Serum eiwitelektroforese APP

Techniek en interpretatie

Pierre Simard, DVM

Overzicht

1. Serumeiwitelektroforese
   1.1. Techniek
   1.2. Pre-analytische fouten
   1.3. Normale elektroforese
   1.4. Hyperproteïnemie
   1.5. Hypoproteïnemie
   1.6. Hypoalbuminemie
   1.7. Hyperglobulinemie
      1.7.1. polyclonaal
      1.7.2. monoclonaal
2. Acute Phase Proteïns
3. Proteomics: een inleiding

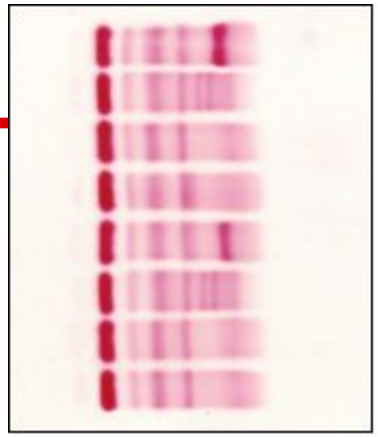
1. Electroforese: Meetprincipe

- Serumeiwitten zijn neg geladen bij een alkalische pH 8.6 - 9.0
- pH wordt constant gehouden dmv bufferoplossing en vormt de mobiele fase
- onder invloed van een elektrisch veld migreren ze naar de anode
- de migratiesnelheid is afhankelijk van hun algehele lading, vorm en grootte

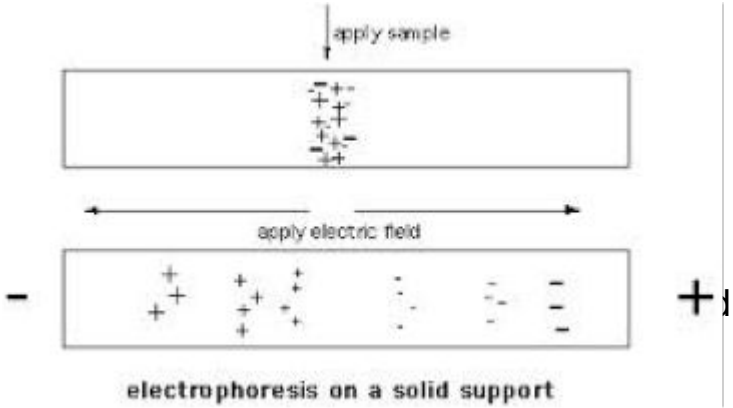
Technieken

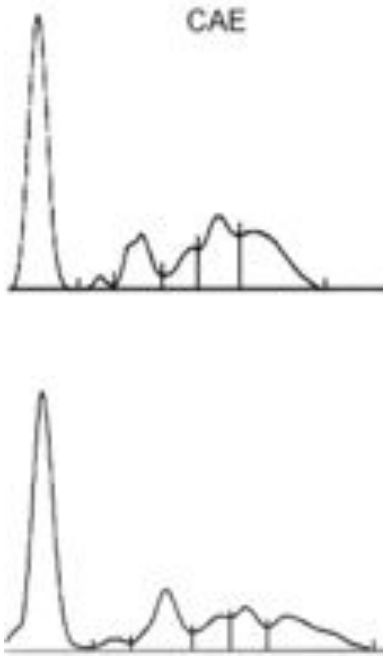
1. Cellulose Acetate Electrophoresis (CAE)
2. Agarose Electrophoresis (AGE)
3. Capillary Zone Electrophoresis (CZE)

Meettechnieken - CAE



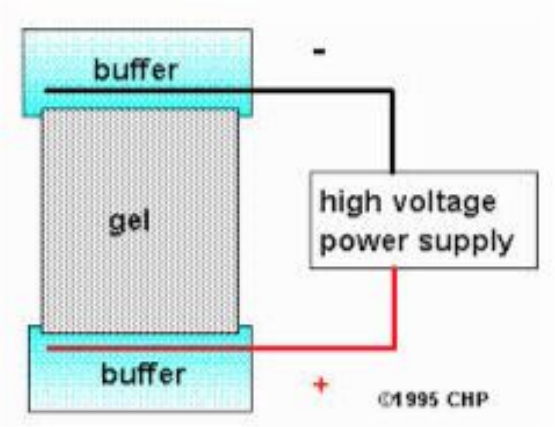
- Gel-gebaseerd
- Scheiding: lading en grootte
- Meting: kleuring en densitometrie
- Voorbereiding gel moeilijk reproduceerbaar
- Verouderd en zo goed als verlaten

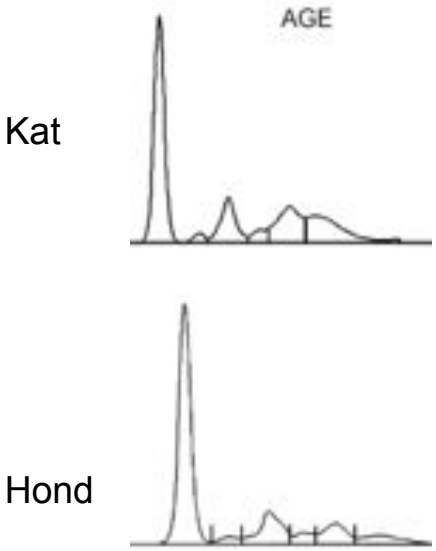




Meettechnieken - AGE

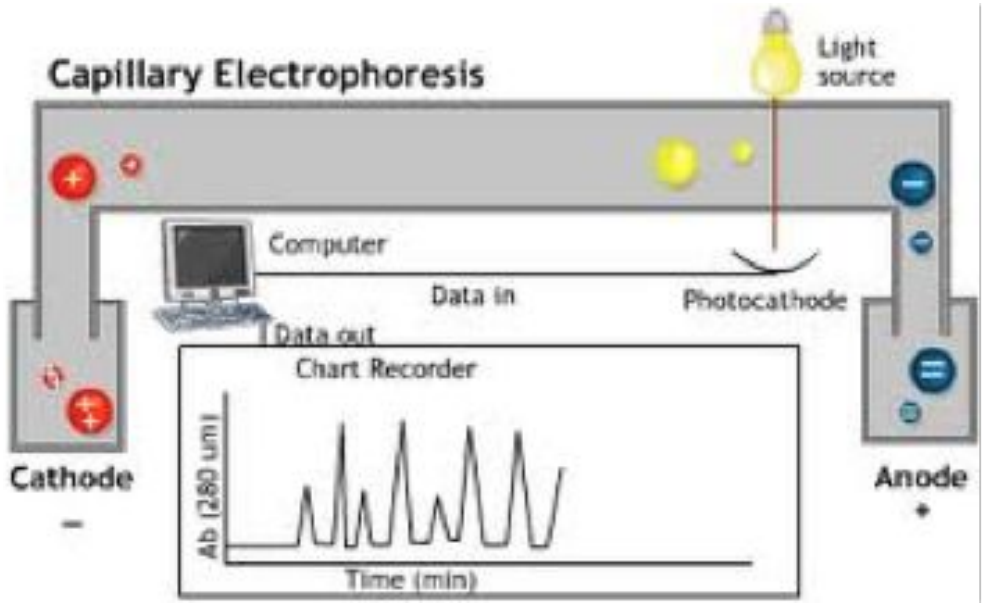
- Gel-gebaseerd
- Scheiding: lading-massa ratio
  - grotere poriën dan CAE
- Meting: kleuring en densitometrie
- Arbeidsintensief

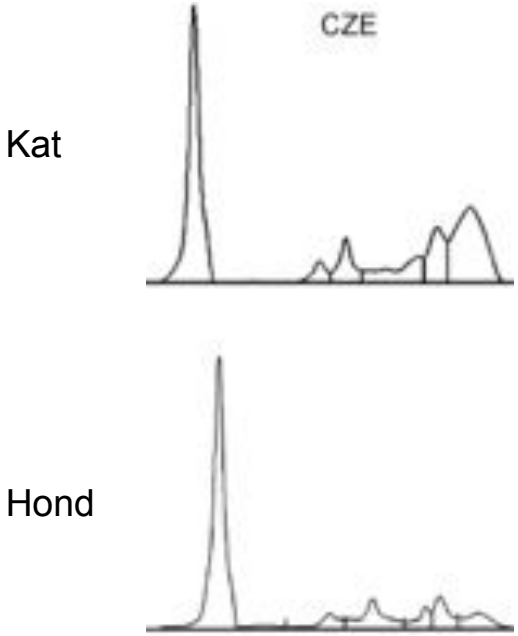




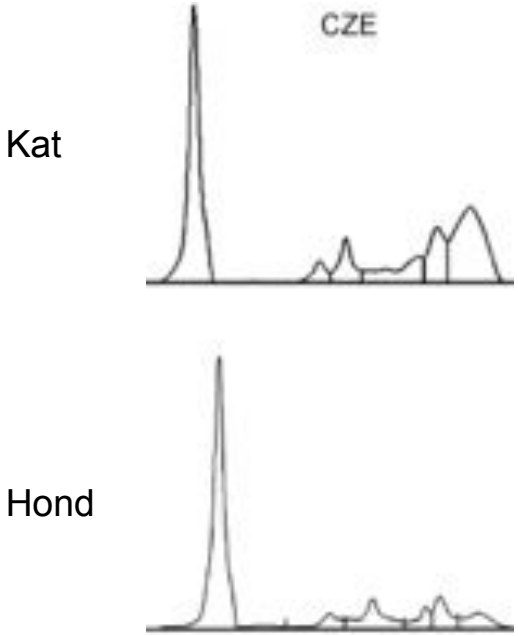
Meettechnieken - CZE

- Migratie doorheen capillair
- Zeer hoog voltage (9000V)
- Scheiding: lading-massa ratio
- Meting: UV spectrofotometrie





Meettechnieken - CZE

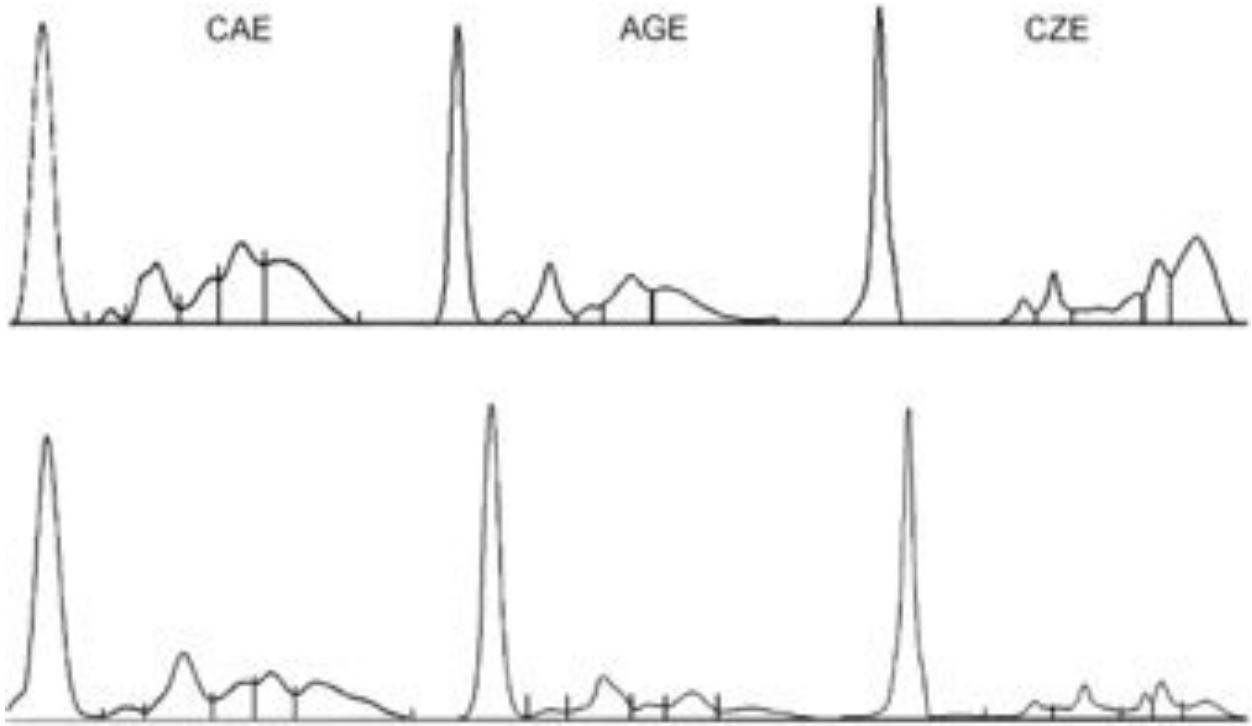


- Automatiseerbaar
- Geen kleuring
- Snelle doorlooptijd
- Hogere resolutie (ie meer pieken)

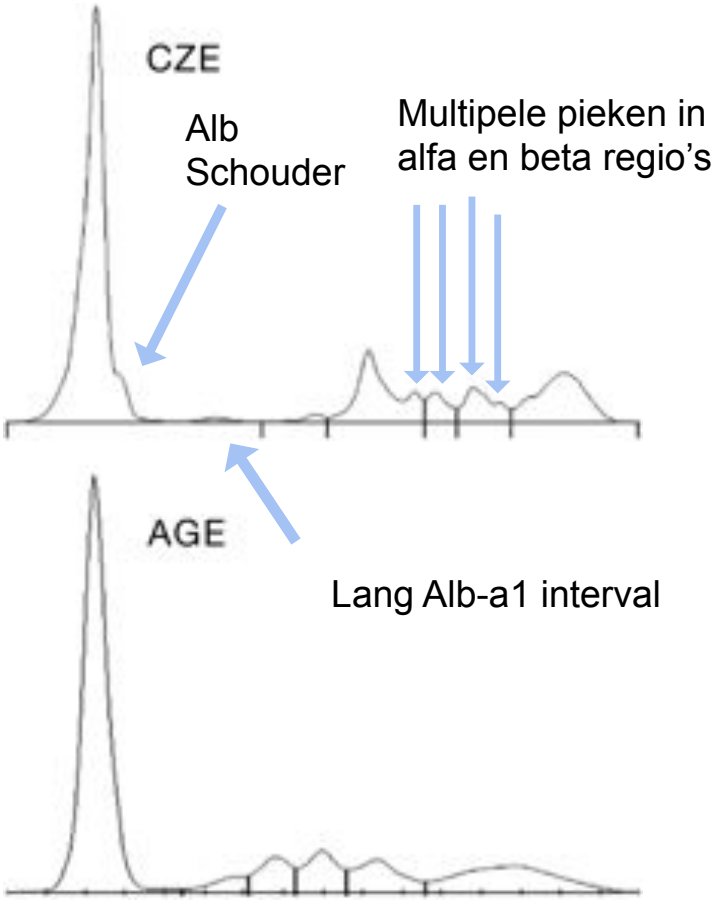
Meettechnieken - overzicht

Kat

Hond



CZE vs AGE



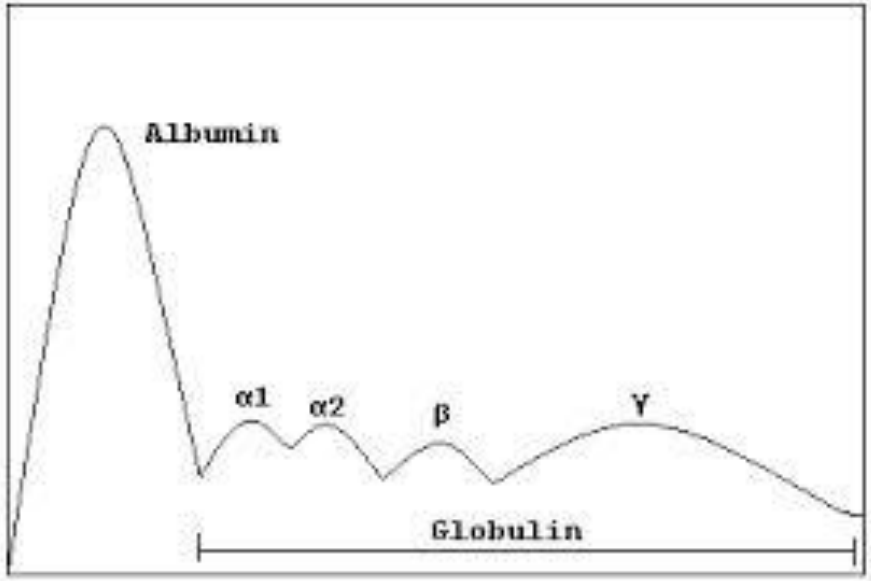
vb. Kat

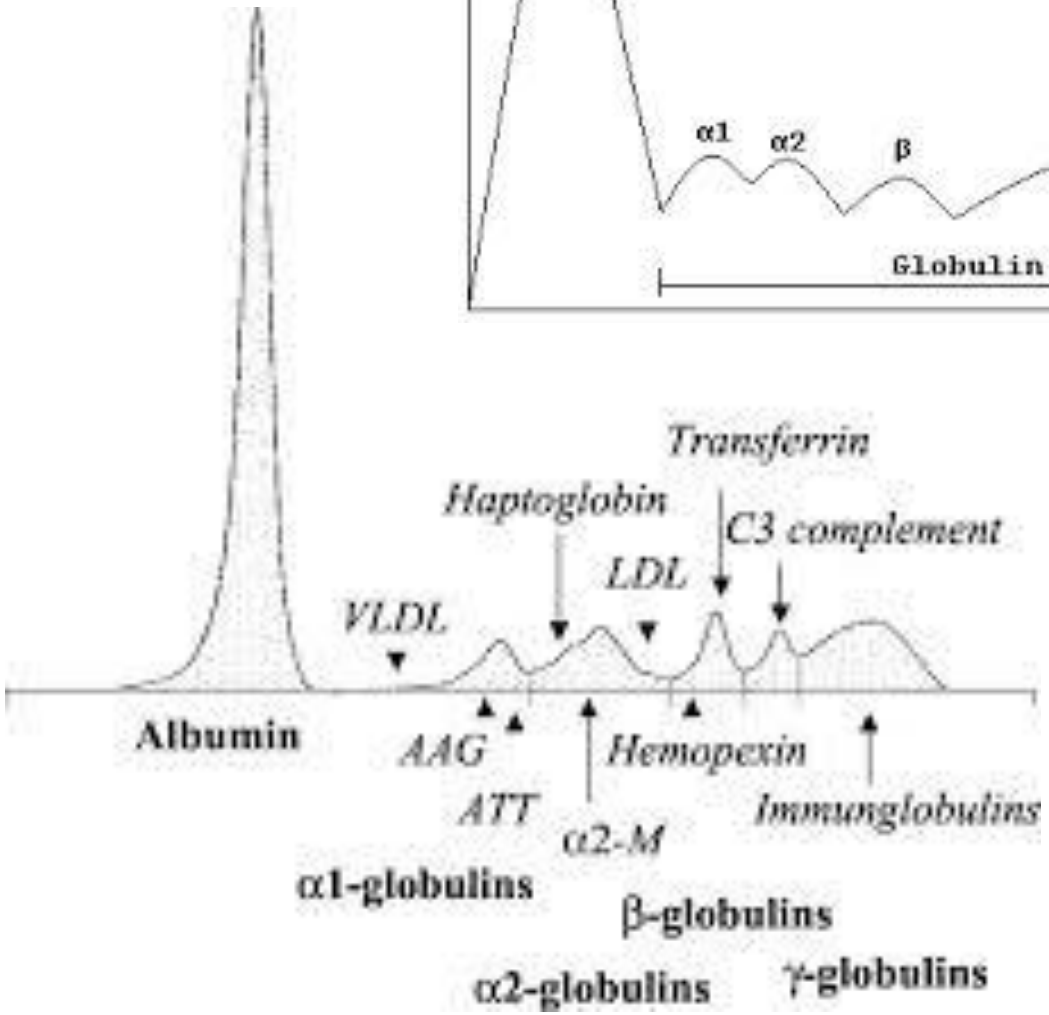
Humaan

Alb

Glob

- a1
- a2
- beta
- gamma





Humaan fracties richtlijnen

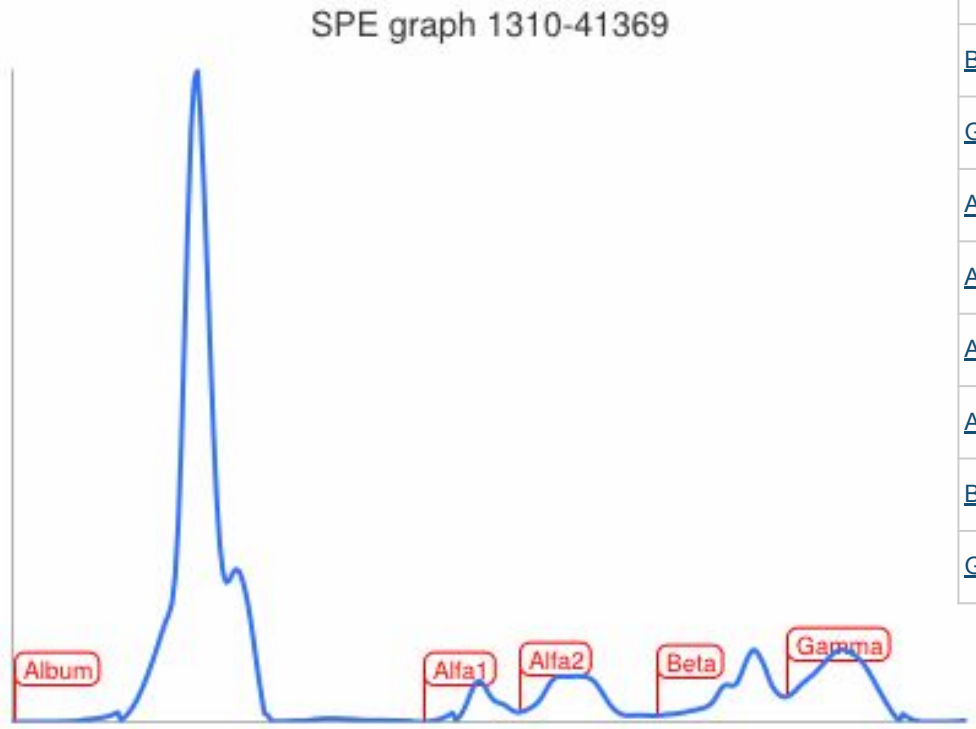
CAE - AGE

- Albumine = eerste piek
- a2 - beta = midden
- gamma = laatste piek

Gaat niet altijd op voor dieren

Hond

Normaal



Albumine %	45,1	63,5
Alfa-1 globulines %	2,6	7.0
Alfa-2 globulines %	8,0	18,7
Beta globulines %	11,4	21,8
Gamma globulines %	5,6	16
Albumine/globuline ratio	0,4	1,2
Albumine g/dL	2.7	4.2
Alfa-1 globulines g/dL	0,1	0,4
Alfa-2 globulines g/dL	0.4	1.2
Beta globulines g/dL	0.6	1,4
Gamma globulines g/dL	0,4	1

Hond

- **Albumine**
  - Lever
  - Functies
    - Oncotische druk
    - Bron aminozuren
    - Transport eiwit
      - Hormonen
      - Medicatie
      - Ca, Mg
    - Negatieve APP

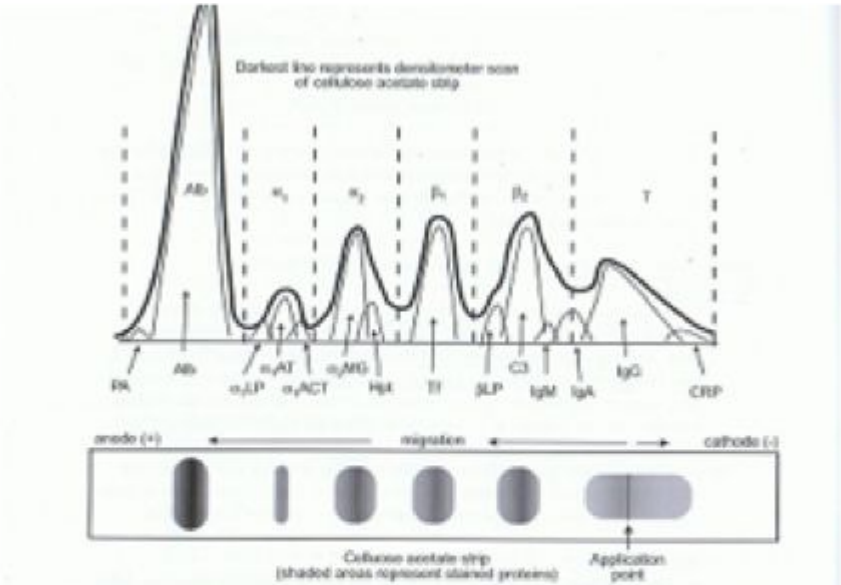
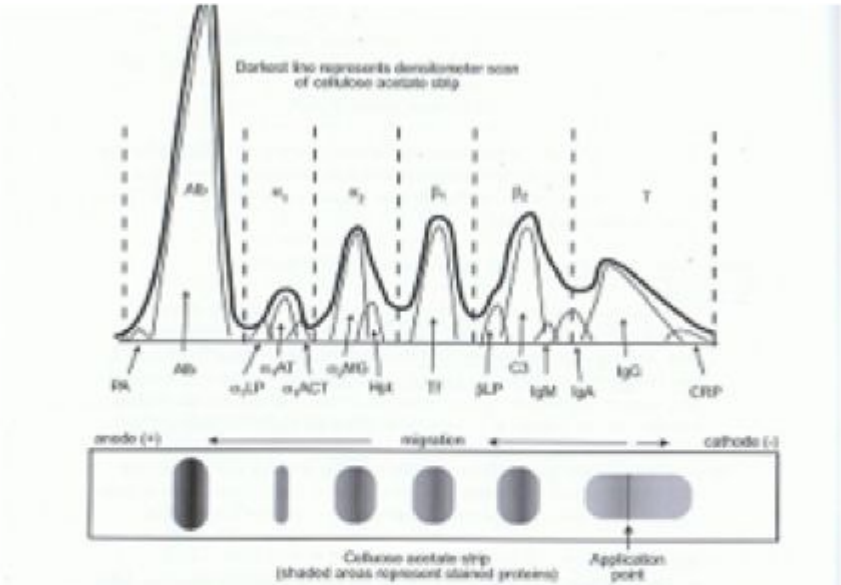


Fig. 7.1. Schematic representation of SPE results (cellulose acetate strip and densitometer tracing). Proteins are separated during electrophoresis in an alkaline medium on cellulose acetate. Albumin migrates the farthest toward the anode, and globulin fractions separate into bands or fractions (e.g., α1-globulins, α2-globulins, β1-globulins, β2-globulins, and γ-globulins). After electrophoresis, the strip is stained with a protein stain (e.g., Ponceau S). Bands that contain the most protein stain the darkest. When scanned with a densitometer, the tracer pen draws a line that corresponds with the intensity of protein staining. The darkest band causes the highest peak on the tracing, and other peaks are relatively lower depending on the relative staining intensities of the corresponding bands. One peak may represent the staining of one protein (e.g., albumin) or may represent the sum of multiple proteins (e.g., the α2-globulin region contains Hpt and α2-macroglobulin). α1ACT, α1-antichymotrypsin; α1AT, α1-antitrypsin; α1LP, α1-lipoprotein; α2MG, α2-macroglobulin; βLP, β-lipoprotein; and PA, prealbumin.

