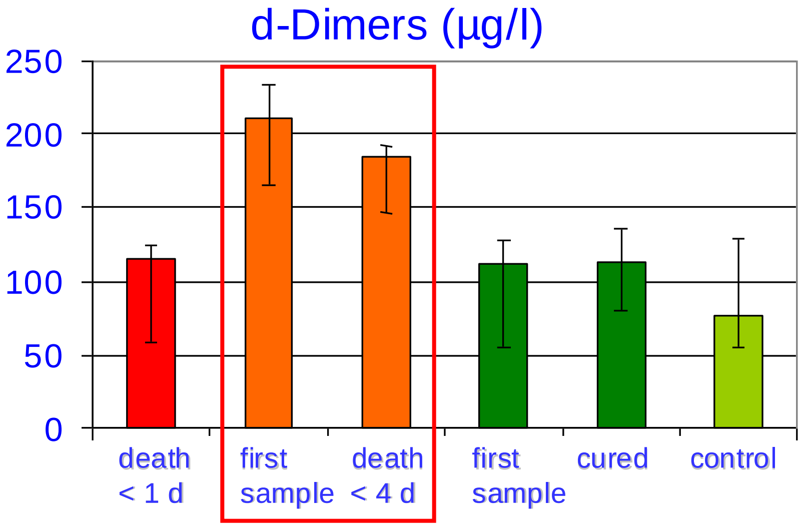
complikations by fat cows

Endotoxins: inflammatory mediators: neuromus-ventricular function (GOFF 2002) :

- Interleukin 1 → ↓ **Blood-Ca**
- Thromboxans, Prostazyklins and vasoaktive Amins → **hypovolämic Shock**
- Hypoglycemia + ↓ **Glucose transfer** → cells → ↑ Lactate + Dysfunktion + **muscle weakness**
- Platelet activating factor (PAF) → thrombi
- + Skeletal + Heart muscle weakness

➢ Platelet activating factor (PAF) → thrombi





Müller, M. Möhring, M. Fürll, A. Sobi-raj,K. Gmeiner, H.-A. Schoon.
Pulmonale Thrombosen beim weiblichen adulten Rind im klinischen Kontext.
Tierärztl. Prax. 2009, 37

4. Therapy by downer cows complikations

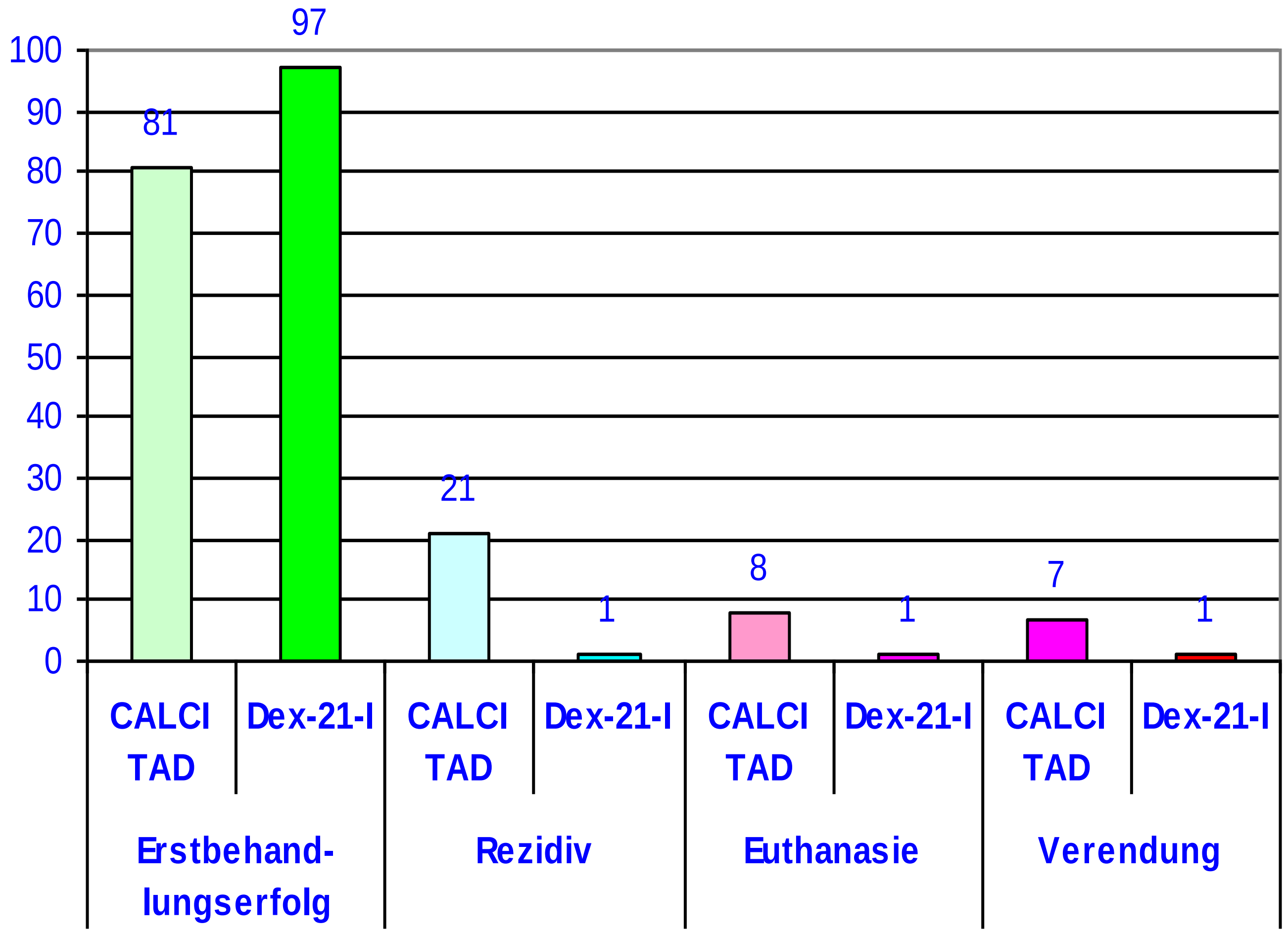
- 9 – 11 g Ca^{++} or more (?)
- PO4
- Mg^{++}
- KCl 0,4g/kg KM/24h
- **Dexamethason**
- NSAA
- Antioxidants
- Trace elements

  Se, Cu, Mn . . .

1923 2006

Milk fever – Therapy results (%) by

a) First treatment , b) additional Dex-21-iso-Nicotinat (Pichon 2007)

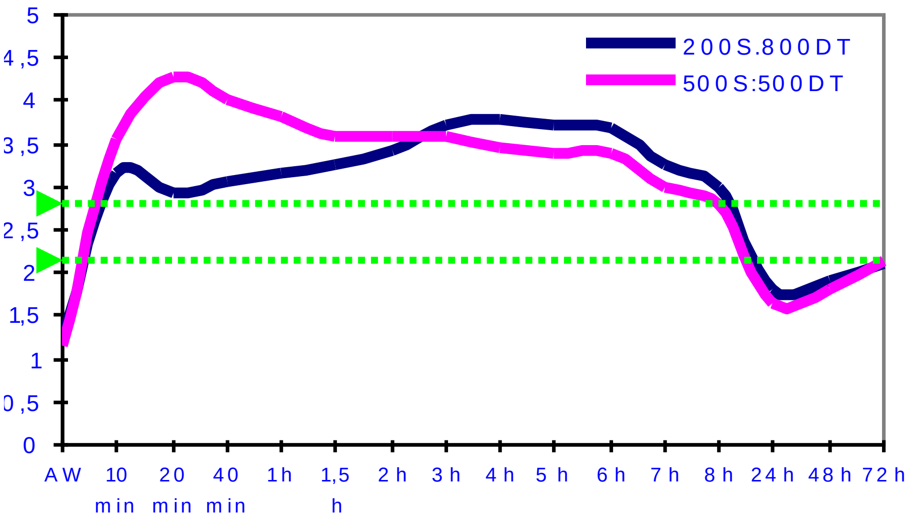


4. Therapy by downer cows (complikations)

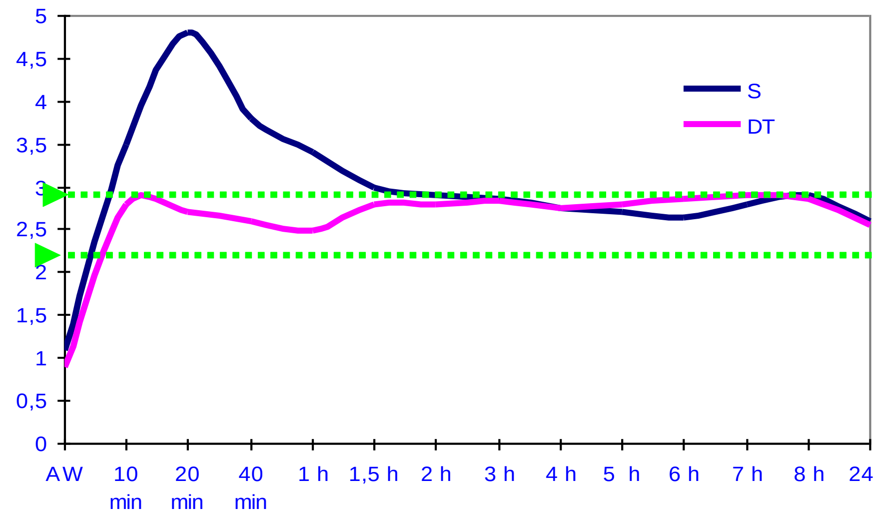
- 9 – 11 g - **more Ca^{++} ?**
- PO4
- Mg^{++}
- Dexamethason
- NSAA
- Antioxidants
- trace elements

  Se, Cu, Mn . . .

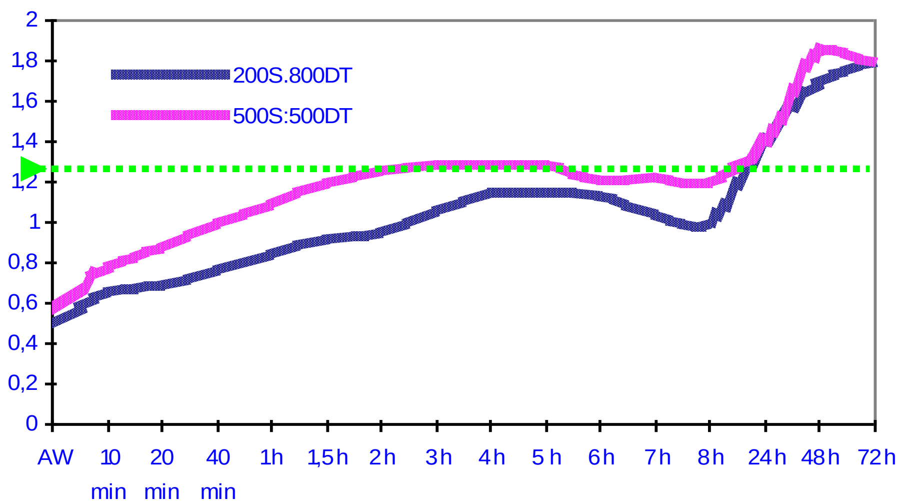
Ca (mmol/lSerum) bei 1000 ml Ca-Borogluconat in Calcamyl® (Jehle 2004)



Ca (mmol/lSerum) bei 600 ml Ca-Borogluconat resp. Calcamyl (Braun et al. 2004)
S = Sturz-, DT = Dauertropfinfusion



Pi (mmol/lSerum) bei 1000 ml Ca-Borogluconat in Calcamyl® (Jehle 2004)



Pi (mmol/lSerum) bei 600 ml Ca-Borogluconat resp. Calcamyl (Braun et al. 2004)
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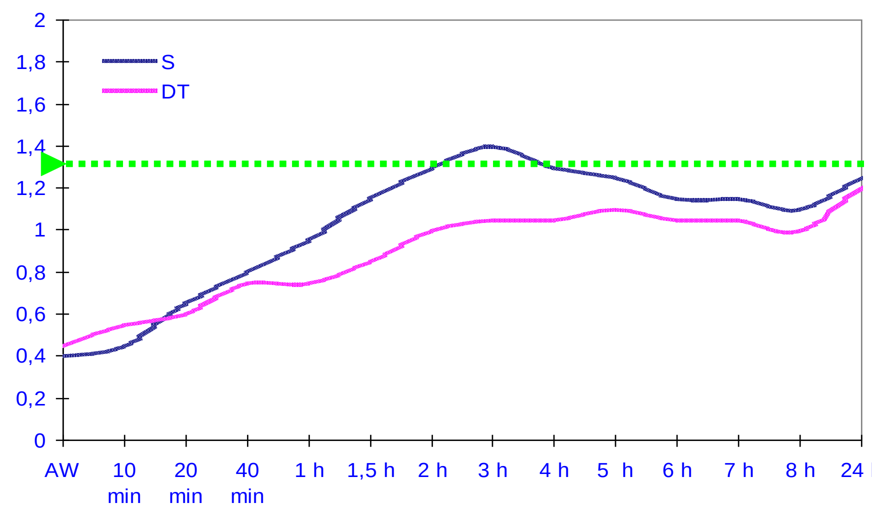


Jehle (2004):

1000 ml Ca-Borogluconat in Calcamyl®

- Only 47% first treatment success.
- ~ not more than 600 ml (Brown et al. 2004)
- Cardiac arrhythmias et al. side effects without serious consequences

4. Therapy by downer cows complikations

- 9 – 11 g Ca^{++}
- PO4
- Mg^{++}
- KCl 0,4 g/kg KM/24h
- Dexamethason
- NSAA
- Antioxidants
- trace elements

  Se, Cu, Mn . . .

