Guļošo govju sindroms (Downer cow):

Ko dara TNFα un kā pret to cīnīties?

1. Piena triekas cēloņi
2. Guļošo govju diferenciāldiagnozes
3. Komplikācijas
4. Terapija komplikāciju gadījumā

1. Cēloņi

etioloģija	patoģenēze
• sārmaina barība (DCAD> 100 meq/kg DM) un audu reakcija • Ca (> 80g / d), • PI (> 50 g / d) • ↑ energy (aptaukošanās) • ↑ vecums, piena g.šķirne • ↑ izslaukums • **↑ radicals/**↓ mikroelementi	↓ Vitamin D3 receptori zarnās + kaulos ↓ parathyroid hormone receptori nierēs+ kaulos ↓ osteoklastu skaits un aktivitāte ↓ brīvpieejamais Ca kaulos ↓ D vitamīna metabolītu sintēze nierēs - ↓ cholesteryl kalziferola aktivācija nierēs un aknās ↓ brīvpieejamais Ca kaulos (mobilizācija) ↓ **osteoclastu nobriešana**

2. Differential diagnosis of "downer cows"

Downer cow

- divas “piena triekas devas" vai

- govs noguļās “24 stundās pēc piena triekas ārstēšanas"

Sekmīga ārstēšana → Hipokalcēmija **Piena trieka**

Ārstēšana nepalīdz → **Downer cow Syndrome**

?

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

(modif. n. Dirksen 1990)

Normāla reakcija	**Izmainīta reakcija**	**Smags vispārējais stāvoklis**
• smaga trauma: lūzums, plīsumi, nobrāzumi, paralīze • Vielmaiņas rādītāji: ↓Pi, ↓ Ca, ↓K • Psihogēni cēloņi (bailes celties, nedrošība, insubordination)	• piena trieka (↓Ca) • Tetania (↓Mg) • Ketoze • Aknu koma	• Vēdera dobuma orgānu slimības: ... Ileuss, peritonitis, zarnas plīsums • intoxications, smags iekaisums dzemdību ceļos • mastitis paralytika

3. Downer cow complications

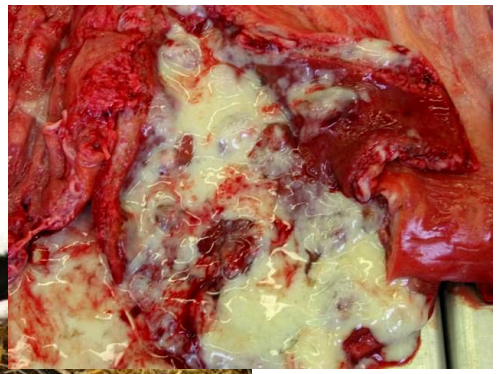
. . . = Piena tiekas

komplikācijas?

- aptaukošanās
- endotoksīni
- TNFα
- ↓Pi
- ↓ antioksidanti
- tromboze

?

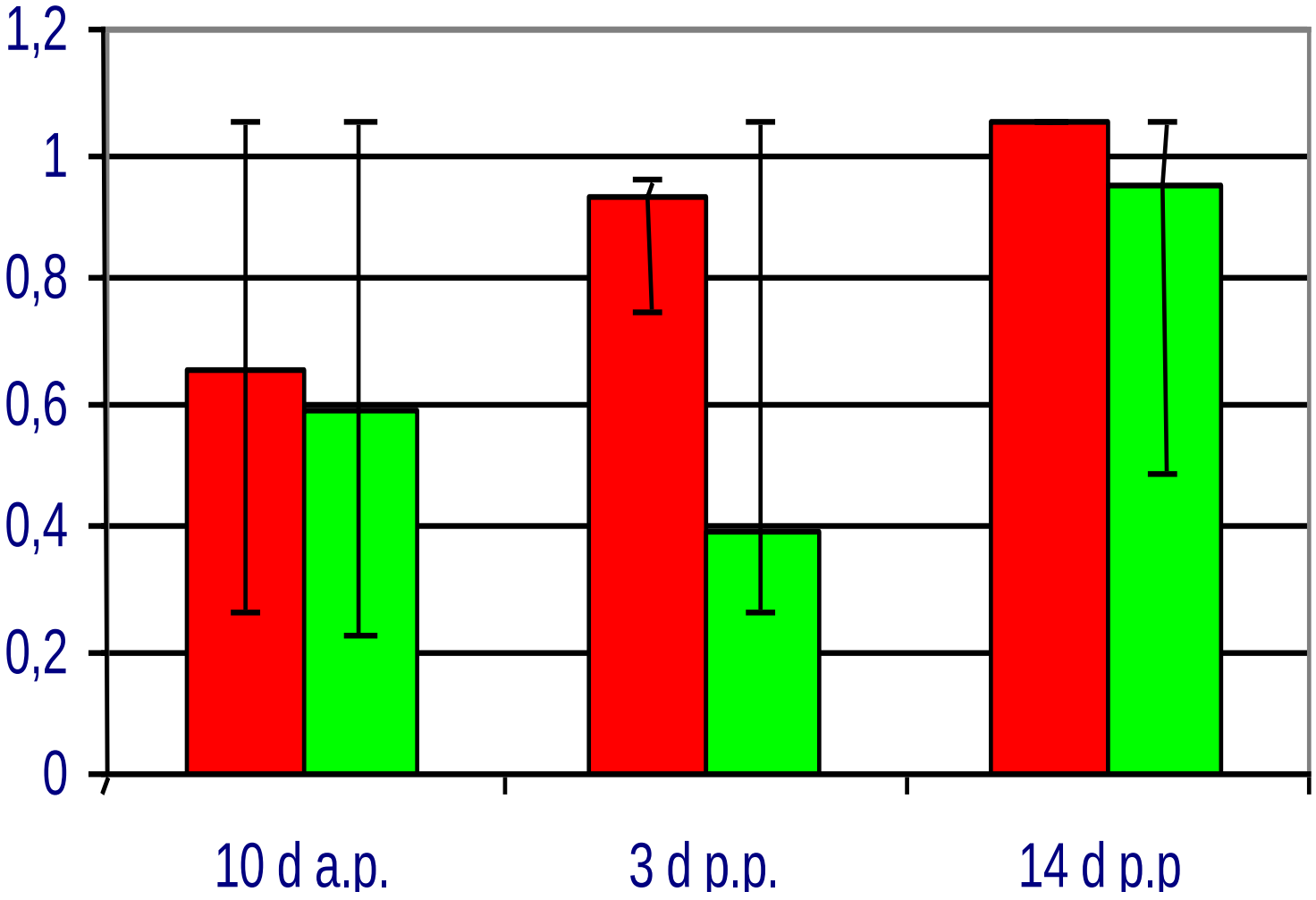
Endotoksīna ietekme



?

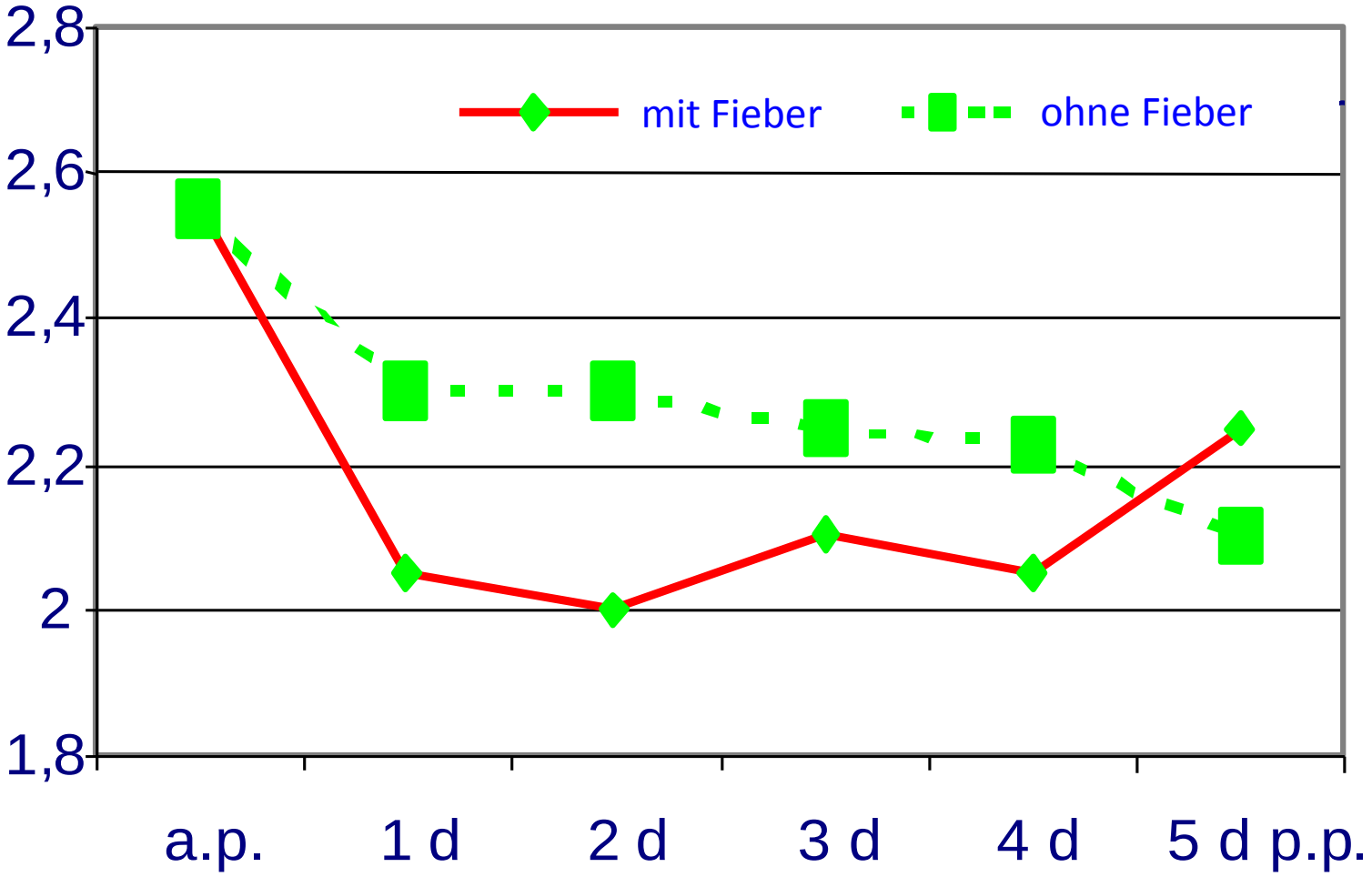
Endotoxin (EU/ml) – milk fever

Endotoksīns pazemina Ca

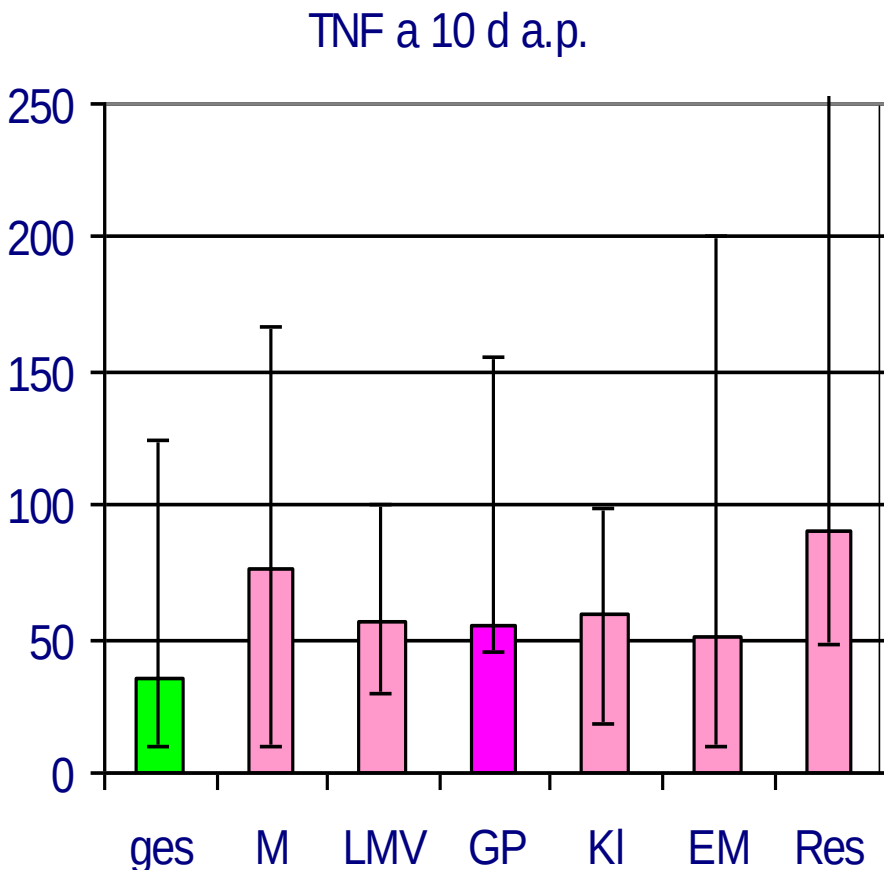


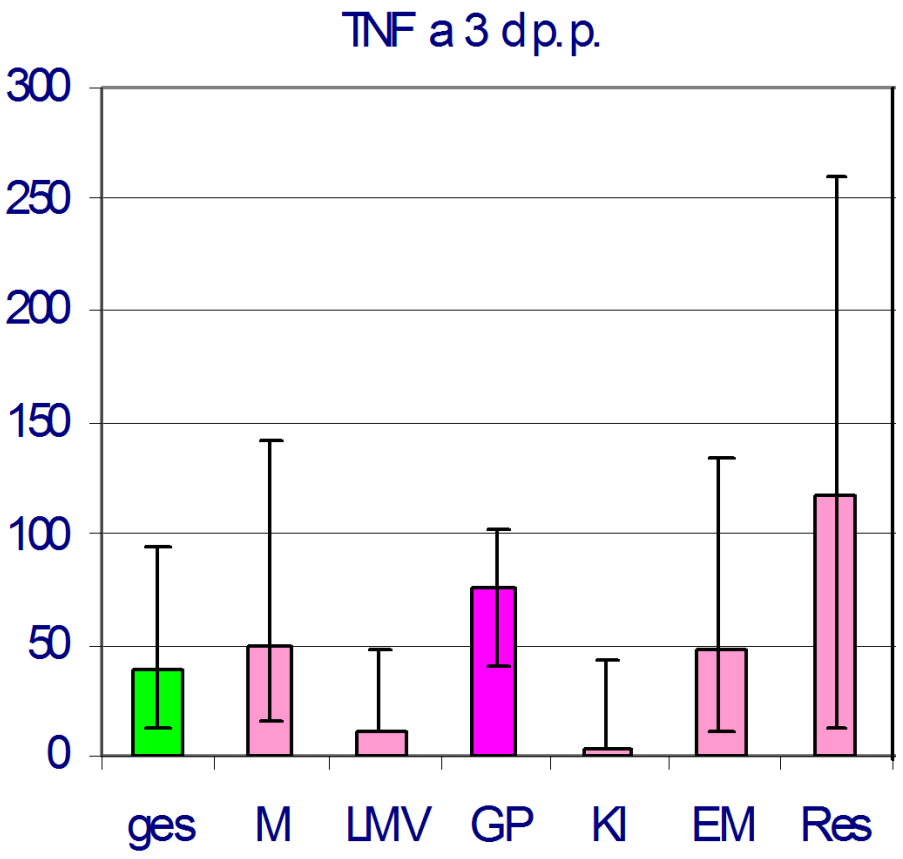
Ca (mmol/l Serum; Fritzsche 1999)

Endotoxin decreases Ca



TNFα koncentrācija govīm ar pēcdzemdību slimībām(unpublished)