Hond

- **α-globuline**
  - Lever
  - Acute ontstekingen APP
  - æ1 antitrypsin
  - æ1 AGP
  - æ1 macroglobulin
  - Ceruloplasmin
  - Protein C
  - Haptogblobulin
  - æ1 lipoproteïnen



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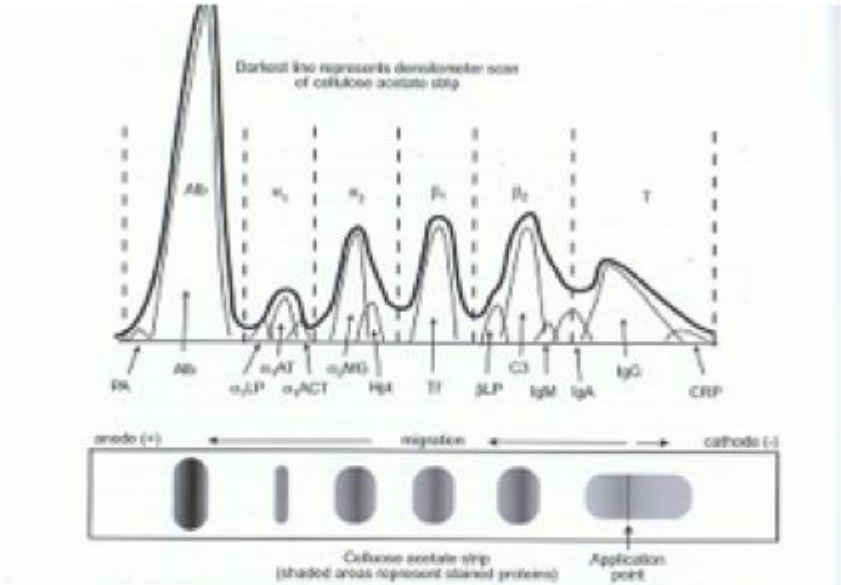
Hond

- **ß-globuline**
  - Lever
    - Fibrinogeen
    - Complement
    - CRP
    - Ferritin
    - Transferrin
    - ß-lipoproteïnen
  - IgA
  - IgM



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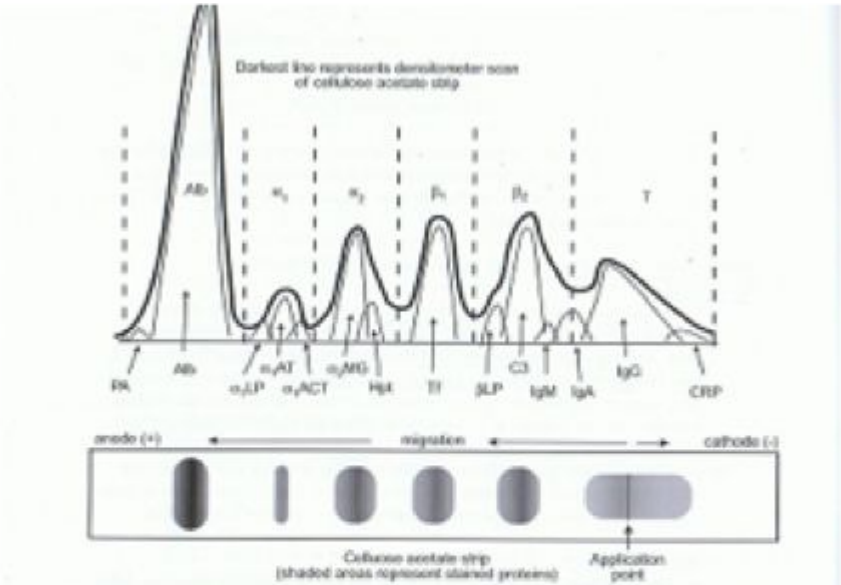
Hond

- **gamma-globuline**
  - Synthese
    - Plasmacellen
    - B-lymfocyten
  - Humorale immuniteit
    - Antistoffen
    - Chronische inflammatie
    - IgE
    - IgC
  - CRP



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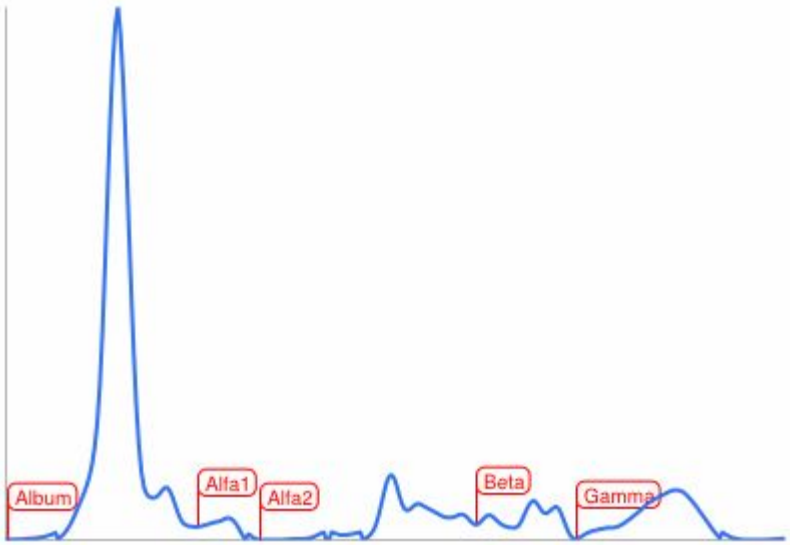
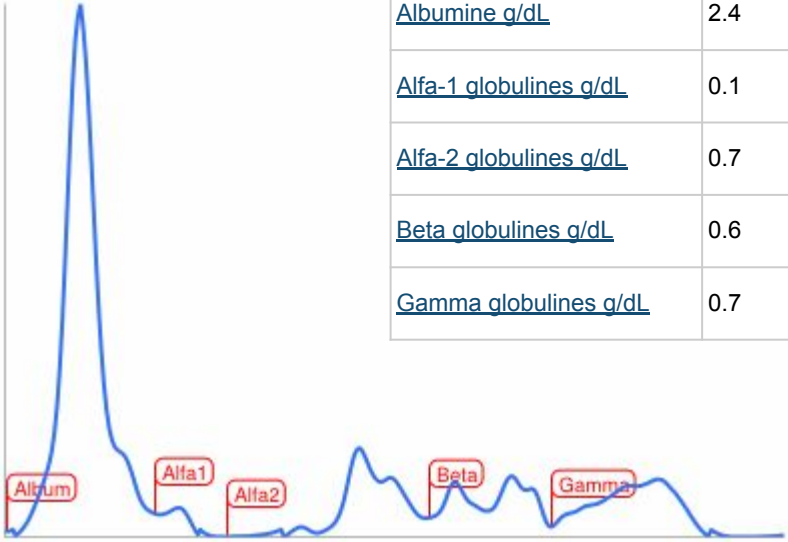
Kat

Normaal patroon

SPE graph 1310-40137



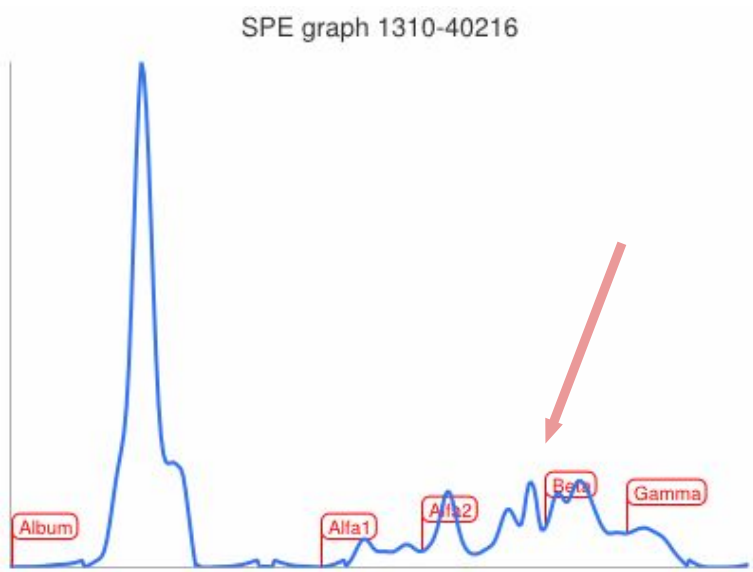
SPE graph

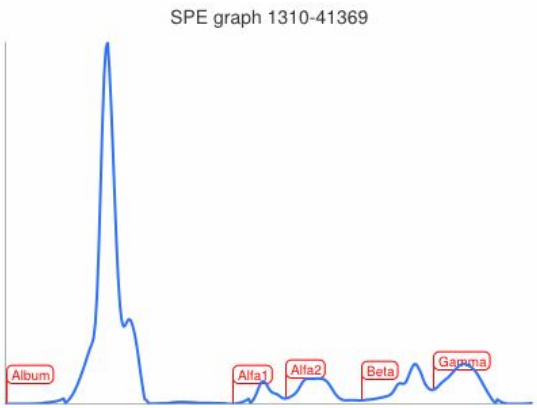


Albumine %	33.8	56.8
Alfa-1 globulines %	1.3	6.0
Alfa-2 globulines %	9.5	21.4
Beta globulines %	9.0	19.0
Gamma globulines %	11.1	34.7
Albumine/globuline ratio	0.5	1.2
Albumine g/dL	2.4	4.1
Alfa-1 globulines g/dL	0.1	0.4
Alfa-2 globulines g/dL	0.7	1.7
Beta globulines g/dL	0.6	1.3
Gamma globulines g/dL	0.7	2.8

Pre-analyse

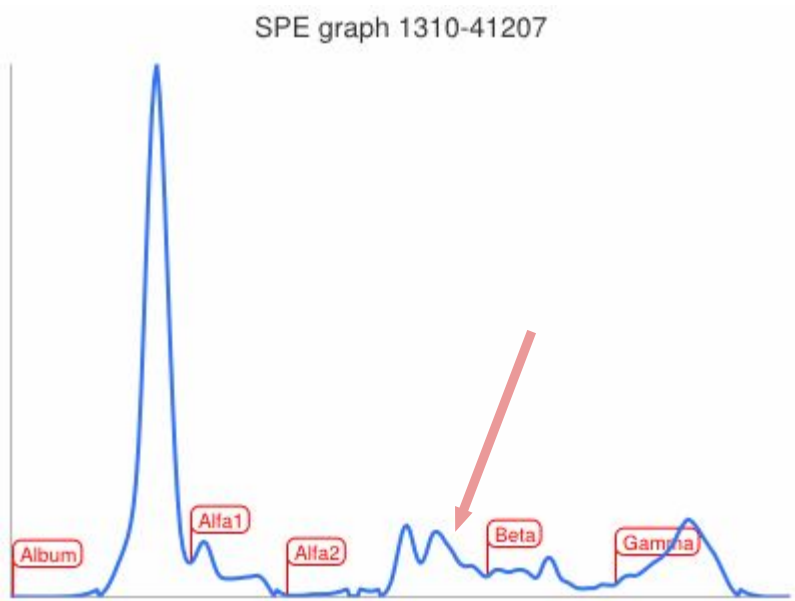
- Hemolyse
  - Geen hemolyse toegelaten
  - Hemoglobine : migreert naar zone tussen alfa2 en beta fractie
  - Hoe meer hemolyse, hoe meer afwijkingen
  - Verlaagt concentratie aan Haptoglobine

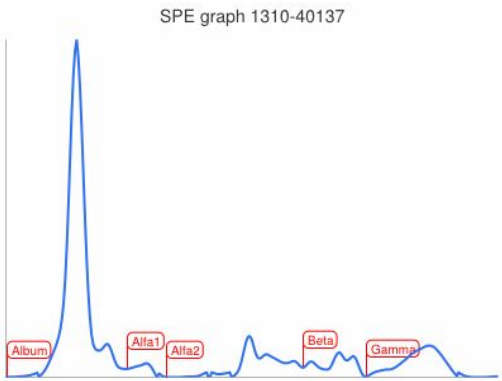




Kat

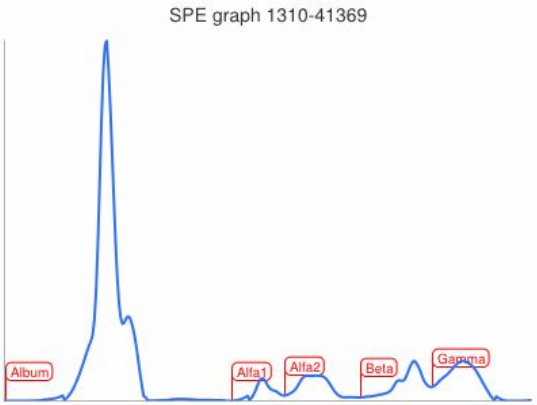
Hemolyse

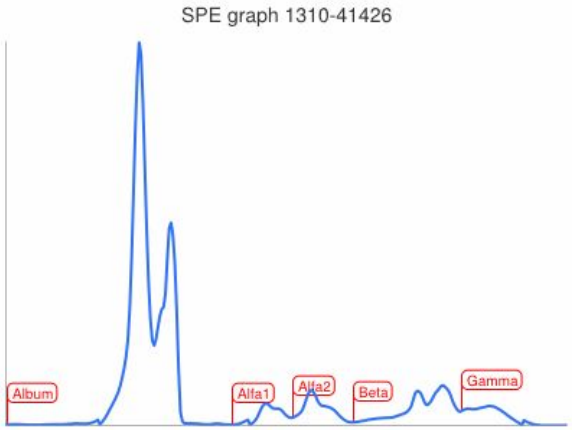


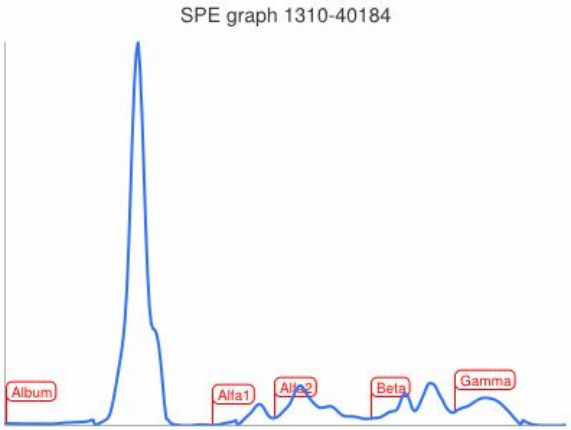


Hond

- Lipemie
  - Chylomicronen en lipoproteïnen storen migratie van andere moleculen

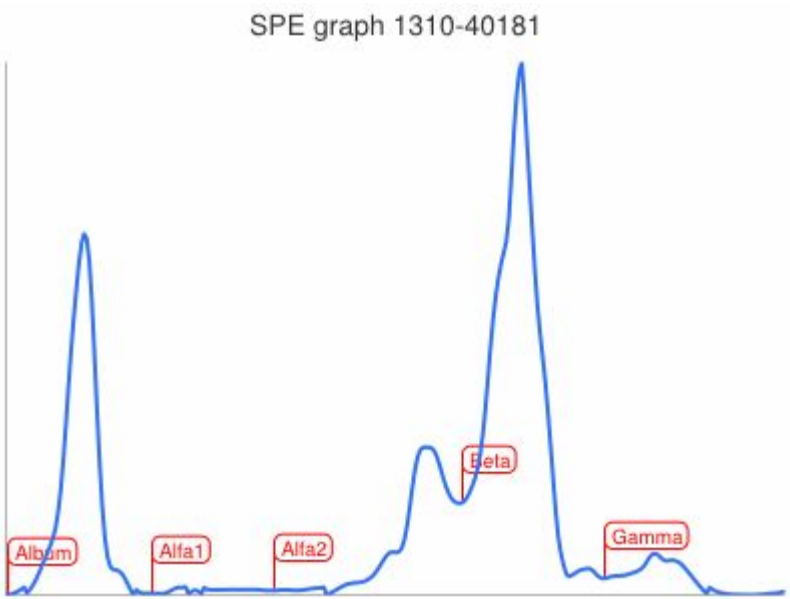


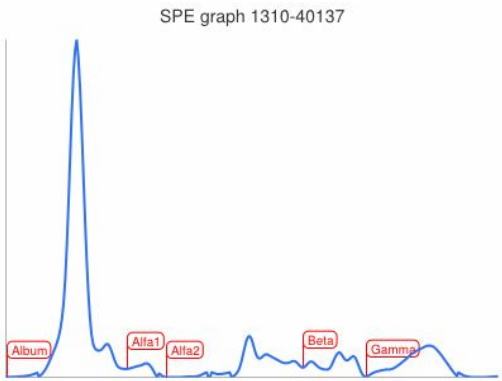




Kat

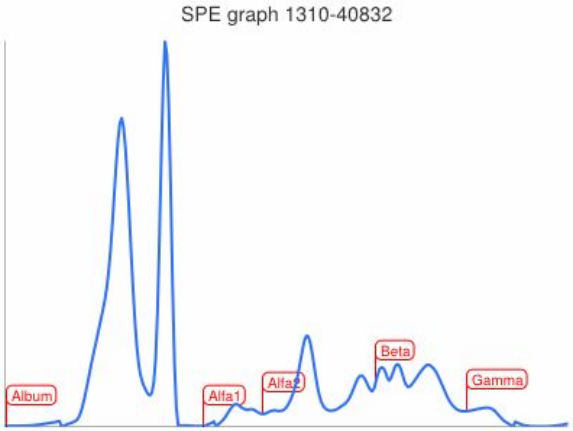
Lipemie

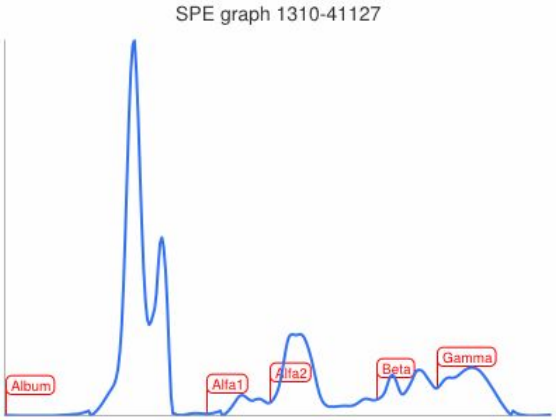

SPE graph 1310-40181
Album
Alfa1
Alfa2
Beta
Gamma

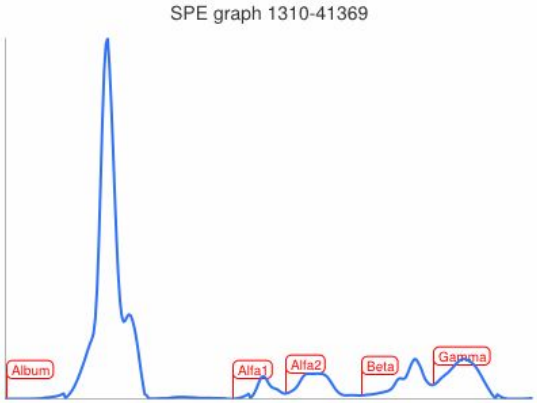

SPE graph 1310-40137
Album
Alfa1
Alfa2
Beta
Gamma

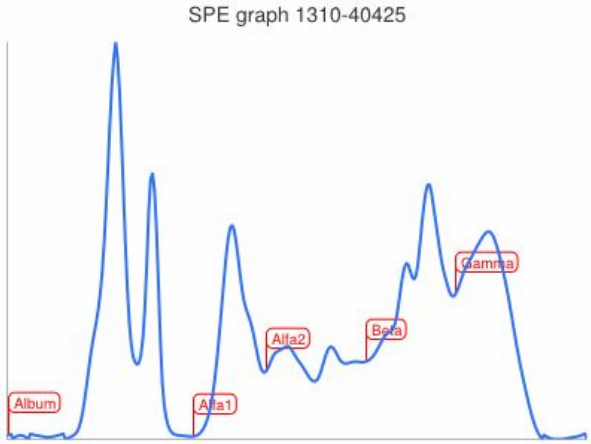
Hond

Lipemie + Hemolyse





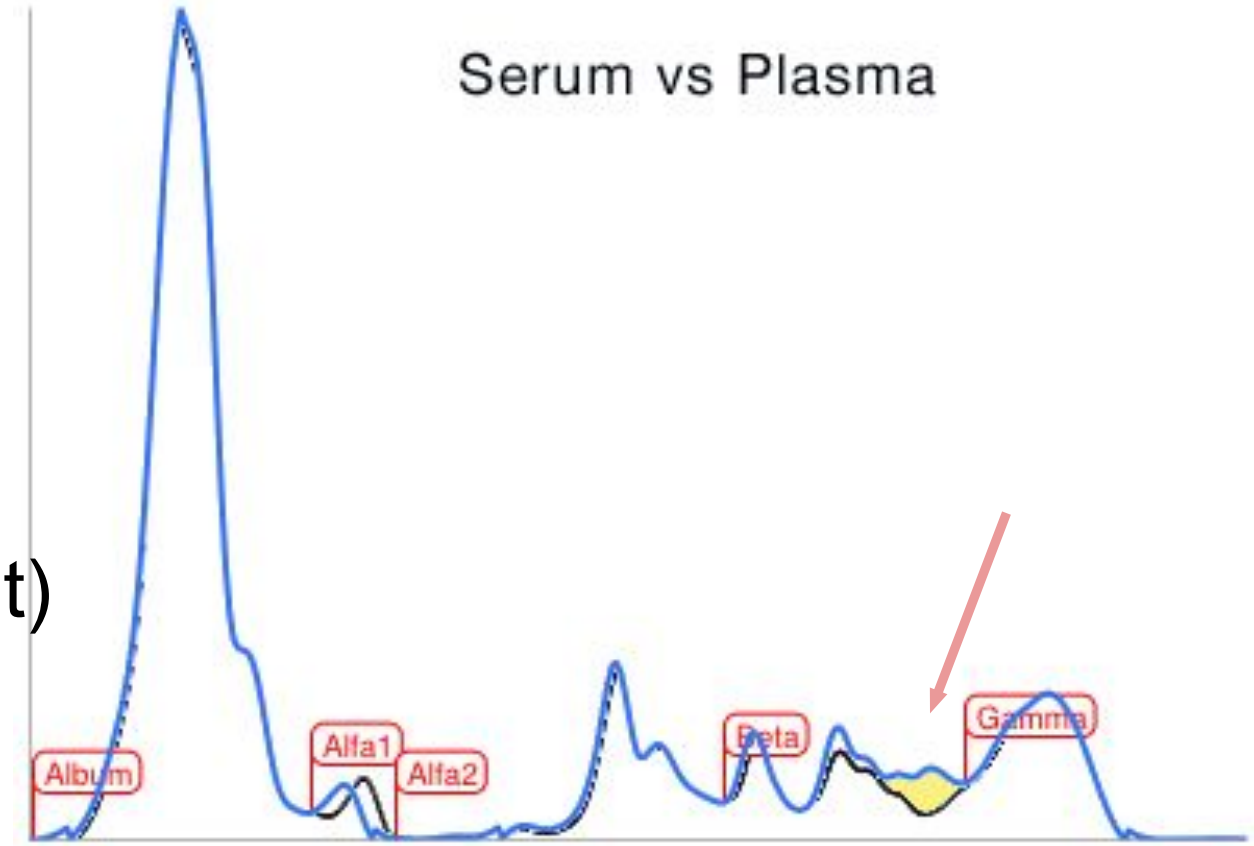




Serum vs Plasma

+ Fibrinogeen

(vb Kat)



Hyperproteïnemie

- **<u>Niet-Selectief: PANhyperproteïnemie</u>**
  - Totaal eiwit gestegen
  - Alle eiwitten (in gelijke mate) gestegen

- Altijd <u>Hemoconcentratie</u> (dehydratatie)
  - Lich. onderzoek en anamnese!!!
  - Labo
    - Erythrocytose
    - Prerenale azotemie
    - Hypersthenurie? afh. van de oorzaak!