„Hypophosphatemic or atypical paresis“ [1,2]

Heinrich Seidel
Leipzig
(1935 bis 1982)

- main symptoms

  unaffected sensorium, normal food intake,

  unable to rise spezially in the hindquarters

- Ca and inorganic P (Pi)

  moderate hypokalzemia (p>0,05)

  strong hypophosphatemia (p<0,01)

  often hypokalemia

- Occurrence

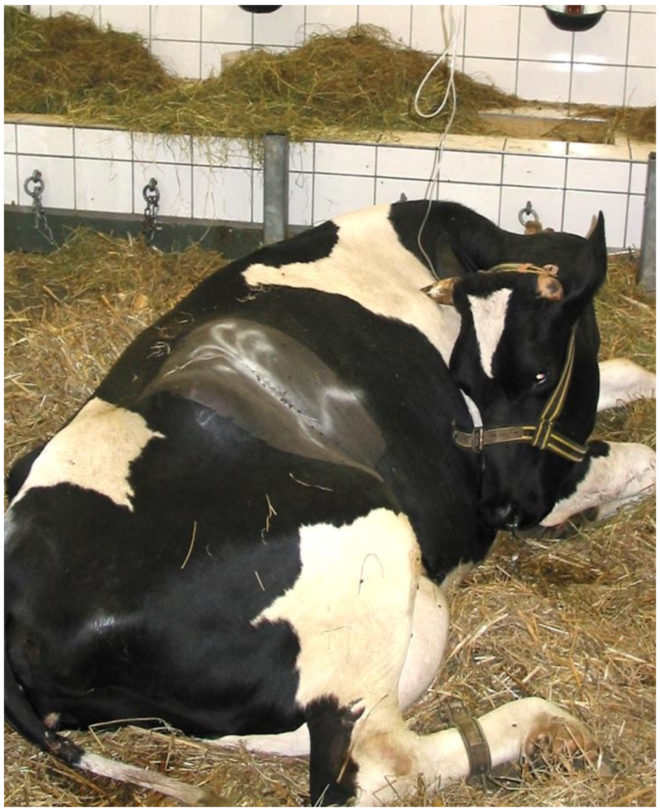
  from parturition to 30 days after parturition

and coworkers

1) **Seidel H., Schröter, J**. (1966):Mineralstoffbestimmungen im Serum sowie in der Milch von festliegenden Rindern. Mh. Vet.-Med. **21**, 606-613

2) **Liebetrau, R., Oetzel, H., Rödiger, W., Schröter, J., Seidel, H., Steitz, J., Trommer, F**. (1975): Klinische und biochemische Untersuchungen an festliegenden Milchkühen. Mh. Vet.-Med. **30**, 324-331

Hypophosphatemia-etiology:



1. puerperal haemoglobinuria / milk cow anemia / Brassica intoxication

1. 2. ↓ phosphate uptake

2. 3. "Pi-binding substances"

3. 4. ↑↑↑ glucose infusions

4. chronic acidosis

5. 6. nonspecific milk fever symptom

6. heavy (st) form of parturient paresis

7. in fatty liver

8. own recumbency form: Atypical paresis

9. effect of inflammation

Retrospective analysis

of 94 patients

(Dislocatio abomasi)

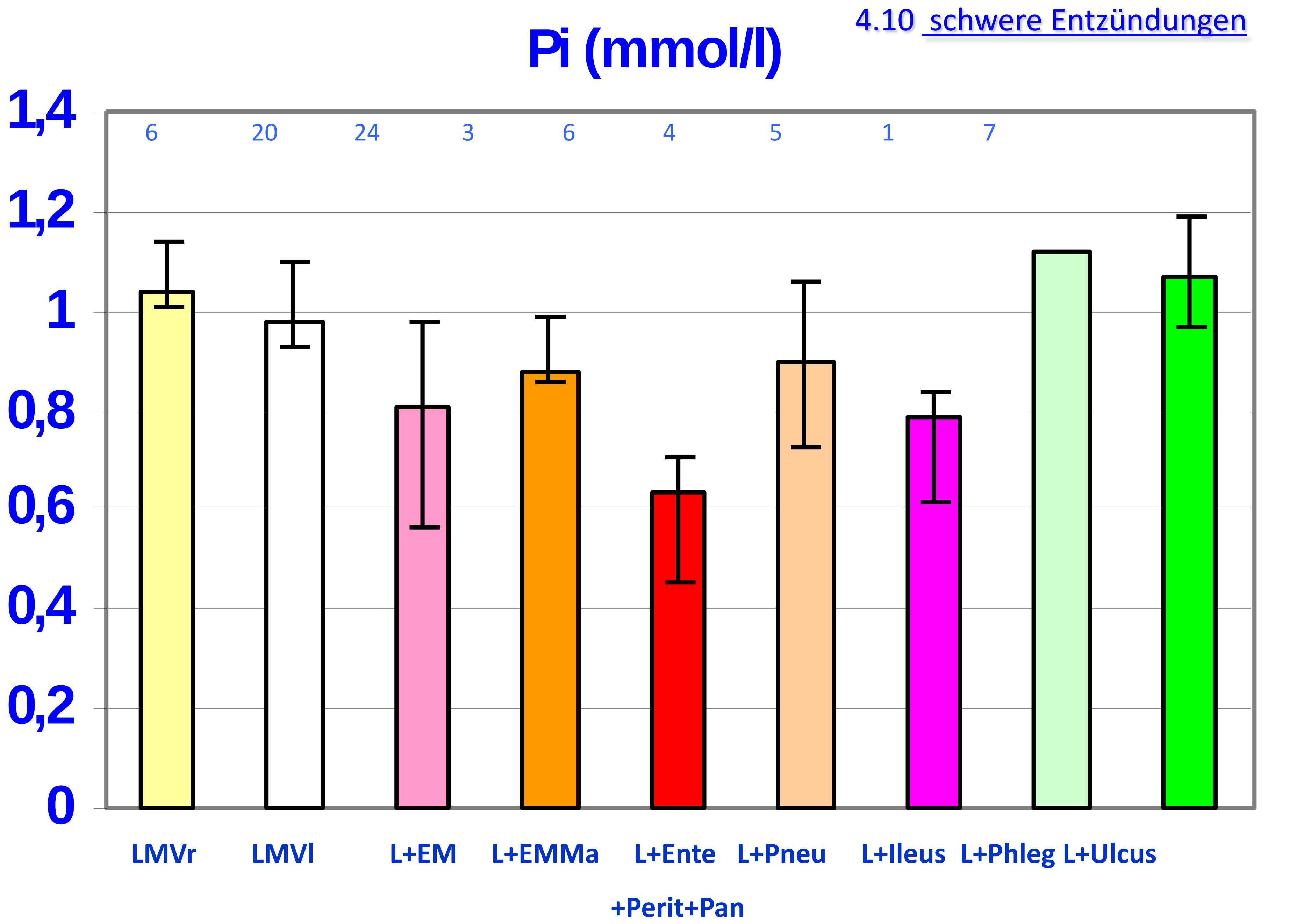
with Pi <1.25 mmol/l:

?

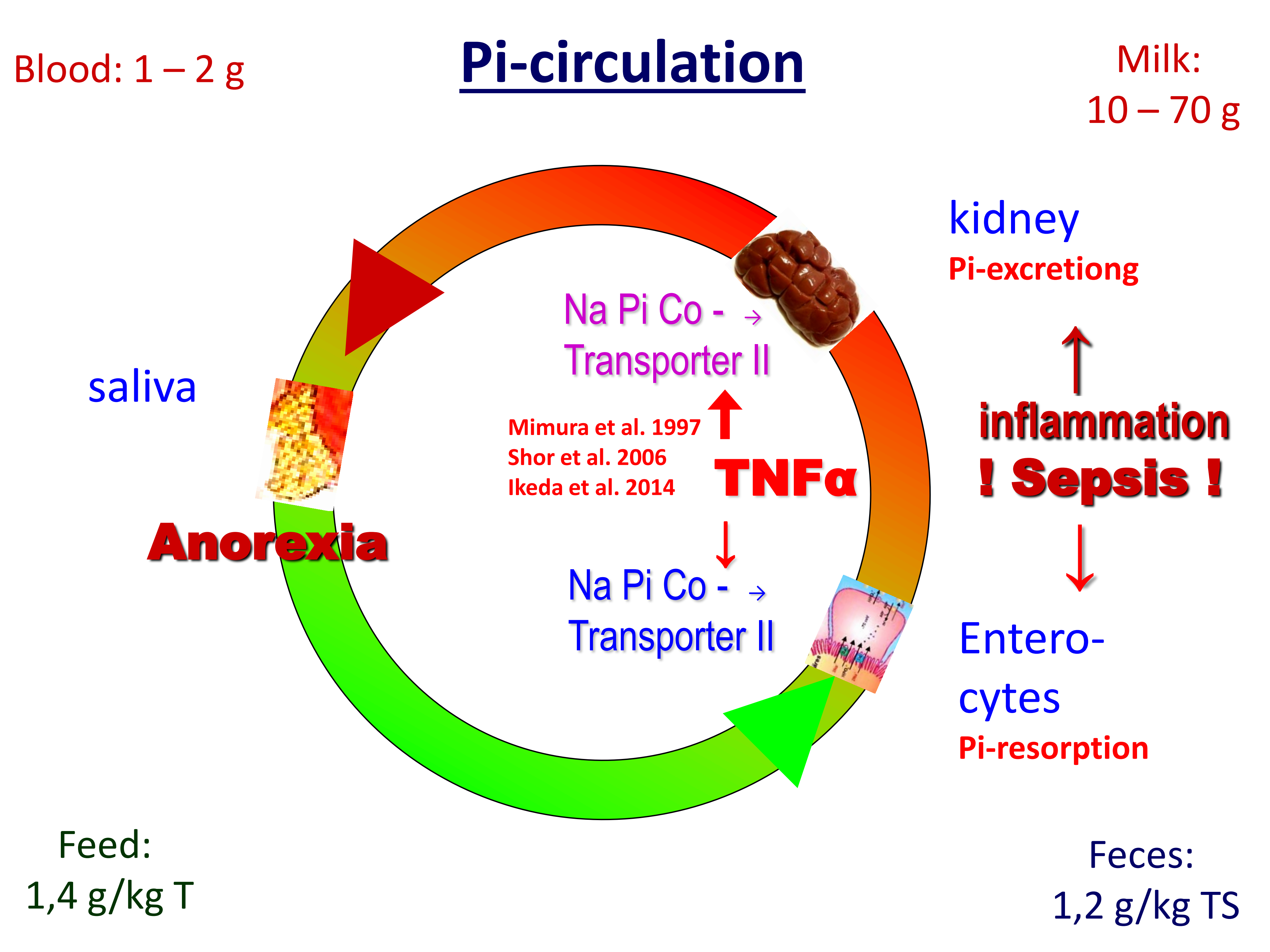
. . . . clinical findings

with

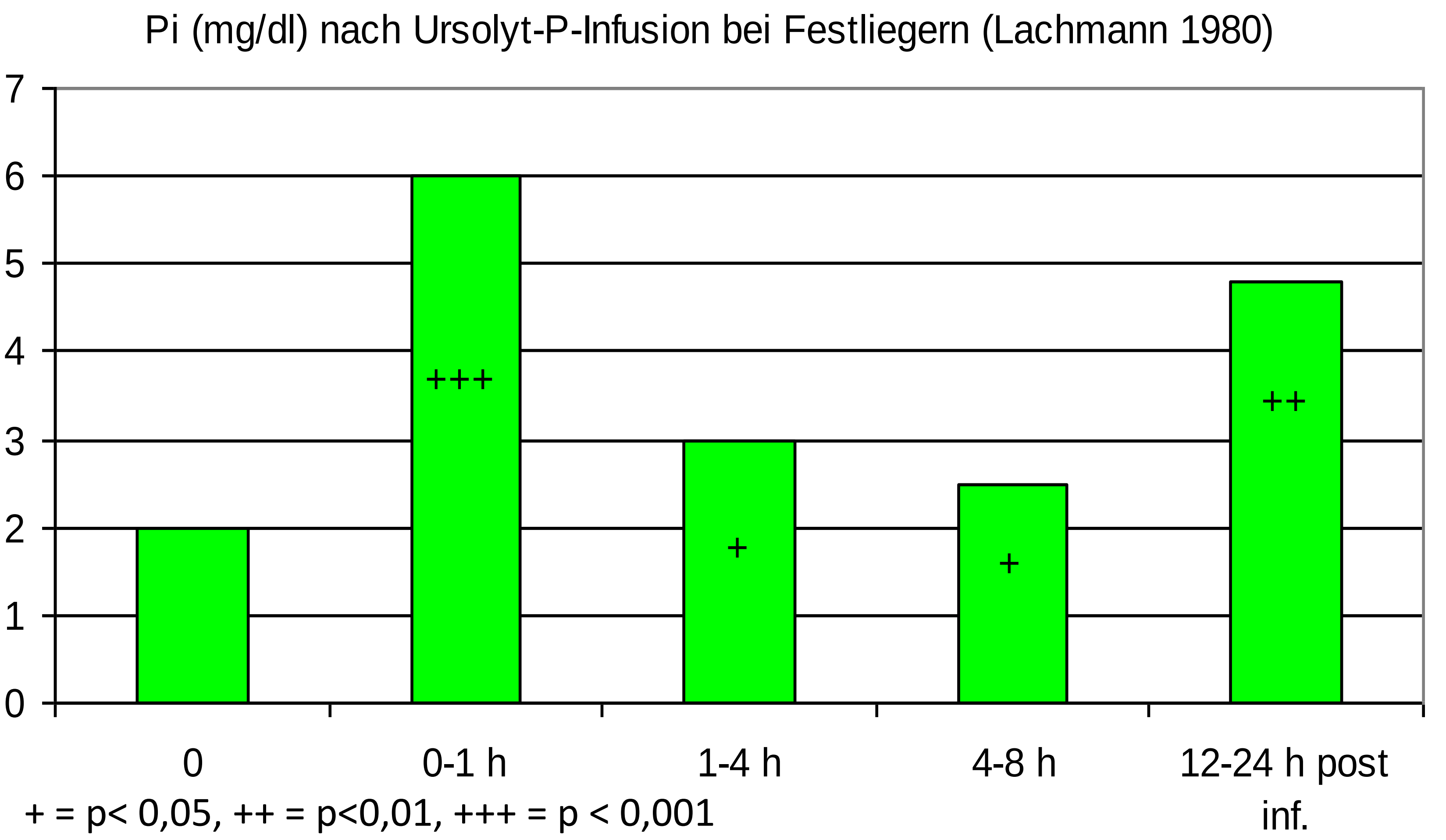
hypophosphatemia



4.10 schwere Entzündungen
Pi (mmol/l)
1,4
1,2
1
0,8
0,6
0,4
0,2
0
6
20
24
3
6
4
5
1
7
LMVr
LMVl
L+EM
L+EMMa
L+Ente
L+Pneu
L+Ileus
L+Phleg
L+Ulcus
+Perit+Pan