TNFα: ↓ P-uzsūkšanos un ↓ Ca-mobilizāciju ↓ osteoklastu nobriešanu

Guļoša govs:

ante partum + post partum ↑ TNFα

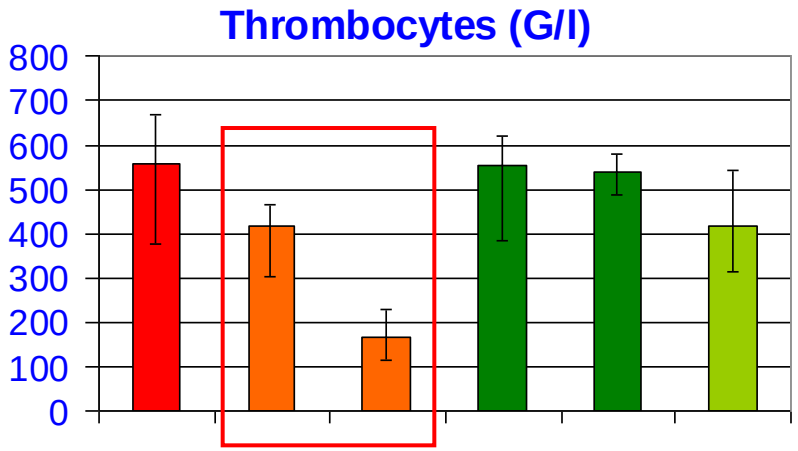
TNFa → ↓Ca^{++}

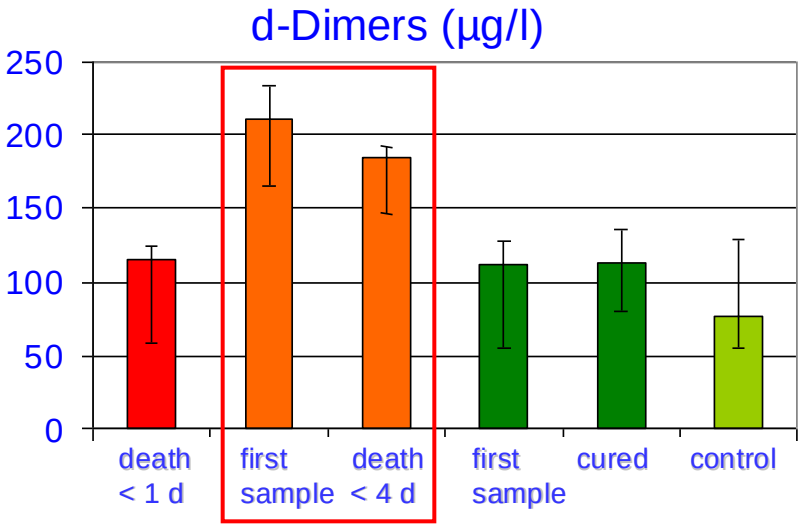
Komplikācijas aptaukošanās gadījumā

Endotoxins: iekaisuma mediatori: neuromus-ventricular function (GOFF 2002) :

- Interleukin 1 → ↓ **Blood-Ca**
- Thromboxans, Prostazyklins and vasoaktive Amins → **hypovolämic Shock**
- Hypoglycemia + ↓ **Glucose transfer** → cells
  → ↑ Lactate + Dysfunktion + **muskuļu vājums**
- Trombocītu aktivācijas faktors(PAF) → trombi
- + Skeleta + Sirds muskuļa vājums

➢ Platelet activating factor (PAF) → thrombi





Müller, M. Möhring, M. Fürll, A. Sobiraj,K. Gmeiner, H.-A. Schoon.

Pulmonale Thrombosen beim weiblichen adulten Rind im klinischen Kontext.

Tierärztl. Prax. 2009, 37

4. Terapija (guļoša govs ar komplikācijām)

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

  Se, Cu, Mn . . .

?

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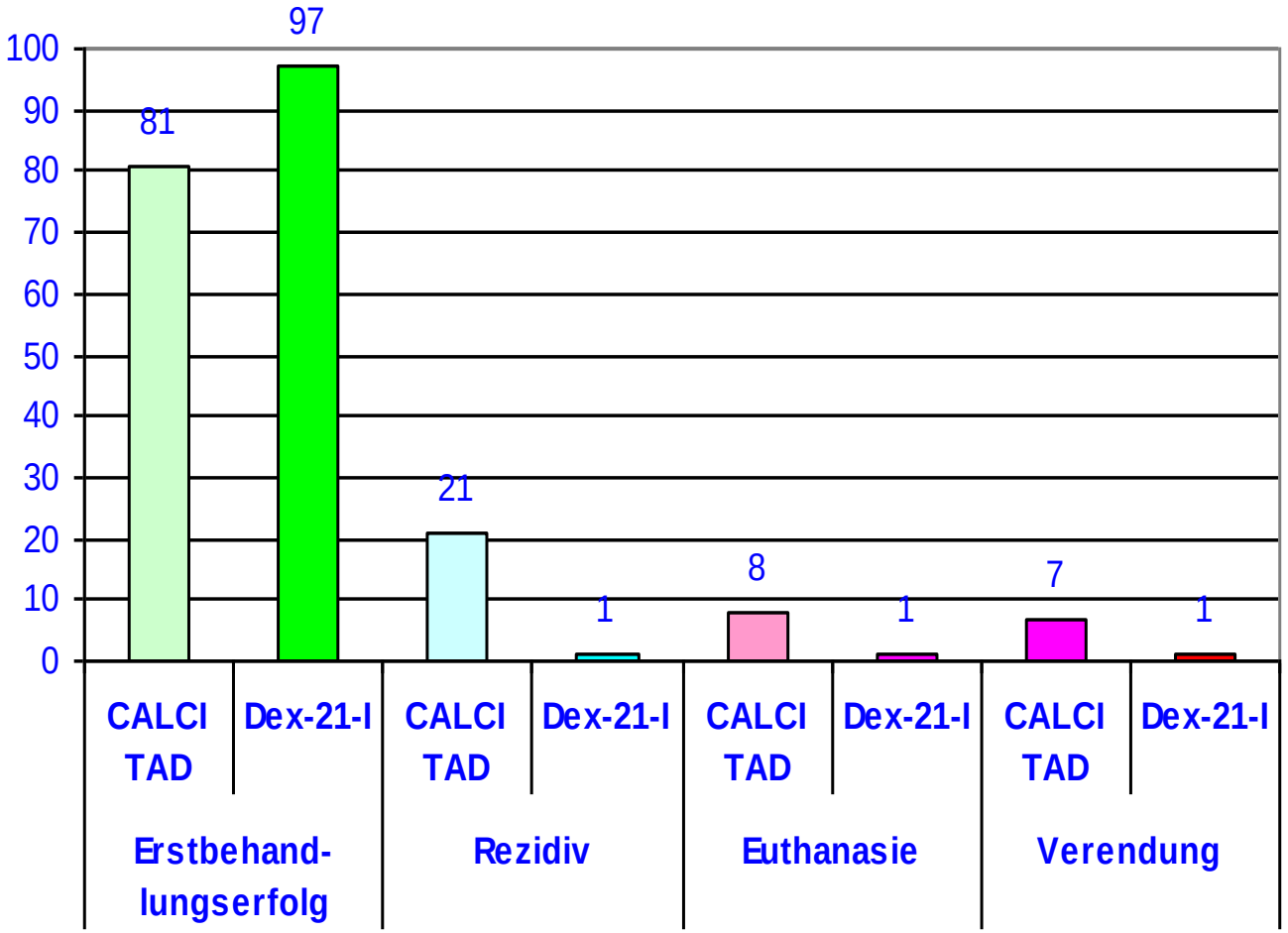
Piena trieka– ārstēšanas rezultāti(%)

a) Pirmreizēja, b) kopā ar Dex-21-iso-Nicotinat (Pichon 2007)

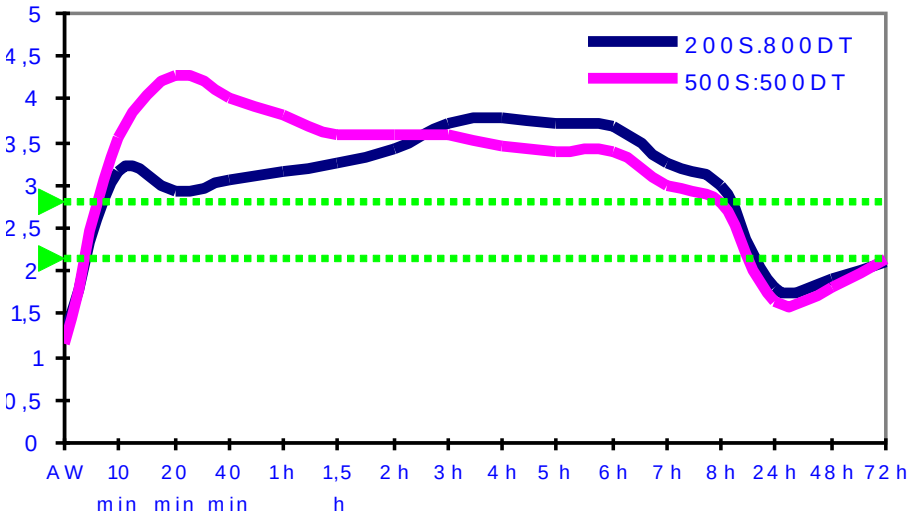


4. Therapy by downer cows (complikations)

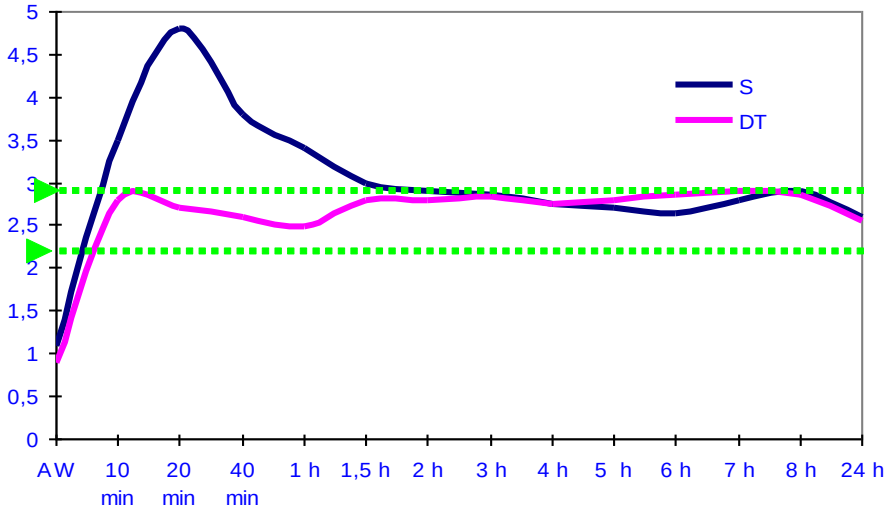
- 9 – 11 g - **more Ca^{++} ?**
- PO_4
- Mg^{++}
- Dexamethason
- NSAA
- Antioxidants
- trace elements

  Se, Cu, Mn . . .

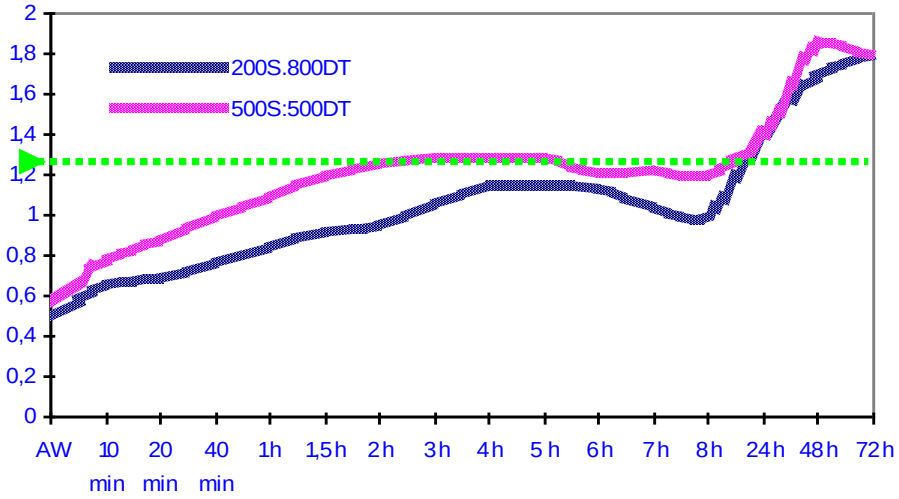
Ca (mmol/lSerum) bei 1000 ml Ca-Borogluconat in Calcamyl® (Jehle 2004)



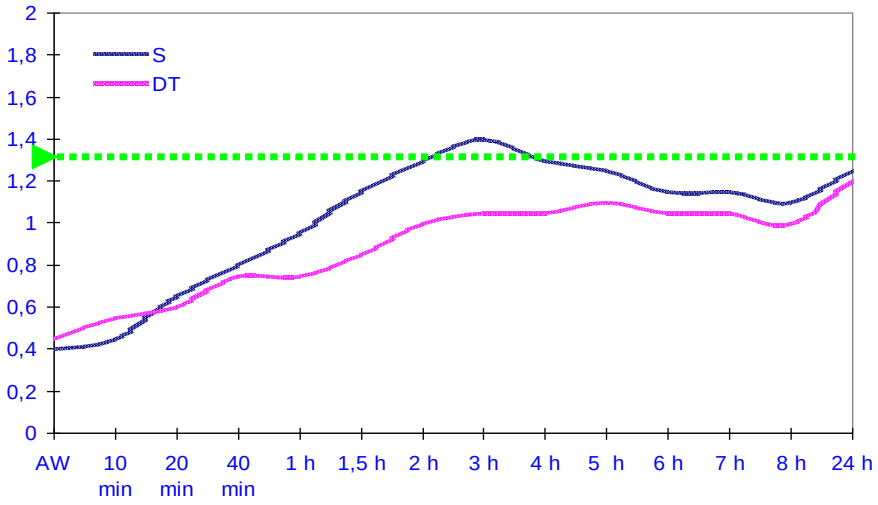
Ca (mmol/lSerum) bei 600 ml Ca-Borogluconat resp. Calcamyl (Braun et al. 2004)
S = Sturz-, DT = Dauertropfinfusion



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)
S = Sturz-, DT = Dauertropfinfusion



Jehle (2004):

1000 ml Ca-Borogluconat in Calcamyl®

- Tikai 47% pirmās devas efektivitāte.
- ~ ne vairāk kā 600 ml (Brown et al. 2004)
- Sirds aritmija u.c. blakusefekti bez nopietnām sekām

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 . . .

„Hipofosfatēmija vai atipiska piena trieka“ [1,2]

Heinrich Seidel
Leipzig
(1935 bis 1982)

- **Galvenās pazīmes**

  govs normāli reaģē, ēd,

  nespēj piecelties, vājas pakaļkājas

- **Ca un neorganiskais P (Pi)**

  viduvēja hipokalcēmija ($p>0,05$)

  izteikta hipofosfatēmija ($p<0,01$)

  reizēm hipokalēmija

- **Sastopamība**

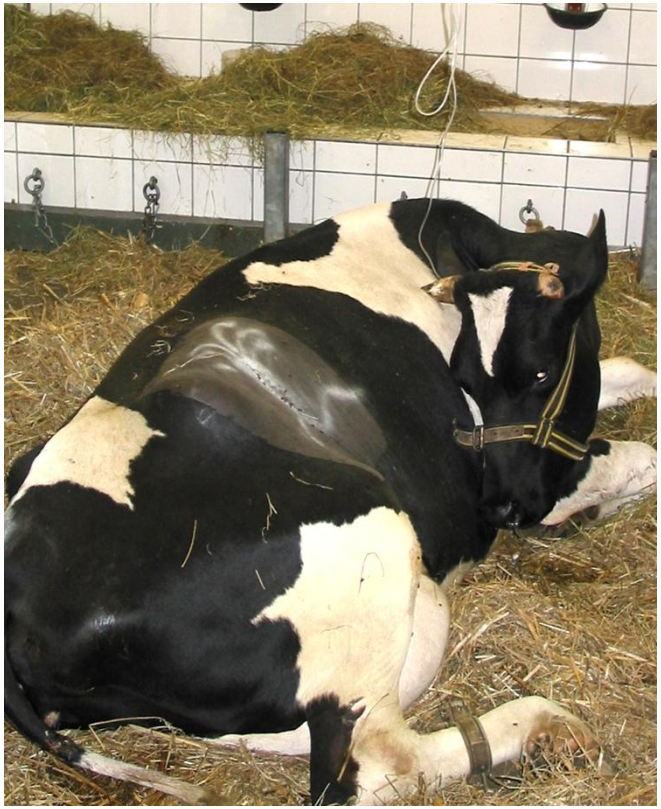
  no dzemdībām līdz 30 diena p.p.