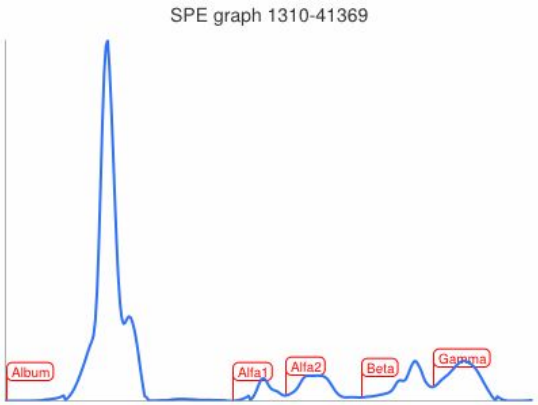
Hyperproteïnemie

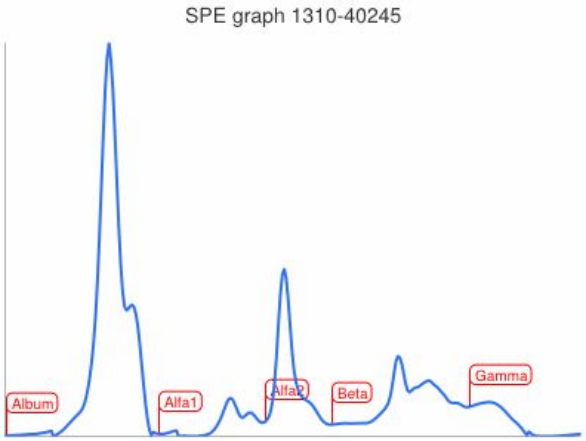
- **<u>Selectief</u>**
  - TP normaal of gestegen
  - Sommige eiwitten meer gestegen dan andere (globulinen)
  - Wat als ontsteking EN dehydratatie?

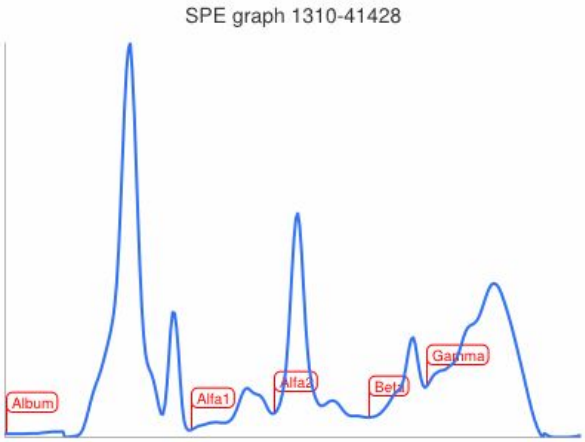
- **Hyperalbuminemie?**
  - Fout labo of lipemie
  - Prednisolone langdurig of Cushing?
  - Hepatocellulair carcinoom (1 geval)

Hond Hyperproteïnemie

- Acute fase respons
  - selectieve stijging van de <u>alfa-</u>fractie

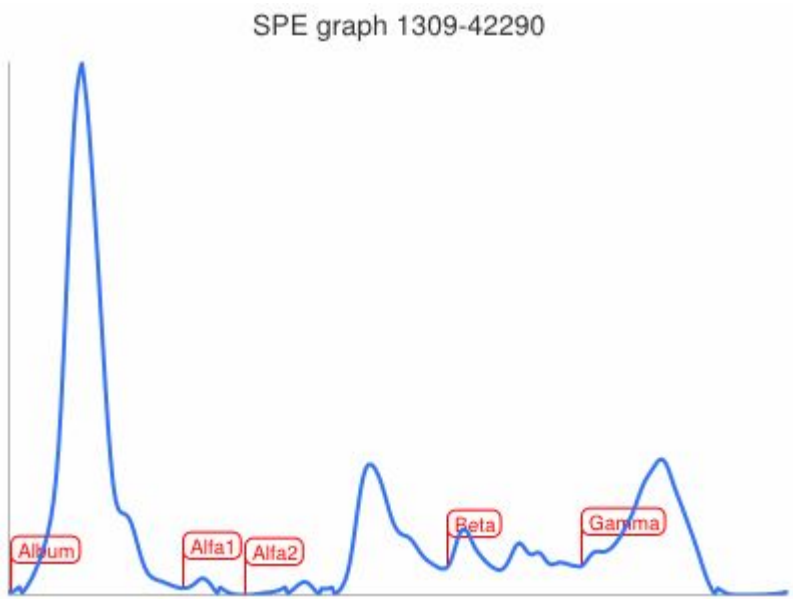


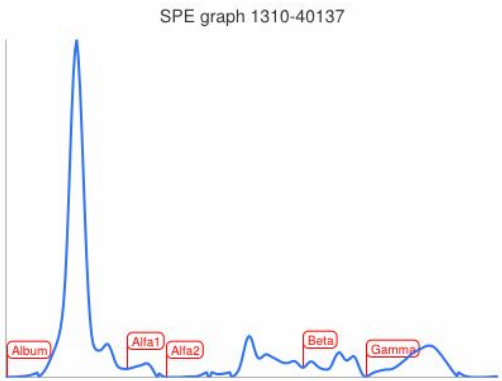




Kat

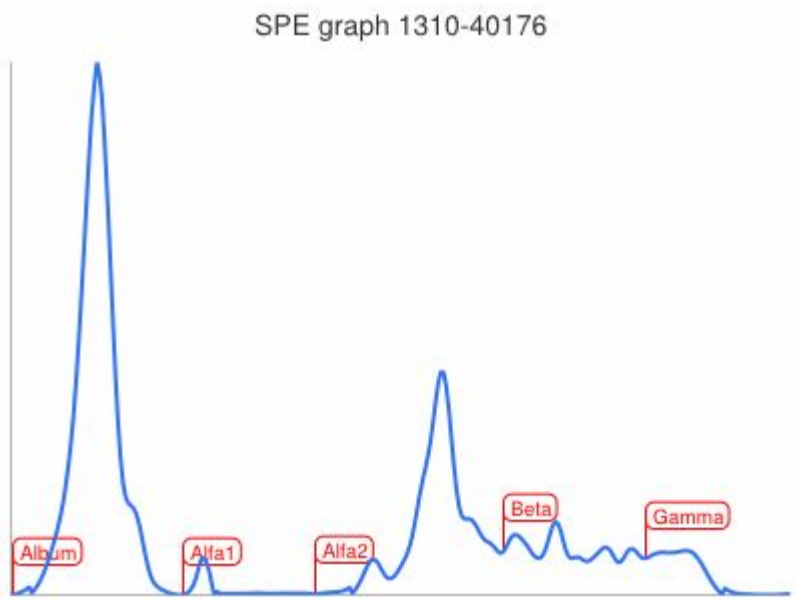
Matige acute fase respons

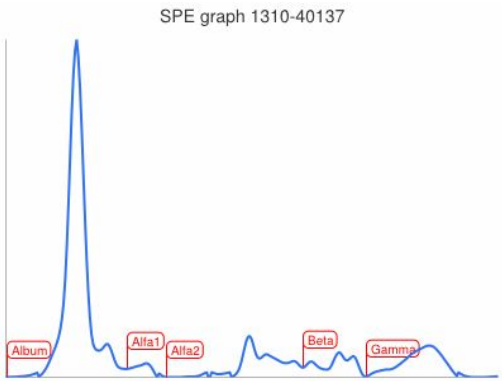




Kat

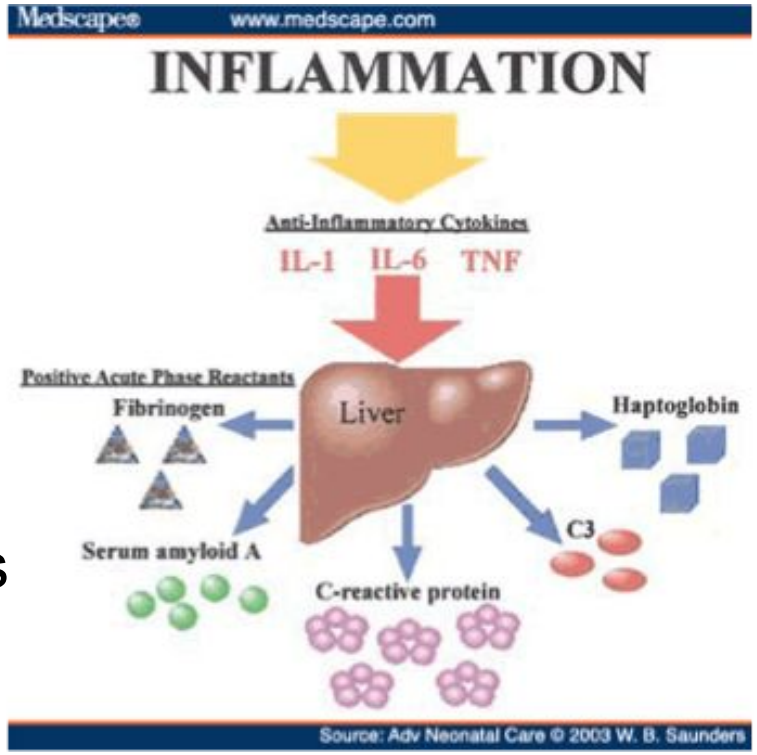
Sterk acute fase respons





Hond Hyperproteïnemie

- Acute fase respons
  - selectieve stijging van de alfa-fractie
  - meestal weinig invloed op TP!!!!
  - Gestegen synthese in hepatocyten o.i.v. Cytokines (IL-6,…)



Ontsteking

ACUTE ONTSTEKING 2-7 DAGEN

- Geen tot milde stijging TP
- HyperGlobulinemie (APP)
  - α1- en/of α2 fractie
  - Gestegen fibrinogeen
- Mogelijks een MILDE hypoalbuminemie of een laag-normaal albumine (half-waardetijd 8d.!!!)
- Δ hematologie

Table 2.16. Major leukogram patterns (see the text for species differences, especially for cattle)

Leukogram pattern	Total WBCs	Segmented neutrophil	Nonsegmented neutrophil	Lymphocyte	Monocyte	Eosinophil
Acute inflammatory	↑	↑	↑	↓	WRI–↑	↓–WRI
Chronic inflammatory	↑	↑	WRI–↑	WRI–↑	WRI–↑	WRI
Steroid leukocytosis	↑	↑	WRI–slight ↑	↓	↑	↓
Physiologic leukocytosis	↑	↑	WRI	↑	WRI–↑	WRI
Acute overwhelming inflammatory	↓	↓	WRI–↑	↓	WRI	↓–WRI
Acute inflammatory with endotoxemia	↓	↓	WRI–↑	↓	WRI	↓–WRI
Granulocytic hypoplasia	↓	↓	WRI	WRI	WRI	WRI
Ineffective neutropoiesis	↓	↓	WRI	WRI	WRI–↑	WRI
Hypoadrenocorticism	WRI	↓–WRI	WRI	WRI–↑	WRI	WRI–↑
Hemic neoplasia	↑↑↑*	?	?	?	?	?

* The neoplastic cell line is expected to be increased. Other cell lines typically are WRI or decreased.

Ontsteking

ONTSTEKING >7 DAGEN

- Milde tot uitgesproken stijging TP
  - Hyperglobulinemie
    - α1- en/of α2 fractie
    - Gestegen fibrinogeen
  - Polyclonale gammopathie
- MILDE tot matige hypoalbuminemie
- Δ hematologie : Anemia of Inflammatory disease

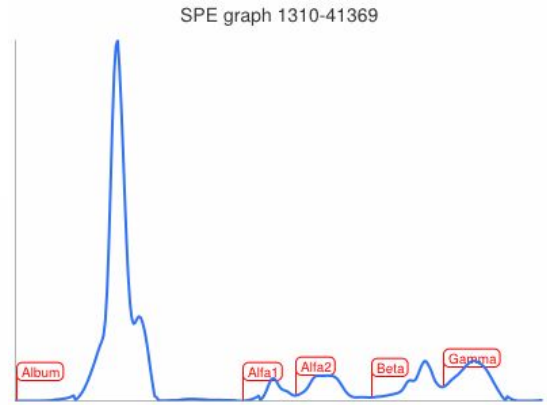
Table 2.16. Major leukogram patterns (see the text for species differences, especially for cattle)

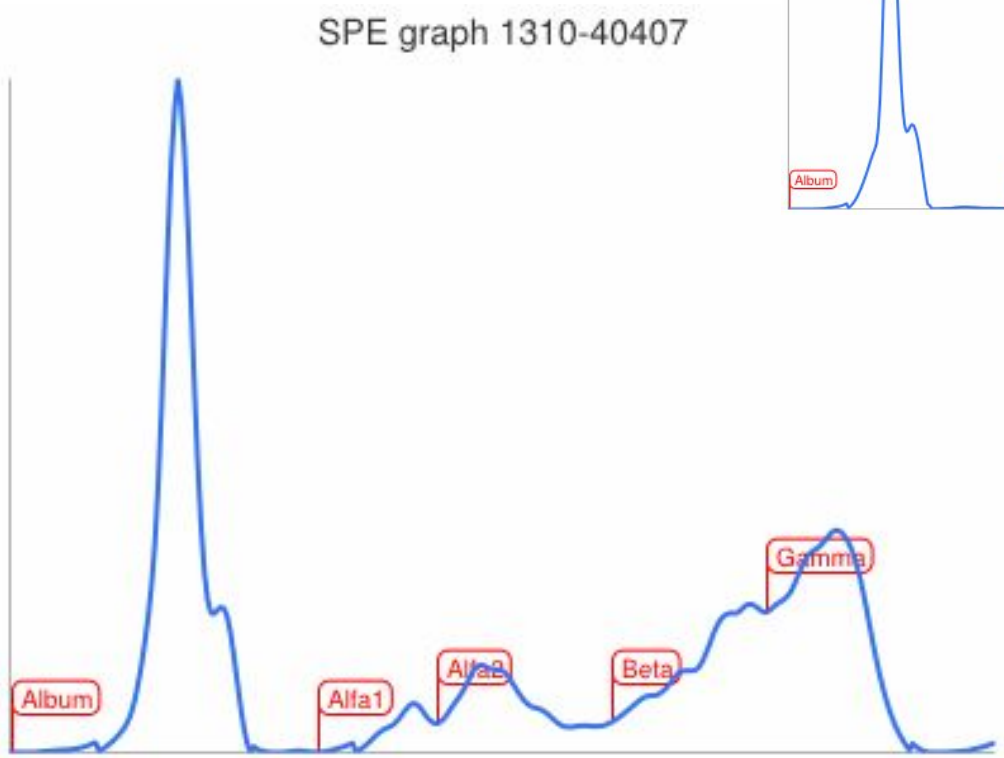
Leukogram pattern	Total WBCs	Segmented neutrophil	Nonsegmented neutrophil	Lymphocyte	Monocyte	Eosinophil
Acute inflammatory	↑	↑	↑	↓	WRI–↑	↓–WRI
Chronic inflammatory	↑	↑	WRI–↑	WRI–↑	WRI–↑	WRI
Steroid leukocytosis	↑	↑	WRI–slight ↑	↓	↑	↓
Physiologic leukocytosis	↑	↑	WRI	↑	WRI–↑	WRI
Acute overwhelming inflammatory	↓	↓	WRI–↑	↓	WRI	↓–WRI
Acute inflammatory with endotoxemia	↓	↓	WRI–↑	↓	WRI	↓–WRI
Granulocytic hypoplasia	↓	↓	WRI	WRI	WRI	WRI
Ineffective neutropoiesis	↓	↓	WRI	WRI	WRI–↑	WRI
Hypoadrenocorticism	WRI	↓–WRI	WRI	WRI–↑	WRI	WRI–↑
Hemic neoplasia	↑↑↑*	?	?	?	?	?

* The neoplastic cell line is expected to be increased. Other cell lines typically are WRI or decreased.

Hond

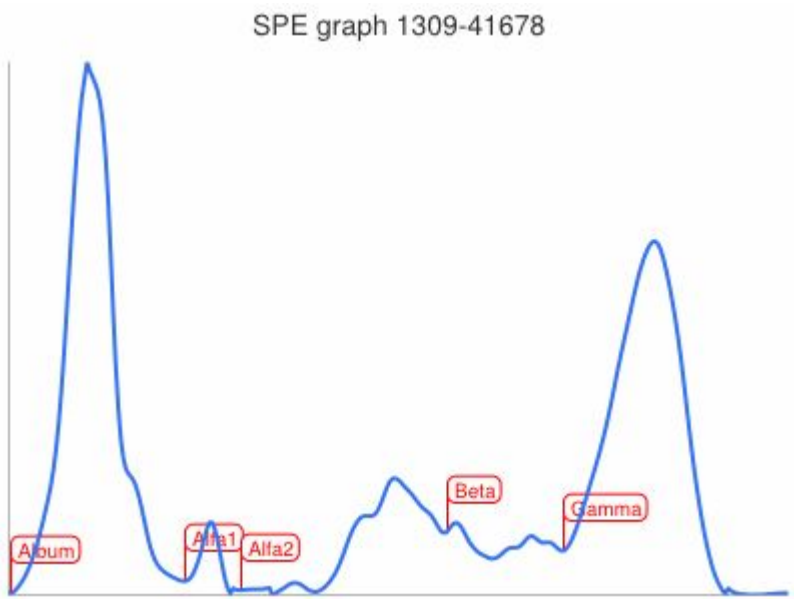
Hypergammaglobulinemie

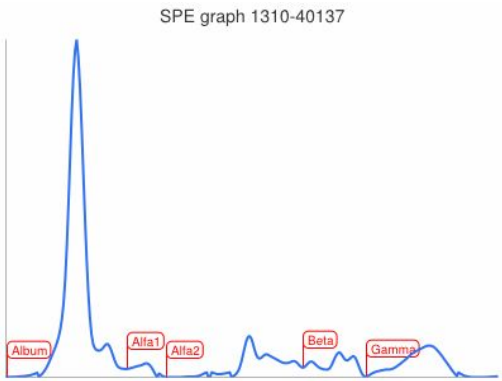




Kat

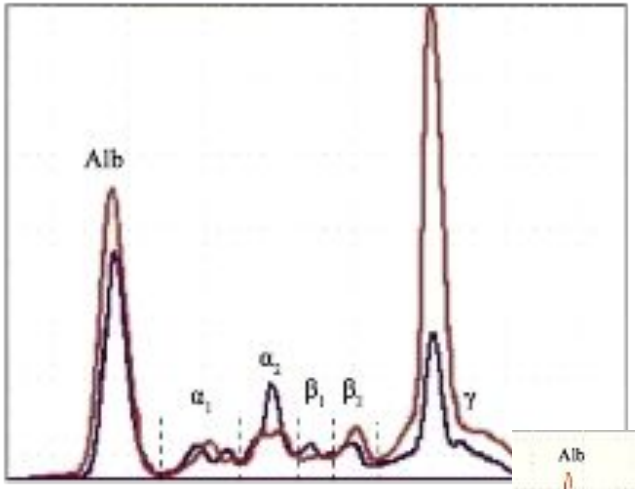
Hypergammaglobulinemie



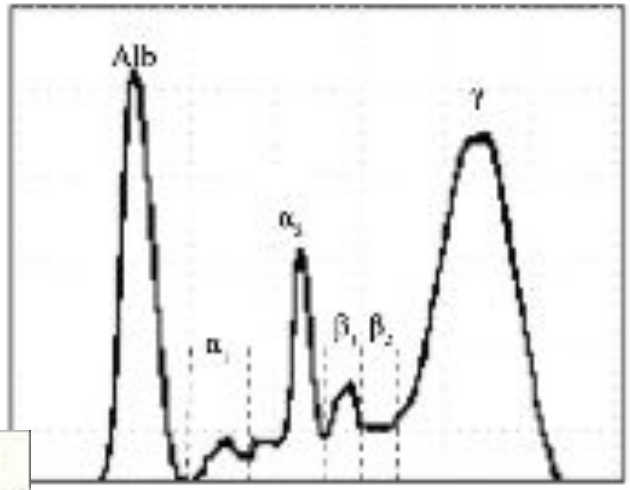


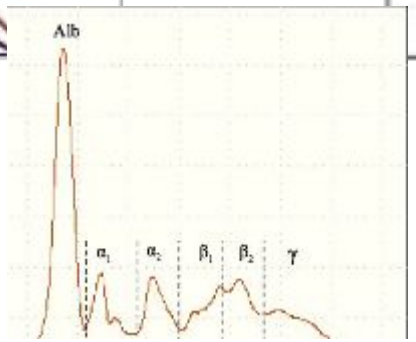
Hypergammaglobulinemie

MONOCLONAAL



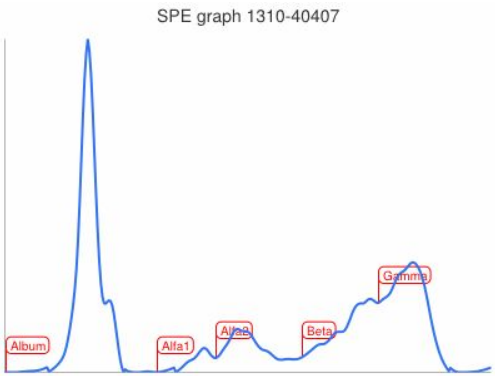
POLYCLONAAL





Polyclonale gammopathie

- Oorzaken
  - Inflammatoire aandoeningen
  - Infectieuze aandoeningen
  - Immuungemedieerde aandoeningen
  - Tumoren



- Chronische aandoeningen
  - polyclonale response: verscheidene immunoglobulinen
  - clonale expressie van verschillende cellijnen
    - plasmacellen
    - B-lymfocyten
- Brede piek, brede basis, ß of gamma

Table 2d. Diagnoses for cats with abnormal SPE results (γ globulin abnormalities), organised according to the DAMNITV system.[20] Categories with no cases are not illustrated (degenerative, traumatic). Cases with more than one SPE abnormality feature in all relevant categories/rows. Cases with >1 diagnosis within the same DAMNITV category are illustrated in bold type. Cases with >1 diagnosis in different DAMNITV categories are illustrated in italics in all relevant categories/columns but count as one case to the total cases with each SPE abnormality.

SPE abnormality/ DAMNITV group	Total cases (% of 136 cats)	No diagnosis reached (total cases = 23)	Anomalous (total cases = 5)	Metabolic (total cases = 4)	Neoplastic (total cases = 14)	Infectious/inflammatory (total cases = 83 cases)	Vascular (total cases = 3)	Traumatic (total cases = 1)	Miscellaneous (total cases = 9)
Increased γ	81 (59.6)	8	PSS (1) *Calicivirus/ nasopharyngeal stenosis (1)*	*Hyperthyroidism/ hypertension (1)* *Chronic renal failure and pyelonephritis (1)*	Pulmonary carcinoma (1) *Myeloid leukaemia/FIV (1)* Lymphoma (3) Splenic plasmacytoma (confirmed) (1) Splenic plasmacytoma (suspected) (1)	FIP (suspected) (21) FIP (confirmed) (14) IBD (neutrophilic/ lymphocytic) (1) IBD (lymphoplasmacytic) (2) Endocarditis (1) Dermatophytosis (1) Non-healing wound (1) Neutrophilic cholangitis (1) Pyogranulomatous pneumonia (mycobacteria suspected) (1) *Calicivirus/nasopharyngeal stenosis (1)* Uveitis (cause unknown) (1) *Chronic renal failure and pyelonephritis (1)* Myeloproliferative disease (FIV positive) (1) IMHA (1) Otitis media (1) **Lymphoproliferative rhinitis/ chronic airway disease (1)** Lymphadenitis (*S aureus*) (1) Lymphadenitis (cause unknown) (1) Lymphoid hyperplasia and inflammatory skin disease (1) Inflammatory CNS disease (1) *Ollulanus tricuspis* infection (1) Alternaria osteomyelitis (1) **Chronic rhinitis/FIV positive (1)** Pancreatitis (2) *Myeloid leukaemia/FIV (1)* *Gingivitis and cerebellar infarcts (1)*	*Hyperthyroidism/ hypertension (1)* *Gingivitis and cerebellar infarcts (1)*		Bone marrow disorder (red cell maturation arrest) (1) Colonic intussusception (1) Megaoesophagus (cause unknown) (1)
Decreased γ	3 (2.2)			Hepatic lipidosis (1)	Lymphoma (1)				Chylothorax (1)

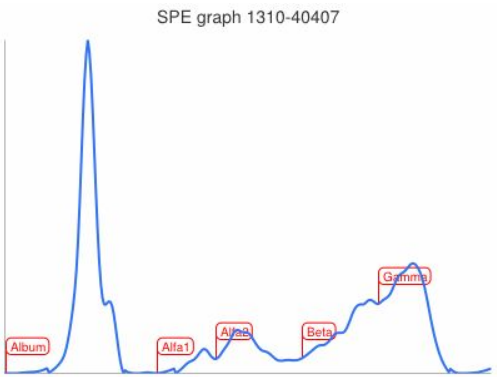
FIP = feline infectious peritonitis, IBD = inflammatory bowel disease, DCM = dilated cardiomyopathy, PSS = portosystemic shunt, IMHA = immune mediated haemolytic anaemia, CNS = central nervous system.