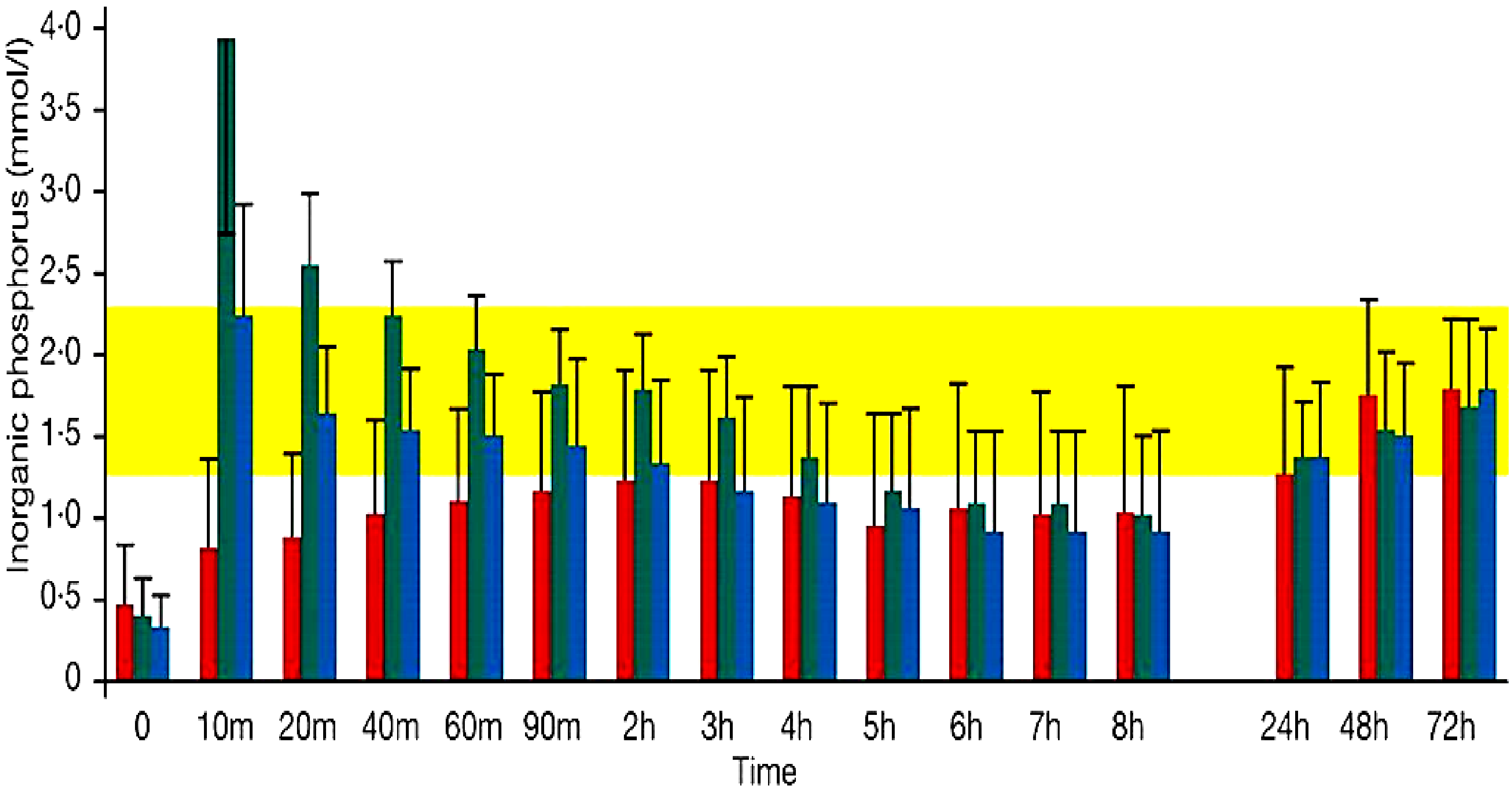

Pi-circulation
Blood: 1 – 2 g
Milk:
10 – 70 g
kidney
Pi-excretiong
Na Pi Co - →
Transporter II
saliva
Mimura et al. 1997
Shor et al. 2006
Ikeda et al. 2014
TNFα
inflammation
! Sepsis !
Anorexia
Na Pi Co - →
Transporter II
Entero-
cytes
Pi-resorption
Feed:
1,4 g/kg T
Feces:
1,2 g/kg TS

Pi concentration (mg / dl serum, $\bar{x}$) by downer cows after iv therapy with 90 g Na_2HP0_4/ $NaHP0_4$/ 500 ml (Lachmann 1980)



Phosphate-buffer increased Pi-blood-concentration

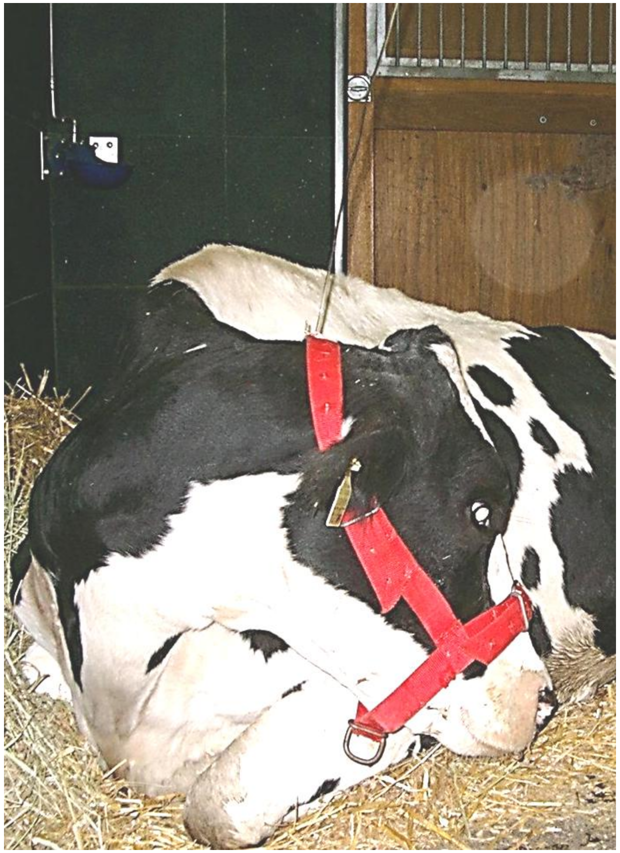
Pi (mmol / l serum) at downer cows after i.v. treatment with Ca-Boro-gluconat (red), additional iv NaH_2PO_4 (green) and NaH_2PO_4 partly in continuous drip (blue)(Braun et al. 2004)



Phosphat-Puffer hebt Pi-Blut-Konzentration

Therapy of “atypical Downers”

(puerperale septicemia)



1. glucose drip infusion
   (0.1 mg glucose / hr / kg) ("insulin")
2. propylene glycol per os 2 x 200 g
3. antiphlogistic (NSAA, GCS)
4. antioxidants (Vit C, -. E)
5. Mineral substitution
   (90 g Na_2HPO_4 / NaH_2PO_4)
6. effective antibiotic
   - pathogens in blood
   - clean up output stove
7. heparin (180 IU / kg BW / d)

4. Therapy by downer cows (complikations)

- 9 – 11 g Ca^{++}
- PO4
- Mg^{++}
- **KCl** 0,4 g/kg KM/24h
- Dexamethason
- NSAA
- Antioxidants
- Trace elements

  Se, Cu, Mn . . .

?

Backgrounds and combat Hypokalemia as a clinical problem

M. Fürll

Medizinische Tierklinik Leipzig

1. Physiological role of potassium

2. 3. K and acid-base balance

3. K in the blood of cows various diseases in practice

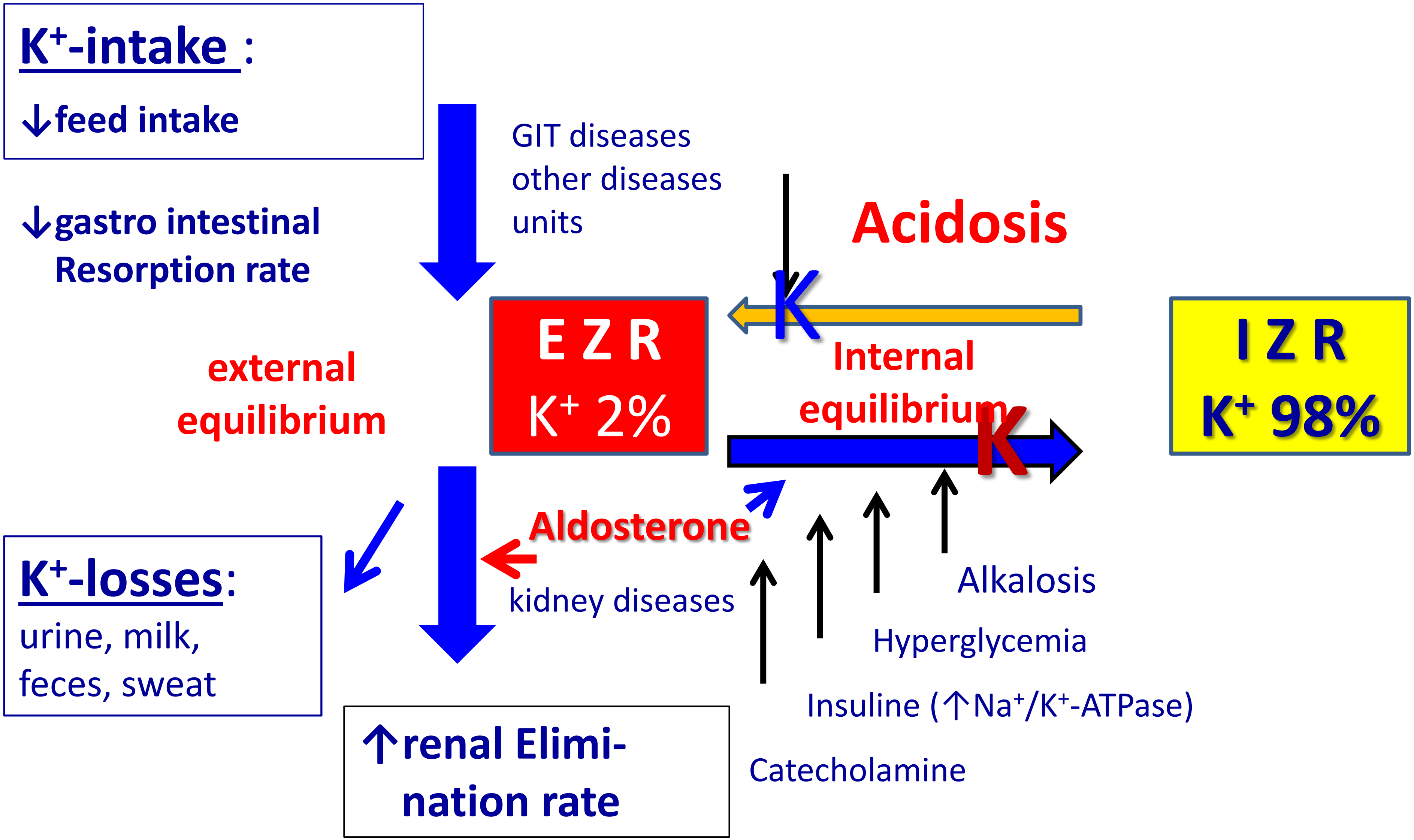
4. K at milk fever cows: findings in practice

5. K in cows with abomasal displacements (DA)

6. Therapy of Hypokalämien

7. Conclusions for clinical practice

Potassium metabolism (mod. N. Sattler et al. 1998)