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. Pēcdzemdību hemoglobīnūrija/ Hb-pienā, anēmija / Intoksikācija (Brassica)
2. 2. ↓ fosfātu uzņemšana ar barību
3. 3. “P – saistoša vielas"
4. 4. ↑↑↑ glikozes infūzijas
5. Hroniska acidoze
6. Netipiska piena trieka
7. Smaga piena trieka
8. Aknu lipidoze
9. Citi cēloņi: Atypical paresis

10. iekaisuma sekas

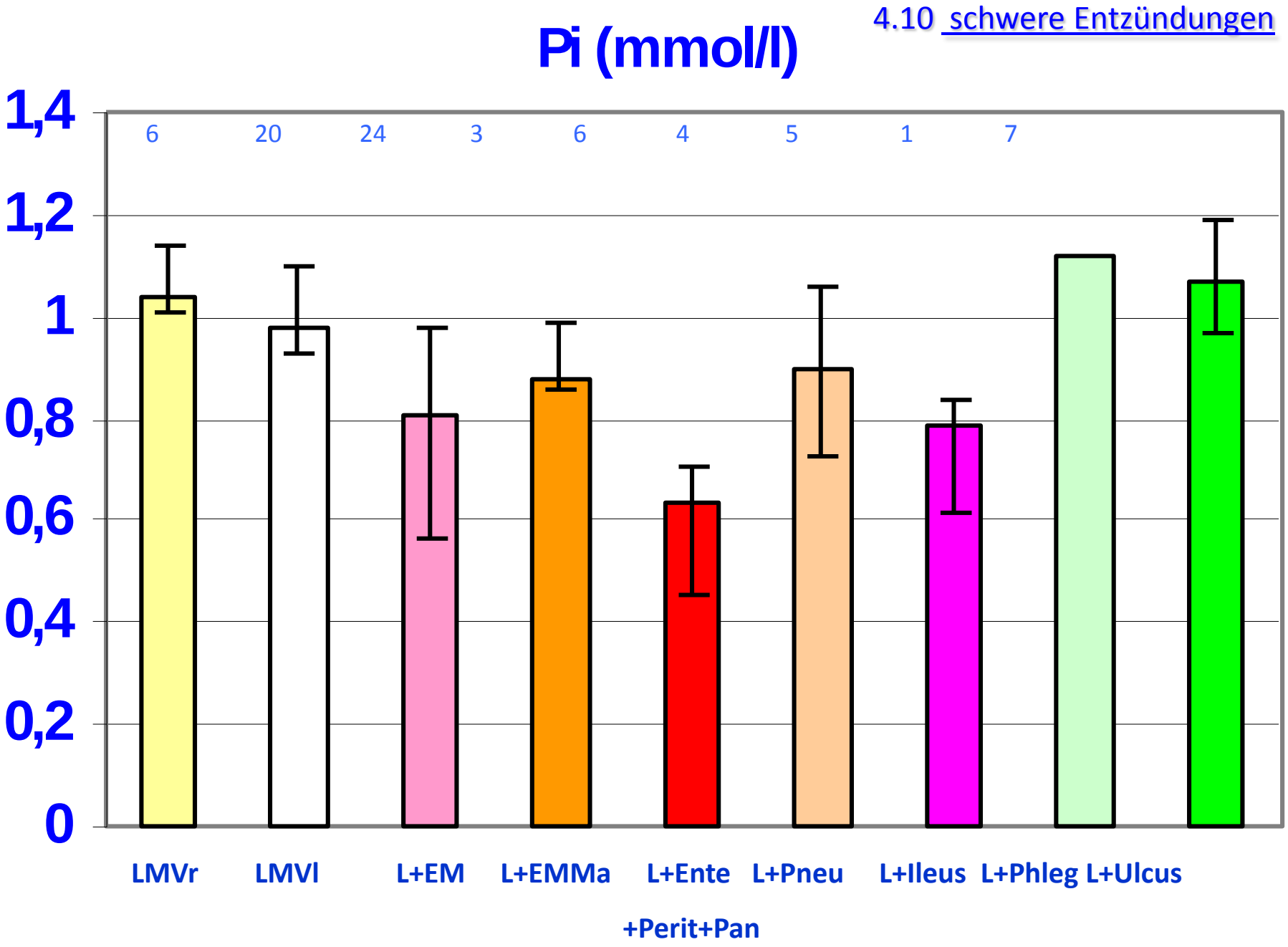
94 gadījumu retrospektīva analīze

(glumenieka dislokācija)

Pi <1.25 mmol/l:

. . . . Hipofosfatēmijas

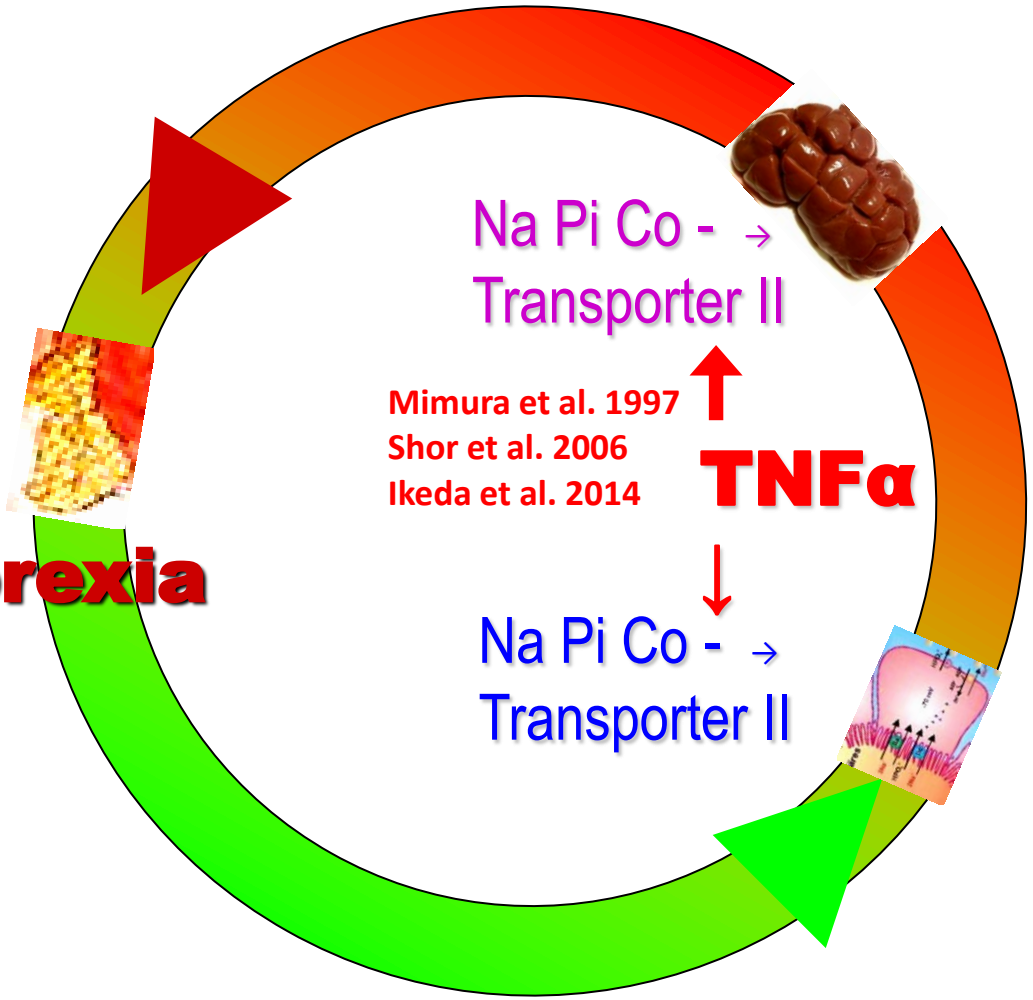
klīniskās pazīmes


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 +Perit+Pan
L+Pneu
L+Ileus
L+Phleg
L+Ulcus

Pi-circulation

Blood: 1 – 2 g

Milk:
10 – 70 g



kidney
Pi-excretiong

saliva

inflammation
! Sepsis !

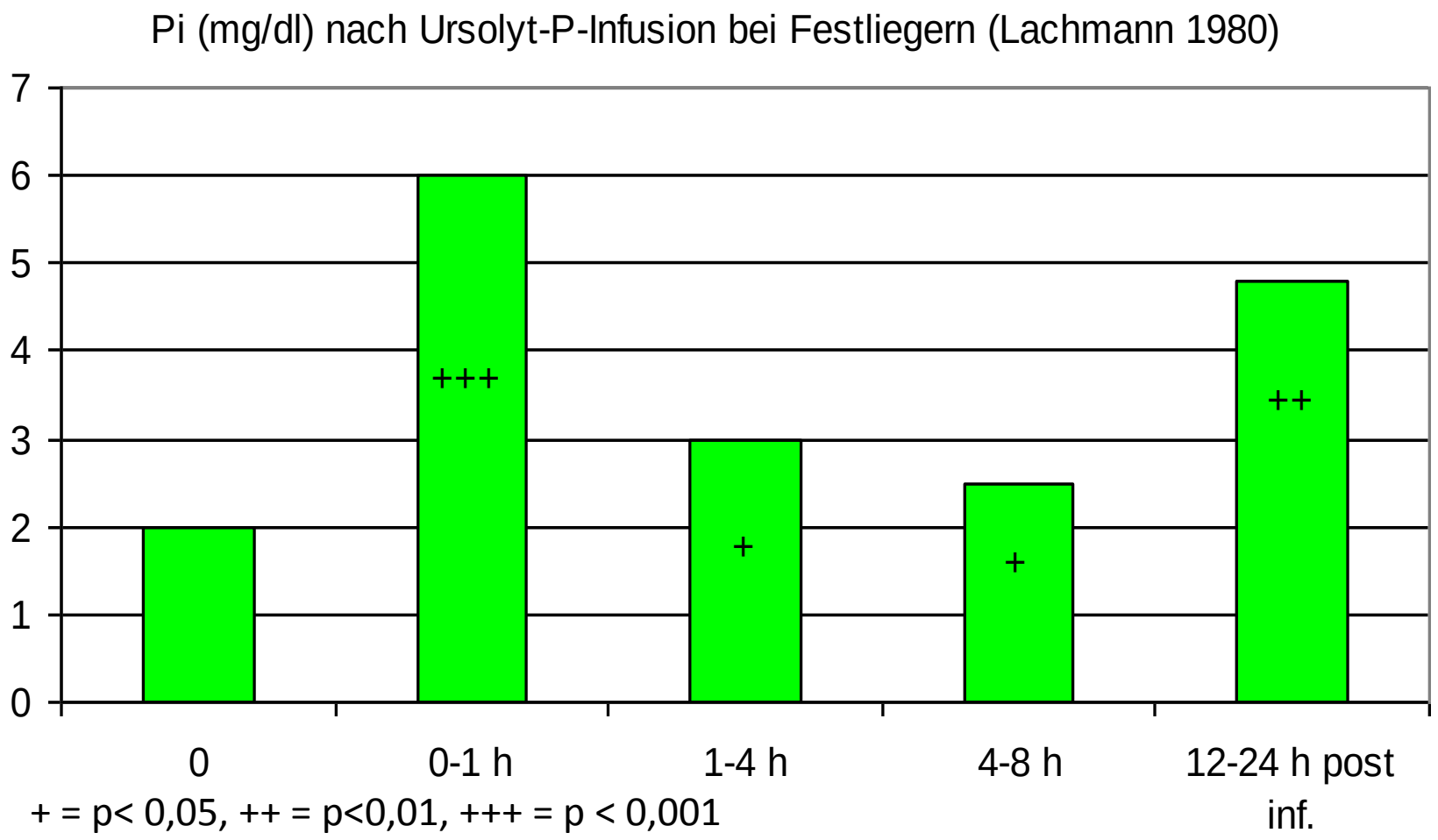
Anorexia

Entero-
cytes
Pi-resorption

Feed:
1,4 g/kg T

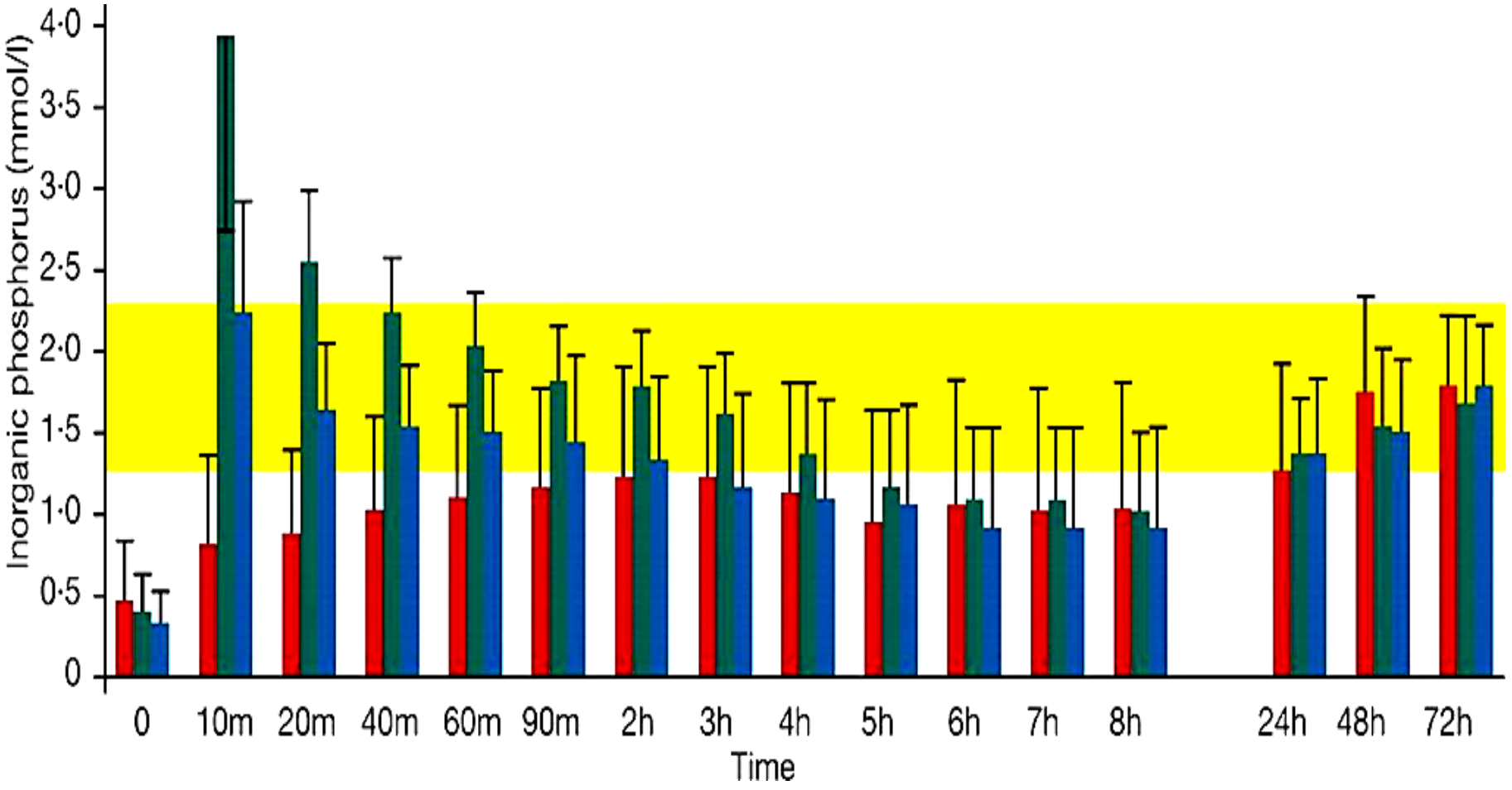
Feces:
1,2 g/kg TS

Pi concentration (mg / dl serum, $\bar{x}$) by downer cows after iv therapy with 90 g Na_2HPO_4/ $NaHPO_4$/ 500 ml (Lachmann 1980)