Serum protein electrophoresis in 155 cats

Samantha S Taylor BVetMed, CertSAM, DipECVIM-CA, MRCVS[1a], **Simon W Tappin** MA, VetMB, CertSAM, DipECVIM-CA, MRCVS[1,a], **Steve J Dodkin** BSc, MSc[2], **Kostas Papasouliotis** DVM, PhD, DipRCPath, DipECVCP, MRCVS[2], **Domingo Casamian-Sorrosal** DVM, CertSAM, CertVC, MRCVS[1], **Séverine Tasker** BSc, BVSc, PhD, DSAM, DipECVIM-CA, PGCertHE, MRCVS[1]

Polyclonale gammopathie Kat

- Meest voorkomende afwijking 33%
  - Polyclonale gammopathie
  - + Compensatoire hypoalbuminemie
- Onderliggende oorzaak
  - Chronische infecties
    - Bacterieel, viraal, mycotisch, parasitair
  - Chronische ontstekingen
    - IBD
    - IMHA



Serum protein electrophoresis in 155 cats

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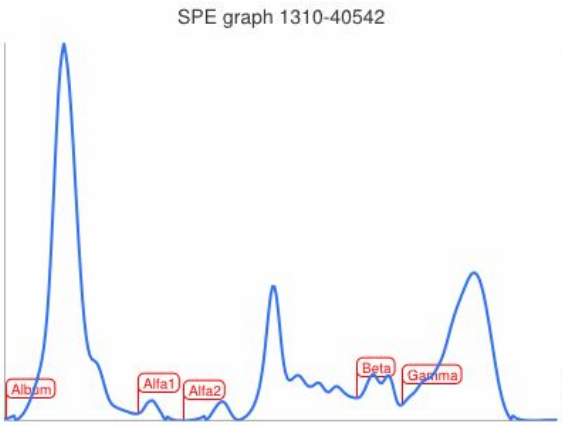
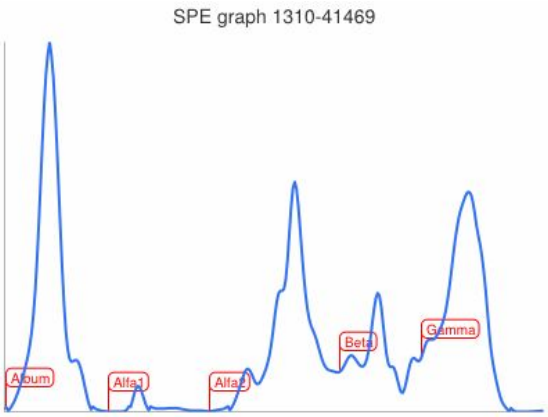
Kat

FIP


SPE graph 1310-40542
Album
Alfa1
Alfa2
Beta
Gamma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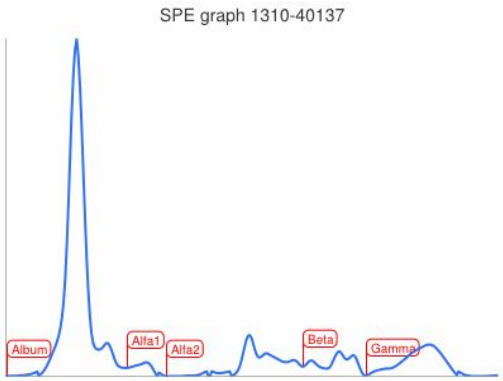
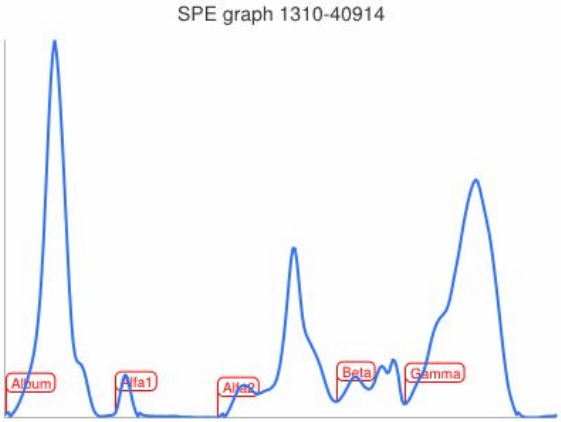
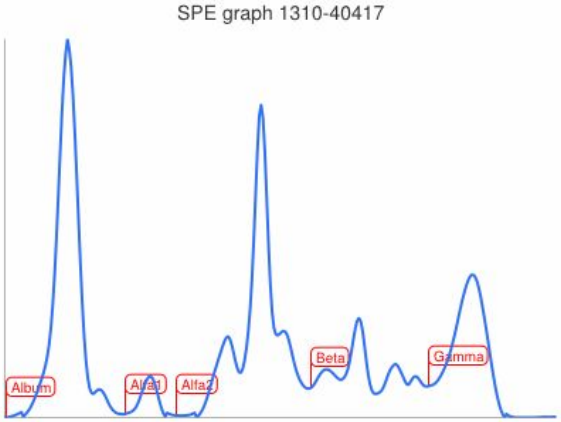
Album
Alfa1
Alfa2
Beta
Gamma

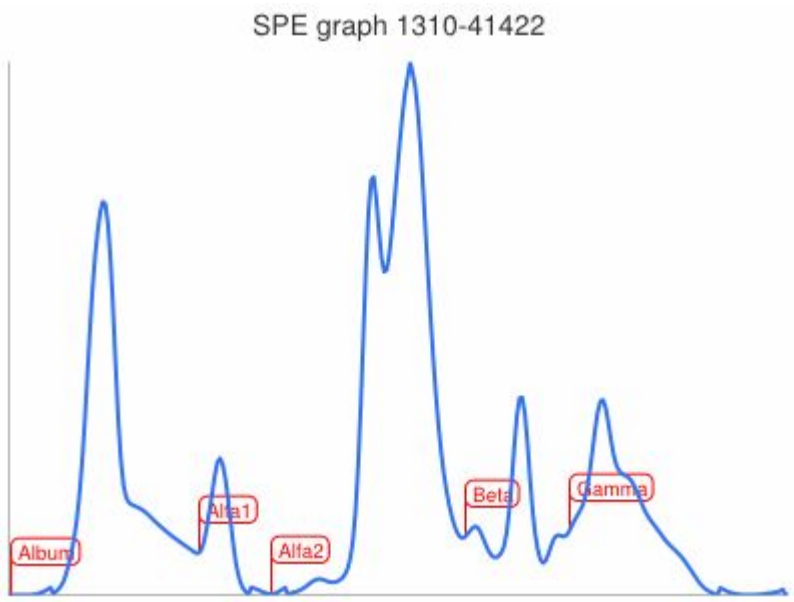

SPE graph 1310-40137
Album
Alfa1
Alfa2
Beta
Gamma

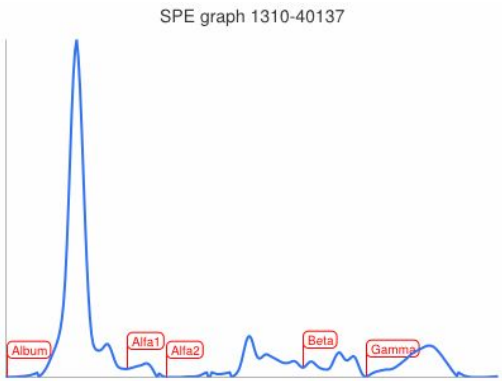

SPE graph 1310-40914
Album
Alfa1
Alfa2
Beta
Gamma


SPE graph 1310-40417
Album
Alfa1
Alfa2
Beta
Gamma

Kat

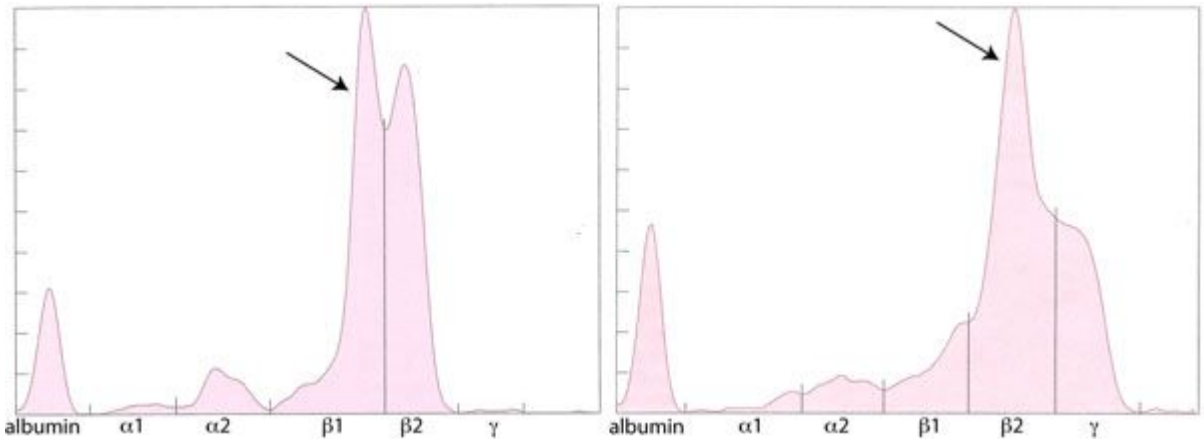
Kat - FIV+, FIP+, creat 6.9 mg/dL





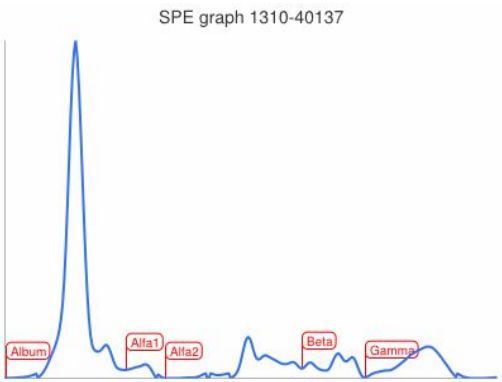
Oligoclonale gammopathie

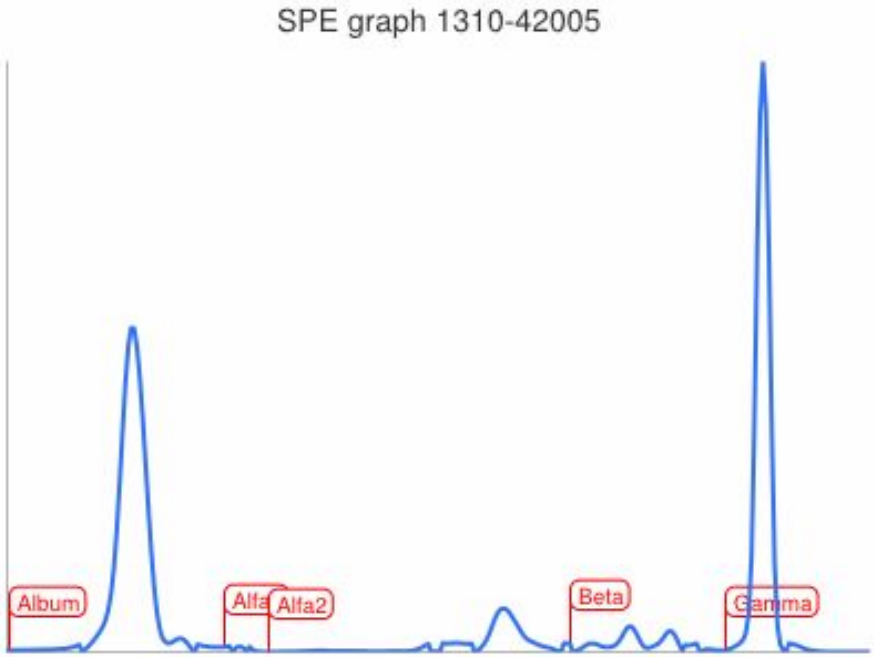
- Nauwe piek op een polyclonale gammopathie OF twee pieken
- Oorzaken
  - Erhlichiose
  - FIP
  - Leishmaniose



Monoclonale gammopathie

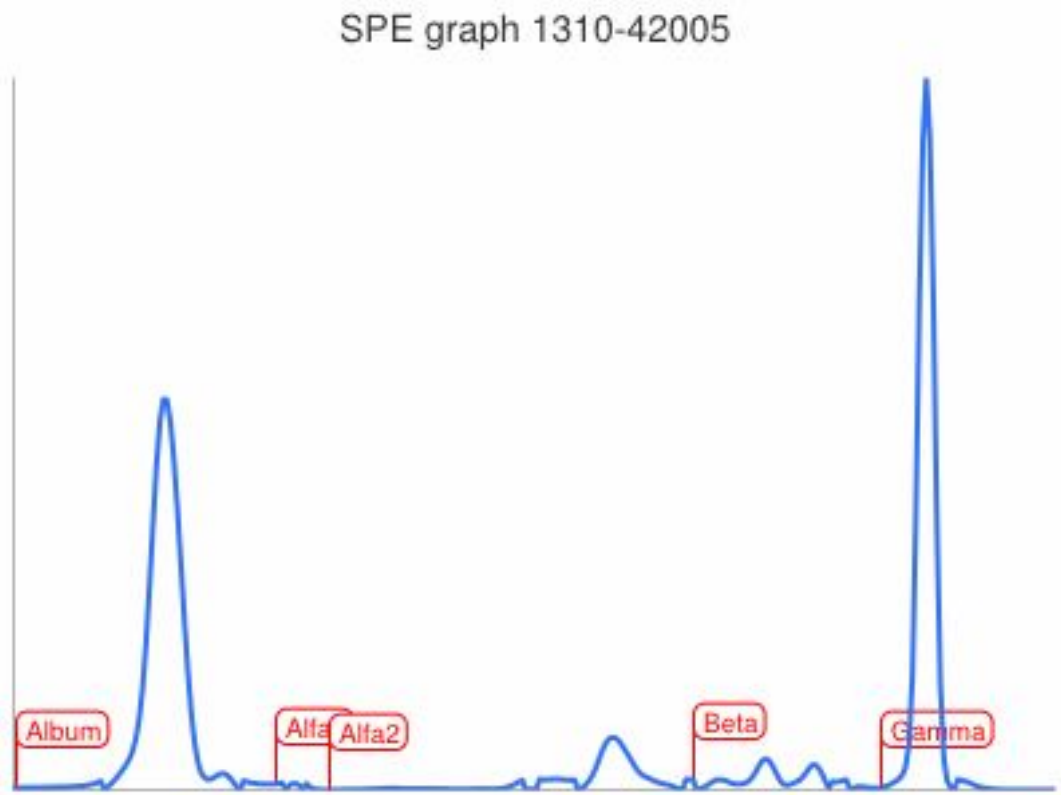
- Nauwe piek, nauwe basis
  - = Paraproteïnemie
  - meestal beta- of gammafractie!!!!
  - æ-fractie: abnormale IG (neo!)

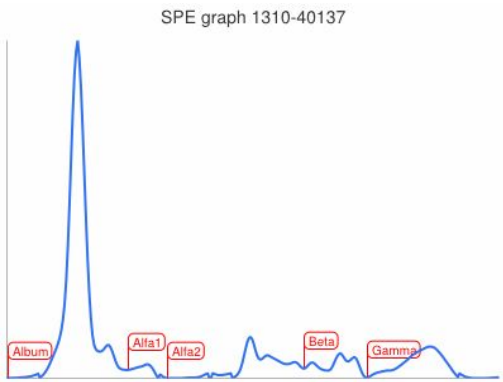




Kat

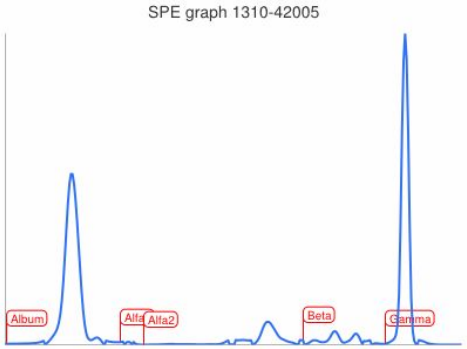
Monoclonale piek





Monoclonale gammopathie Kat

- Zelden : 4/155 katten
- Onderliggende oorzaak
  - Plasmacel neoplasie 2
    - Multipel myeloom
    - Plasmacytoom extramedullair
  - Lymphoma 1
  - FIP 1
- Andere studies
  - Lymfocytaire plasmacytaire stomatitis (uitzonderlijk)
  - Anaplasmose (zeer zelden)



Serum protein electrophoresis in 155 cats

Samantha S Taylor BVetMed, CertSAM, DipECVIM-CA, MRCVS[1*], Simon W Tappin MA, VetMB, CertSAM, DipECVIM-CA, MRCVS[1,a], Steve J Dodkin BSc, MSc[2], Kostas Papasouliotis DVM, PhD, DipRCPath, DipECVCP, MRCVS[2], Domingo Casamian-Sorrosal DVM, CertSAM, CertVC, MRCVS[1], Séverine Tasker BSc, BVSc, PhD, DSAM, DipECVIM-CA, PGCertHE, MRCVS[1]

Monoclonale gammopathie Kat

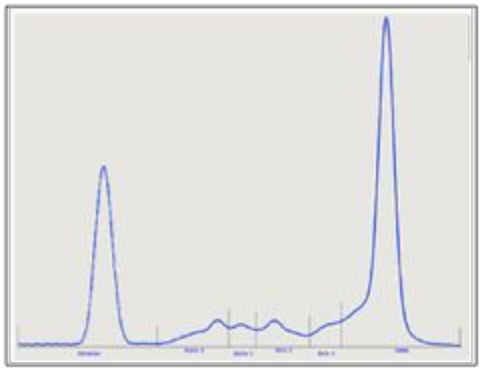


Figure 1 Protein electrophoresis of serum indicating a narrow spike in the gamma (γ) region

Primary bronchial carcinoma associated with bone marrow metastasis and paraneoplastic monoclonal gammopathy in a cat

Mario Cervone[1] and Stéphanie Beurlet[2]

Journal of Feline Medicine and Surgery Open Reports
1–5
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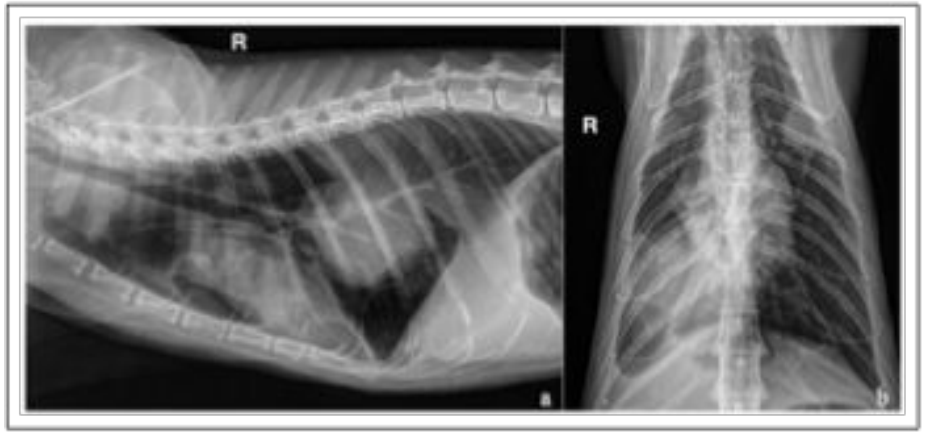


Monoclonale gammopathie Kat

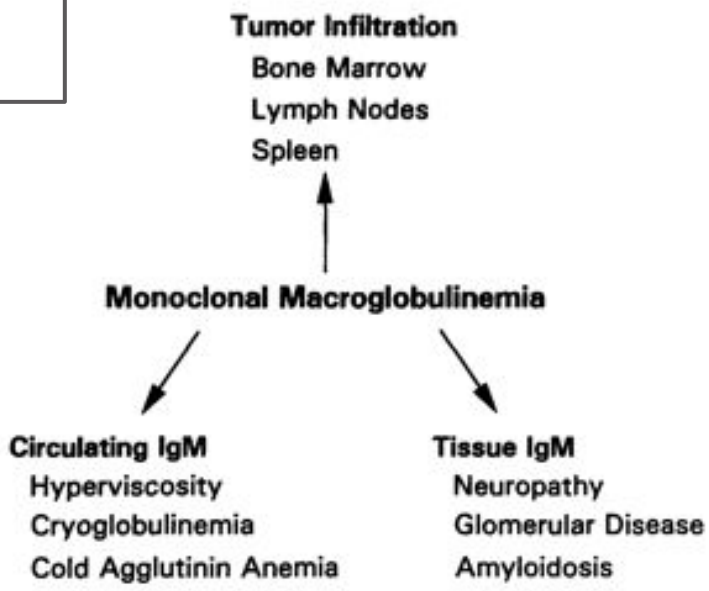
NOTE

A Case of Feline Macroglobulinemia

Takatsugu YAMADA, Akie OGURA, Jun INOUE, Hajime TSUJIMOTO, Kenichiro ONO, Naoaki GOTO[1], Isamu TOMODA, Kosaku FUJIWARA[1], and Kazuya USUI

Department of Veterinary Medicine and Department of Veterinary Pathology[1], Faculty of Agriculture, University of Tokyo, 1-1-1 Yayoi, Bunkyo, Tokyo 113

(Received 21 December 1982/Accepted 24 February 1983)



Monoclonale gammopathie

TABLE 3: Location of monoclonal 'spike' and diagnosis in dogs with monoclonal gammopathies

Location of monoclonal spike	Diagnosis (number of dogs)
α-2	Multiple myeloma (1)
β-1	Multiple myeloma (1)
β-2	Splenic plasmacytoma (1)
	Lymphoma (stage V) (1)
γ	ND (1)
	Multiple myeloma (2)
	Hepatic plasmacytoma (1)

ND No diagnosis reached

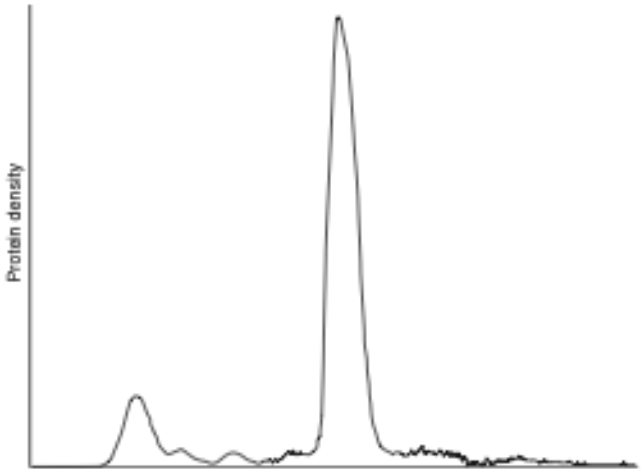


FIG 3: Serum protein electrophoresis densitometer trace illustrating monoclonal gammopathy with the monoclonal 'spike' in the α-2 region and also exhibiting profound background suppression

PIEK NIET ALTIJD
IN GAMMAFRACTIE

Serum protein electrophoresis in 147 dogs

S. W. Tappin, S. S. Taylor, S. Tasker, S. J. Dodkin, K. Papasouliotis, K. F. Murphy

Monoclonale gammopathie

- Prevalentie : zelden 8/147 5,7%

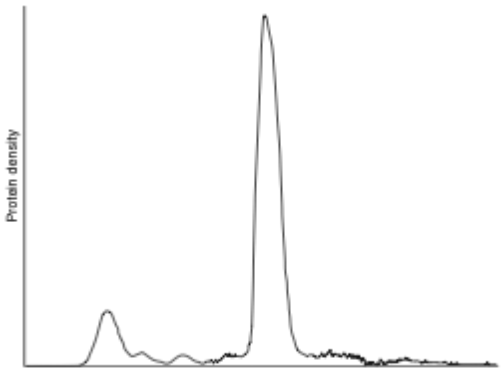


FIG 3: Serum protein electrophoresis densitometer trace illustrating monoclonal gammopathy with the monoclonal 'spike' in the α-2 region and also exhibiting profound background suppression

- Oorzaken bij de hond
  - Lymfoproliferatieve aandoeningen
    - Multipel myeloom
    - Plasmacytoom van de milt, lever, andere
    - Lymfoom
    - Chronische lymfoïde leukemie

Serum protein electrophoresis in 147 dogs

S. W. Tappin, S. S. Taylor, S. Tasker, S. J. Dodkin, K. Papasouliotis, K. F. Murphy

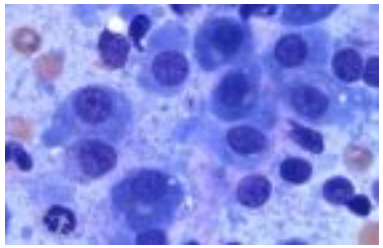
Monoclonale gammopathie

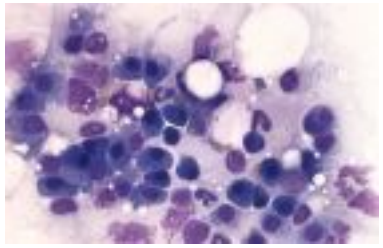
- JAAHA 2002 Giraudel
  - Multipel Myeloom 9/18
  - Wäldenström's macroglobulinemie 1/18
  - Chronische lymfoïde leukemie 1/18
  - Lymfoom 1/18
  - Plasmacytoma 1/18
  - Ehrlichiosis 2/18
  - Leishmaniosis 3/18
- 1 geval chronische pyoderma (JVIM)
- Dirofilariose

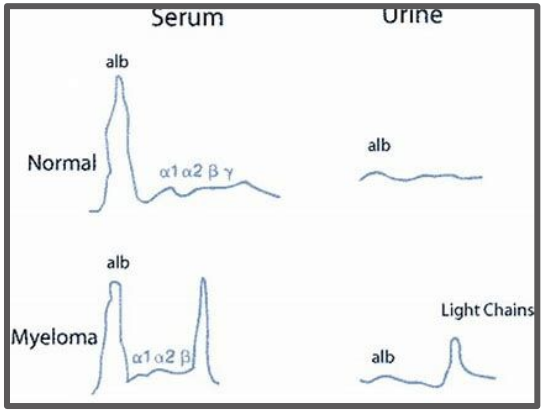
Monoclonal Gammopathies in the Dog: A Retrospective Study of 18 Cases (1986-1999) and Literature Review

Monoclonale gammopathie

- Multipel Myeloom 9/18
  - Diagnose: 3 van 4 criteria
  - Beenmerg
  - Monoclonale gammopathie
    - biclonaal zelden
    - niet-secreterend: zeer zelden
  - Bence-Jones proteïnurie
    - light-chains; 25-40%
    - dipstick negatief!!
  - RX Osteolytische zones!!