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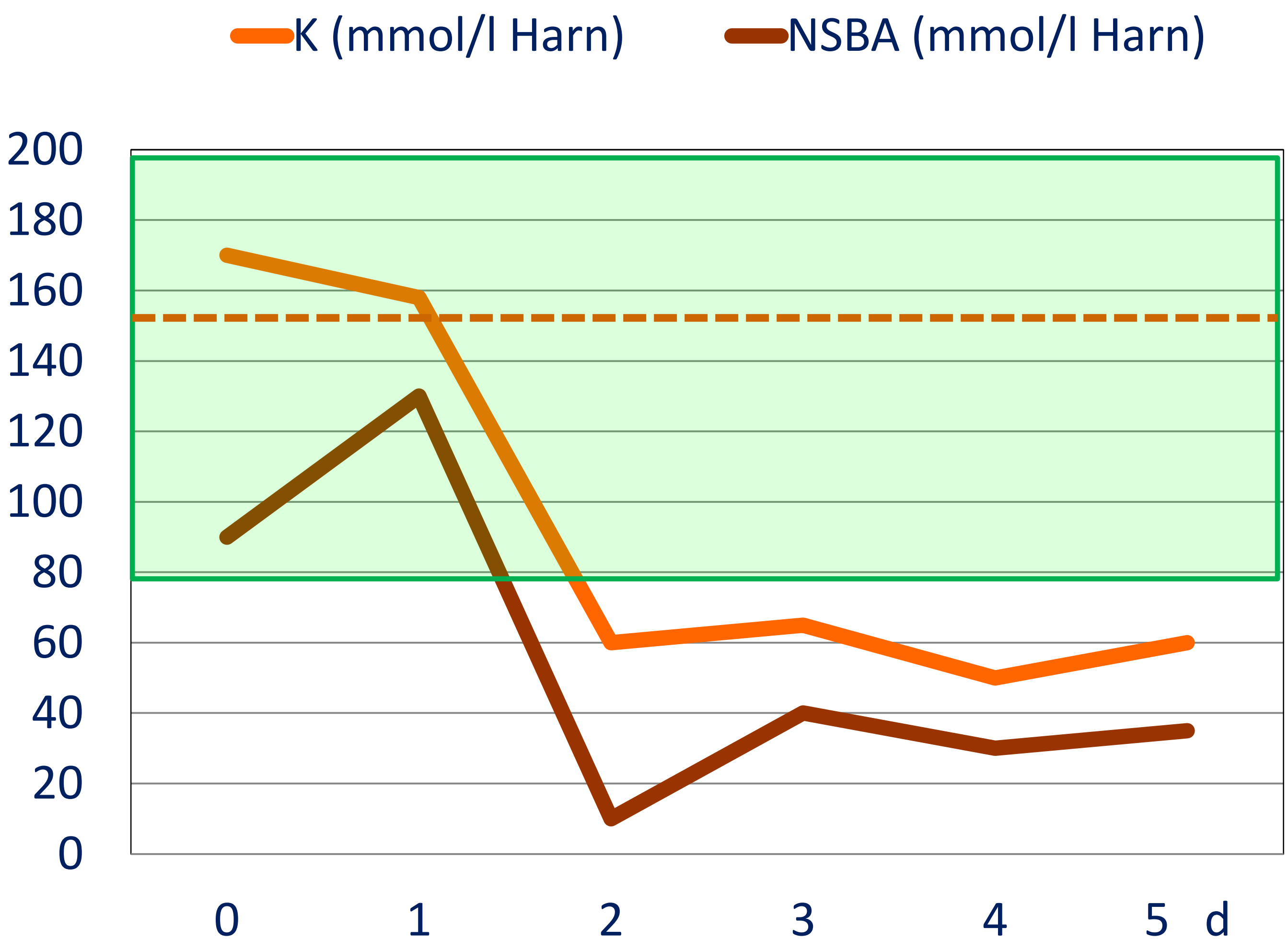
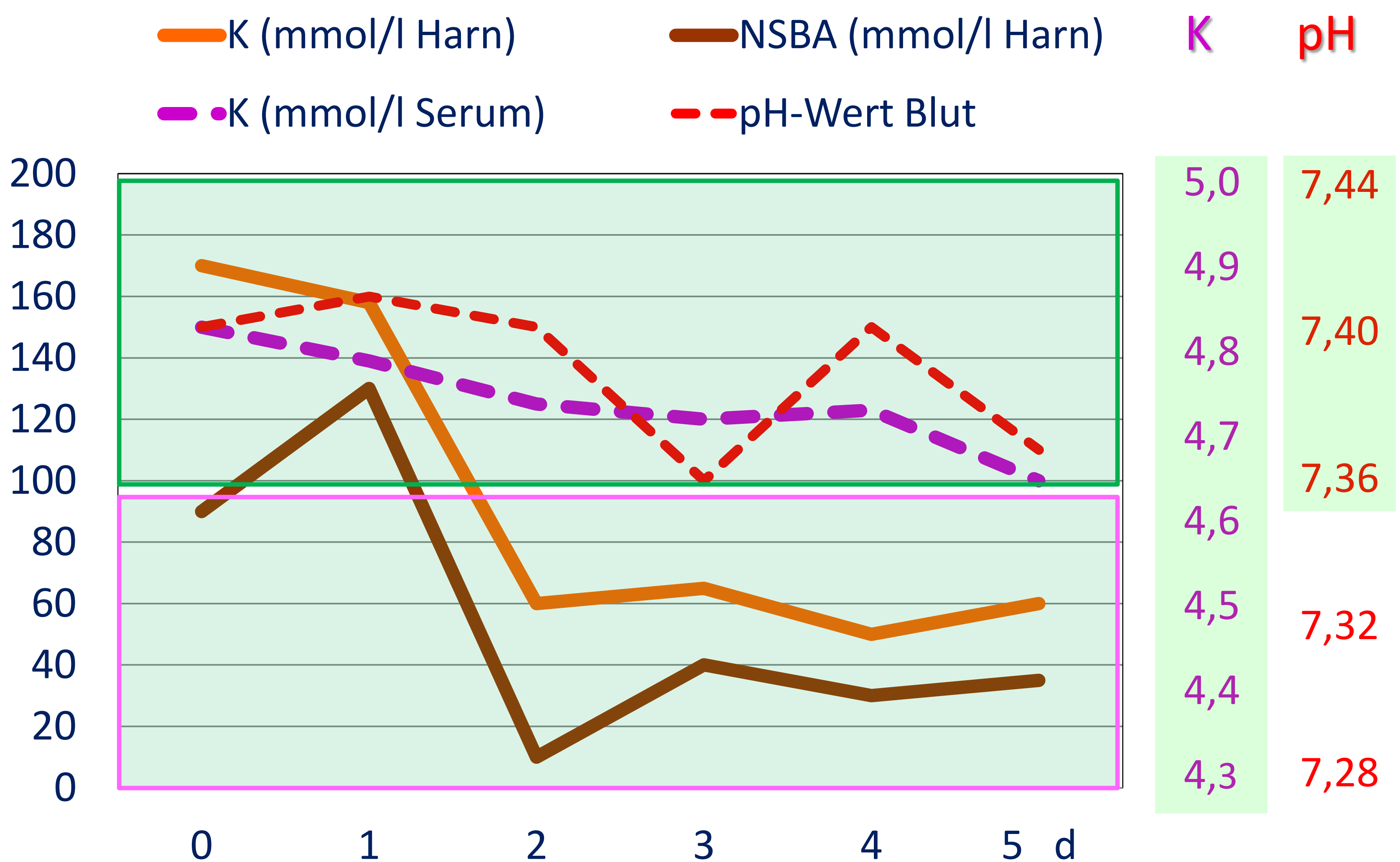
K and NABE in blood and urine (mmol / l) and pH in the blood at 5 days fasting sheep



K and NABE in blood and urine (mmol / l) and pH in the blood at 5 days fasting sheep



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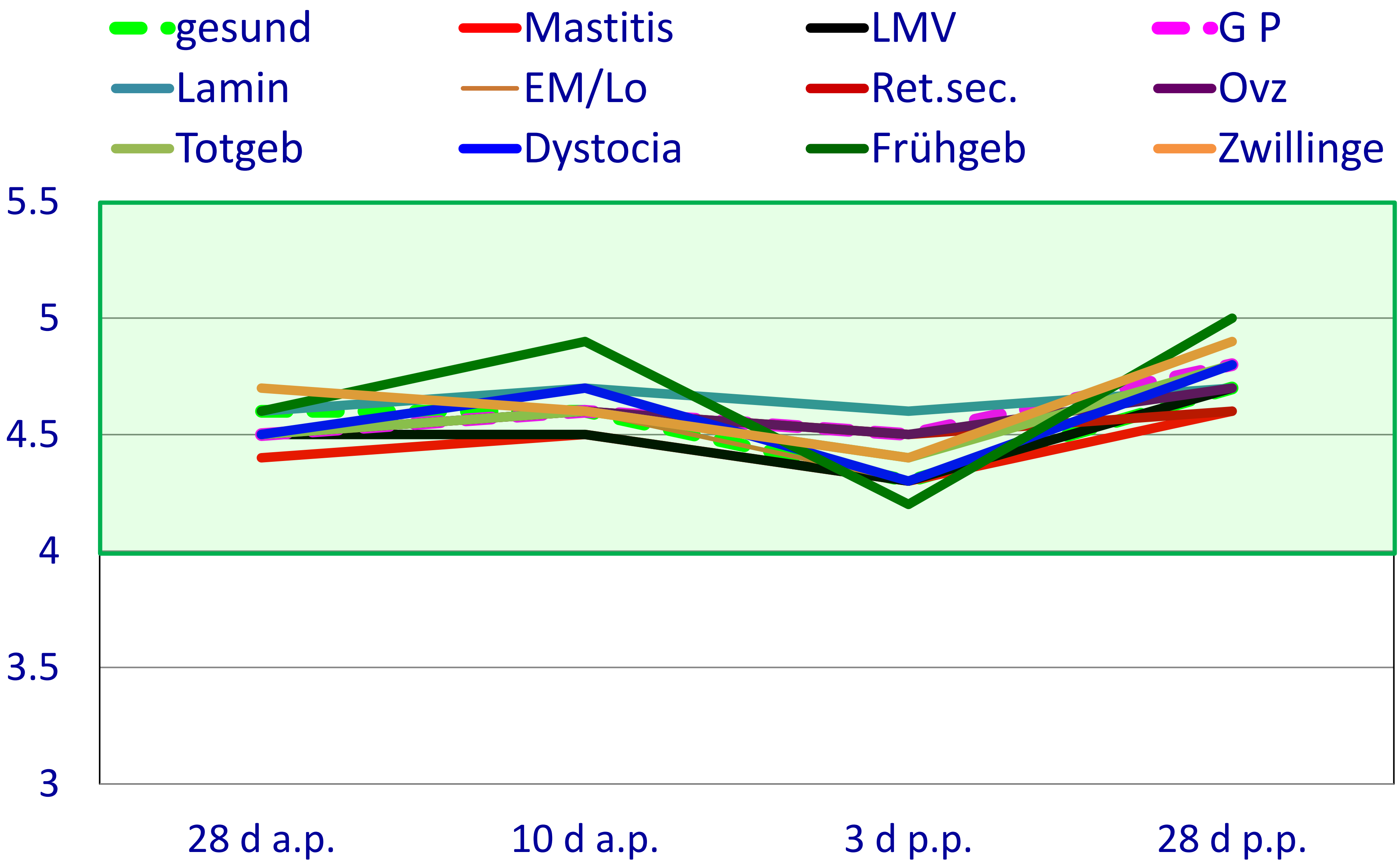
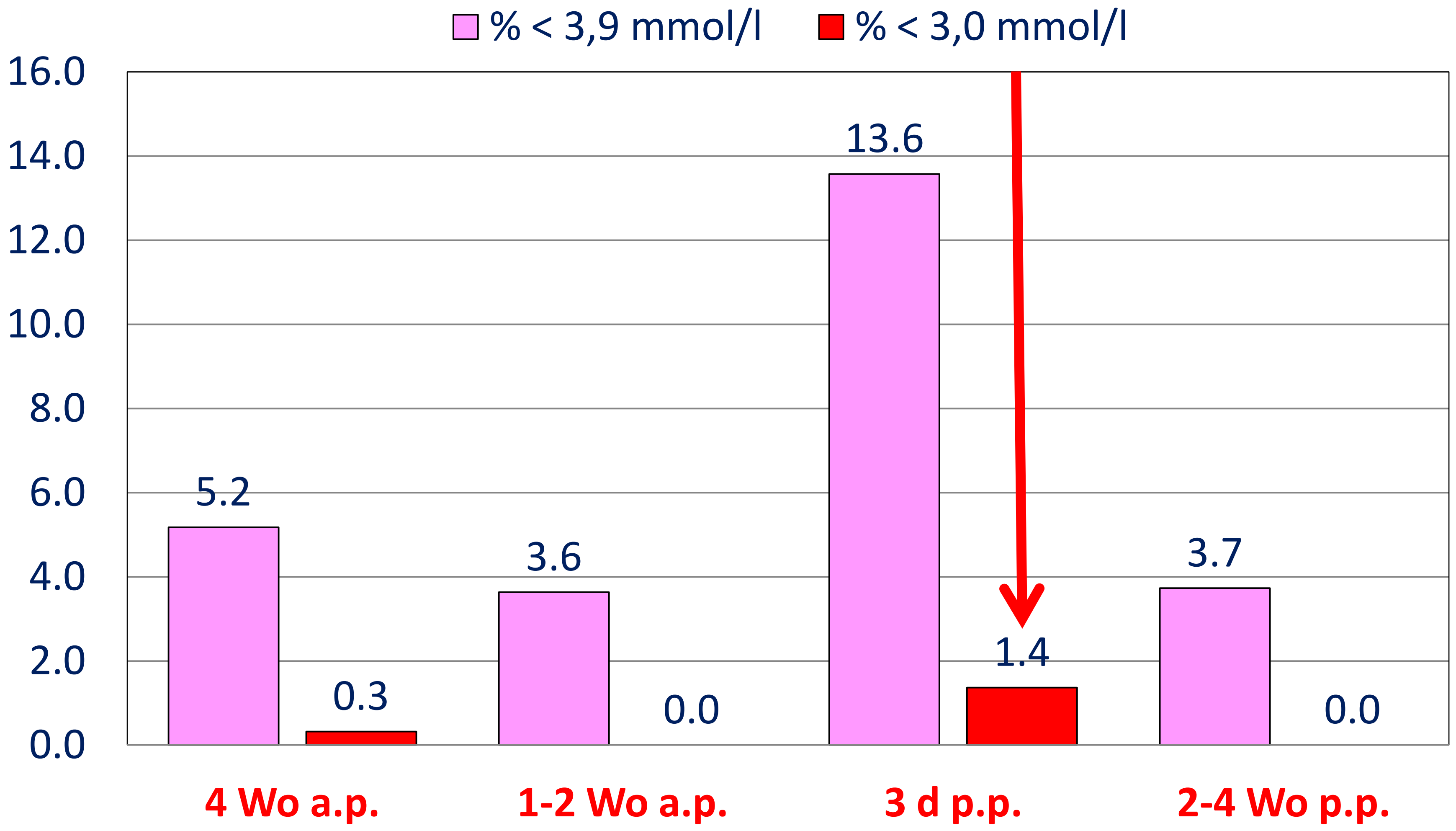
3. K in the blood of cows various diseases in practice

When we need to expected hypokalemia?