Phosphate-buffer increased Pi-blood-concentration

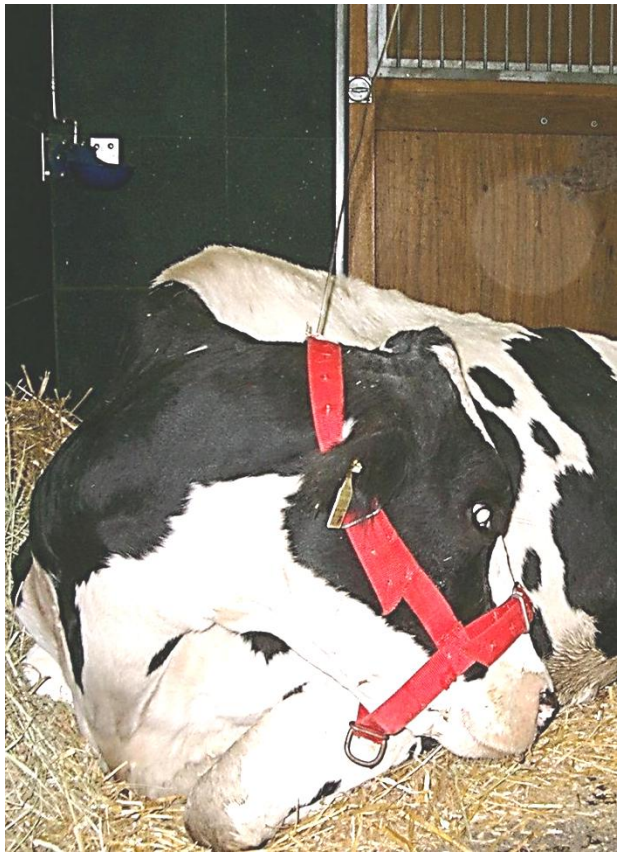
Pi (mmol / l serum) at downer cows after i.v. treatment with Ca-Boro-gluconat (red), additional iv NaH_2PO_4 (green) and NaH_2PO_4 partly in continuous drip (blue)(Braun et al. 2004)



Phosphat-Puffer hebt Pi-Blut-Konzentration

Atipisko “Downer cow” ārstēšana

(pēcdzemdību septicēmija)



1. Glikoze šķ. pilienu infuzijas veidā
   (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. antibiotikas
   - ierosinātāji var būt asinīs
   - clean up output stove
7. heparin (180 IU / kg BW / d)

4. Therapy by downer cows (complications)

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

  Se, Cu, Mn . . .

?

1923

2006

Hipokalēmijas cēloņi un klīniskie aspekti

M. Fürll

Medizinische Tierklinik Leipzig

1. Kālija fizioloģiskā loma

2. K un skābju-bāzu līdzsvars

3. K līmenis asinīs dažādu slimību gadījumos

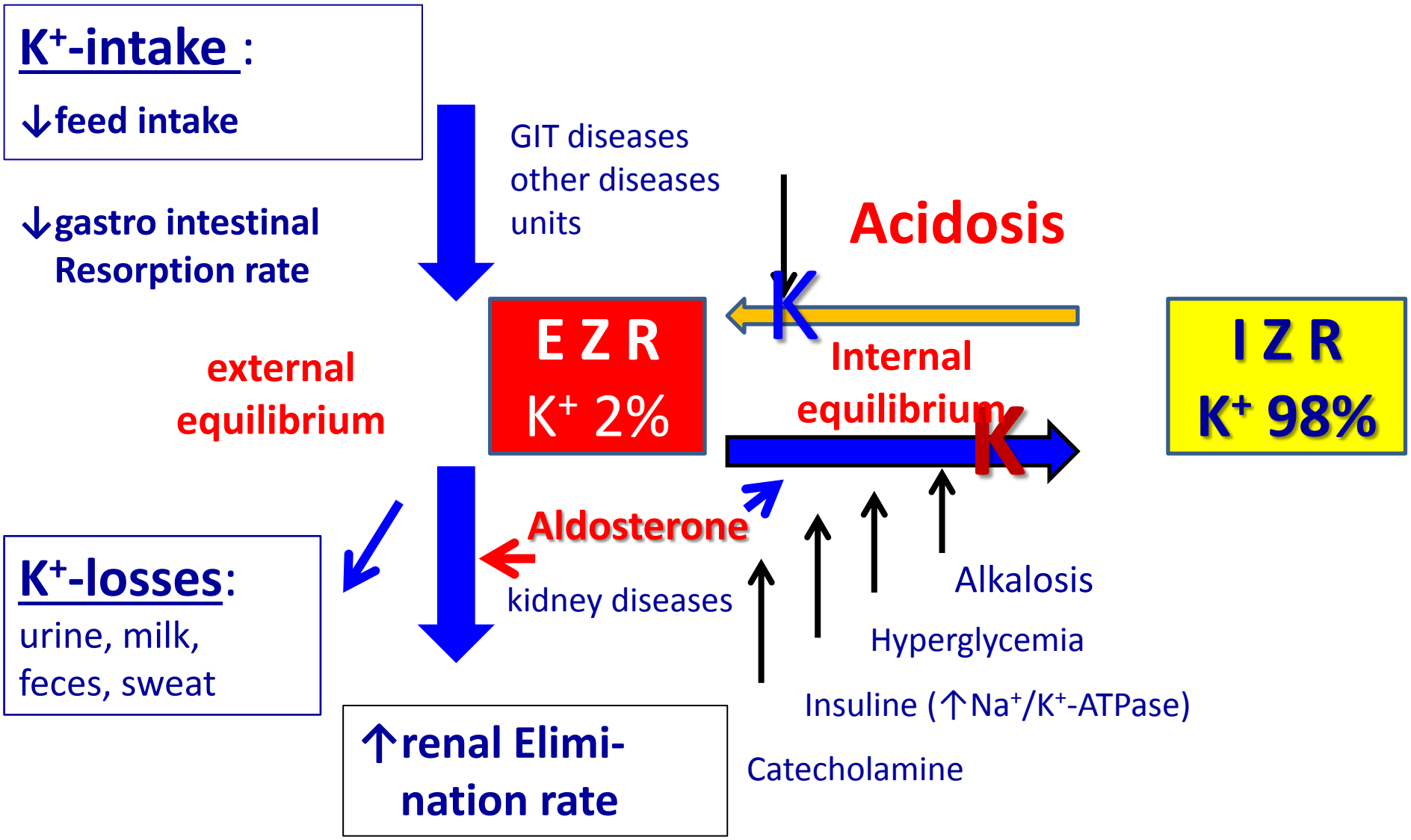
4. K piena triekas gadījumā: gadījumi praksē

5. K glumenieka dislokācijs gadījumā (DA)

6. Hipokalēmijas terapija

7. Secinājumi

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



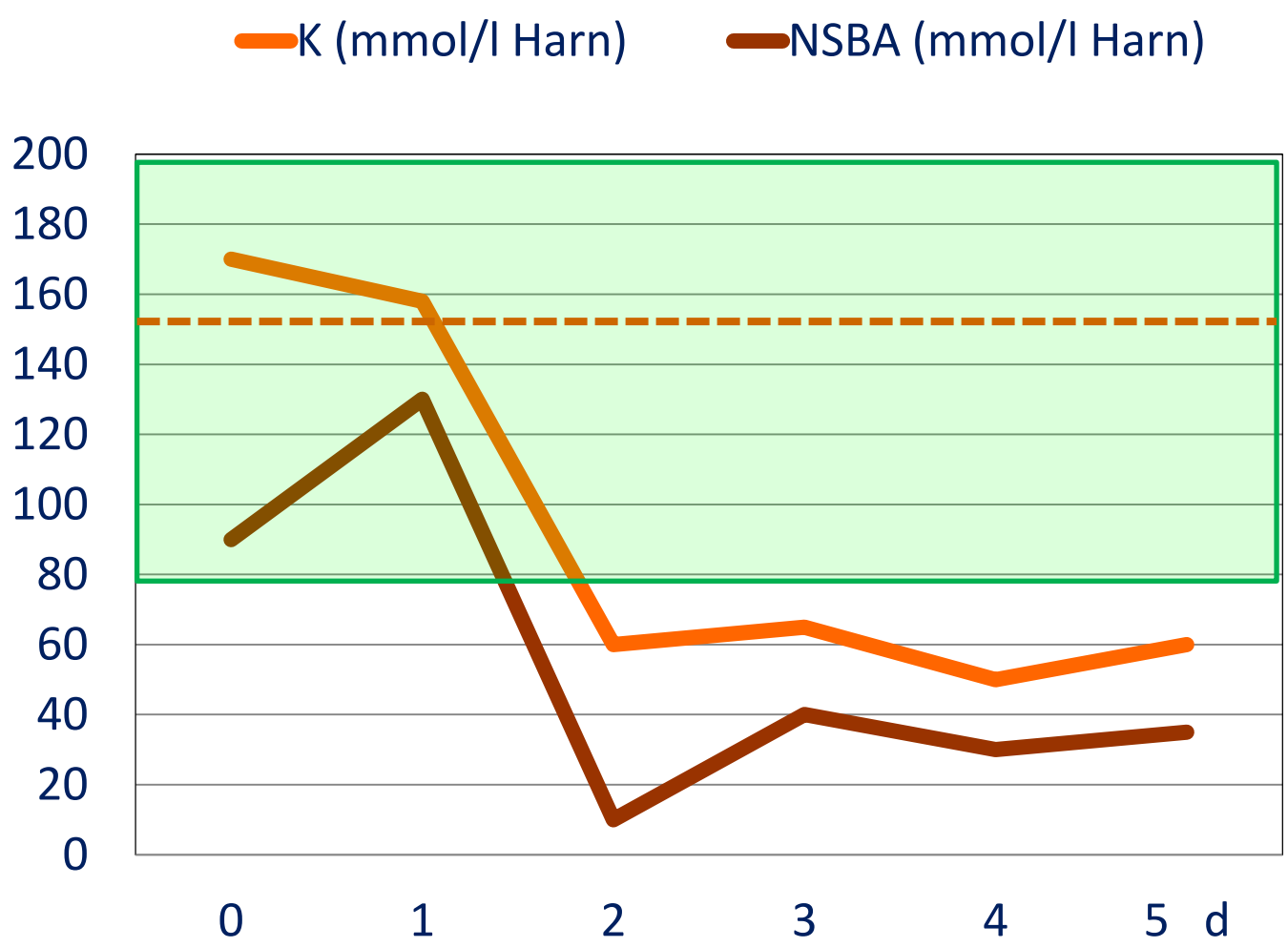
Backgrounds and combat Hypokalemia as a clinical problem