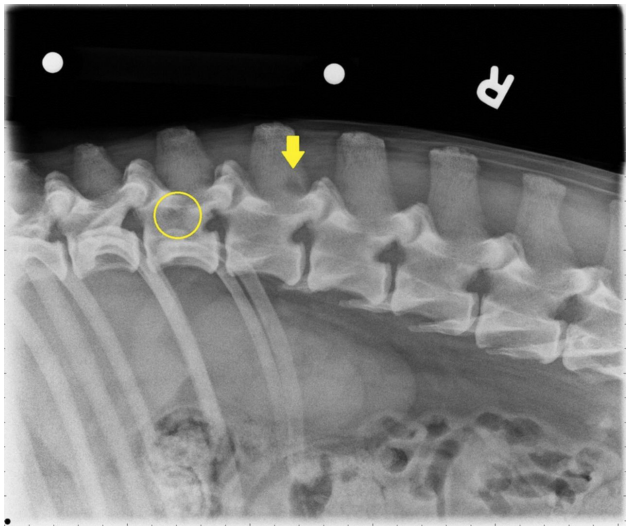


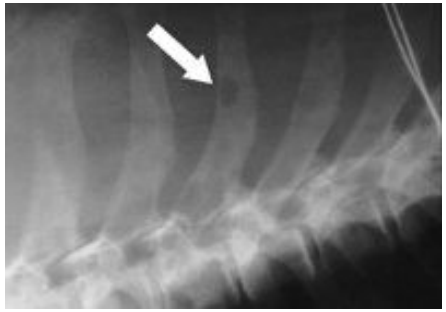




Monoclonale gammopathie

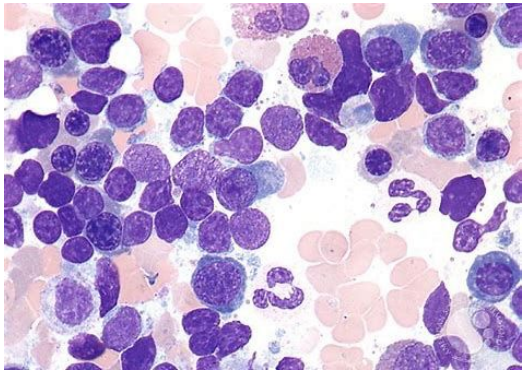
- Multipel Myeloom 9/18
  - osteolytische zones!!
    - “punch-hole”
  - H 60%; K 10%!!!!





Monoclonale gammopathie

- Wäldenström's macroglobulinemie 1/18
  - zeer zelden
  - hond, kat, mens
  - lymfoplasmacytair lymfoom
    - beenmerg (zelden milt, lever)
    - nooit perifeer bloed
  - hyperviscositeit syndrome, stollingstoornissen, Ca, cytopenies, cardiovasculaire en renale problemen
  - Dx: beenmergpunctie, cytologie
  - Tx: chemo:
    - chlorambucil/predni
    - melphalan/predni



Monoclonale gammopathie

- JAAHA 2002 Giraudel
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  - Leishmaniosis 3/18
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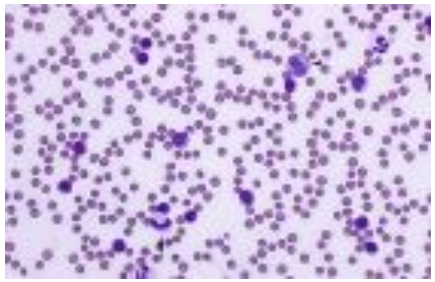
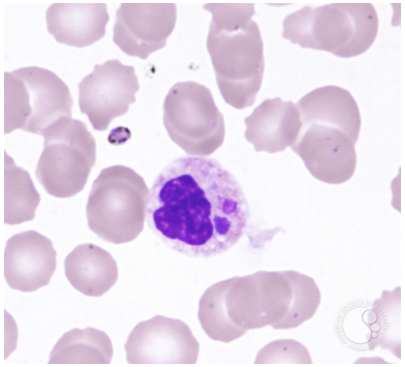
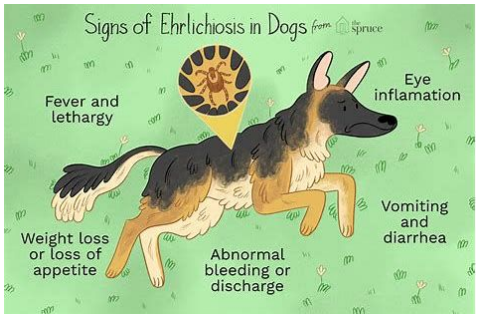






Panhypoproteïnemie

- ALLE fracties
- Oorzaken
  - Fysiologisch (jonge dieren)
  - Proportioneel verlies
    - Bloeding (acuut!!!!)
    - GI verlies (PLE)
    - Protein losing dermatopathy (!!Brandwonden)
    - Peritonitis,pleuritis, vasculitis **"THIRD SPACE LOSS"**
      - NIET bij hartaandoeningen indien normale lever
        - Herhaalde abdominocentese zonder problemen?
  - Proportioneel gedaalde synthese???
    - alb. en APP: lever
    - globulinen: lymfocyten en plasmacellen

Hypoproteïnemie
Bloeding

- <12u (tot 24u)
  - Hct, Hb, Telling, Totaal Eiwit NORMAAL
  - !!!klinische tekens!!
    - hypotensie
    - grauwe mucosae, CRT+++
- 12u-3d.
  - Hct, Hb, Telling, Totaal Eiwit LAAG
  - interstitieel vocht naar bloedbaan
- 3-7d.
  - Hct, Hb, Telling LAAG
  - Totaal Eiwit NORMAAL
- 2-4 weken Normaal

Hypoproteïnemie
PLE

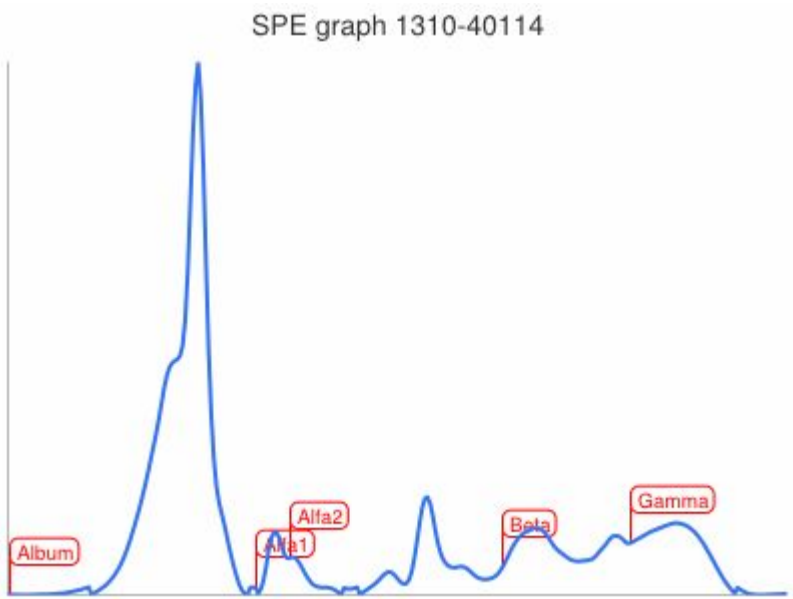
- Verlies van eiwit via intestinale secretie
  - Veralgemeende aandoeningen slijmvlies
  - Aandoening lymfoïde systeem
  - Intestinale bloedingen
- Ziekten
  - Veralgemeende aandoeningen van het slijmvlies
    - Lymfoom, IBD, eosinofiele enteritis, parvo
  - Lymfangiectasie
  - Bloedverlies
    - Trichuris, ancylostoma
    - Tumoren
    - Parvo
- Beginfase: soms alleen albumine gedaald

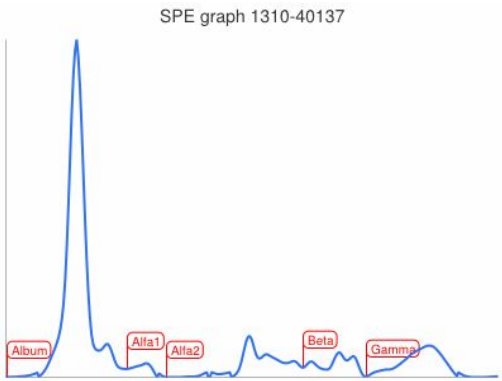
Hypoalbuminemie

- Verlies
  - PLE
  - PLN (glomerulonefritis)
  - Dermaal
  - Septische Peritonitis
- Sequestratie en Dilutie
  - Effusies
  - Overhydratatie
  - Hartfalen
- Verminderde productie
  - Leverfalen (cirrhose)
  - Acute Phase response
  - Cachexie
- Opname
  - Malnutritie/Dieet
  - Malabsorptie
  - Maldigestie

Kat

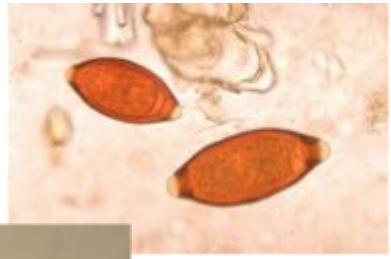
Levertumor - hypoalb





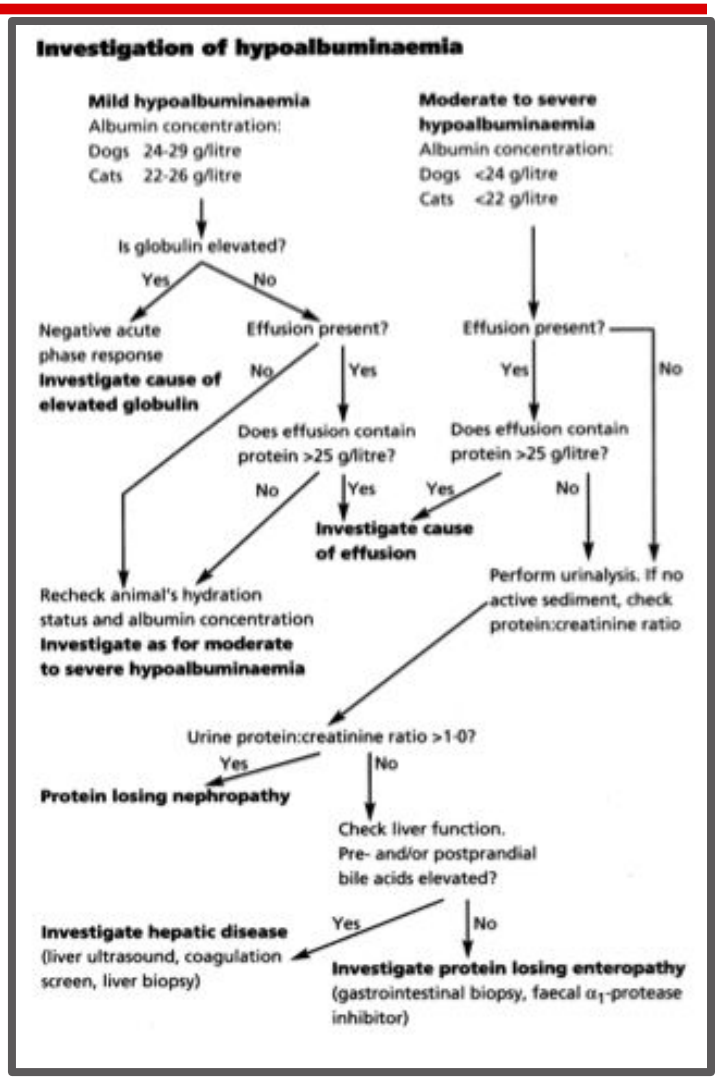
Hypoalbuminemie

- Anamnese
  - Dieet/Rantsoen
  - Bloedingen (uitwendig)
- Lichamelijk onderzoek
- Labo
  - Urine
    - Eiwit en eiwit/creatinine ratio urine
    - Sediment
  - Faeces: parasieten!!
  - Bloed
    - leverenzymen, galzuren
    - TLI
    - Vit B12



Hypoalbuminemie

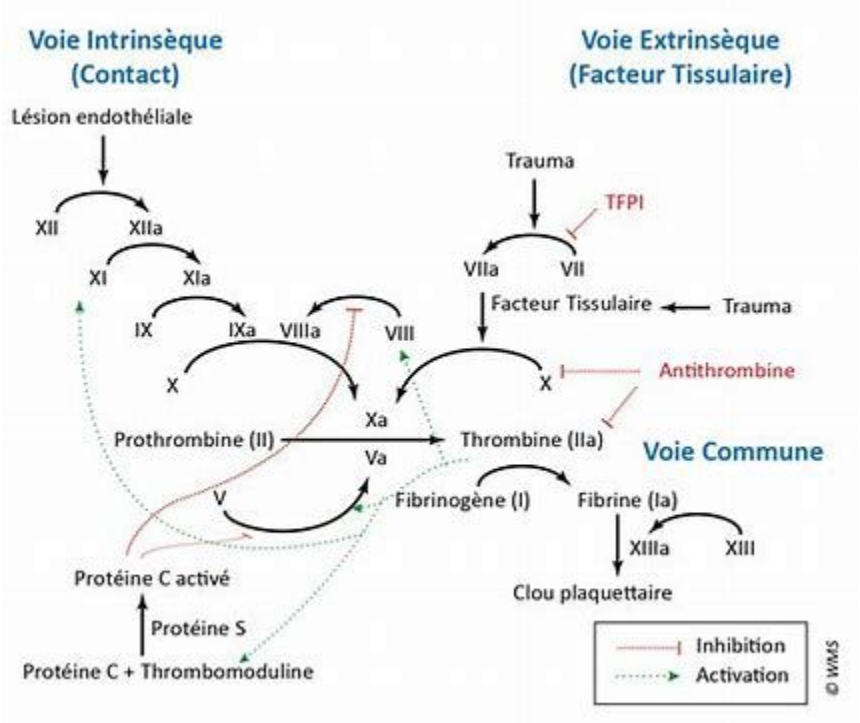
- Echografie
  - nieren
  - lever (tumor, …..)
  - darmen!!!
  - effusie
- Cytologie
  - opgezette (mesenteriale) lnn
  - lever
- Biopten!!
  - darmen
  - lever

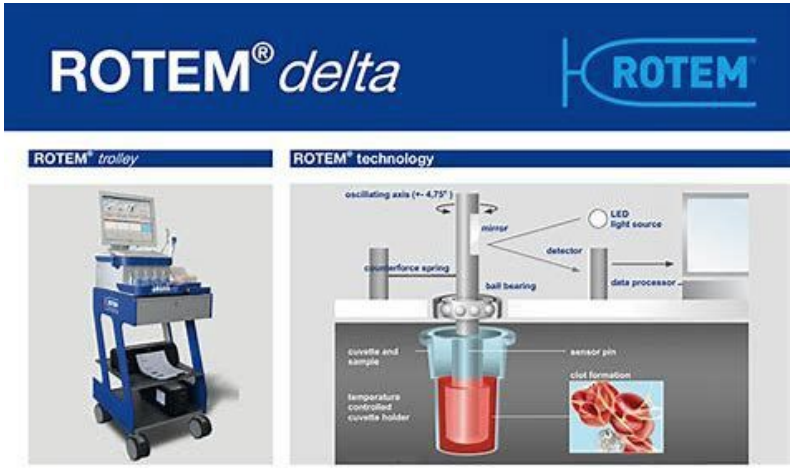


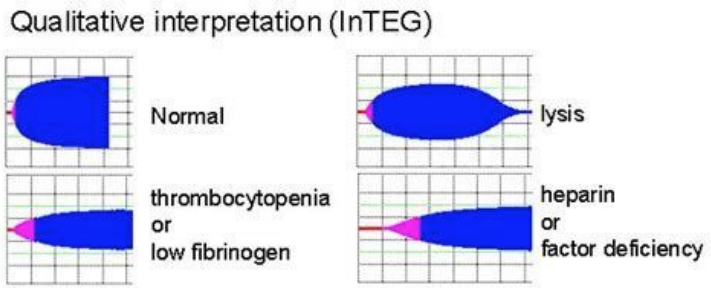
Hypoalbuminemie

Albumine < 2 g/dl

Bepaal AT3 TEG







Hypoalbuminemie
PLN

IRIS International Renal Interest Society

IRIS Staging of CKD (modified 2017)

UP/C value		Substage
Dogs	Cats	
<0.2	<0.2	Non-proteinuric
0.2 to 0.5	0.2 to 0.4	Borderline proteinuric
>0.5	>0.4	Proteinuric

Controleer 2 stalen met 14 dagen tussen
UPCR >3 Significante proteïnurie
Glomerulonefropathie

Hypoalbuminemie
PLN

Volume 27, Issue s1

Special Issue:International Renal Interest Society

Consensus Clinical Practice Guidelines for Glomerular Disease in Dogs

Pages: S1-S75

November/December 2013

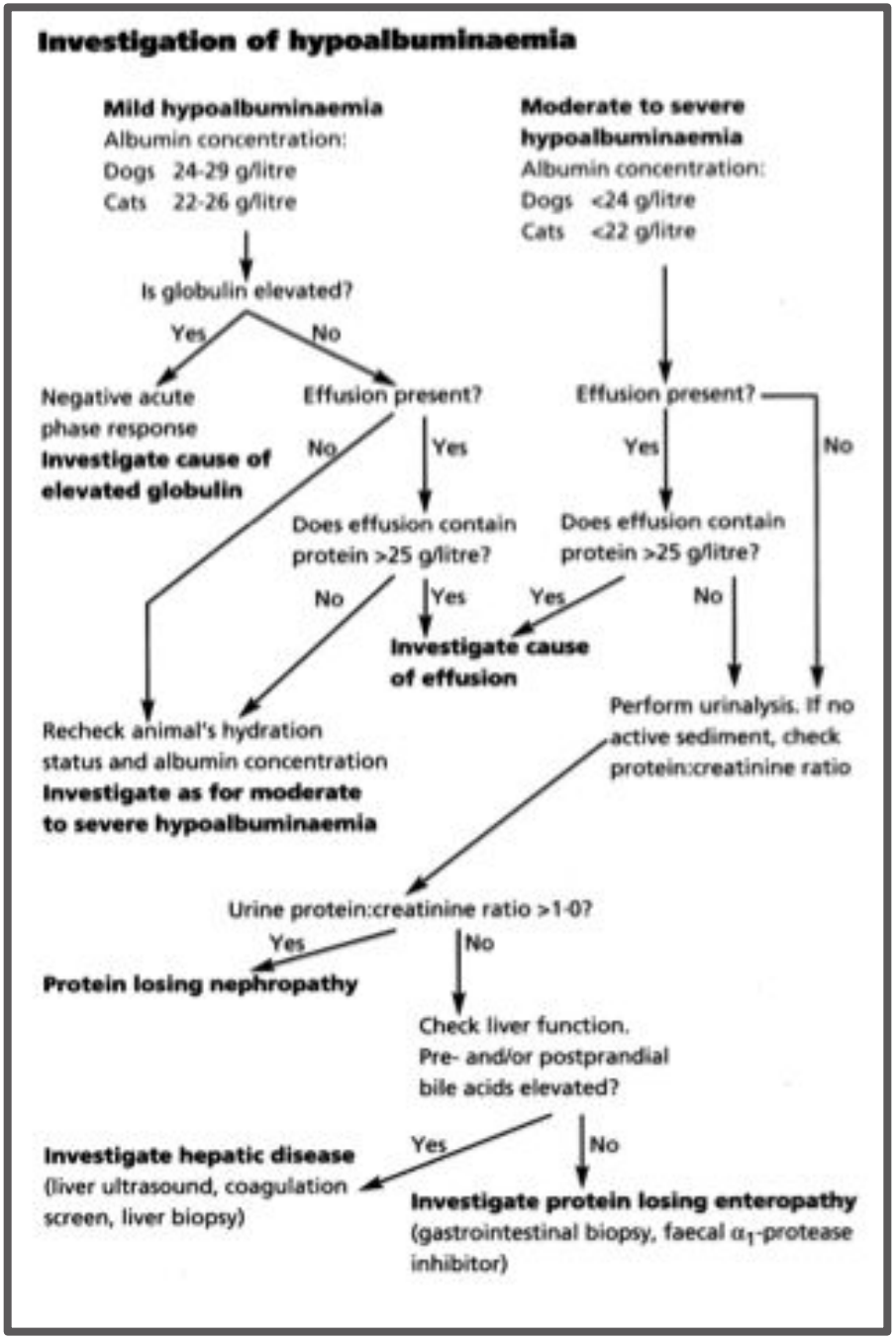
Table 3. Diagnostic priorities based on canine glomerular disease tier.

	Tier I Uncomplicated Renal Proteinuria			Tier II Renal Proteinuria with Hypoalbuminemia without Azotemia			Tier III Renal Proteinuria with Azotemia		
	Essential	Recommended	Potentially helpful	Essential	Recommended	Potentially helpful	Essential	Recommended	Potentially helpful
Hx, PE, BPM CBC, Chem UA ± culture UPCs[a]	X			X			X		
Investigate "evident" extrarenal disease		(X)			(X)			(X)	
Abdominal ultrasound	[b]	X		X			X		
Chest radiographs	[b]		X		X			X	
Work-up for hypertension	(X)			(X)			(X)		
Work-up for infectious diseases[a]	X			X			X		
Work-up for hypo-albuminemia				X			(X)		
Classify and work-up for azotemia[a]							X		
Renal biopsy[a]		[b]	X		X			X	
AT, TEG, SDS-PAGE, save samples for DNA, etc.			X			X			X

(X) if appropriate; Hx, history; PE, physical examination; BPM, blood pressure measurement; Chem, biochemical profile; UA, urinalysis; AT, antithrombin; TEG, thromboelastography; SDS-PAGE, sodium dodecyl sulfate-agarose gel electrophoresis.

[a]See text.

[b]A small minority of respondents made this recommendation.