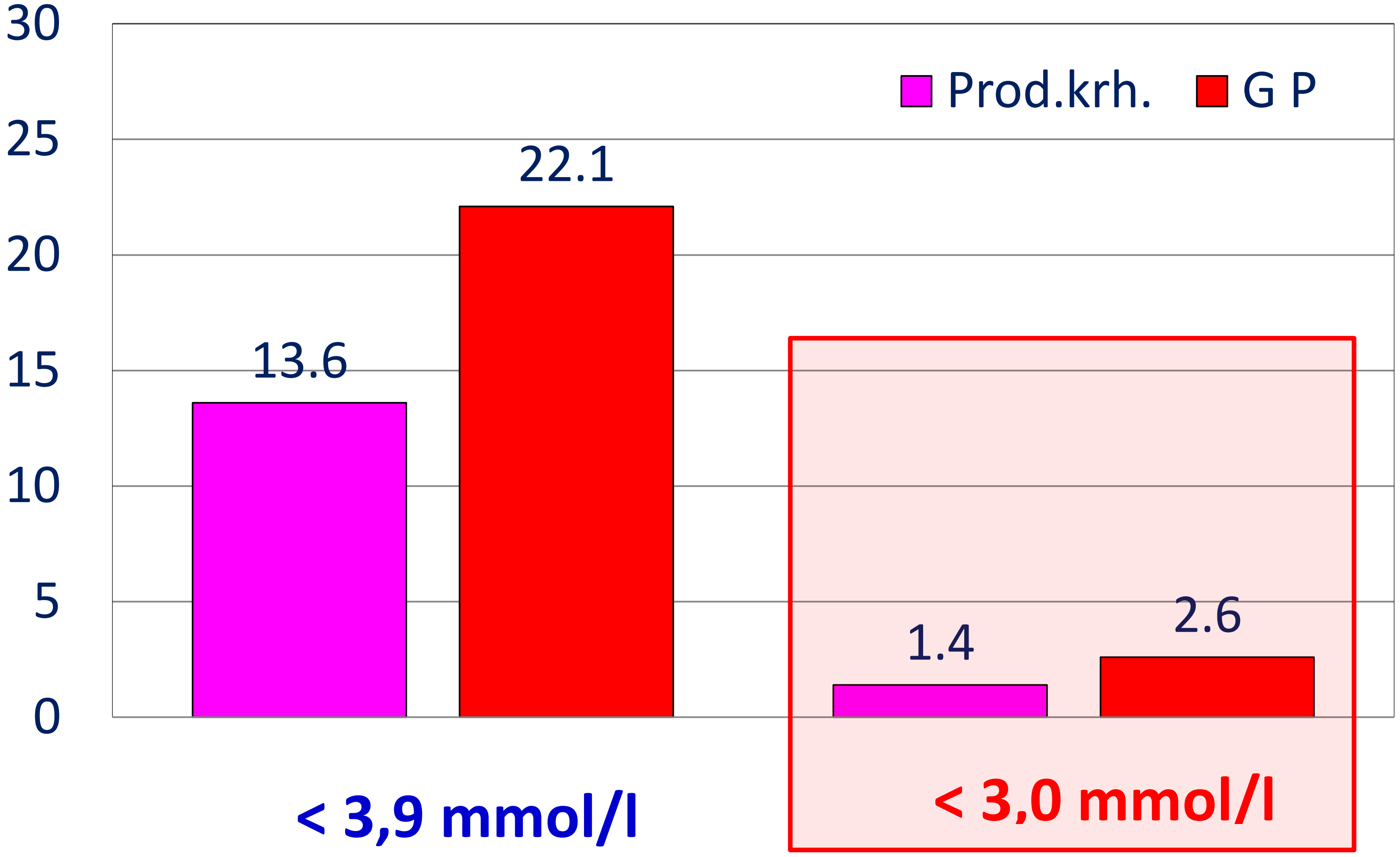
K (mmol / l) in healthy and ill cows (Hädrich 2007)



Share (%) K-sample <3.9, respectively. 3.0 mmol / l periparturient cows in 3444



Share (%) K <3.9 resp. <3.0 at production diseases and parturient paresis 3 d pp



MF cows usually **without hypokalemia however :**

2,6%

< 3,0 mmol/l

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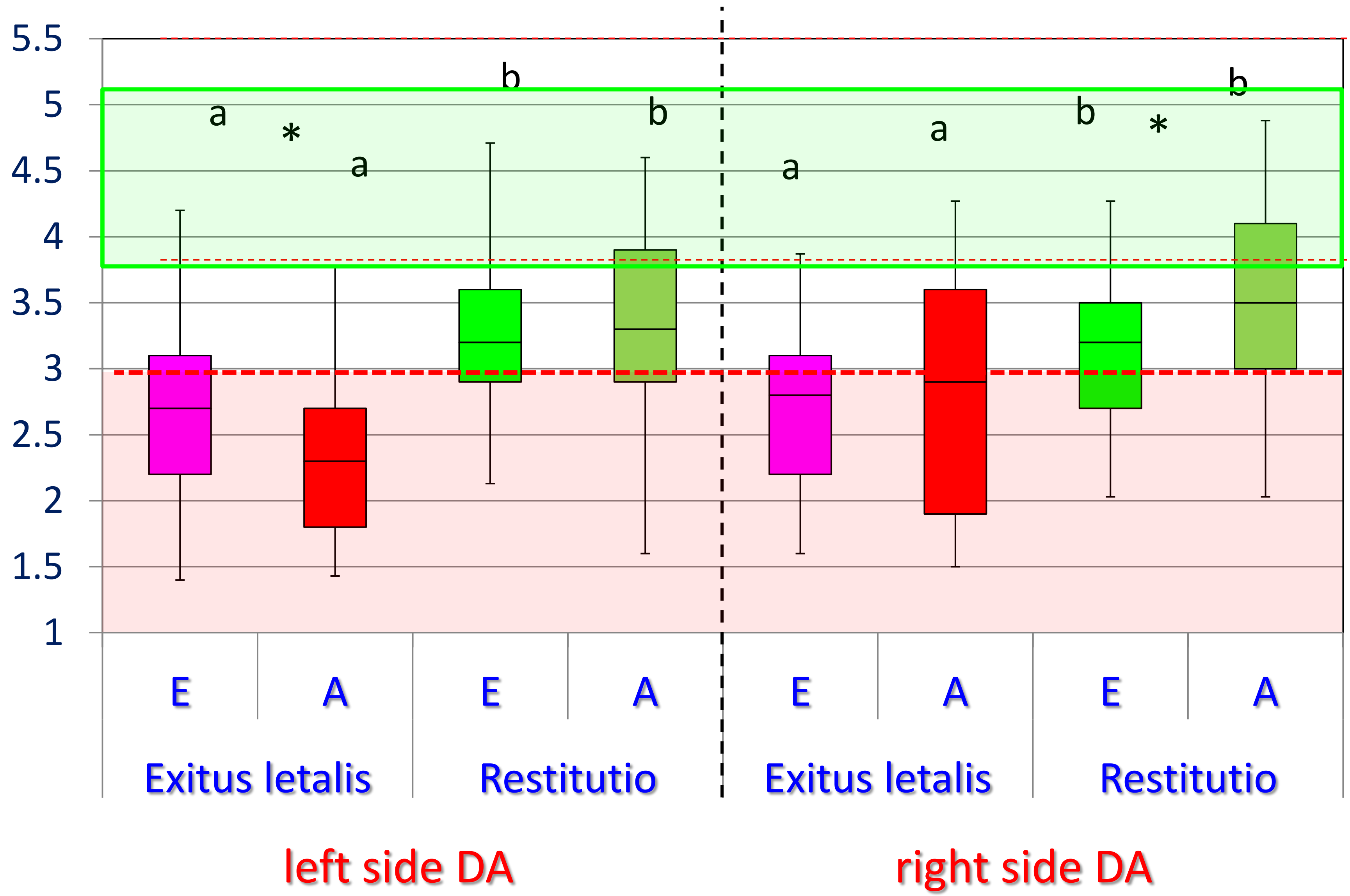
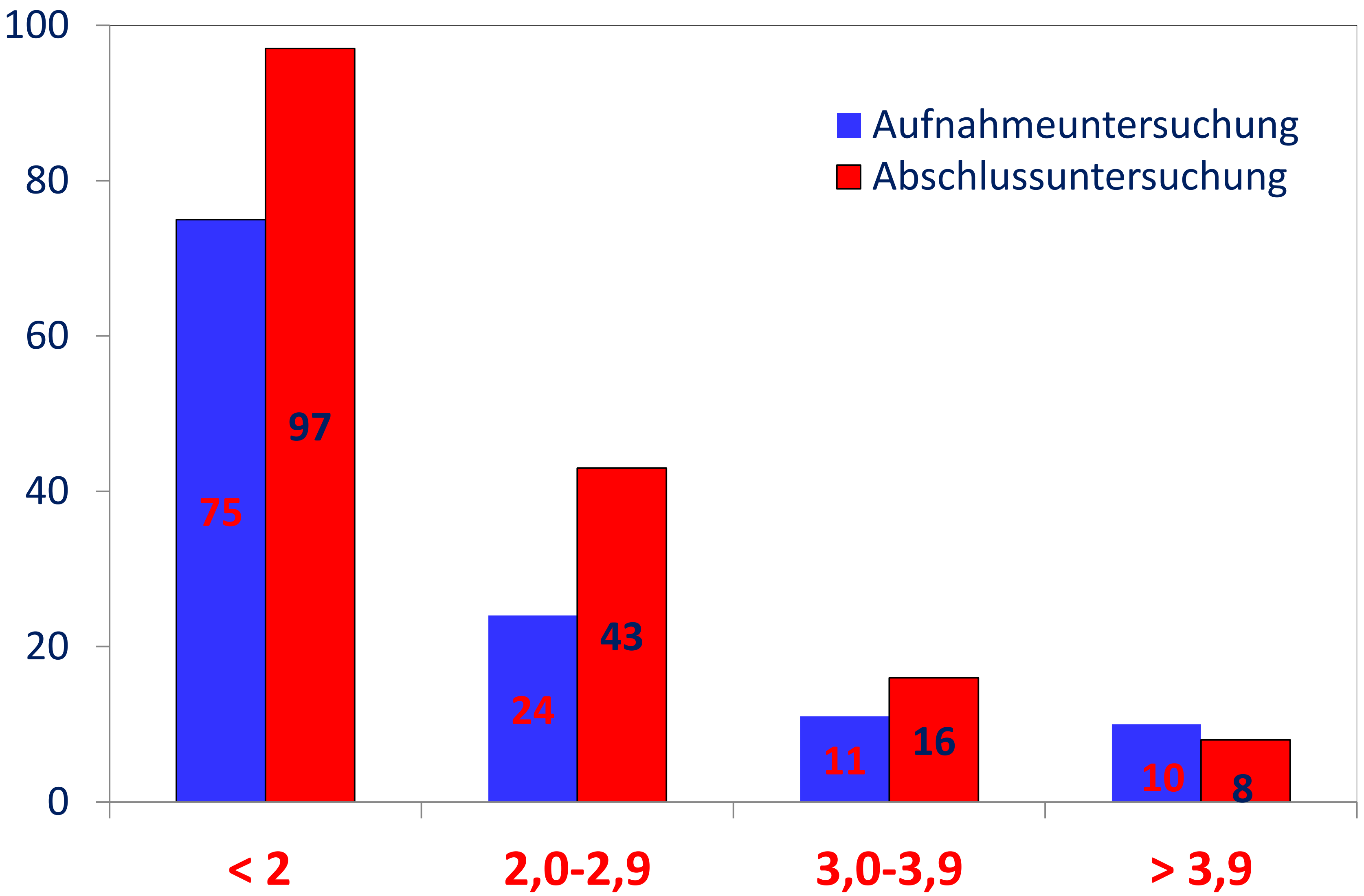
K-relevance to etiology and therapy?

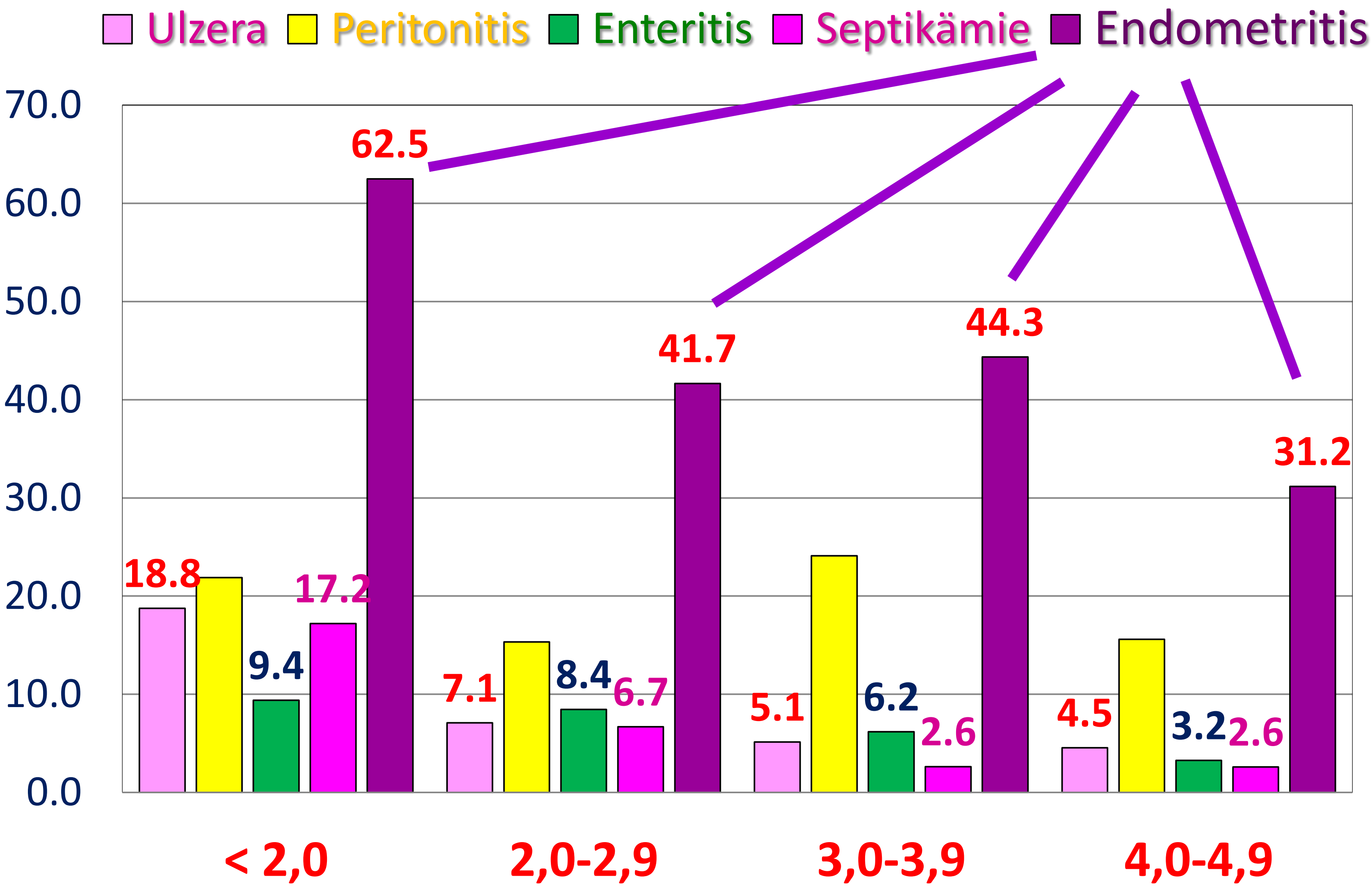
K (mmol/l Serum) **in DA cows at initial (E) and last (A) examination with restitution or Ex.letalis** (Meyer-Müller 2014)