M. Fürll

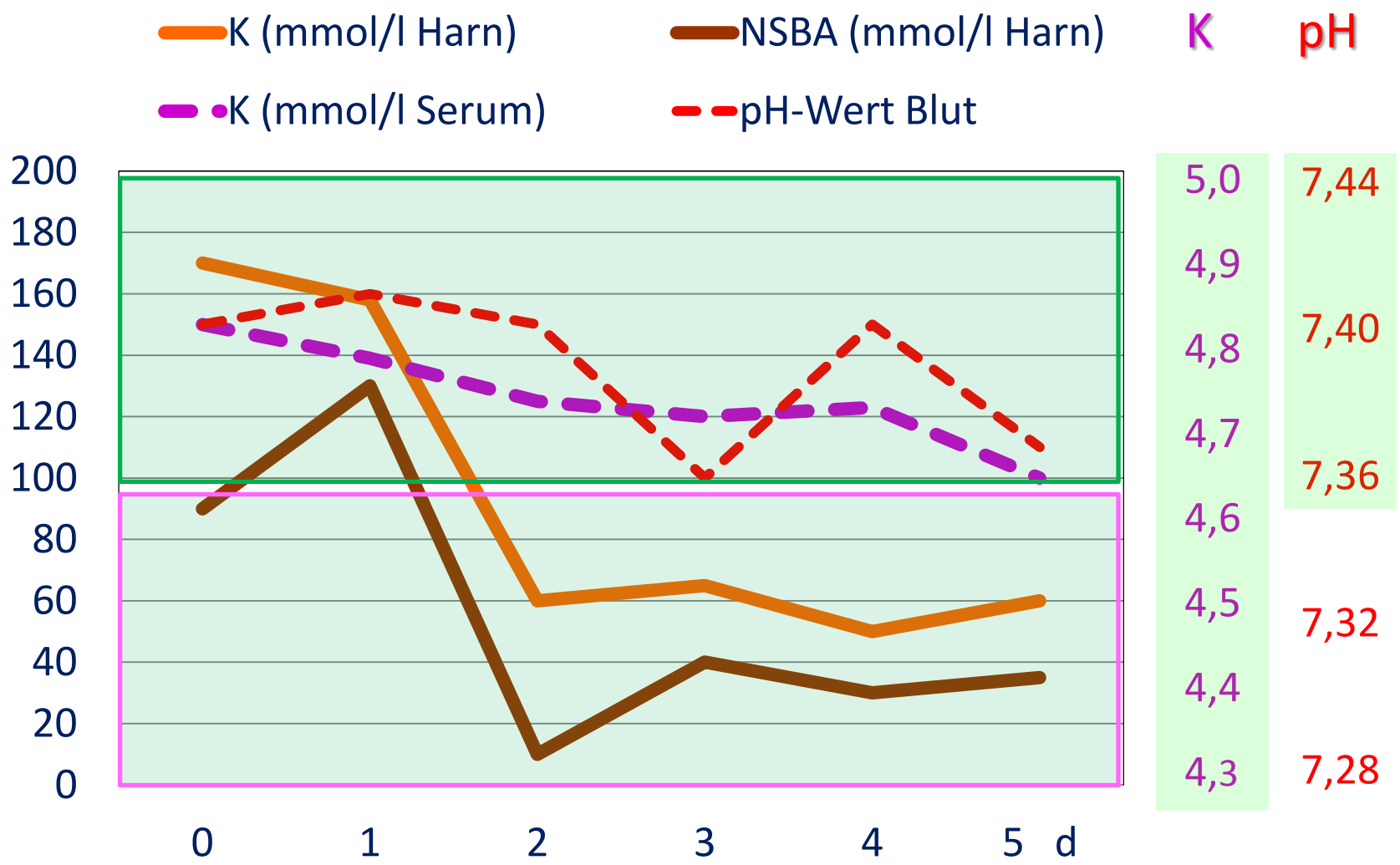
Medizinische Tierklinik Leipzig

1. Physiological role of potassium
2. **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

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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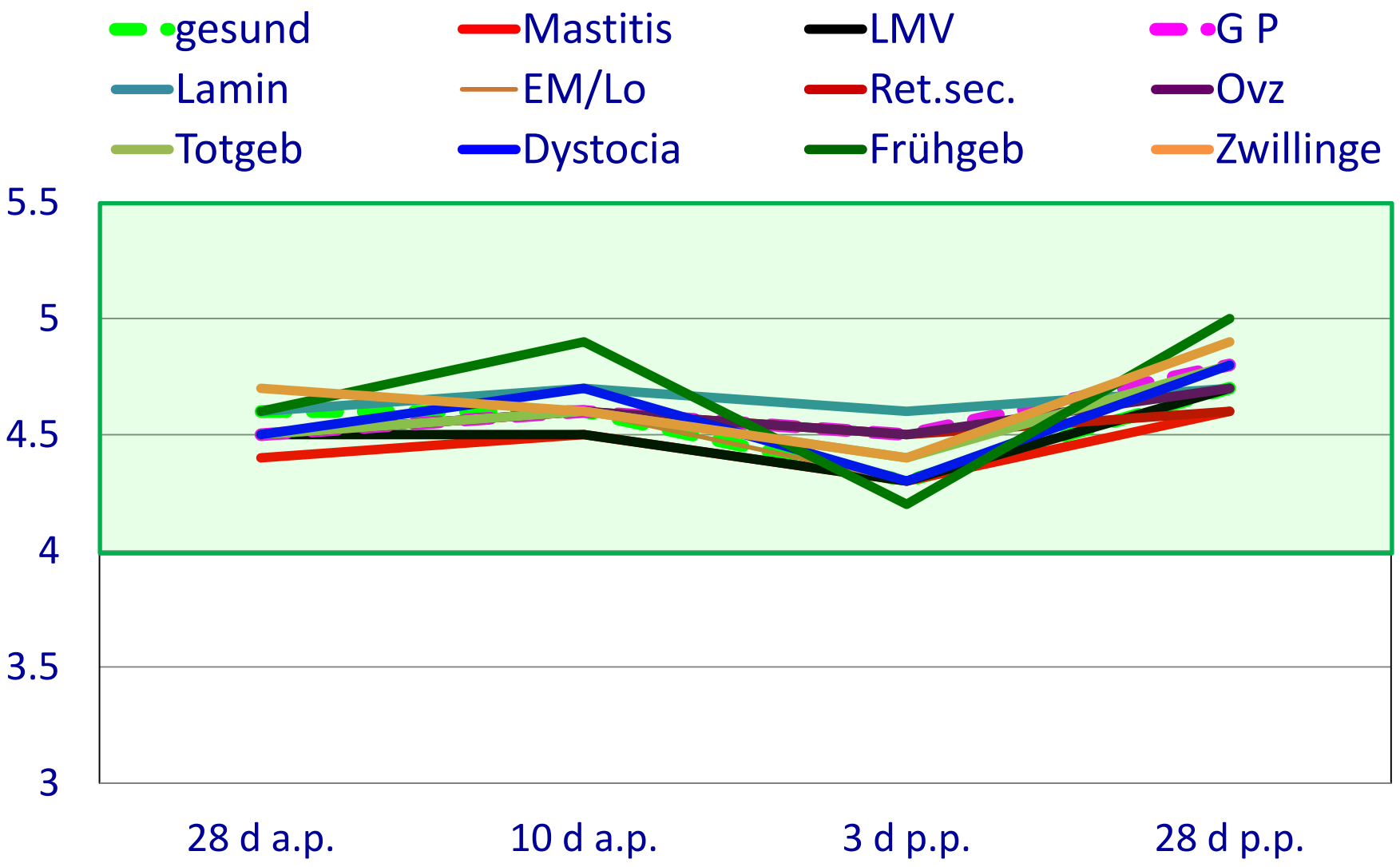
1. Physiological role of potassium

2. 3. K and acid-base balance

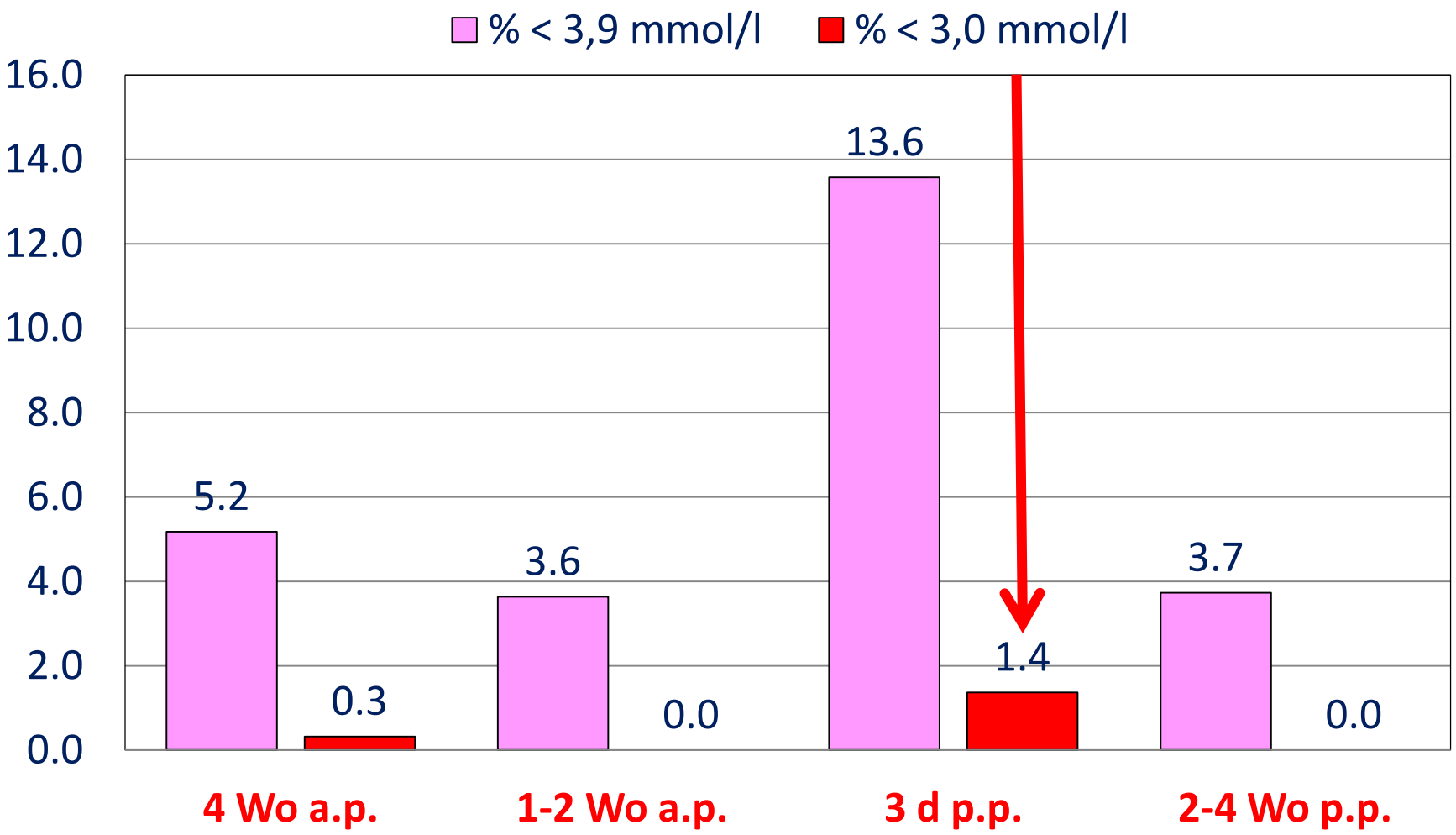
3. K in the blood of cows various diseases in practice

Kad parādās hipokalēmija?

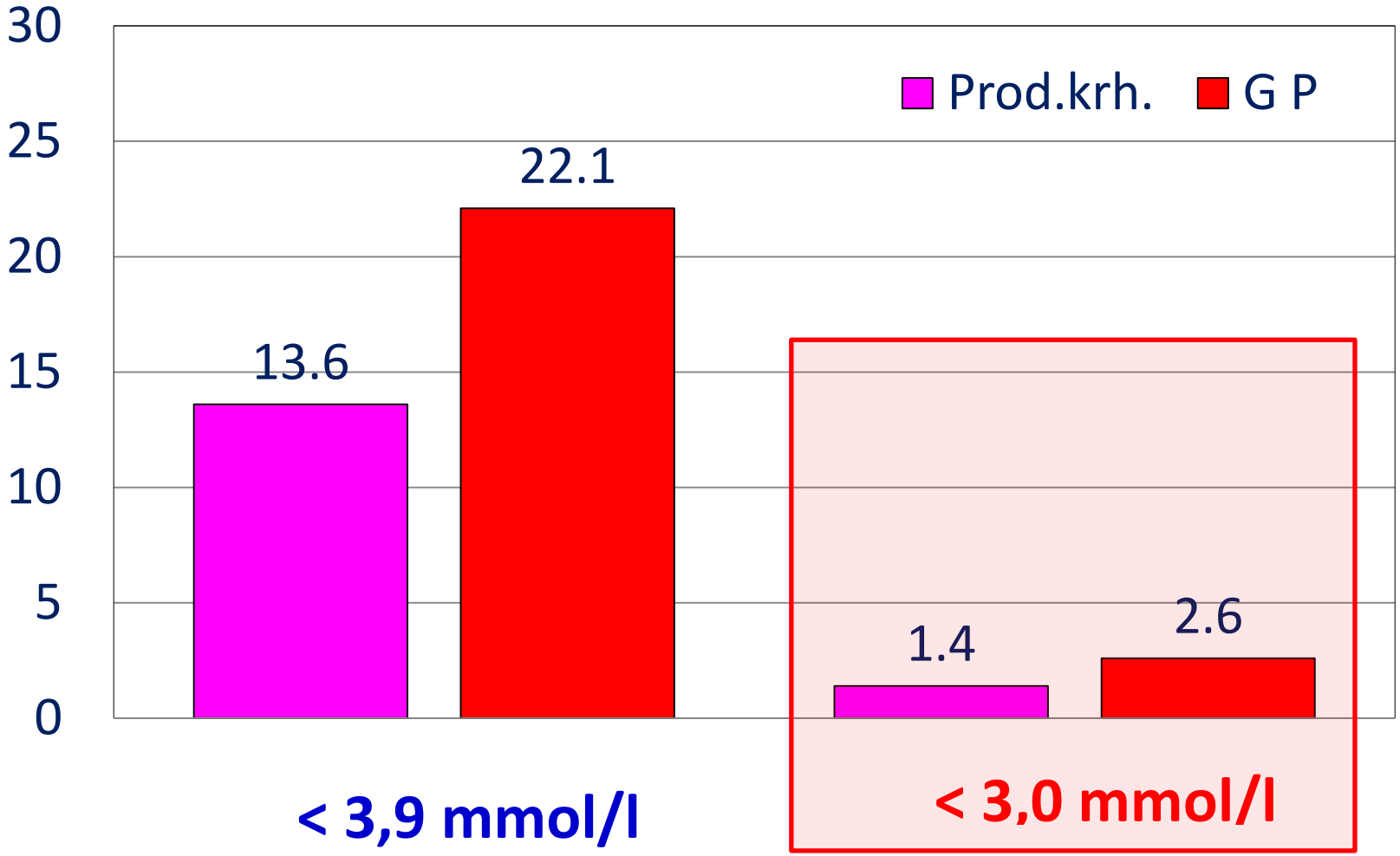
K (mmol / l) in healthy and ill cows (Hädrich 2007)



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



Piena trieka parasti ir bez hipokalēmijas **tomēr** :