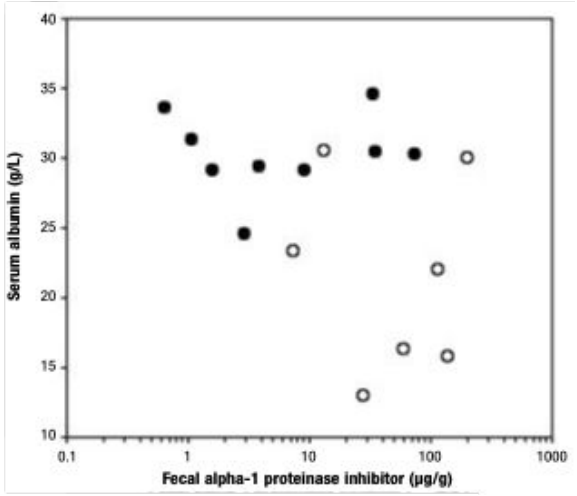

Investigation of hypoalbuminaemia
Mild hypoalbuminaemia
Albumin concentration:
Dogs 24-29 g/litre
Cats 22-26 g/litre
Moderate to severe hypoalbuminaemia
Albumin concentration:
Dogs <24 g/litre
Cats <22 g/litre
Is globulin elevated?
Yes
No
Negative acute phase response
Investigate cause of elevated globulin
Effusion present?
No
Yes
Does effusion contain protein >25 g/litre?
No
Yes
Investigate cause of effusion
Recheck animal's hydration status and albumin concentration
Investigate as for moderate to severe hypoalbuminaemia
Effusion present?
Yes
No
Does effusion contain protein >25 g/litre?
Yes
No
Perform urinalysis. If no active sediment, check protein:creatinine ratio
Urine protein:creatinine ratio >1·0?
Yes
No
Protein losing nephropathy
Check liver function. Pre- and/or postprandial bile acids elevated?
Yes
No
Investigate hepatic disease (liver ultrasound, coagulation screen, liver biopsy)
Investigate protein losing enteropathy (gastrointestinal biopsy, faecal α1-protease inhibitor)

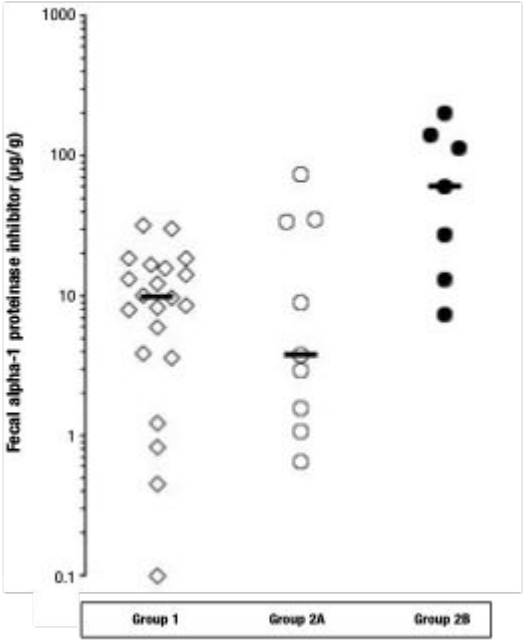
Hypo-albuminemie
PLE

Fecal α_1-Proteinase Inhibitor Concentration in Dogs with Chronic Gastrointestinal Disease

K. F. Murphy, A. J. German, C. G. Ruaux, J. M. Steiner, D. A. Williams, E. J. Hall

- Merker voor eiwitverlies
  - screening bij diarree: stijgt reeds voor hypo-alb!!
  - bevestiging PLE
  - biopsie





Echografie
Darmen Normaal Beeld

- Darm: 5 lagen
  - lumen
  - mucosa
  - submucosa
  - muscularis
  - serosa
- Dikte
  - hond vs. kat
  - hond: gewicht
  - duo/jej/ileum

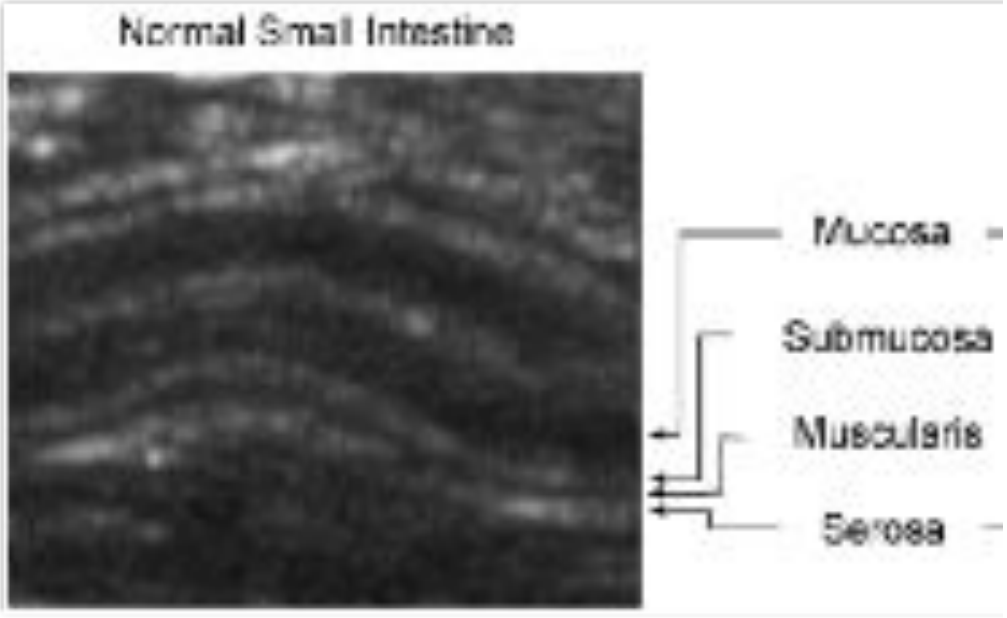


Table 1
Range of normal gastric and intestinal segment wall thicknesses

GI Segment	Canine (mm)	Feline (mm)
Stomach	3–5	1.1–3.6
Duodenum	2–6	1.3–3.8
Jejunum	2–4.7	1.5–3.6
Ileum		2.5–3.2
Colon		1.1–2.5

Table 1.

Normal range of wall thickness for different segments of the intestinal tract in cats (4) and dogs (2)

Wall thickness (mm)	Cats	Dogs
Duodenum	2.0 - 2.4	3 - 6
Jejunum	2.1 - 2.5	2 - 5
Ileum	2.5 - 3.2	2 - 4

Table 2.

Normal range of wall thickness (mm) for the different segments of the intestinal tract in dogs based on body weight (5)

Body weight (kg)	Duodenum	Body weight (kg)	Jejunum
< 20	≤ 5.1	< 20	≤ 4.1
20 - 29.9	≤ 5.3	20 - 39.9	≤ 4.4
≥ 30	≤ 6	≥ 40	≤ 4.7

Echografie

- Echografisch onderzoek
  - Totale dikte van de wand
  - Lagen en respectievelijke dikte!!!!
  - Echogeniciteit van de lagen
  - Motiliteit (peristaltiek)
  - Aanwezigheid van vocht (lumen en abdomen)
  - Lymfeklieren
    - omvang en vorm
    - echogeniciteit
  - Verdeling van de letsels
    - focaal
    - multifocaal
    - diffuus

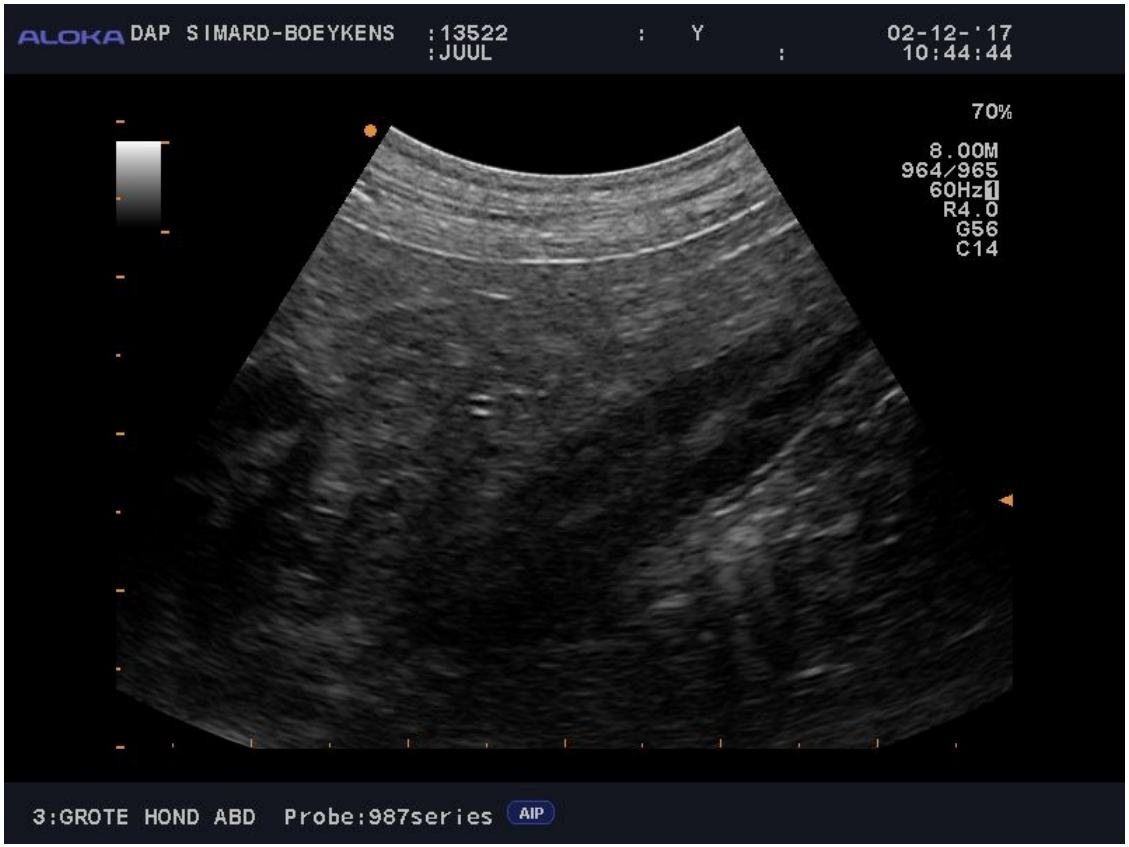
PLE

- Pathofysiologie
  - lymfatische obstructie
  - verhoogde permeabiliteit
    - infiltratie: inflammatie vs. neoplasie
  - mechanische oorzaken
    - ulcus, erosie, congestie
- Inflammatie
  - IBD!!!
- Lymfangiectasie
- Neoplasie
  - lymfoom (adenocarcinoom?)
- Parasieten (bloeding)

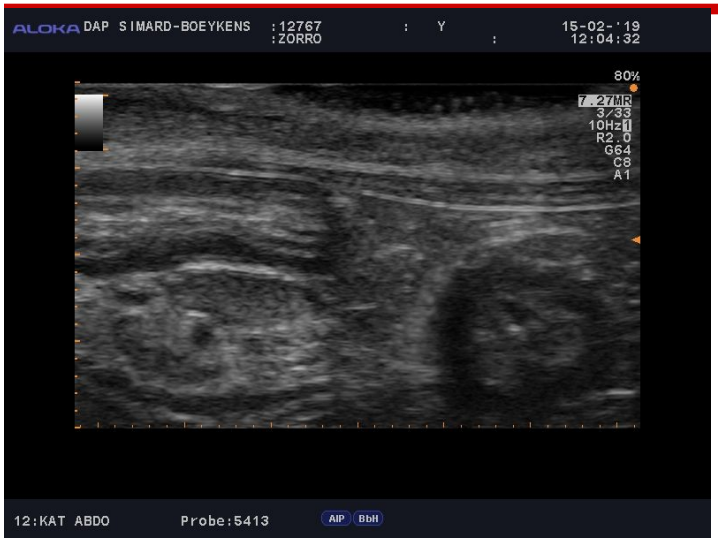
IBD

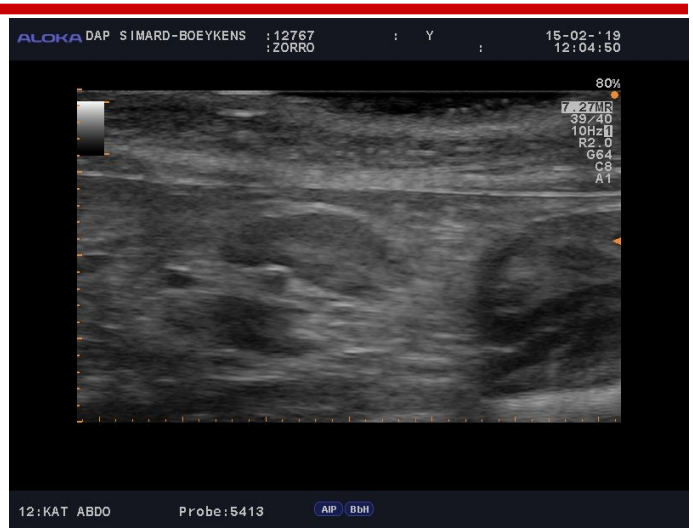
- Radiografie 000
- Echografie
  - normaal !!!!
  - wand verdikt
    - mucosa verdikt
    - kat soms muscularis verdikt
  - echogeniciteit
    - mucosa: toegenomen
      - diffuus
      - gespikkeld
      - loodrechte striatie (lymfangiestasie)
  - lymfeklieren
    - normaal of matig vergroot
    - normale vorm (langwerpig)

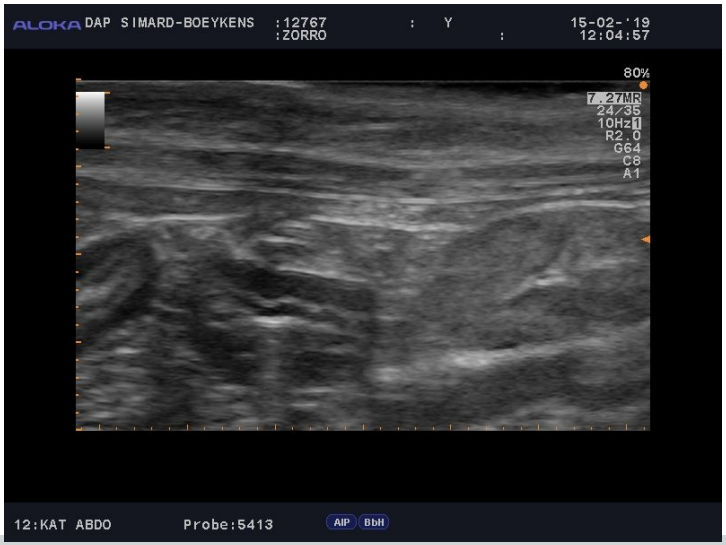
IBD


ALOKA
DAP SIMARD-BOEYKENS :13522
:JUUL
: Y
:
02-12-'17
10:44:44
70%
8.00M
964/965
60Hz
R4.0
G56
C14
3:GROTE HOND ABD Probe:987series
AIP

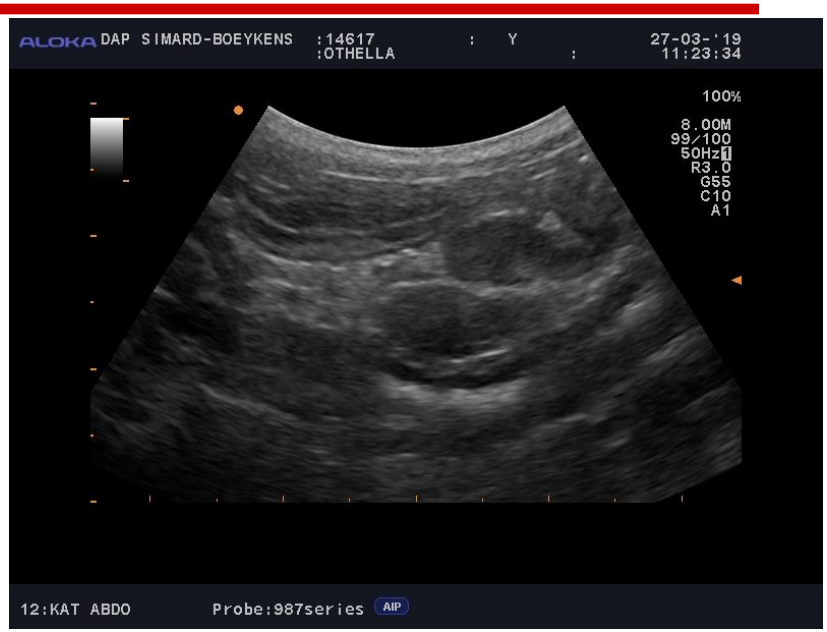
IBD

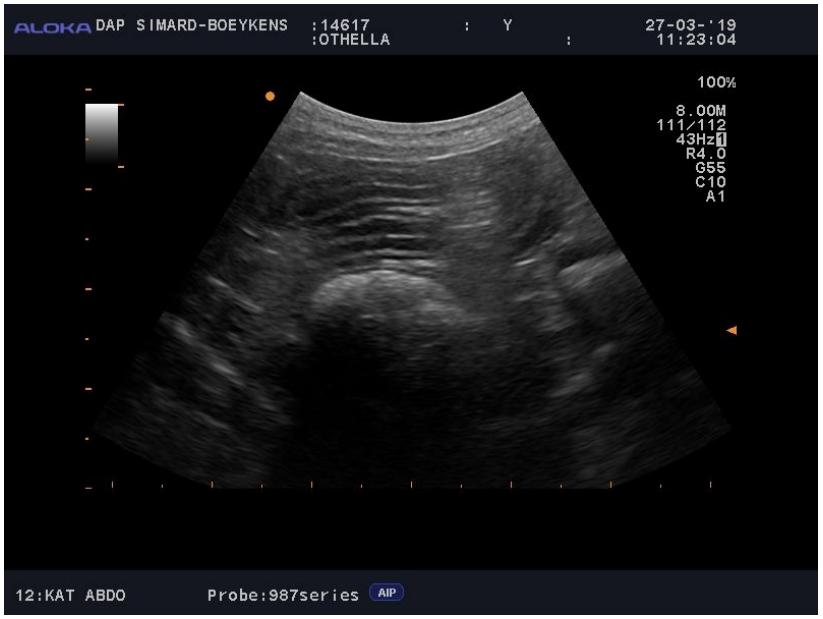

ALOKA DAP SIMARD-BOEYKENS :12767 :ZORRO : Y : 15-02-'19 12:04:32
80%
7.27MR
3/33
10Hz
R2.0
G64
C8
A1
12:KAT ABDO
Probe:5413
AIP
BbH


ALOKA DAP SIMARD-BOEYKENS :12767 :ZORRO : Y : 15-02-'19 12:04:50
80%
7.27MR
39/40
10Hz
R2.0
G64
C8
A1
12:KAT ABDO
Probe:5413
AIP
BbH


ALOKA DAP SIMARD-BOEYKENS :12767 :ZORRO : Y : 15-02-'19 12:04:57
80%
7.27MR
24/35
10Hz
R2.0
G64
C8
A1
12:KAT ABDO
Probe:5413
AIP
BbH

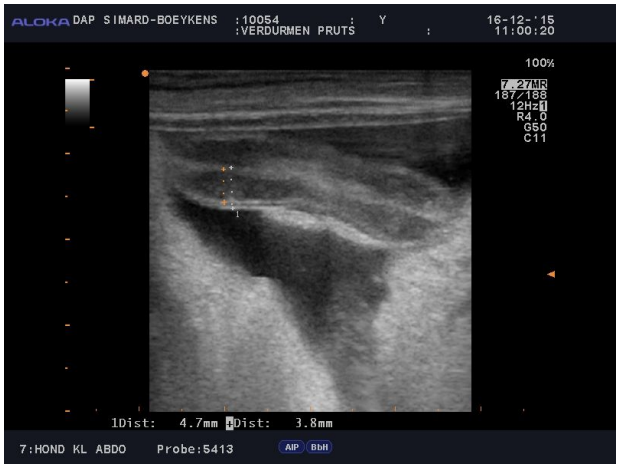
IBD

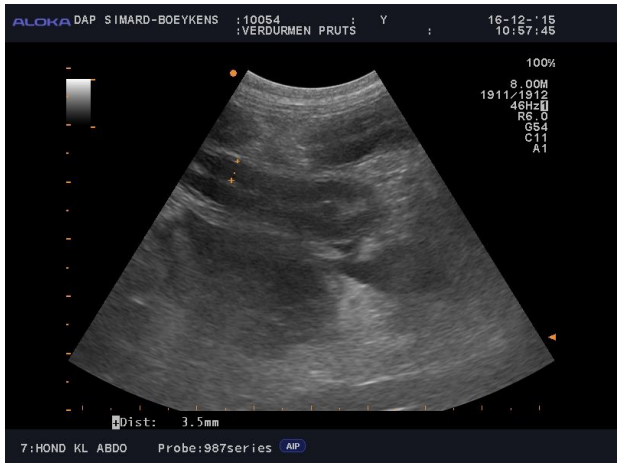

ALOKA DAP SIMARD-BOEYKENS :14617 :OTHELLA : Y : 27-03-'19 11:23:34
100%
8.00M
99/100
50Hz
R3.0
G55
C10
A1
12:KAT ABDO
Probe:987series
AIP


ALOKA DAP SIMARD-BOEYKENS :14617 :OTHELLA : Y : 27-03-'19 11:23:04
100%
8.00M
111/112
43Hz
R4.0
G55
C10
A1
12:KAT ABDO
Probe:987series
AIP

Lymfangiestasie

Lymfangiestasie





Lymfoom: diffuus

- Radiografie 000
- Echografie
  - +/- gelijk aan IBD!!!!
  - normaal indien beperkt tot mucosa!!!
  - verdikking muscularis
    - eerder T-cel lymfoom
- Full Thickness biopten!!!!!!!

J Vet Intern Med 2010;24:289–292

Ultrasonographic Evaluation of the Muscularis Propria in Cats with Diffuse Small Intestinal Lymphoma or Inflammatory Bowel Disease

A. L. Zwingenberger, S. L. Marks, T. W. Baker, and P. F. Moore

Ultrasonographic thickening of the muscularis propria in feline small intestinal small cell T-cell lymphoma and inflammatory bowel disease

Journal of Feline Medicine and Surgery
2014, Vol 16(2) 89–98
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DOI: 10.1177/1098612X13498596
jfms.com
SAGE

Lise A Daniaux[1], Michele P Laurenson[1], Stanley L Marks[2], Peter F Moore[3], Sandra L Taylor[4], Rachel X Chen[4] and Allison L Zwingenberger[5]

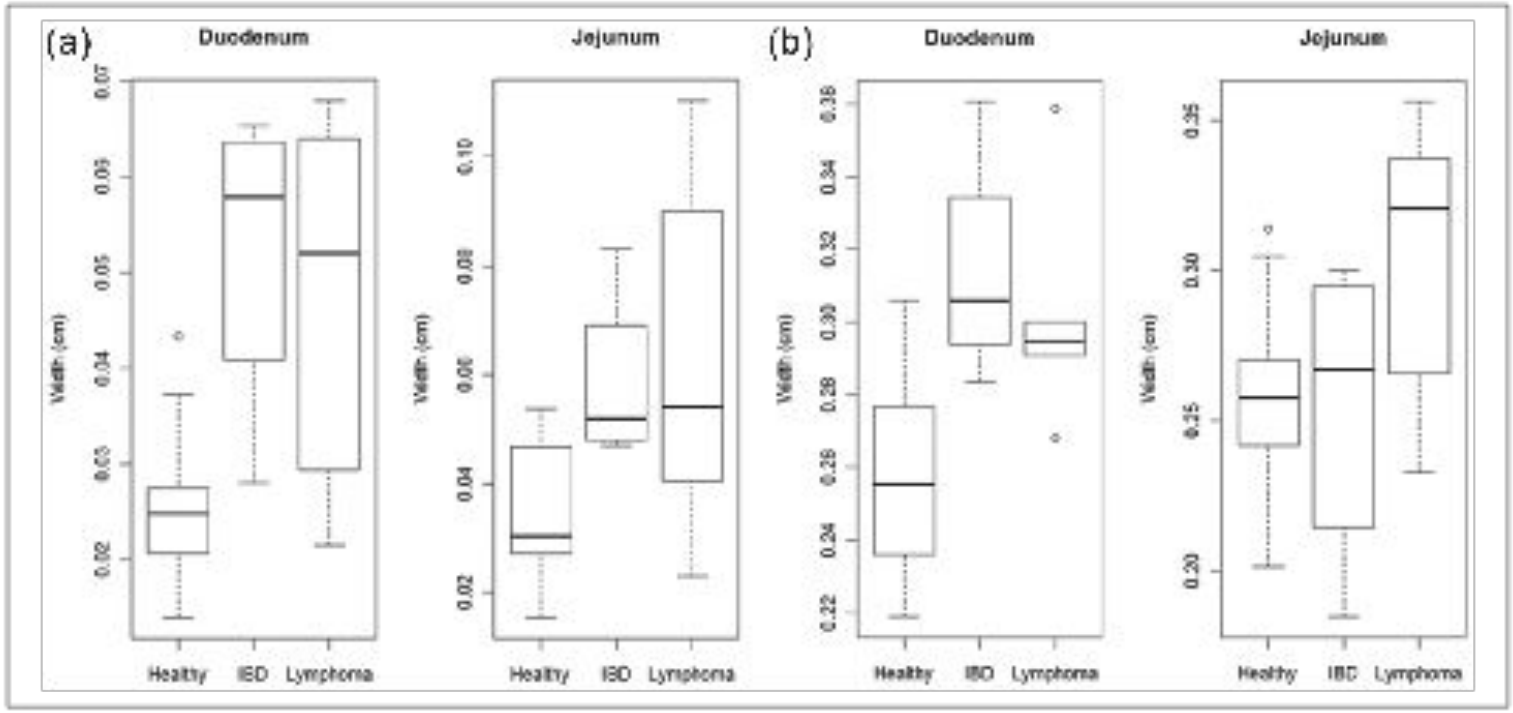
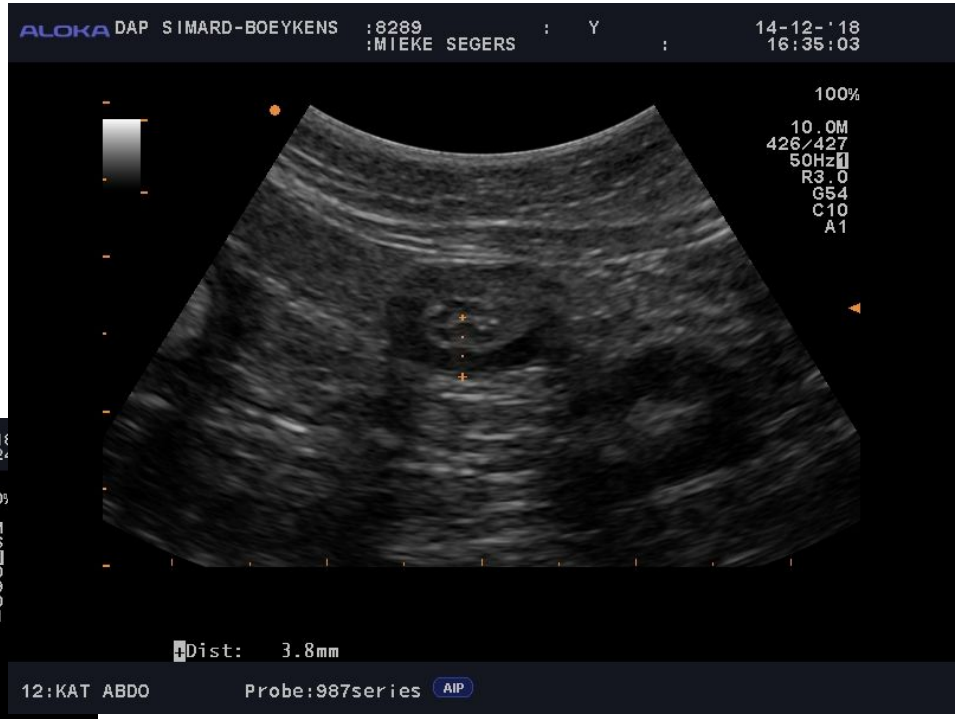