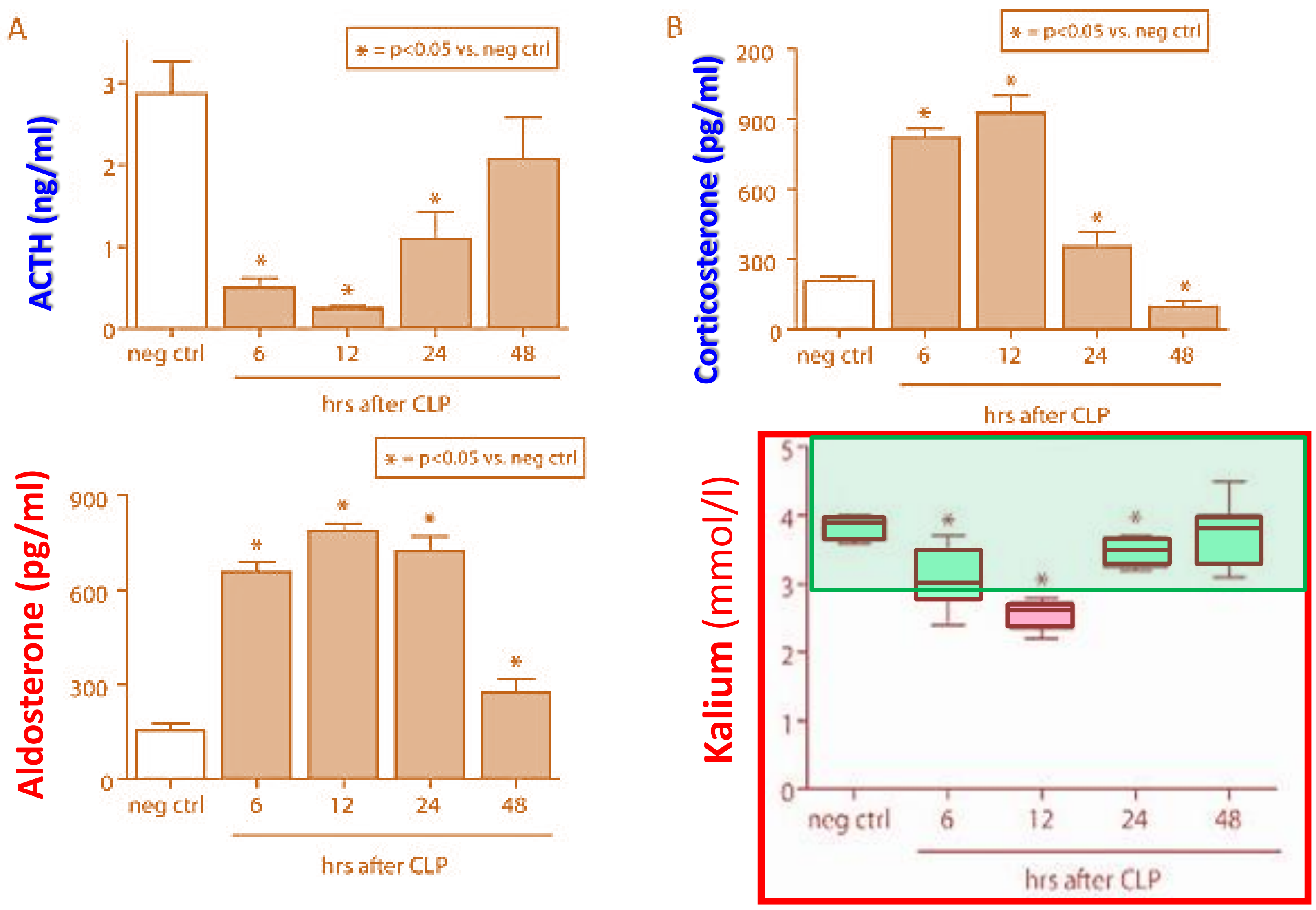
Mortality (%) in function of[K+]



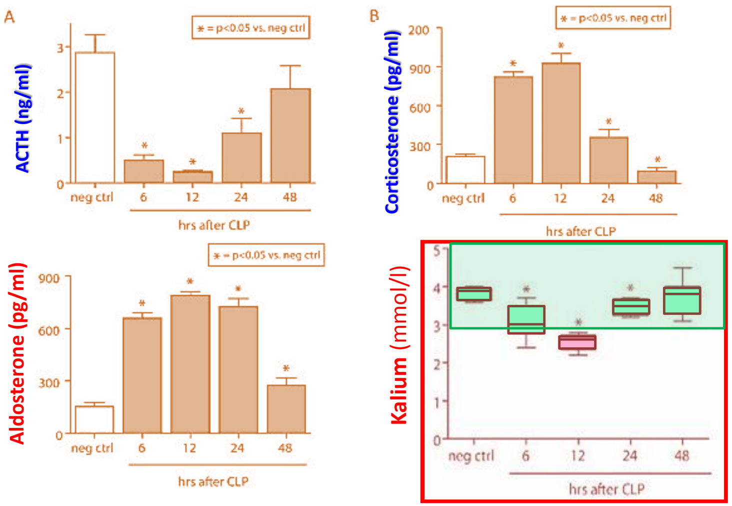
K-classes and morbidity in DA cows



K during septicemia (Flierl et al. 2011)



K during septicemia (Flierl et al. 2011)



Septikemia

↙ Nebennierenrinde ↘

↑ ACTH ↑ Aldosteron

↓ ↓

↑Corticosteron ↓ Kalium

K^+-Aufnahme :

↓Futteraufnahme

Äußeres Gleich-gewicht

E Z R
K^+ 2%

K

Inneres Gleich-gewicht

K

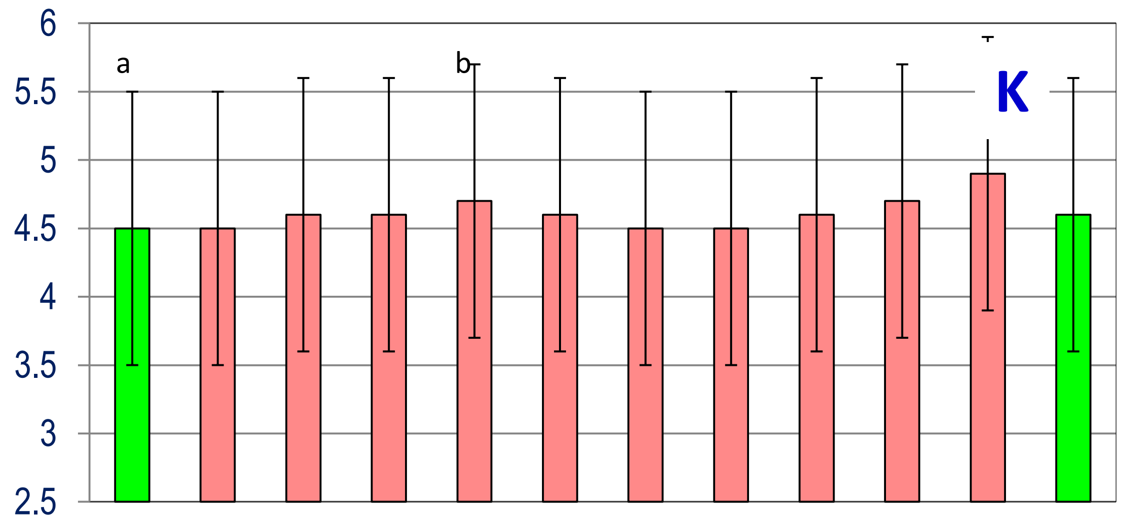
I Z R
K^+ 98%

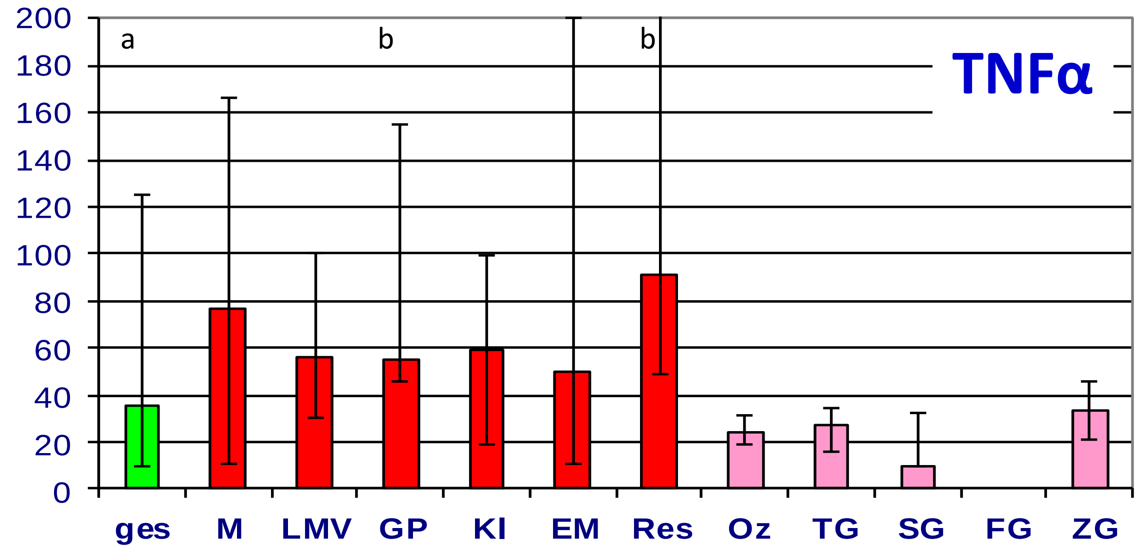
↑renale Elimi-nationsrate

Aldosteron

K (mmol / l) and TNF (pg / mml) ap 10 days with 25 cows per group(Fürll et al. 2006, Hädrich 2007)

r p<0,05	TNFα 10 d ap
K	- 0,25
Leukos	- 0,30
Lactat	0,58
B H B	0,33
Insulin	0,22





Hypophosphatemia - **Hypokalemia**

TNFα: Hemmung des NaPiCo-Transporters II		**„Sepsis“→ activation of adrenal cortex** (Flierl et al. 2011)	
↓Pi-Resorption an **Enterozyten**	↓Pi-Rückre-sorption/**Nieren**	**↑aldosteron-secretion**	↑corticosteron-secretion
↓ Pi-Aufnahme	**↑ Pi-Ausscheidung**	**↑ K – excretion**	↑Na-↓K influence ?
Hypophosphatämie		**Hypokalemia**	

Hypophosphatemia - Hypokalemia

TNFα→ inhibition of NaPiCo-transporter II (Shor et al. 2006, Ikeda et al. 2014)	**↑TNFα → activation of adrenal cortex** (Flierl et al. 2011)

↓Pi-resorption at **enterozytes**	↓Pi-reab-sorption/**renes**	**↑aldosterone-sekretione**	↑corticosteron-sekretione
↓ Pi-intake	**↑ Pi-excretion**	**↑ K-excretion**	↑Na-↓K

Hypophosphatemia	**Hypokalemia**

usually coupled

Backgrounds and combat Hypokalemia as a clinical problem

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Therapy of „Hypokalemia"

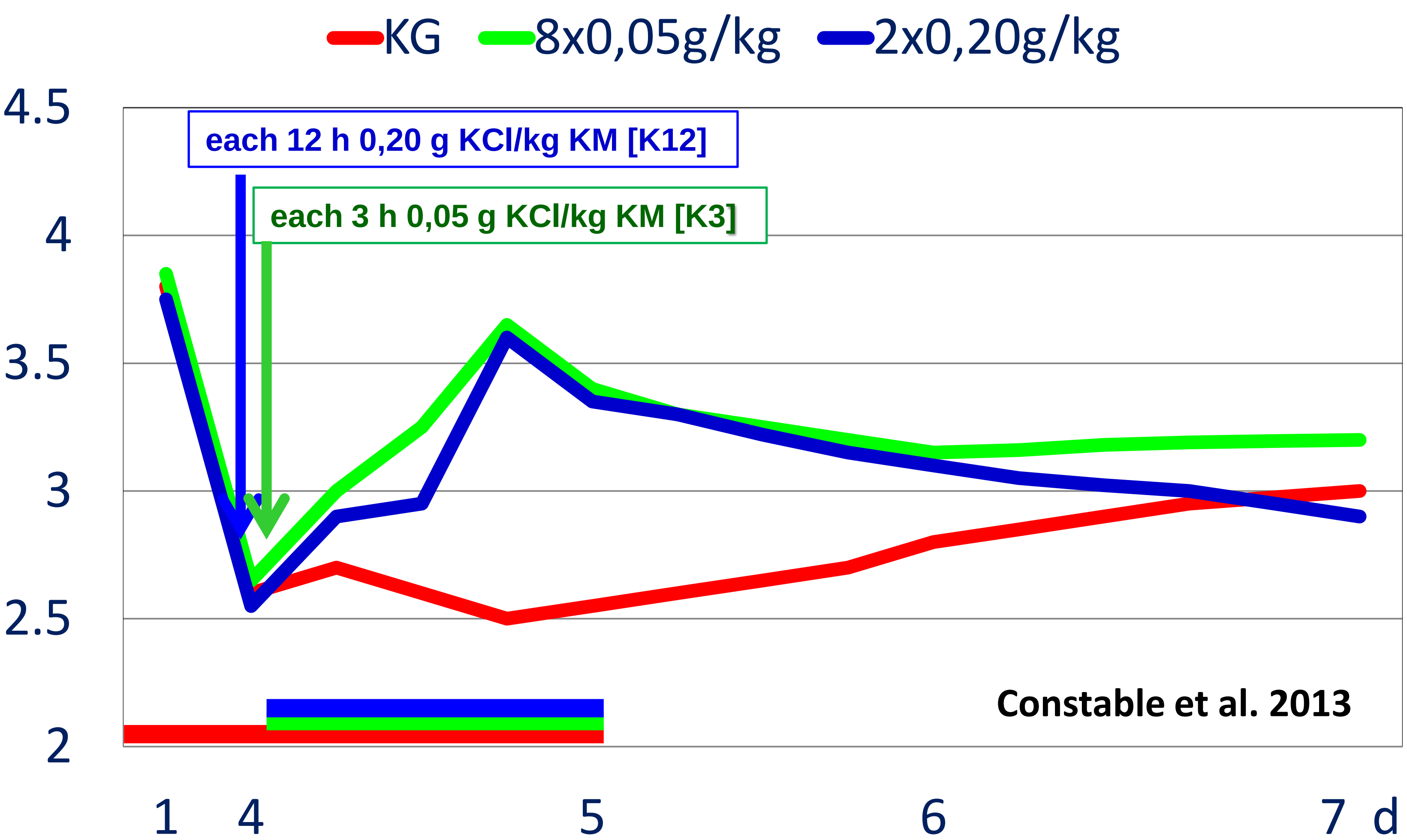
1. **Inflammation (sepsis) therapy** (BALK u. CASEY 2000):

- **Antioxidants**: **Vitamin C (5g), - E (1g); Se (10 mg)**
- **Glucocorticoids**: **Dexamethason 0,02 mg/kg KM**