2,6%

< 3,0

mmol/l

Backgrounds and combat Hypokalemia as a clinical problem

M. Fürll

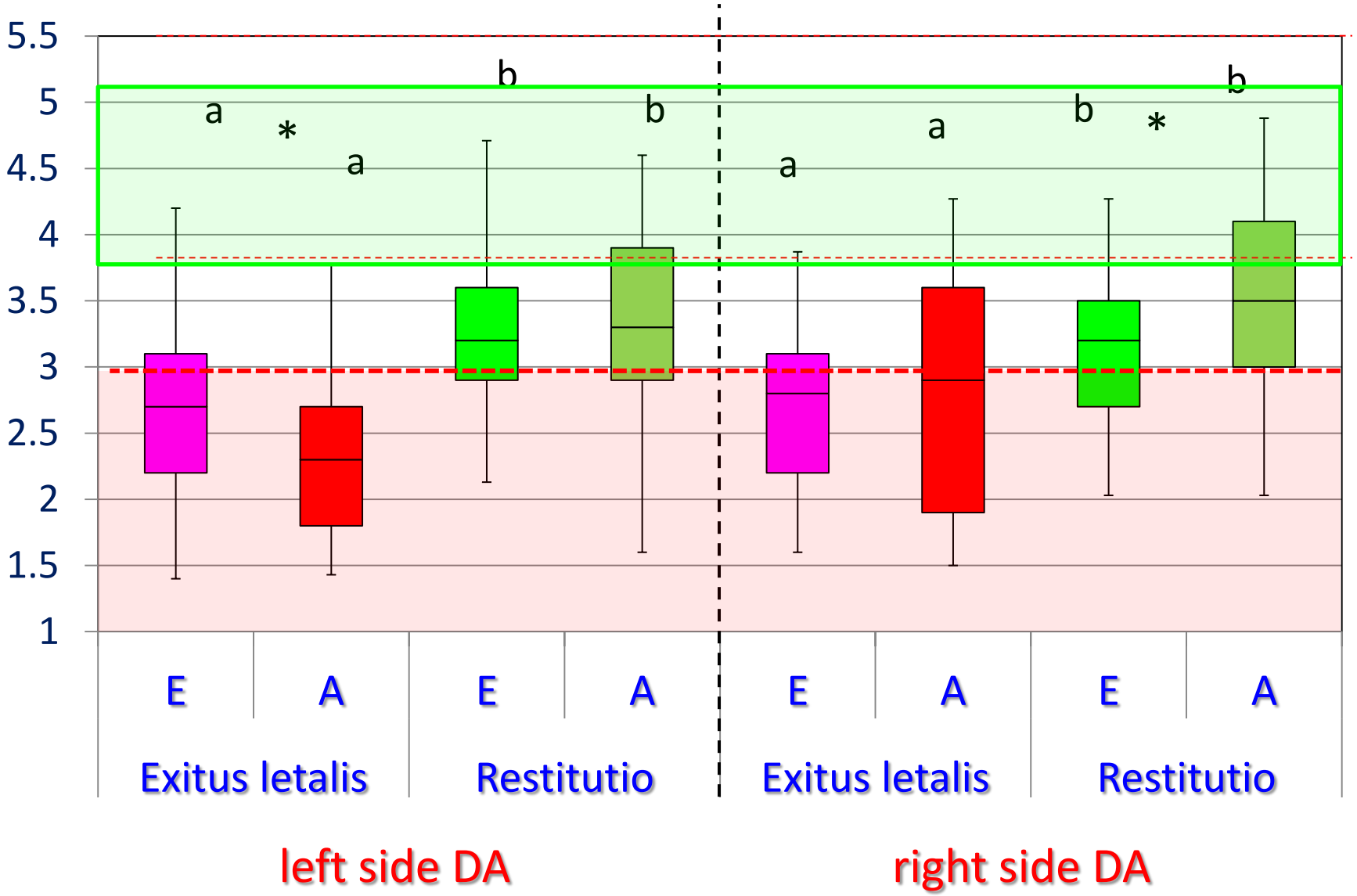
Medizinische Tierklinik Leipzig

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)**

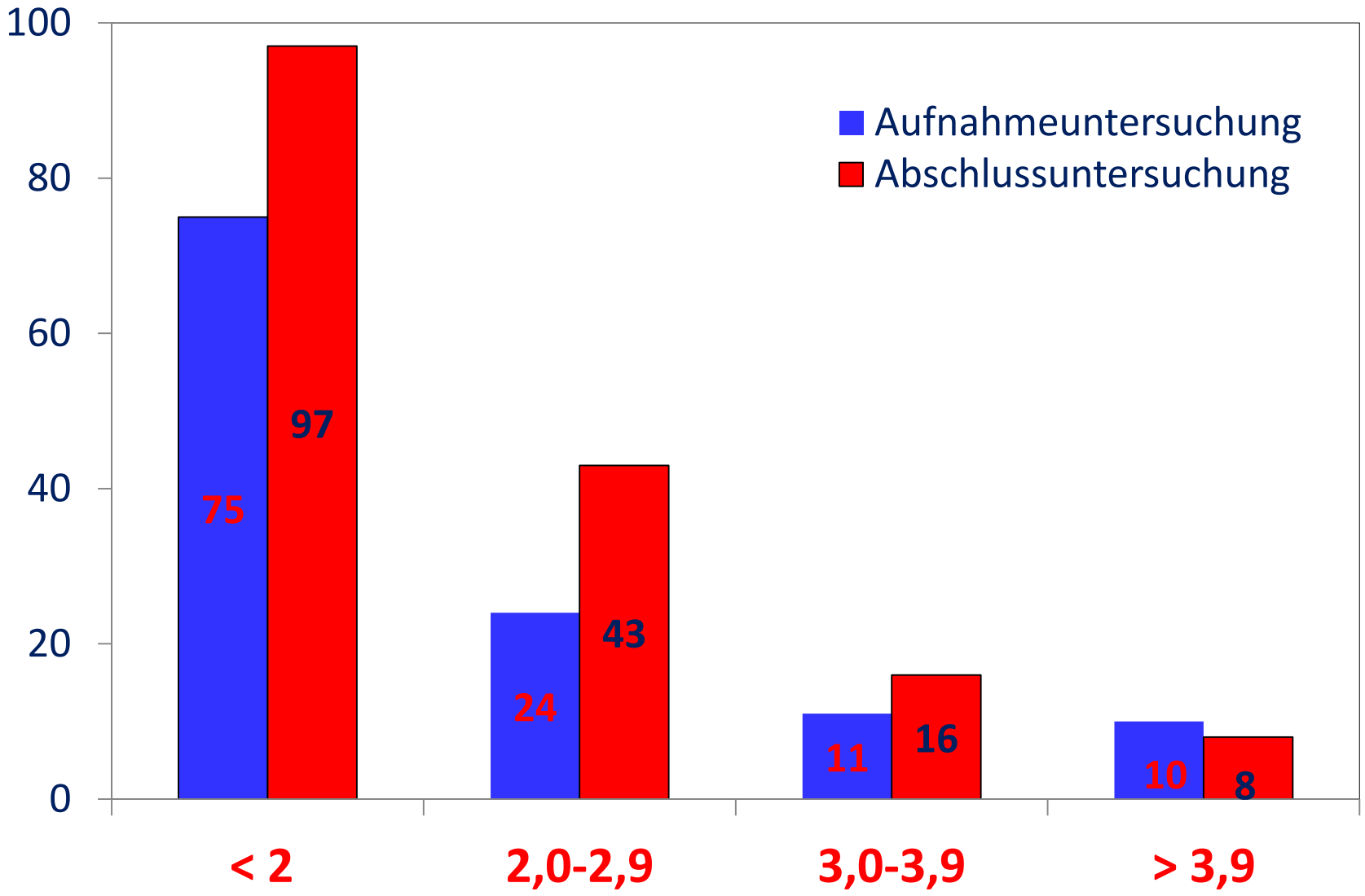
K-nozīme etioloģijā un terapijā?

6. Conclusions for clinical practice

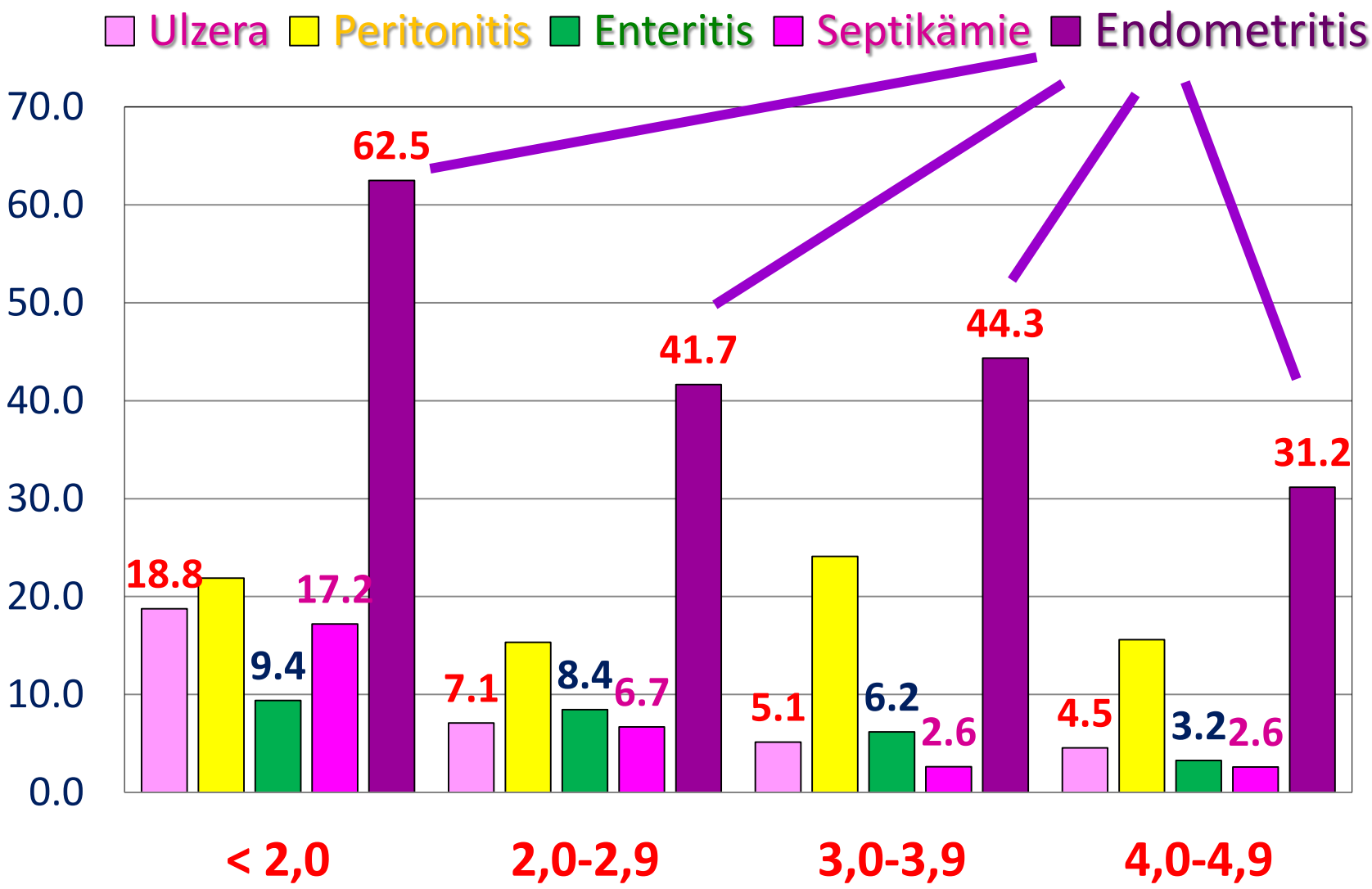
K (mmol/l Serum) in DA cows at initial (E) and last (A) examination with restitution or Ex.letalis (Meyer-Müller 2014)



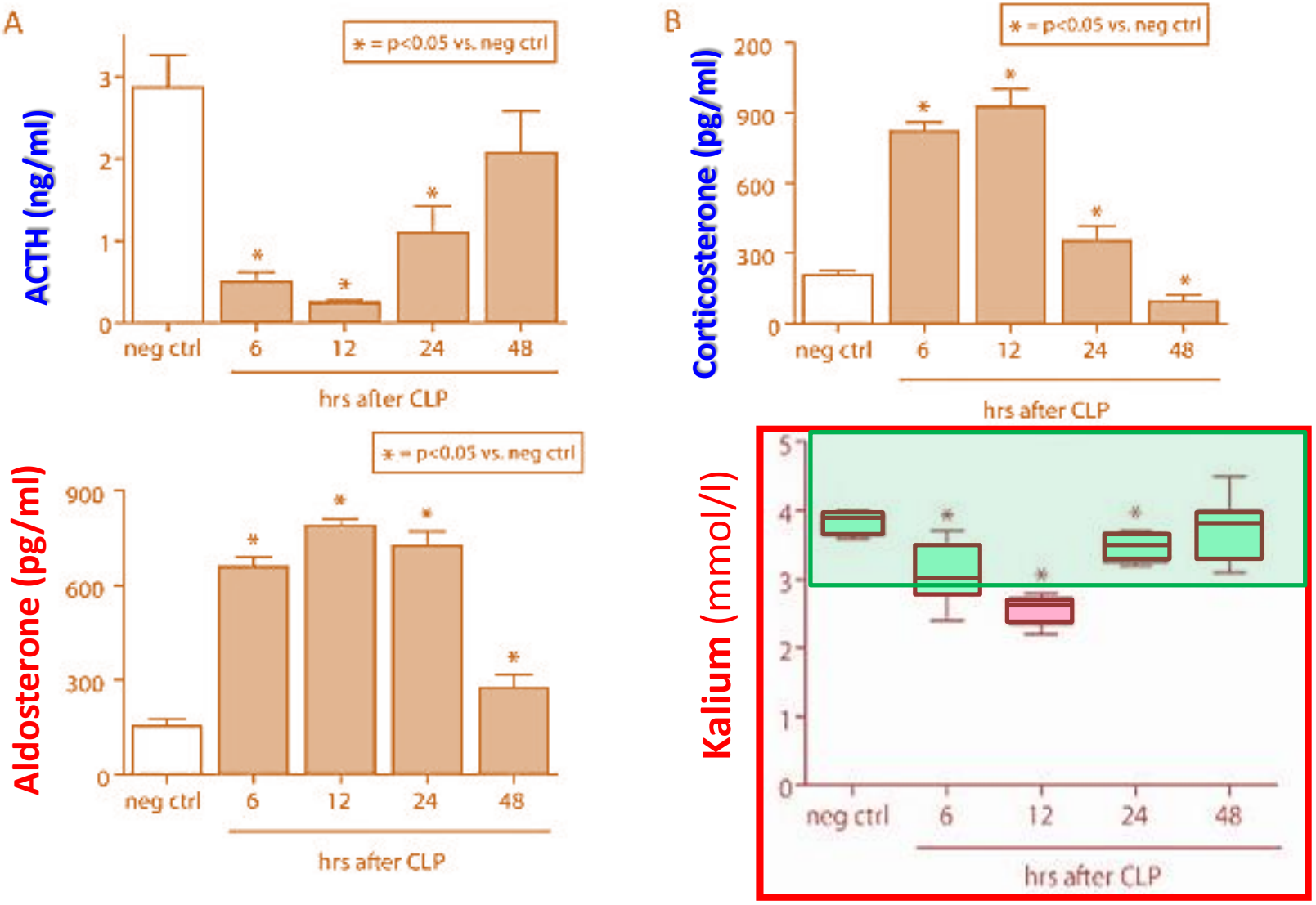
Mortality (%) in function of[K+]



K-classes and morbidity in DA cows



K during septicemia (Flierl et al. 2011)



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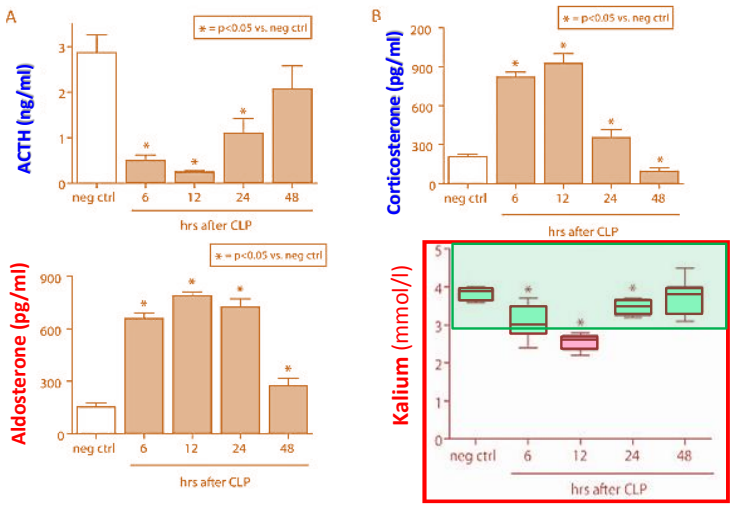


Septikemia

↙ Nebennierenrinde ↘

↑ ACTH → ↑ Corticosteron

↑ Aldosteron → ↓ **Kalium**

K⁺-Aufnahme :

↓Futteraufnahme

Äußeres Gleich-gewicht

E Z R
K⁺ 2%

K

Inneres Gleich-gewicht

K

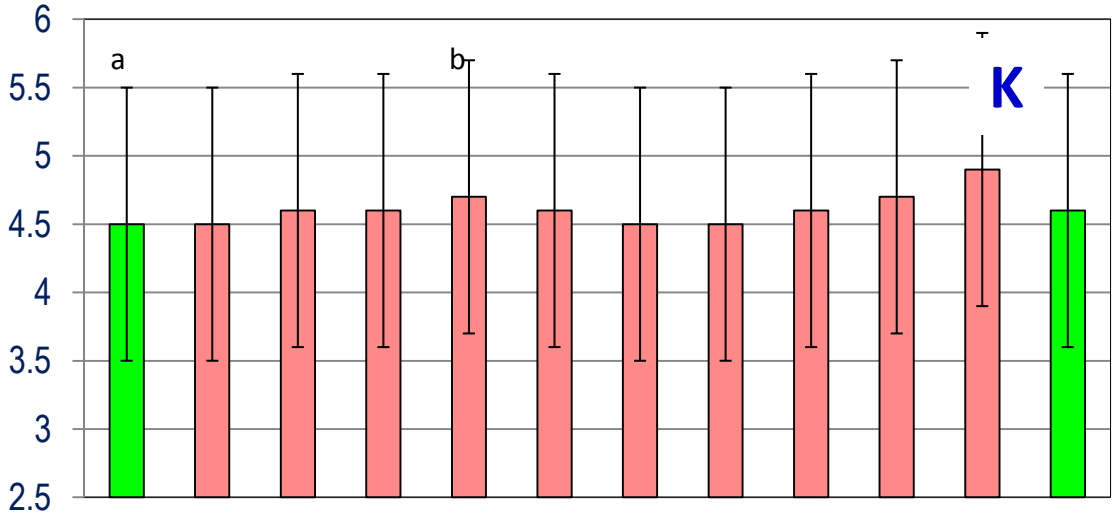
I Z R
K⁺ 98%

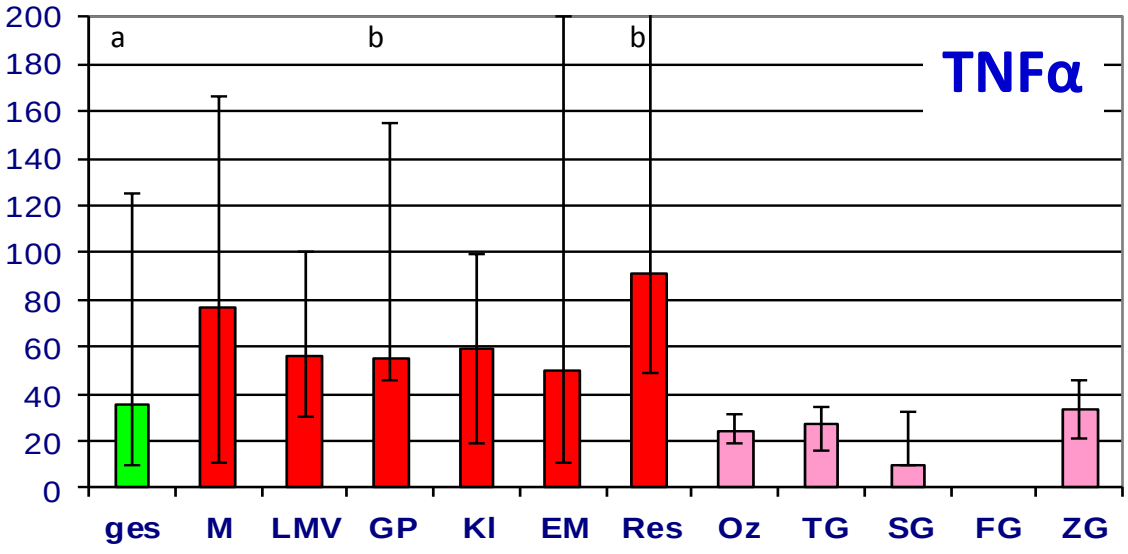
↑renale Elimi-nationsrate

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

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 Hypokalemia**
7. Conclusions for clinical practice