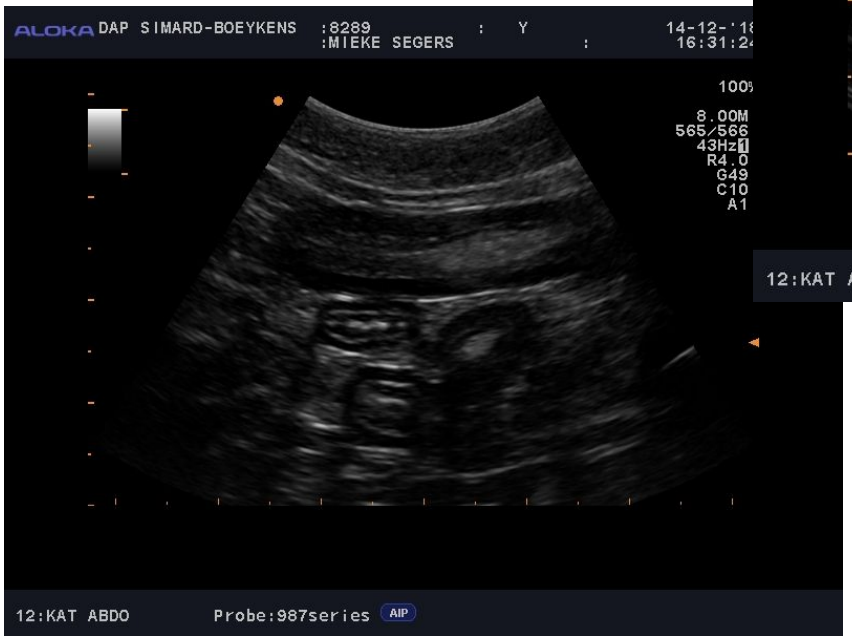
Figure 1 Thickness (cm) of the muscularis propria (a) and the full intestinal wall (b) in the duodenum and jejunum for healthy cats and cats with lymphoma or inflammatory bowel disease

Lymfoom

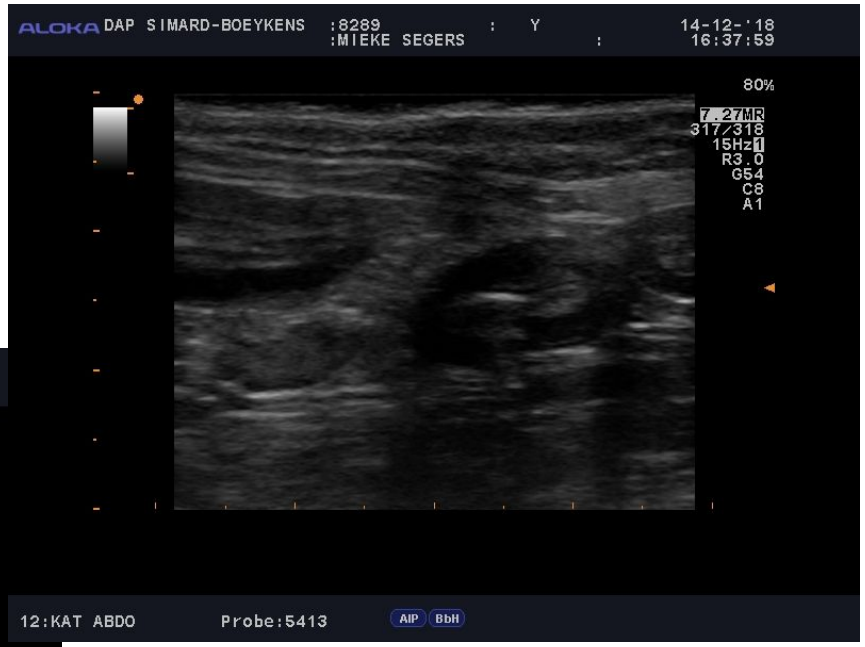
- Lymfeklieren
  - meestal rond
    - breedte>½ lengte
  - hypo-echogeen
  - IBD
    - eerder hyperechogeen
    - normale structuur

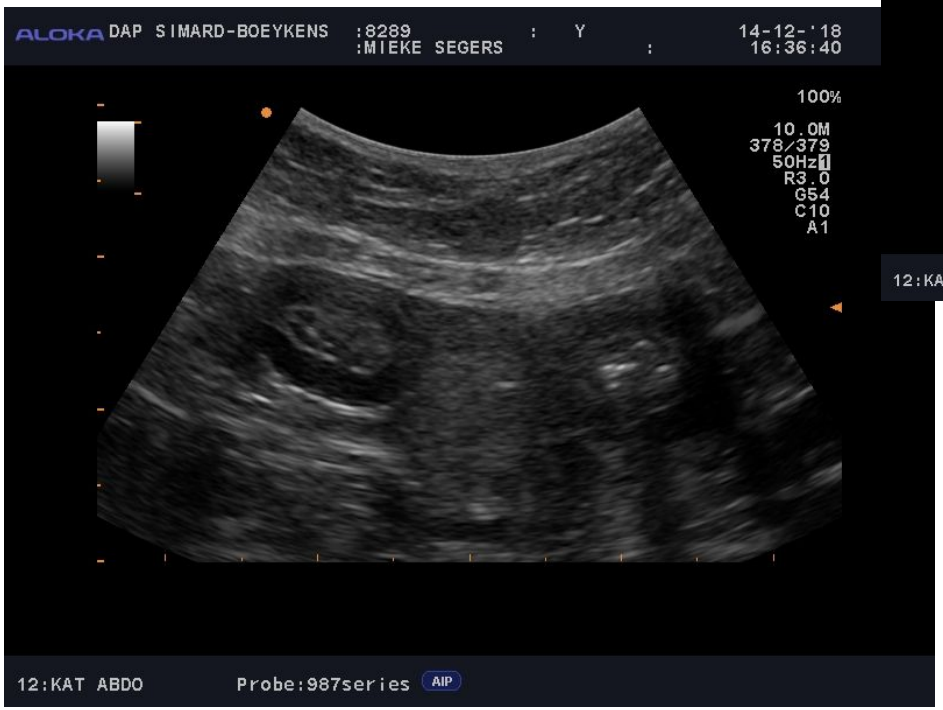
Lymfoom


ALOKA DAP SIMARD-BOEYKENS :8289 : Y 14-12-'18
:MIEKE SEGERS : 16:35:03
100%
10.0M
426/427
50Hz
R3.0
G54
C10
A1
Dist: 3.8mm
12:KAT ABDO Probe:987series AIP

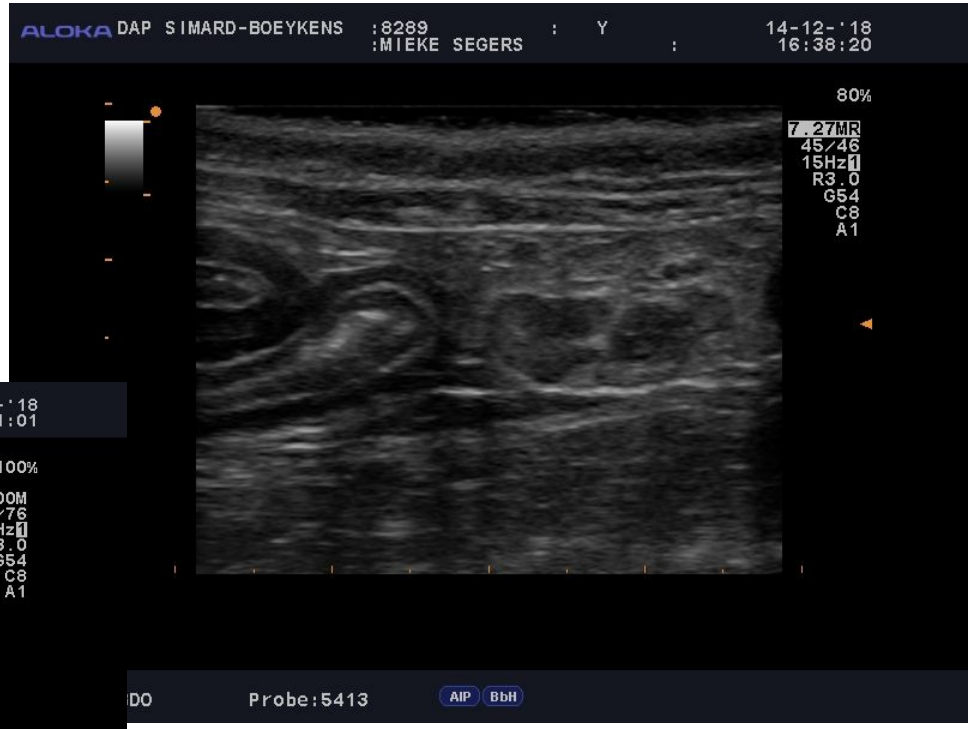

ALOKA DAP SIMARD-BOEYKENS :8289 : Y
:MIEKE SEGERS :
8.00M
565/566
43Hz
R4.0
G49
C10
A1
12:KAT ABDO Probe:987series AIP

Lymfoom


ALOKA DAP SIMARD-BOEYKENS :8289 : Y 14-12-'18
:MIEKE SEGERS : 16:37:59
80%
7.27MR
317/318
15Hz
R3.0
G54
C8
A1
12:KAT ABDO Probe:5413
AIP BbH

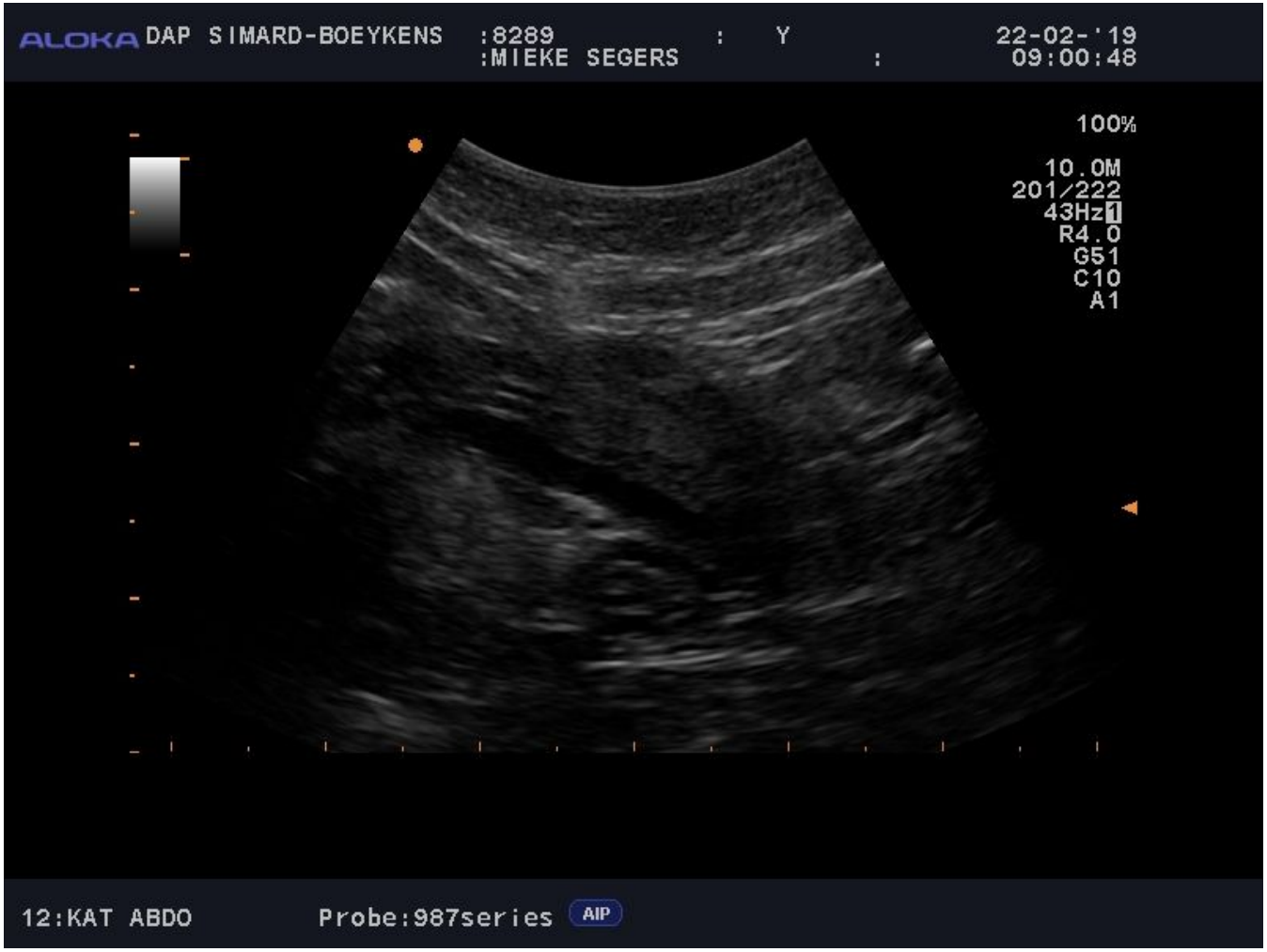

ALOKA DAP SIMARD-BOEYKENS :8289 : Y 14-12-'18
:MIEKE SEGERS : 16:36:40
100%
10.0M
378/379
50Hz
R3.0
G54
C10
A1
12:KAT ABDO Probe:987series
AIP

Lymfoom

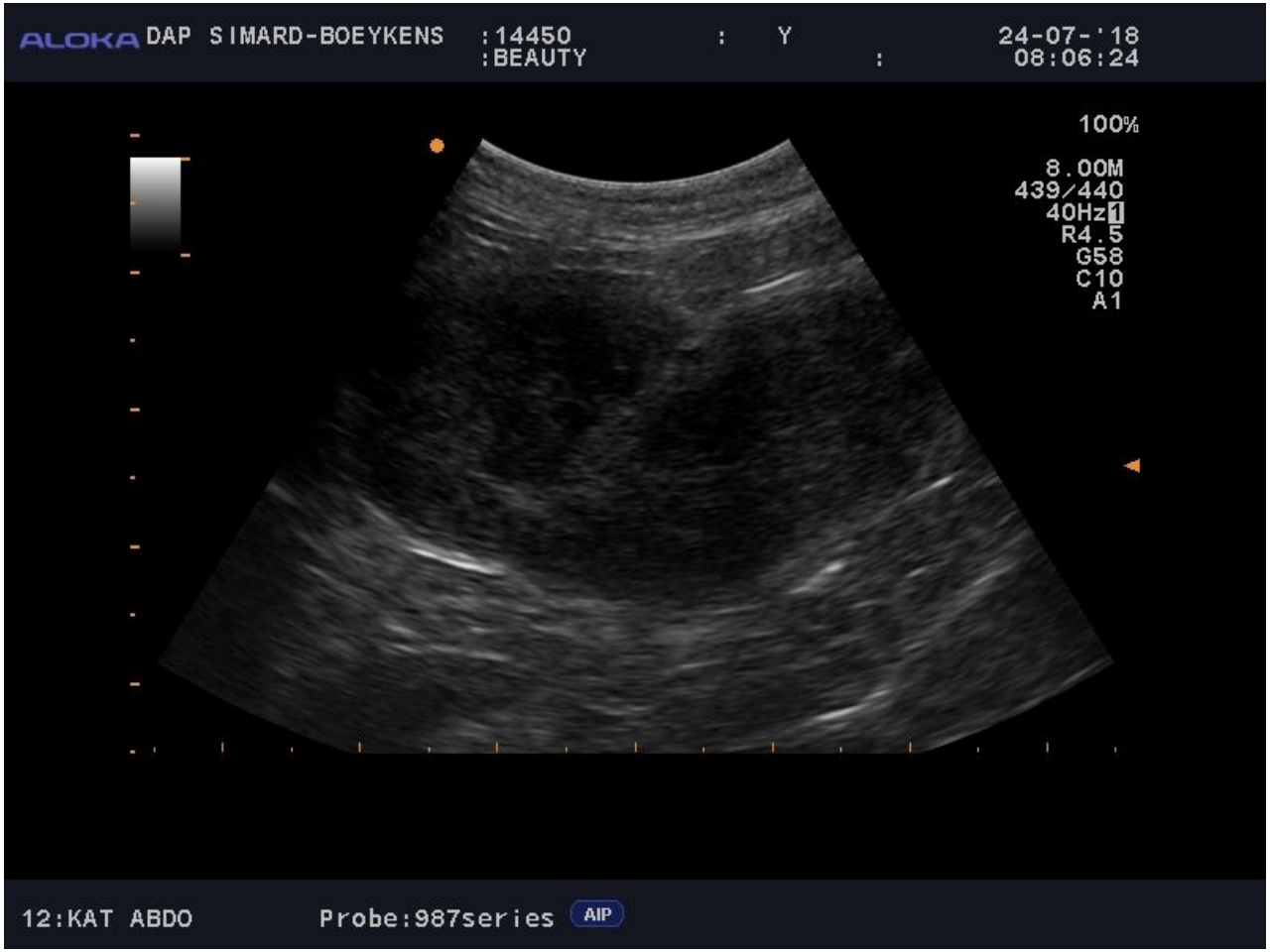

ALOKA DAP SIMARD-BOEYKENS :8289 : Y 14-12-'18
:MIEKE SEGERS : 16:38:20
80%
7.27MR
45/46
15Hz
R3.0
G54
C8
A1
DO Probe:5413
AIP BbH

ALOKA DAP SIMARD-BOEYKENS :8289 : Y 14-12-'18
:MIEKE SEGERS : 16:41:01
.06
.06
F31
100%
5.00M
75/76
4Hz
R3.0
G54
C8
A1
12:KAT ABDO Probe:5413
AIP BbH

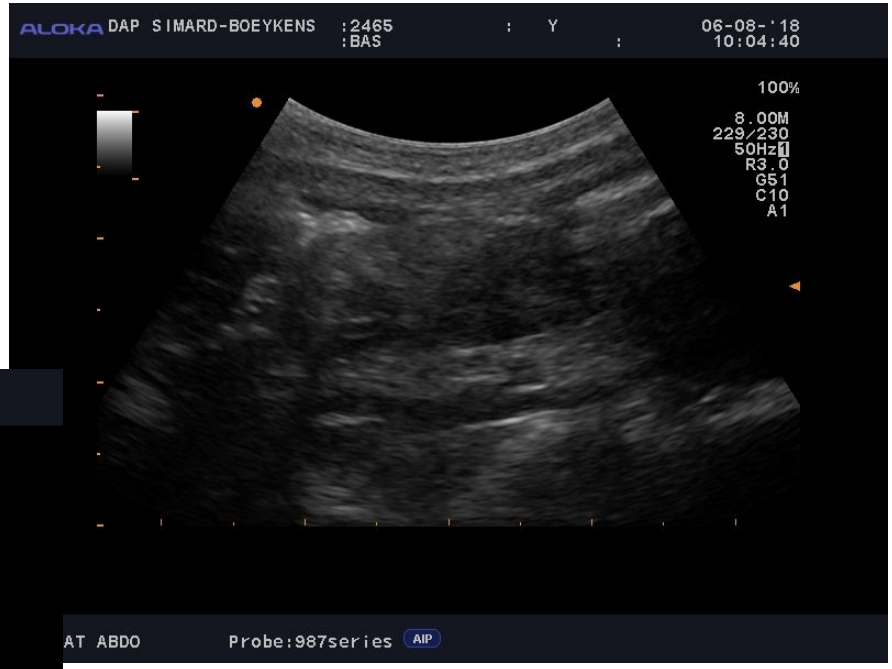
Lymfoom

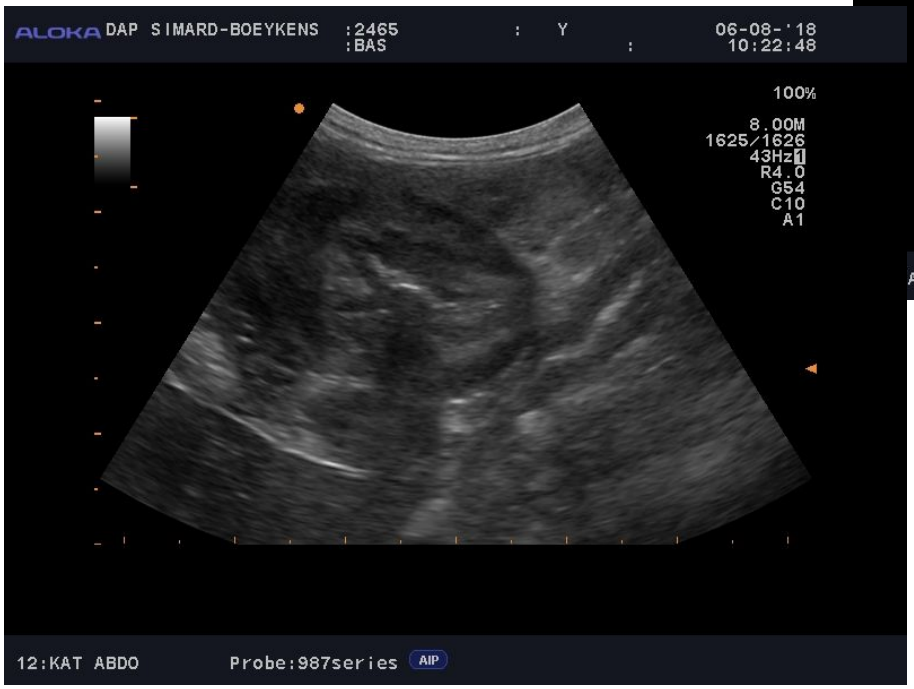

ALOKA
DAP SIMARD-BOEYKENS :8289 : Y 22-02-'19
:MIEKE SEGERS : 09:00:48
100%
10.0M
201/222
43Hz
R4.0
G51
C10
A1
12:KAT ABDO
Probe:987series
AIP

Lymfoom

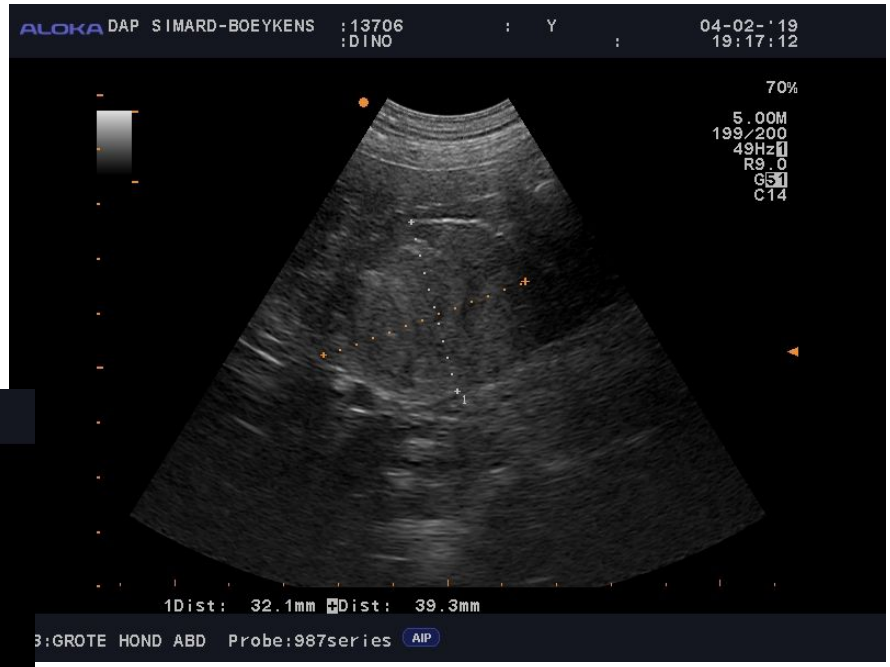

ALOKA
DAP SIMARD-BOEYKENS
:14450
:BEAUTY
Y
24-07-'18
08:06:24
100%
8.00M
439/440
40Hz
R4.5
G58
C10
A1
12:KAT ABDO
Probe:987series
AIP