↑

„inflammatory metabolism“

KCl-Substitution by Hypokalemia



→ **oral 0,4 g KCl** /kg KM/d

Therapy of „Hypokalemia"

1. **Inflammation (sepsis) therapy** (BALK u. CASEY 2000):

2. **Hypokalmia-Therapy**

- **KCL:** **0,4 g KCl** /kg KM/Tag **oral**

  i.v. 100 bis **200** mmol KCl/Tag per **DT**

- **Kaliumphosphat B. Braun**

  Dosierung: 0,2 – 0,5 mmol/kg KM/Tag (Mensch)

- **Kaliumphosphat “Fresenius”** 1molar Infusionszusatz-Ampullen (Mensch)

  Dosierung: 0,4 mmol Phosphat/kg KG/Tag

"Atypical paresis" – second treat-ment:

- basic treatment

+ 500 ml - 90 g Na_2HPO_4/NaH_2PO_4

+ 0,4 g KCl /kg KM/Tag oral

+ GCS

+ AO

7. K - conclusions for clinical practice

- Cows are amply supplied with K
- ↑ K promotes diseases such as GP and Infertility
- K is closely related to ABS
- K + in blood urine does not reflect the K-supply
- K decreases in urine + blood in inanition
- **↓ K occurs in practice in inflammatory diseases**
- **↓ K <2 mmol / l are hopeless at NNR activation**
- **↓ K and ↓ Pi are usually coupled**
- **K therapy: K substitution = anti inflammation drugs**

4. Therapie in Downer cow complications

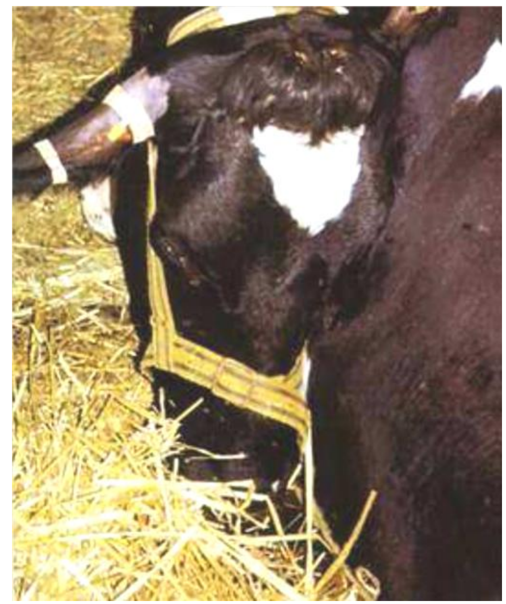
- 9 – 11 g Ca^{++}
- PO4
- Mg^{++}
- KCl 0,4 g/kg KM/24h
- Dexamethason
- NSAA
- Antioxidants
- trace elements

Se, Cu, Mn . . .

?

Potential relevance of selenium and other trace elements in the pathogenesis of milk fever (MF)

1923



2014

M. Heilig, D. Bäuml, M. Fürll, Medizinische Tierklinik Leipzig

Experimental design

➢ **195 "Fleckvieh" cows** (FV)**:**

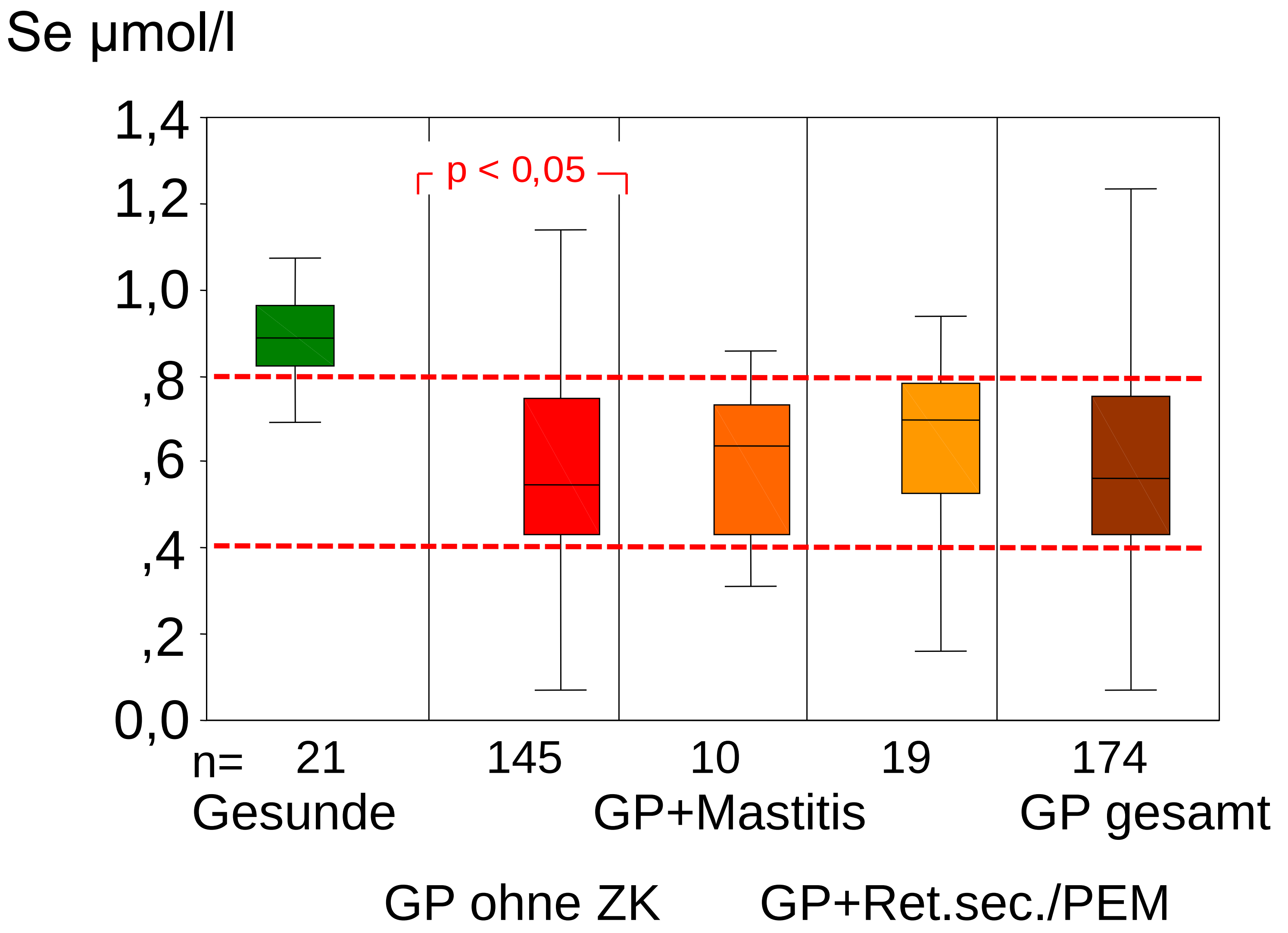
- 21 untreated FV-cows (KG)

- **174 MF cows** (GP)

➢ **Controls**:

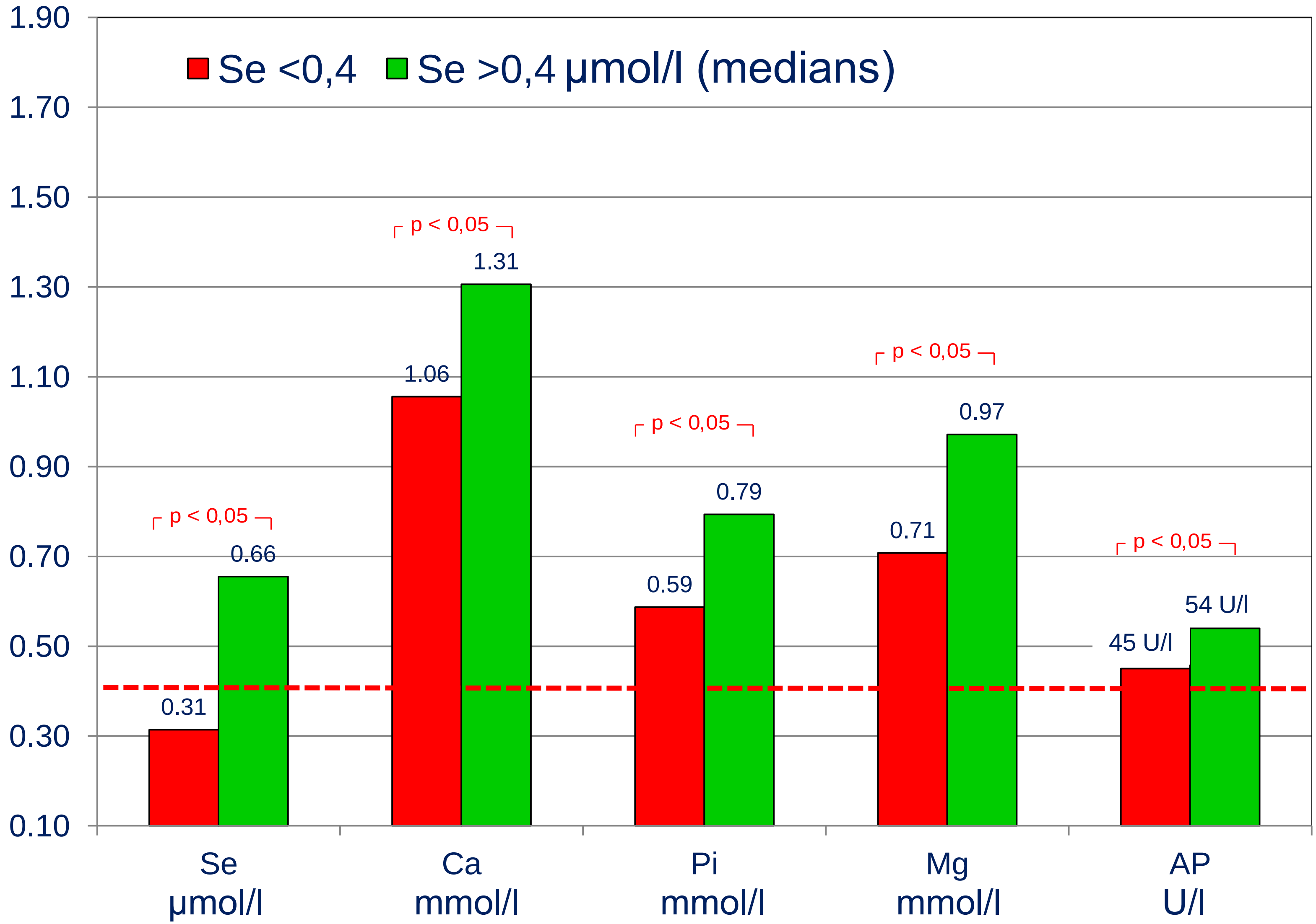
1. Clinical and laboratory controls before treatment
2. to treatment success
3. if necessary at secondary treatments