„Hipokalēmijas“ terapija

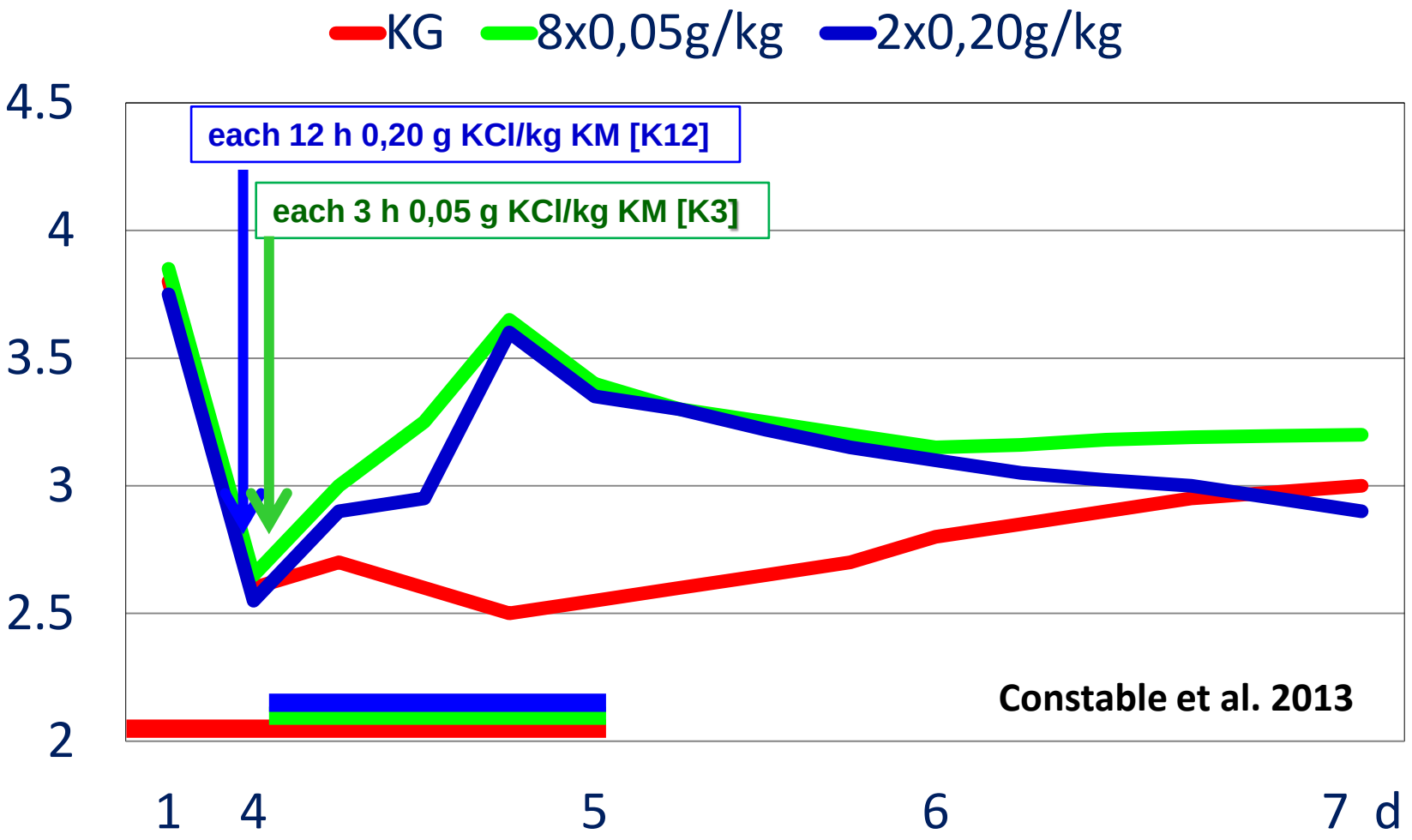
1. **Pretiekaisuma (sepses) terapija** (BALK u. CASEY 2000):

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

↑

„inflammatory metabolism“

KCl-Substitution by Hypokalemia



→per os **0,4 g KCl** /kg KM/d

Therapy of „Hypokalemia"

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

2. **Hypokalemia-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“ – otrā ārstēšanas reizē:

- pamatterapija

+ 500 ml - 90 g Na_2HPO_4/NaH_2PO_4

+ 0,4 g KCl /kg(ķ.s.)/dienā oral

+ GCS

+ AO

7. K – rekomendācijas praksei

- Govis vispār ir bagātīgi nodrošinātas ar K
- ↑ K izraisa slimības GP un neauglību
- K saistīts ar ABS
- K + asinīs un urīnā neparāda govs nodrošinājumu
- K urīnā/asinīs samazinās badojoties
- **↓ K iekaisumu gadījumos**
- **↓ K <2 mmol / l are hopeless at NNR activation**
- **↓ K un ↓ Pi parasti saistīti**
- **K terapija: K substitūcija = pretiekaisuma līdzekļi**

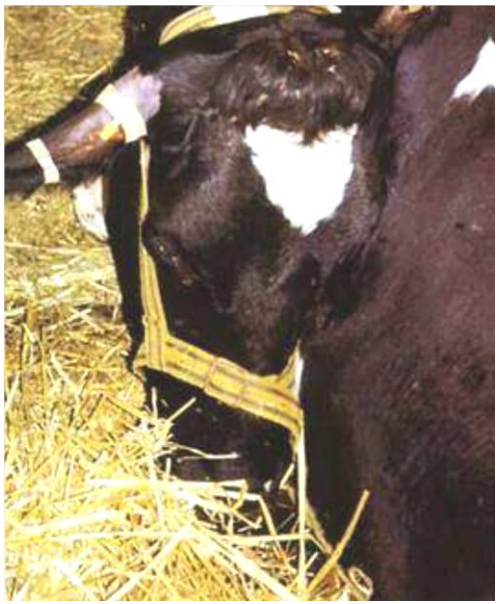
4. Therapie in Downer cow complications

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

  Se, Cu, Mn . . .

Se un citu mikroelementu loma piena trieka patoģenēzē (MF)

1923



2014

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

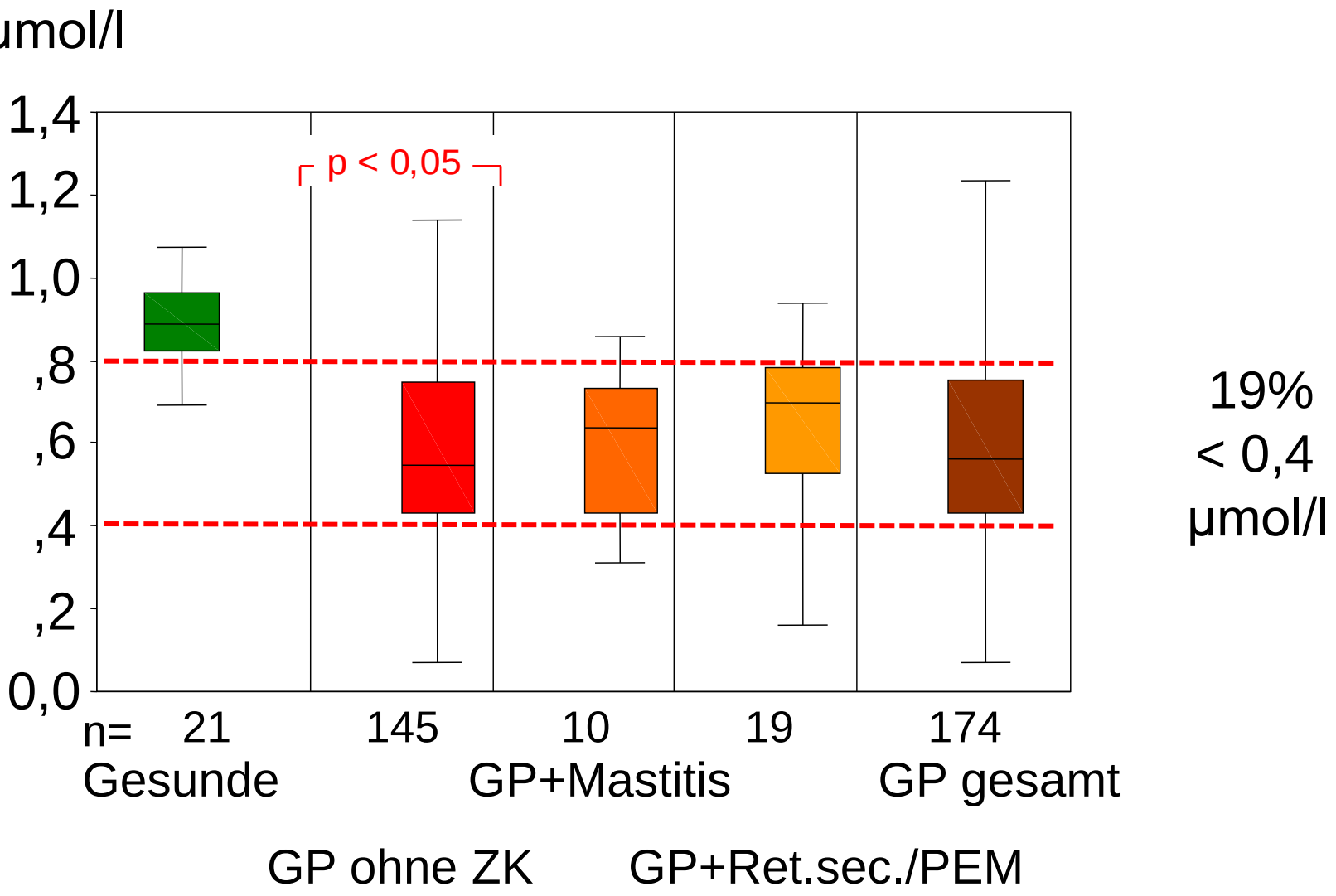
Experimental design / eksperimenta dizains

- **195 “Fleckvieh” cows** (FV)**:**
  - 21 untreated FV-cows (KG)
  - **174 MF cows** (GP)

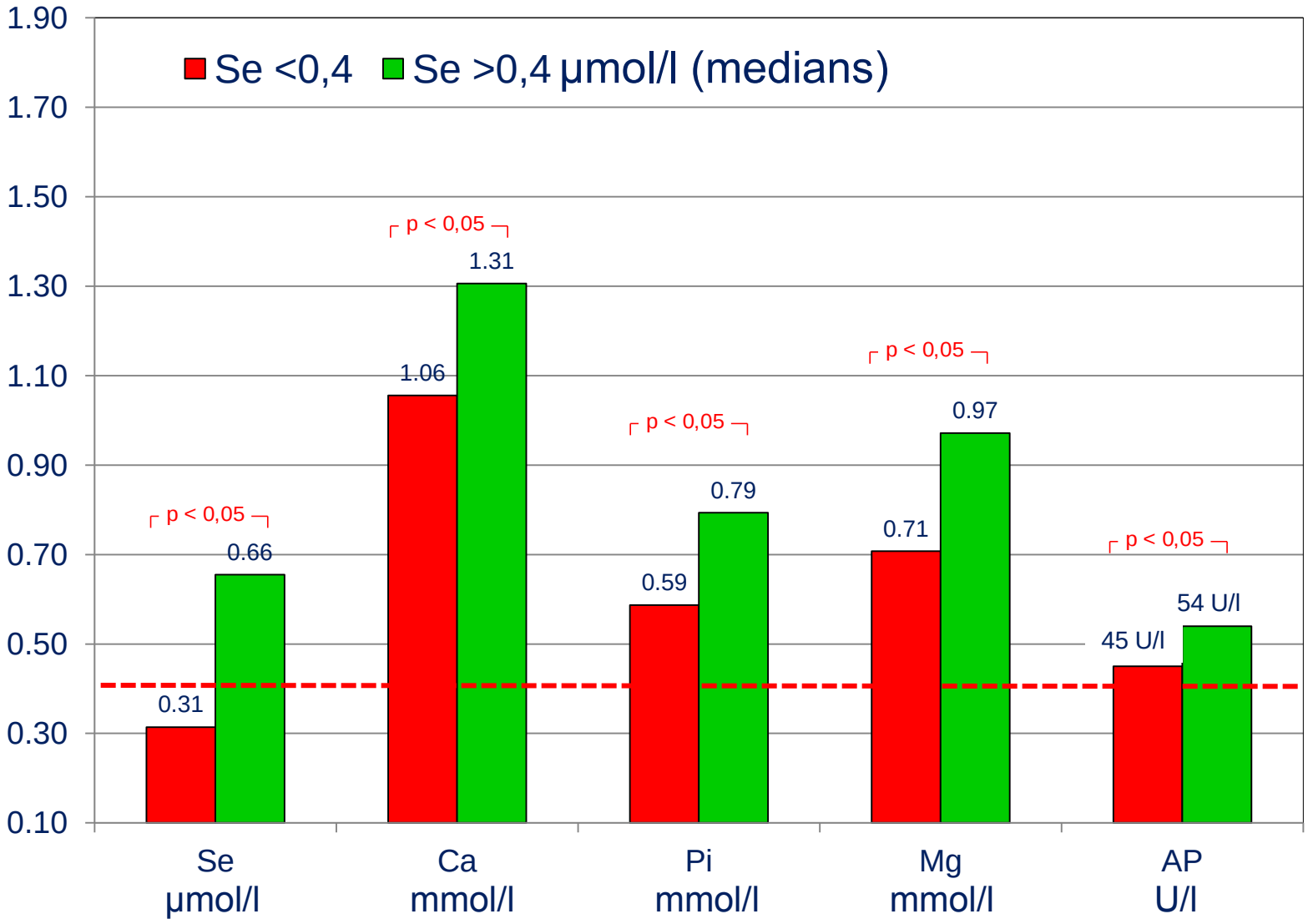
- **<u>Controls</u>:**

1. Klīniska un laboratoriska izmeklēšana pirms ārstēšanas
2. pēc ārstēšanas
3. pie atkārtotas ārstēšanas

Laboratory results: Selenium



Laboratory results: Se < > 0,4 µmol/l



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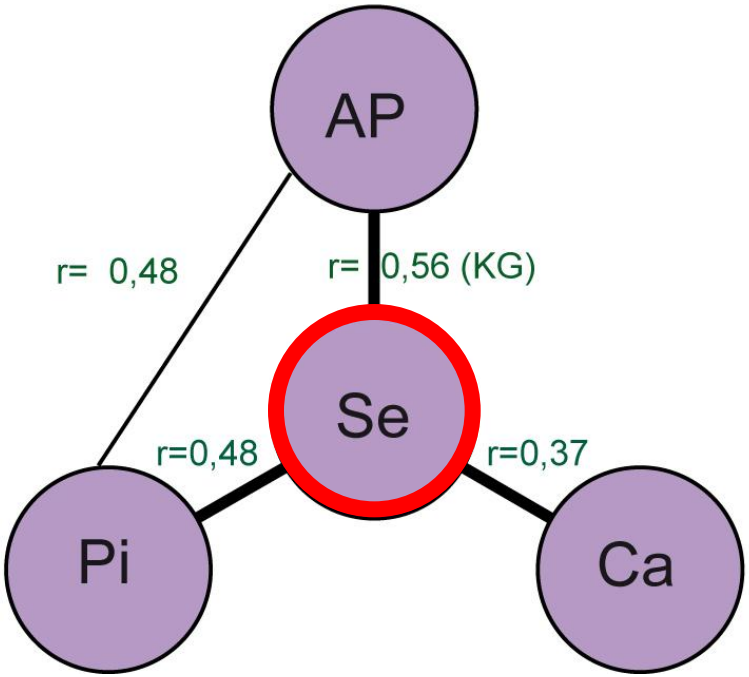
Laboratory results: Selenium



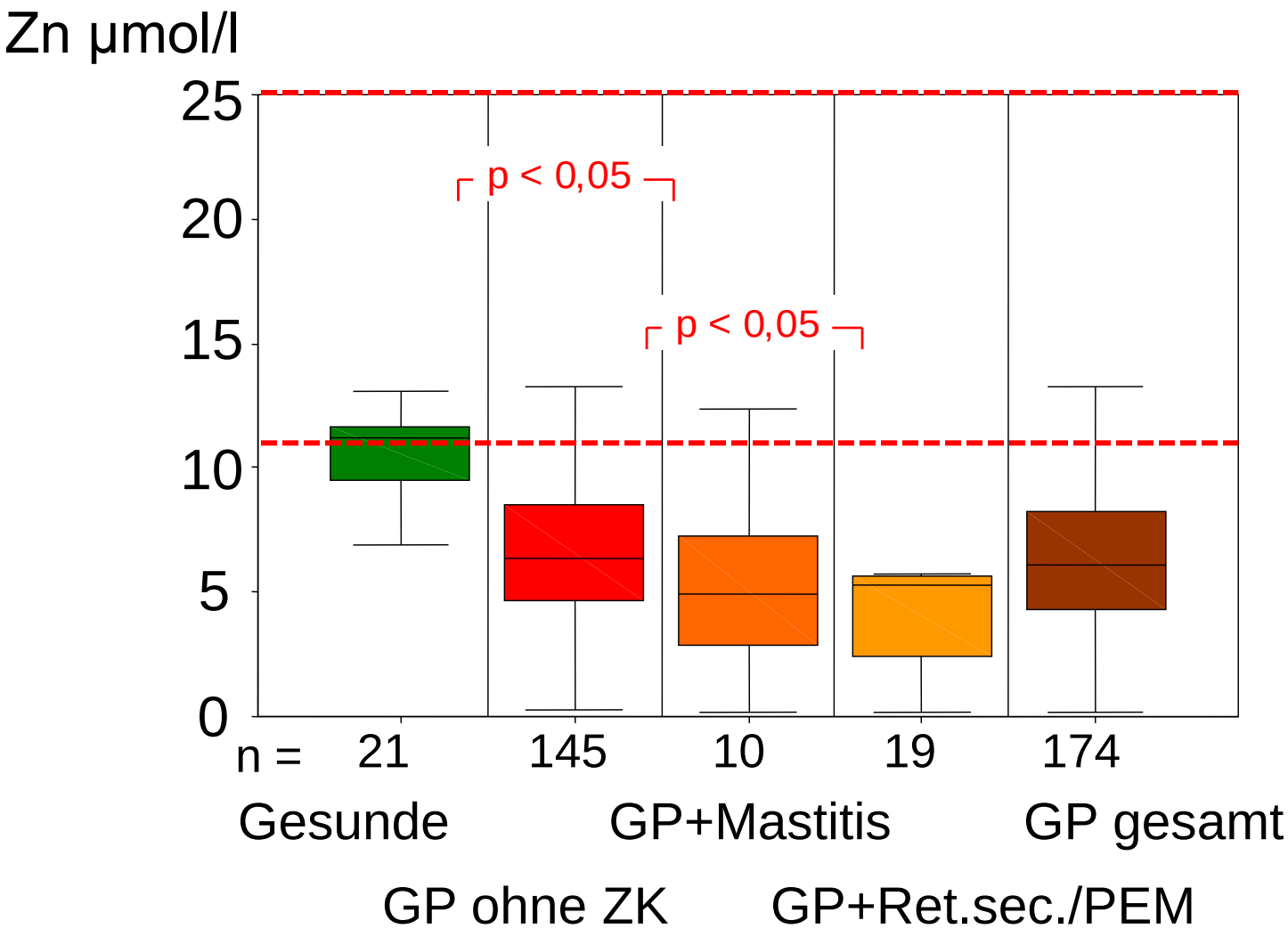
- Pēc sārmainās forfatāzes (AP) var zināmā mērā spriest par Ca mobilizāciju

- AP piena triekas grupā zemāka kā kontroles grupā

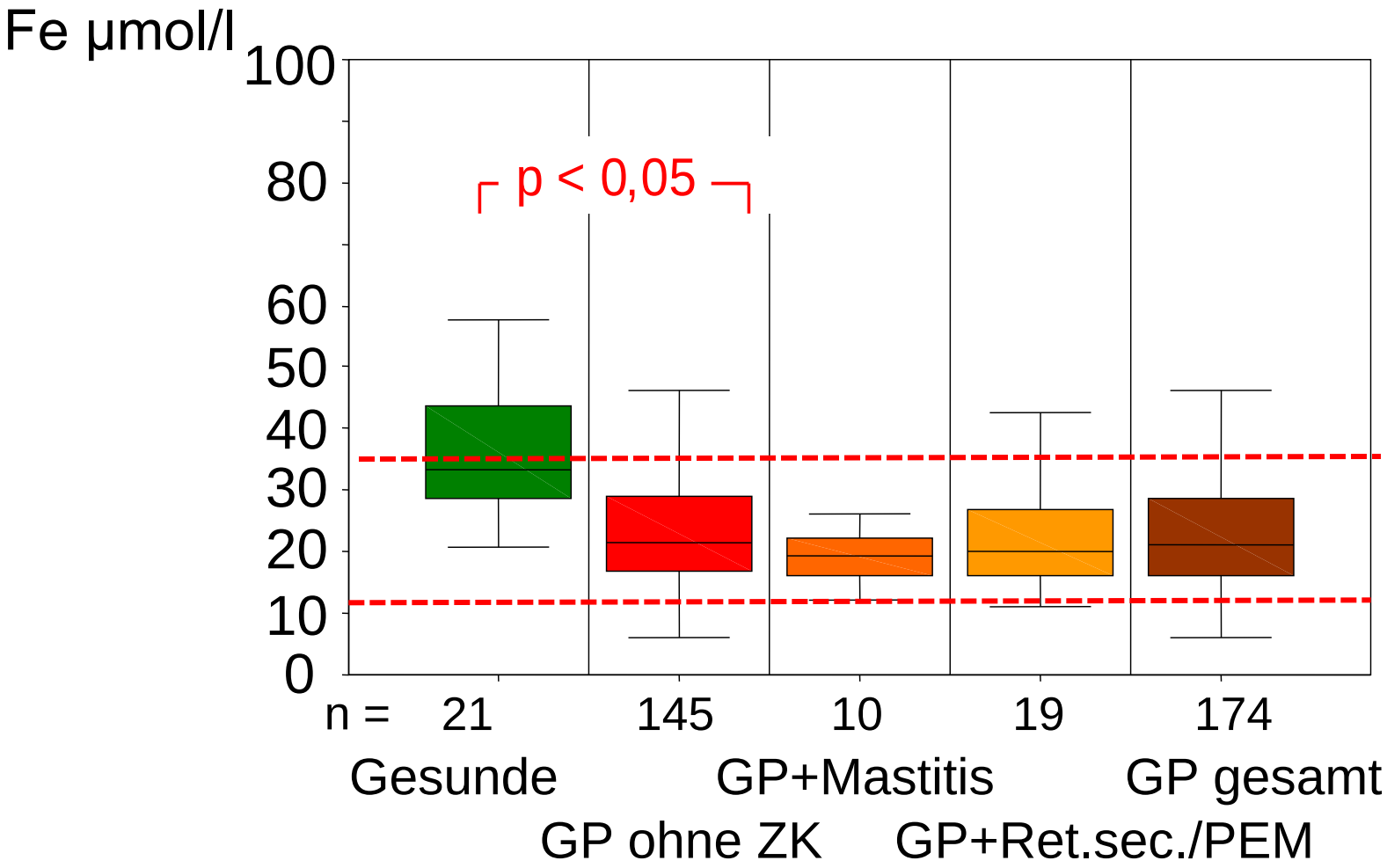
- Se pozitīva korelācija ar AP, Ca un Pi

Se iespējams ir saistīts ar piena triekas patoģenēzi

Laboratory results: Zink

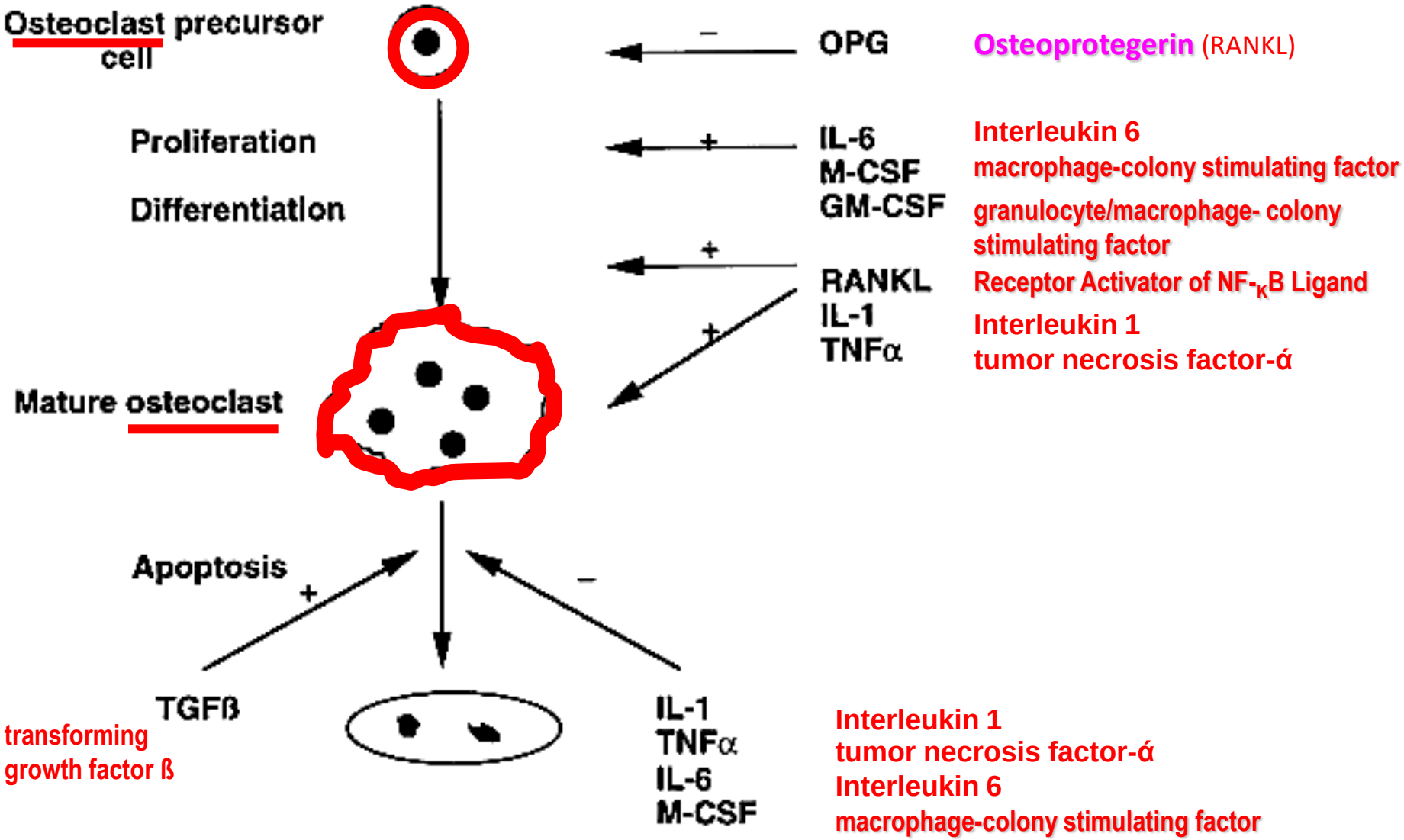


Laboratory results: Ferrum



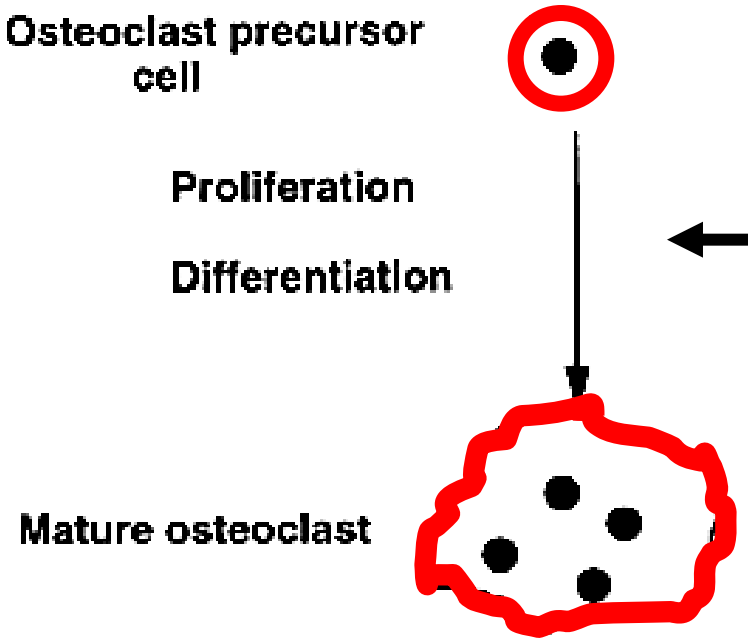
Citokīnu ietekme uz osteoklastu veidošanos un darbību

(Compston 2001)



Effects of cytokines on osteoclast production and activity

(Compston 2001)



cytokines

antioxidants: **Se, Cu, Zn, Mn**

antiphlogistica: **NSAID**

SAID

Secinājumi

➡ **Piena triekas gadījumā**:

- ↓**Ca, Pi, Se, Zn, Cu, TEAC**

➡ - Mn un Fe – normas robežās

➡ - **Cu**: augsta korelācija ar procesiem kaulaudos

20% gadījumos pazemināts

➡ - ↑ **TNFα**, ↑ Haptoglobin

∑: Ieteikumi “guļošu govju” ārstēšanai

- 9 – 11 g Ca^{++}
- PO4
- Mg^{++}
- KCl 0,4 g/kg dzīvm./24h
- Dexamethason
- NSAA (nesteroīdi pretiekaisuma līdz.)
- Antioksidanti
- Mikroelementi Se, Cu, Mn . . .

! ! ! !

1923

2006