Laboratory results: Selenium



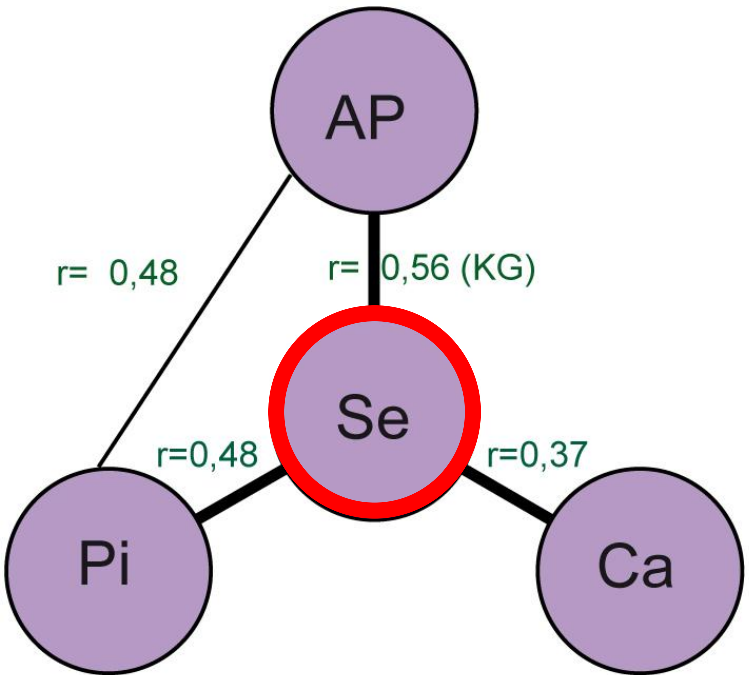
19%
< 0,4
µmol/l

Laboratory results: Se < > 0,4 µmol/l



M. Heilig, D. Bäuml, M. Fürll

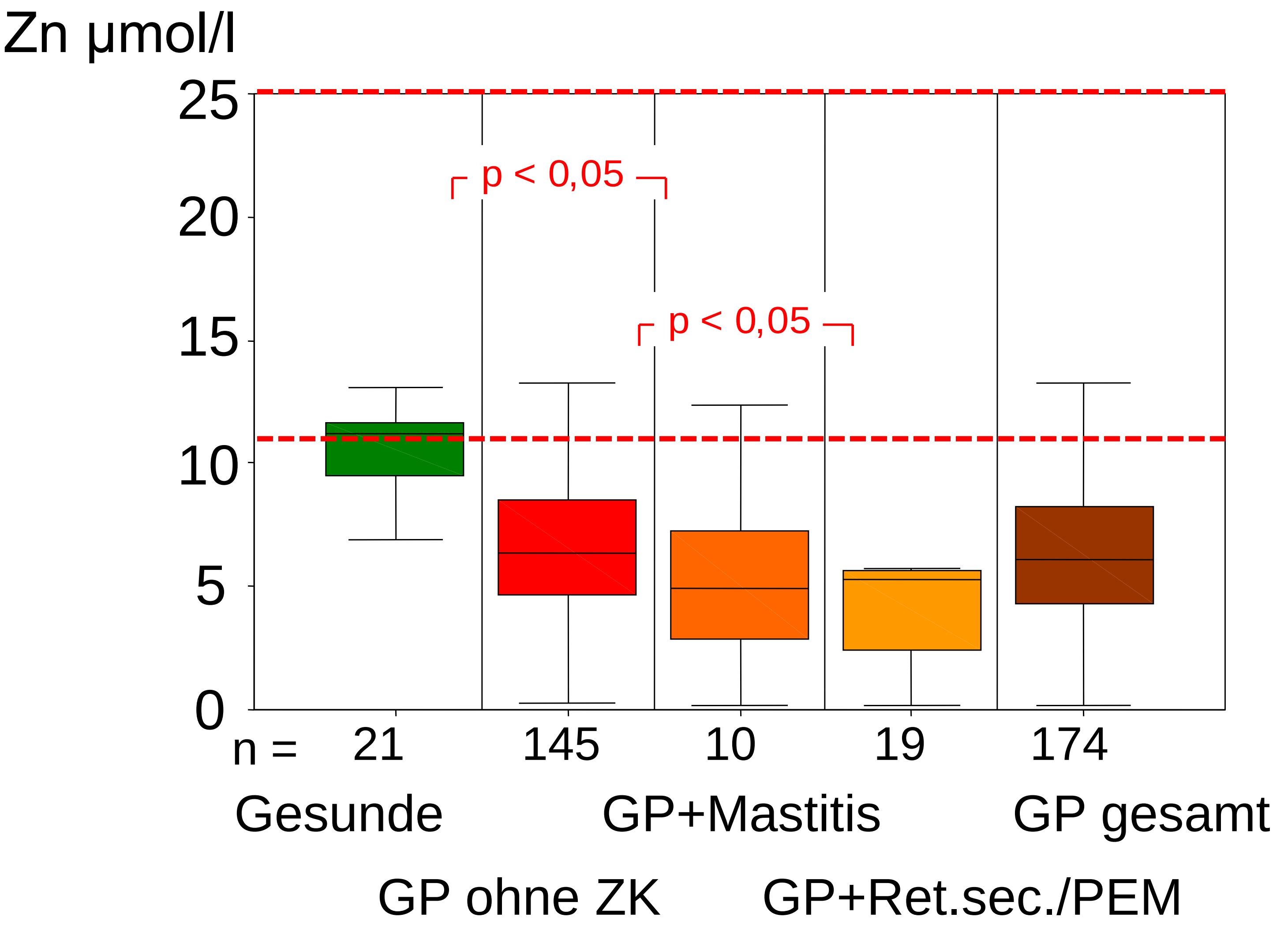
Laboratory results: Selenium



- Alkaline phosphatase reflects in spec. extent Ca mobilization
- AP in MF cows significant lower compared with KG
- Se correlates significant positivly with AP, Ca and Pi

Se may affect pathophysiological MF

Laboratory results: Zink



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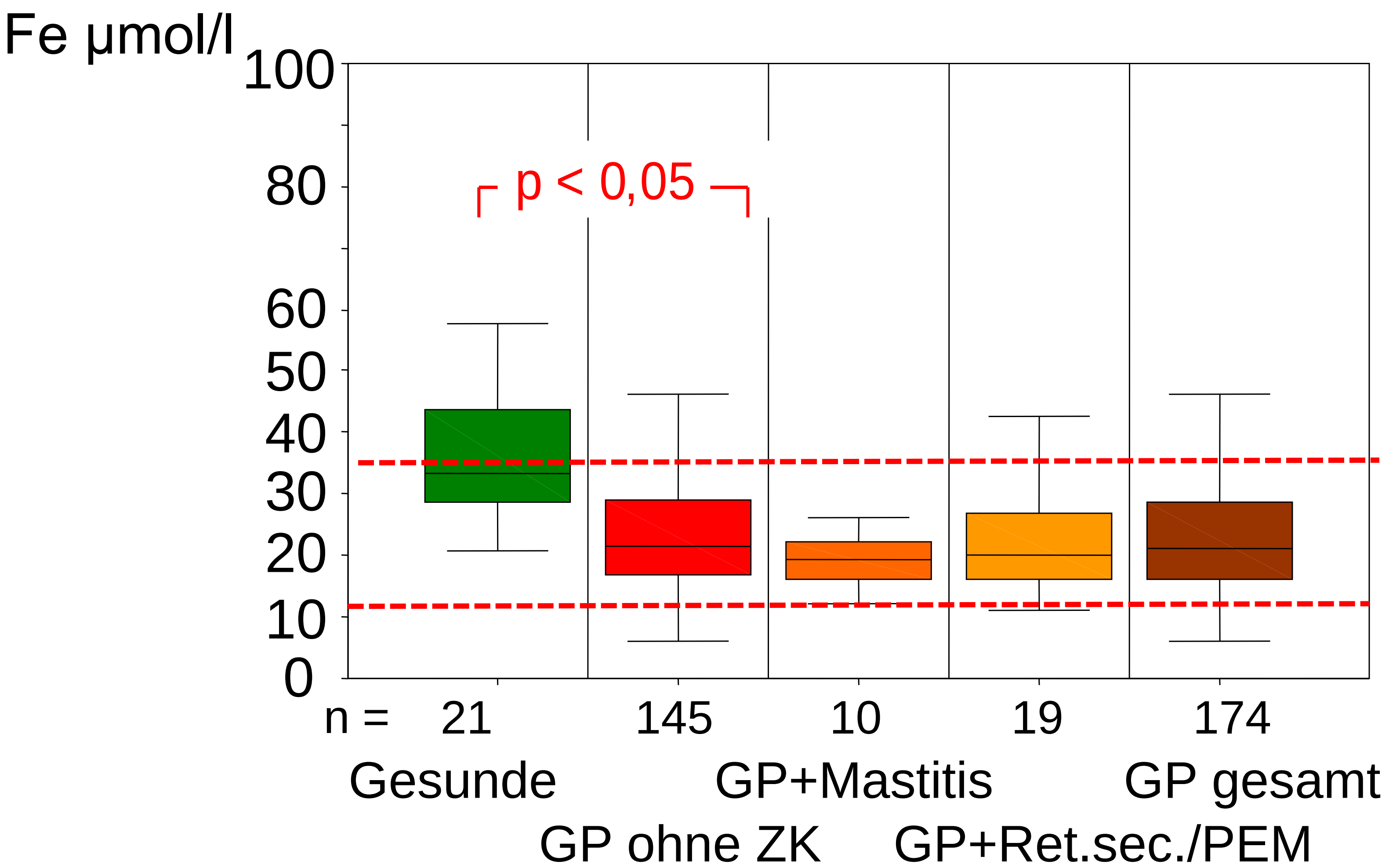
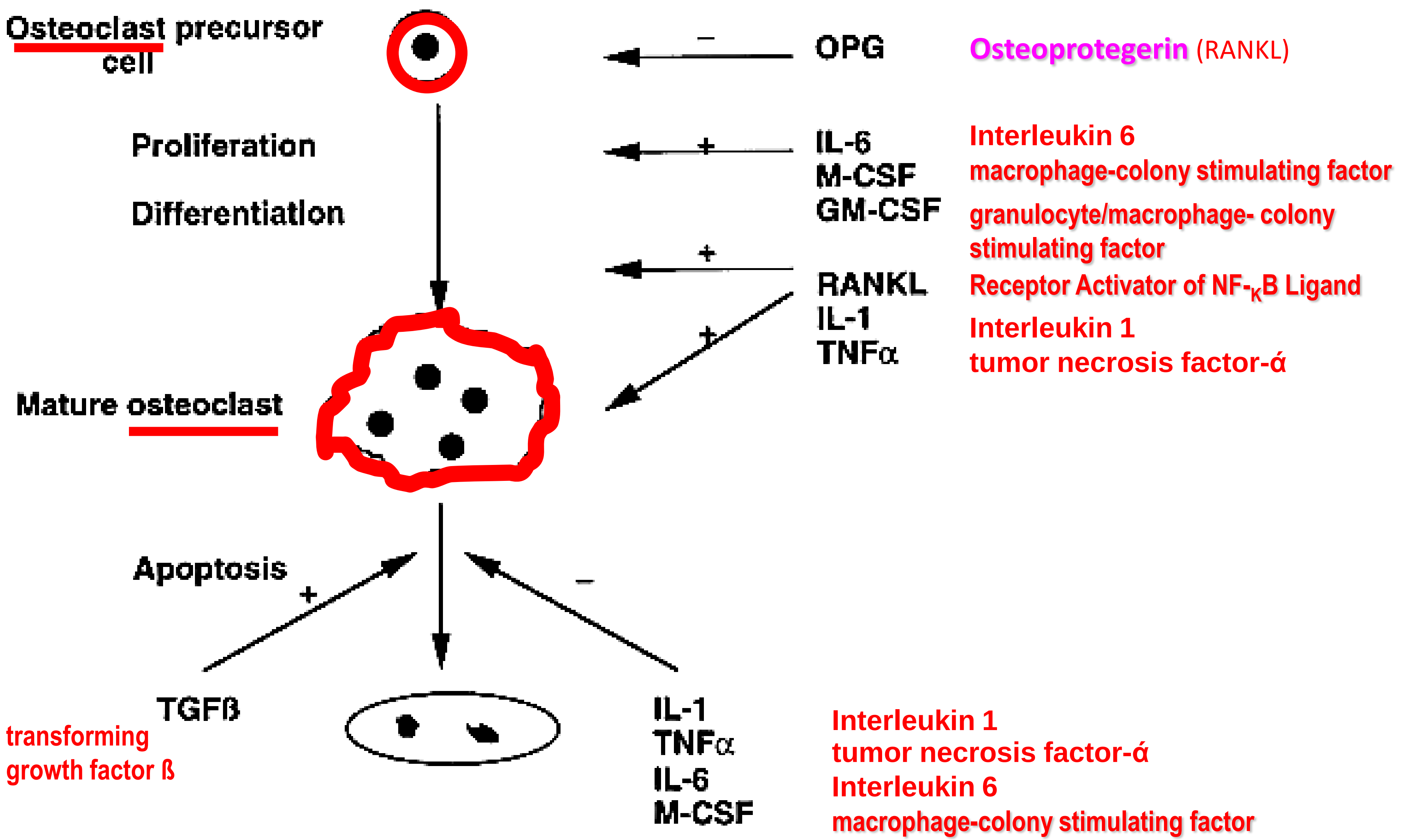
Laboratory results: Ferrum



Effects of cytokines on osteoclast production and activity

(Compston 2001)



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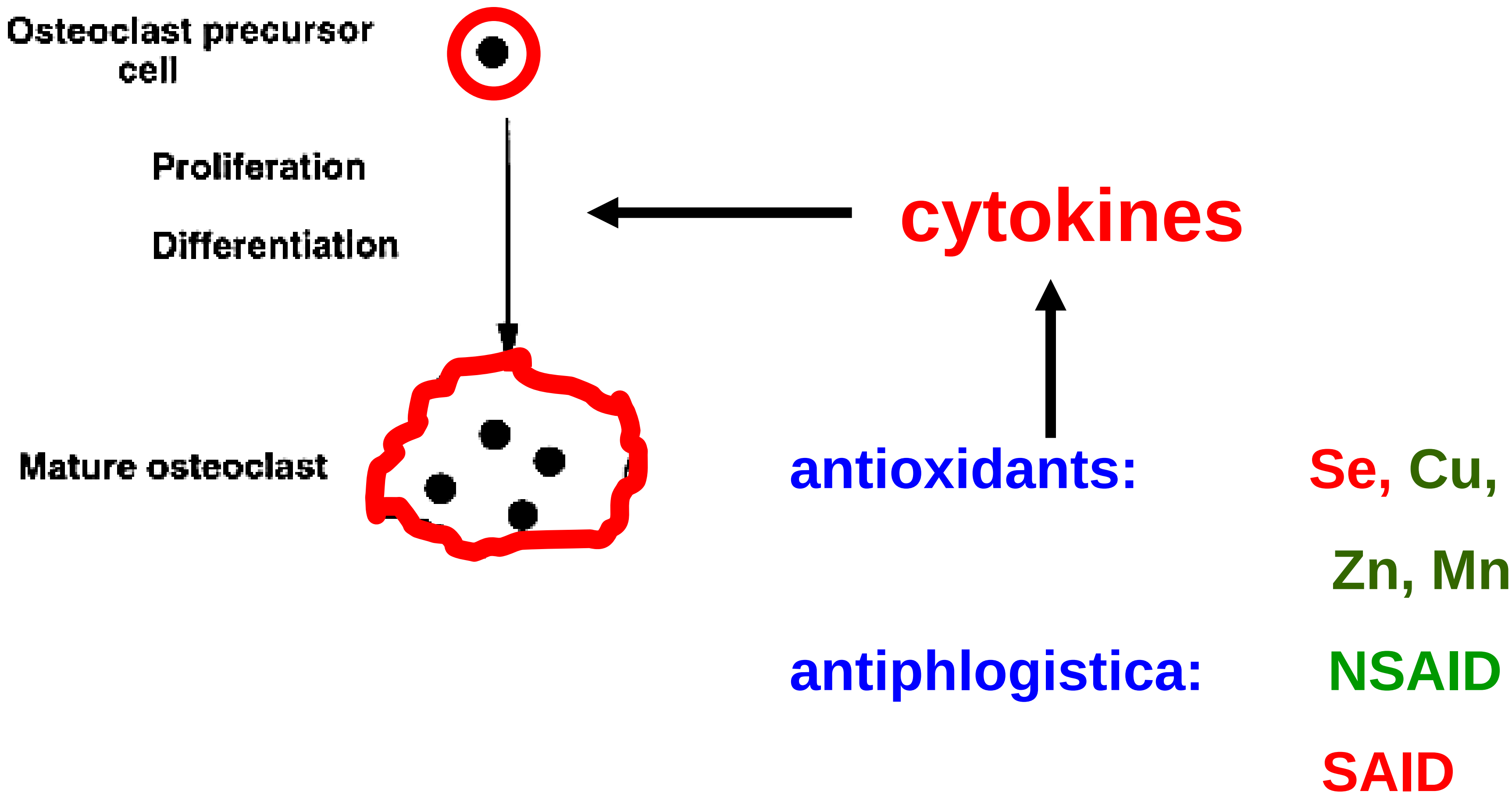

Conclusions

Cows with MF:

- **↓Ca, Pi, Se, Zn, Cu, TEAC**

- Mn and Fe - in normal range

- **Cu**: strong correlated with bone metabolism

20% below normal range

- ↑ **TNFα**, ↑ Haptoglobin

Σ: Therapy by downer cows complikations

- 9 – 11 g Ca^{++}
- PO4
- Mg^{++}
- KCl 0,4 g/kg KM/24h
- Dexamethason
- NSAA
- Antioxidants
- Trace elements

  Se, Cu, Mn . . .

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