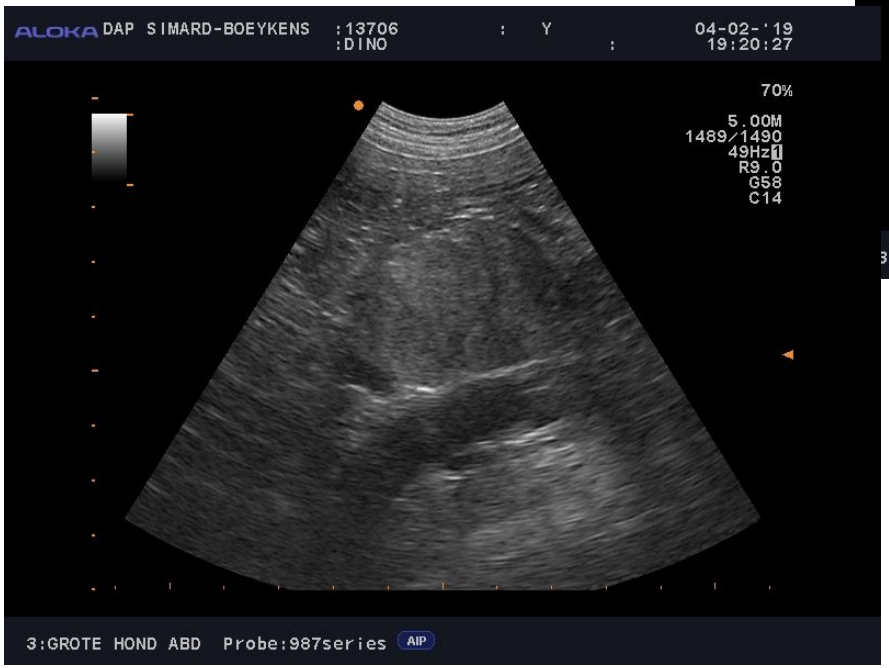
Lymfoom


ALOKA DAP SIMARD-BOEYKENS :2465 :BAS : Y : 06-08-'18 10:04:40
100%
8.00M
229/230
50Hz
R3.0
G51
C10
A1
AT ABDO
Probe:987series
AIP

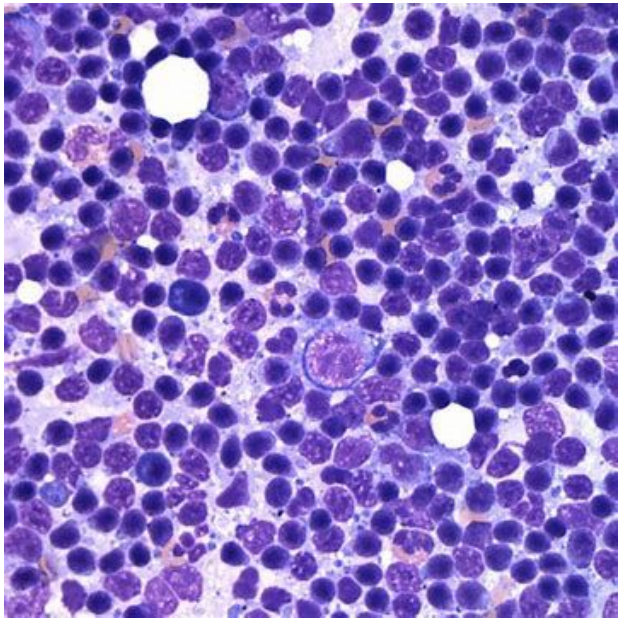

ALOKA DAP SIMARD-BOEYKENS :2465 :BAS : Y : 06-08-'18 10:22:48
100%
8.00M
1625/1626
43Hz
R4.0
G54
C10
A1
12:KAT ABDO
Probe:987series
AIP

Lymfoom

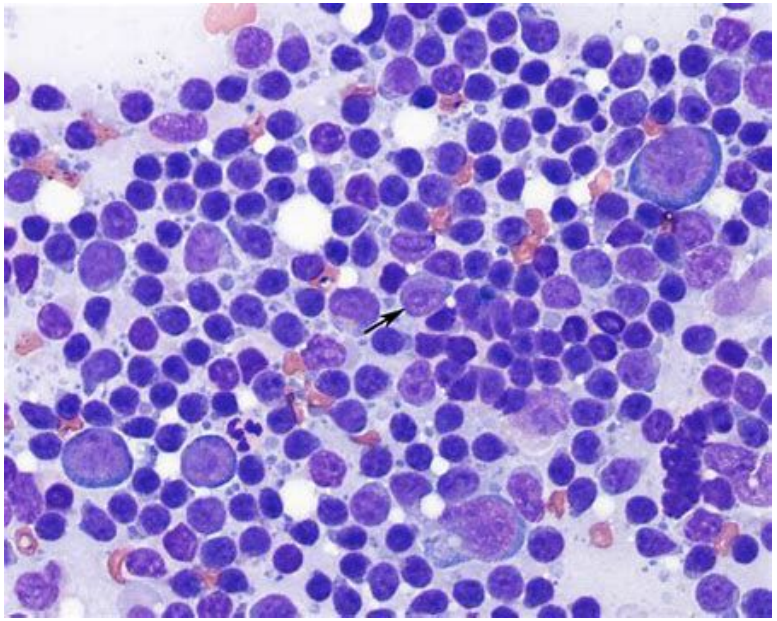

ALOKA DAP SIMARD-BOEYKENS :13706 : Y 04-02-'19
:DINO : 19:17:12
70%
5.00M
199/200
49Hz
R9.0
G51
C14
1Dist: 32.1mm Dist: 39.3mm
3:GROTE HOND ABD Probe:987series AIP


ALOKA DAP SIMARD-BOEYKENS :13706 : Y 04-02-'19
:DINO : 19:20:27
70%
5.00M
1489/1490
49Hz
R9.0
G58
C14
3:GROTE HOND ABD Probe:987series AIP

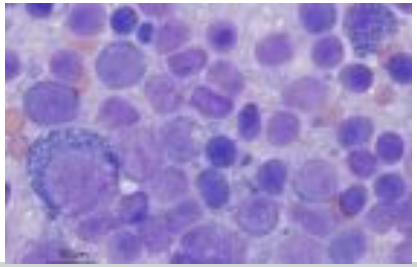
Lymfoom



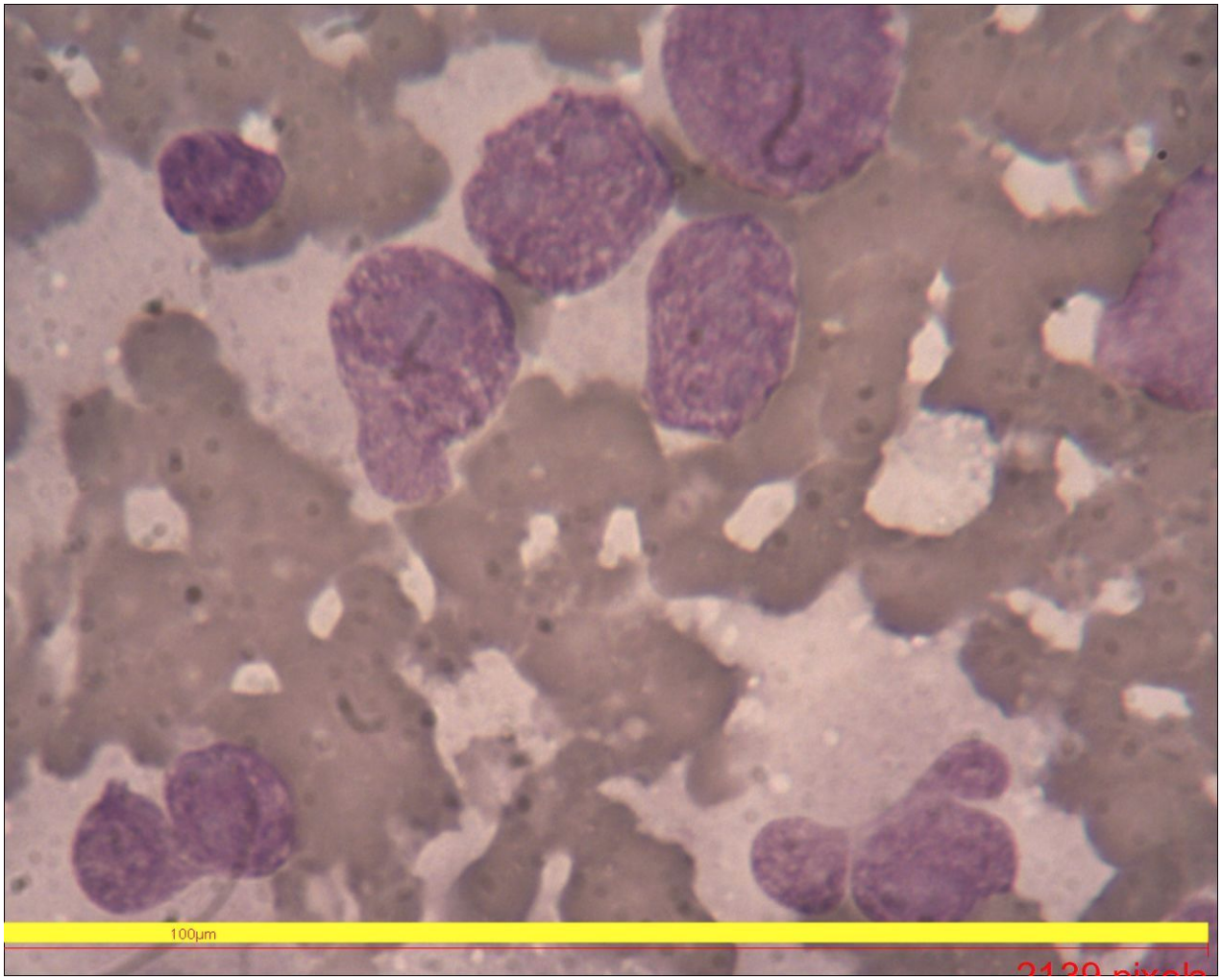
Normale lymfeklier



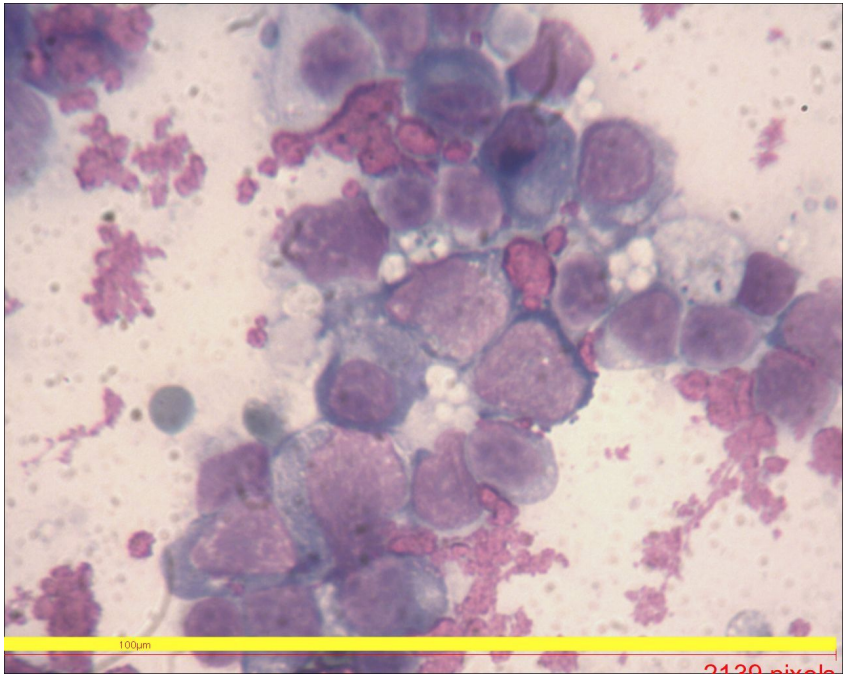
Reactieve lymfeklier

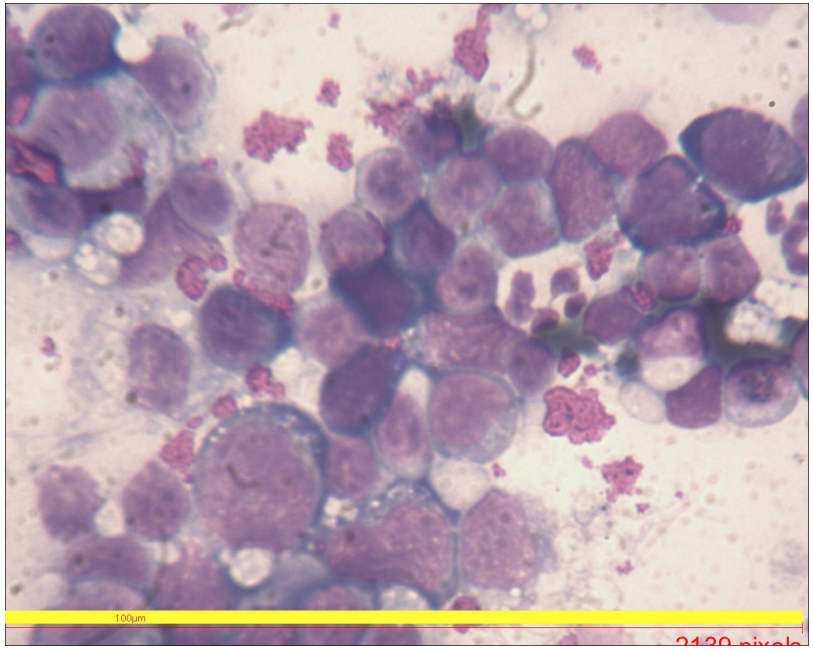


Lymfoom



Lymfoom





Gelokaliseerde darmtumor

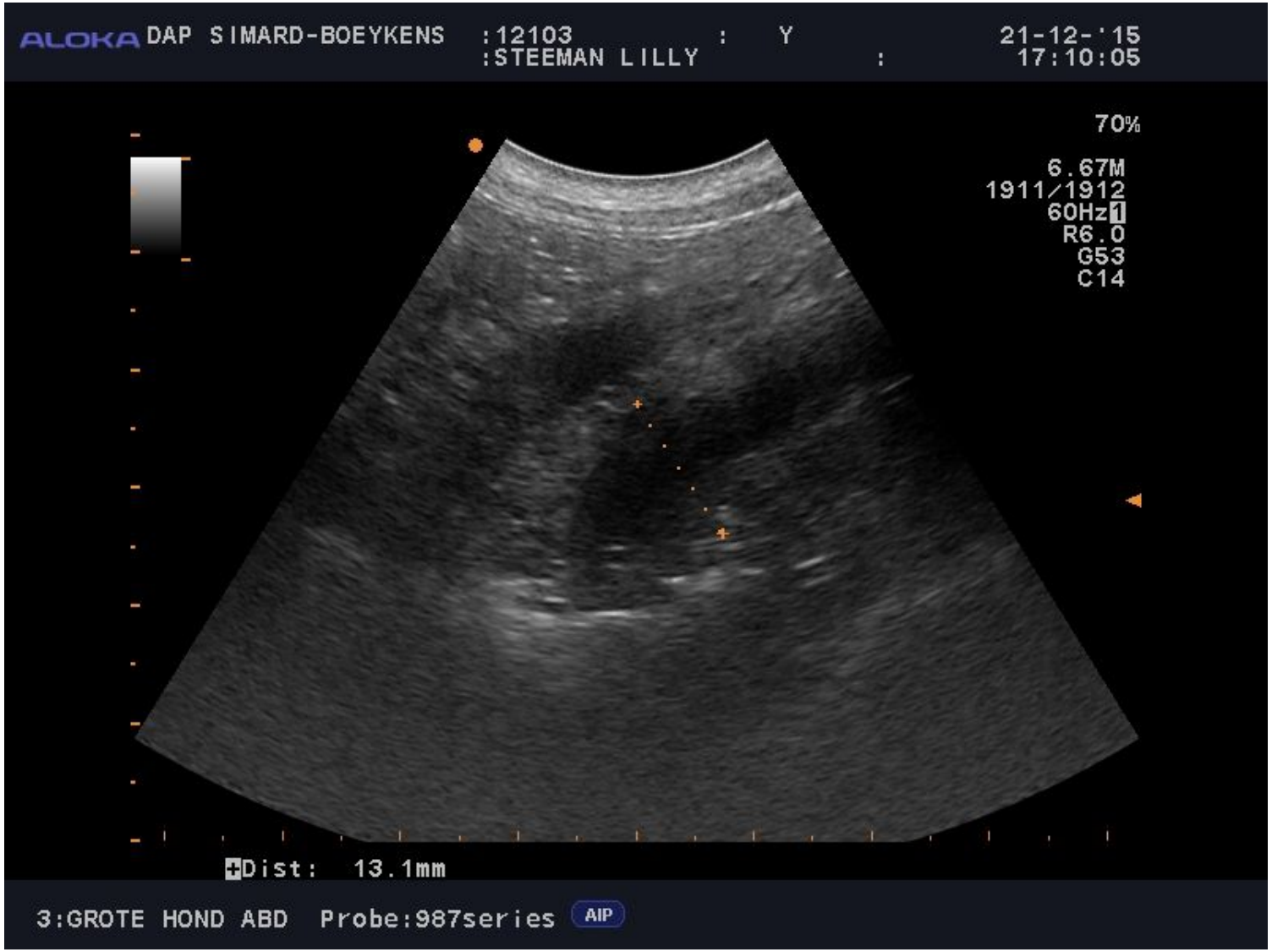
- Radiografie
  - massa (soms)
  - ileus (soms)
  - chronische onvolledige obstructie
    - “gravel sign”

Gelocaliseerde darmtumor

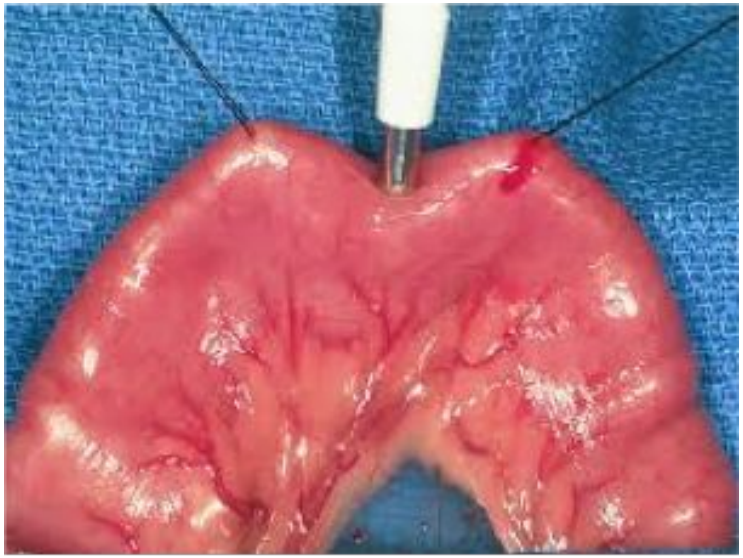
- Echografie
  - >>>RX
  - wand verdikt
  - verlies van normale lagen!!!!
  - verlies peristaltiek thv tumor
  - ileus voor de tumor
  - soms abnormale lymfeklieren
- Diagnose
  - cytologie!!! biopsie!!
  - adenocarcinoom
  - lymfoom
  - leiomyoma, leiomyosarcoma

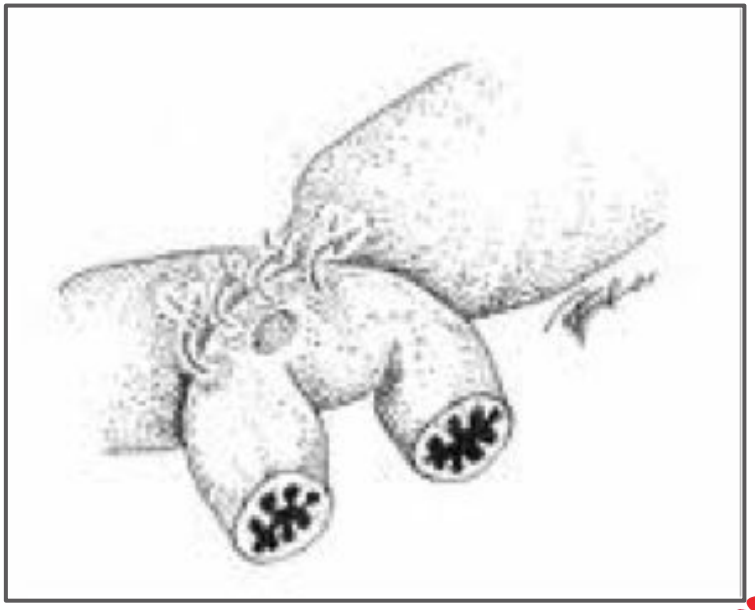
Figure 13.

Longitudinal sonogram of duodenum of a dog with smooth-muscle tumor. The mass is echogenic and homogeneous.


ALOKA
DAP SIMARD-BOEYKENS
:12103
:STEEMAN LILLY
Y
21-12-'15
17:10:05
70%
6.67M
1911/1912
60Hz
R6.0
G53
C14
Dist: 13.1mm
3:GROTE HOND ABD
Probe:987series
AIP

Serosal Patching





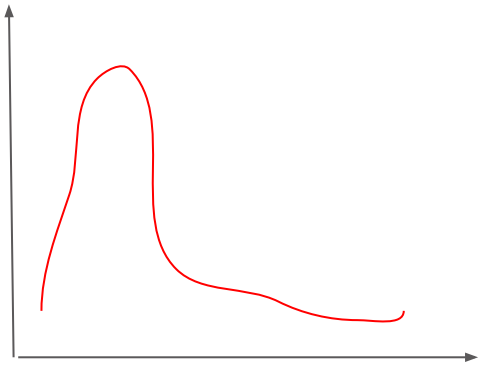
2. Acute Phase Proteïns APP

- 3 belangrijke eigenschappen
  - Zeer snelle respons : vroegste marker van ontsteking
  - Niet specifiek
  - Species afhankelijk

- Biologische rol : niet goed gekend
  - Modulatie immuun respons en ontstekingsreactie
  - Bescherming tegen infectie
  - Herstel beschadigd weefsel

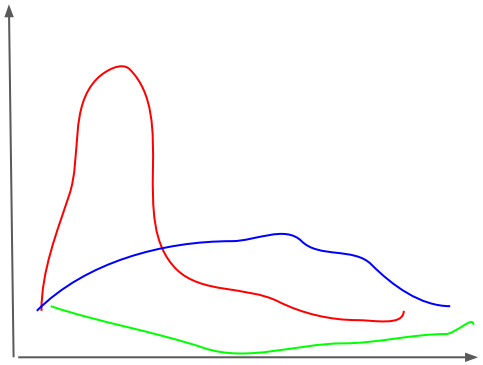
2. Acute Phase Proteïns APP

- MAJOR APP's
  - lage circulerende concentraties
  - sterke stijging 10-100*
  - snelle stijging 24-48u
  - snelle daling



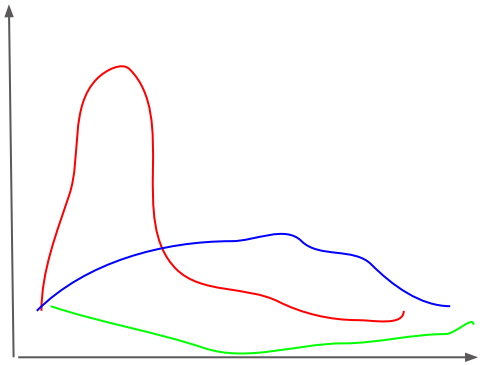
- Hond
  - CRP, SAA
- Kat
  - SAA, æGP

2. Acute Phase Proteïns APP



- Moderate :
  - matige stijging 2-10*
  - trage stijging 4-7d.
  - graduele daling
- Negative : daling
- Hond
  - Moderate : Ceruloplasmine, Haptoglobin, AGP
  - Negative: Albumine, Transferrine
- Kat
  - Moderate : Haptoglobin

2. Acute Phase Proteïns APP



- Pre-analytische factoren
  - Zeer stabiel
  - Beperkte invloed van anticoagulantia
  - Invloed van hemolyse, lipemie en bilirubinemie
    - Afhankelijk van marker
    - Afhankelijk van de testmethode

Table 2. Effects of interfering substances in some methods for analysis of acute phase proteins.[37,71,66,95]

Acute Phase Protein	Method	Hemolysis	Lipemia	Bilirubinemia
C-reactive protein (CRP)	ELISA	Increased*	Increased*	Decreased*
	Immunoturbidimetric	Decreased by 90% when Hb = 80 mg/dL	Not evaluated	Not evaluated
Serum amyloid A	ELISA	No effect	No effect	No effect
Haptoglobin (Hp)	Spectrophotometric	Decreased by 25–30% maximum when Hb = 0.3–10 mg /mL	No effect	No effect
	Immunoturbidimetric	Decreased by 70–80% when Hb >25 mg/dL	Increased when triglycerides >100 mg/dL	Not evaluated
Ceruloplasmin	Spectrophotometric	Increased when Hb <2.5 mg/dL; decreased when Hb >2.5 mg/dL*	Increased*	Increased*

*No significant impact on clinical interpretation.

2. Acute Phase Proteïns APP

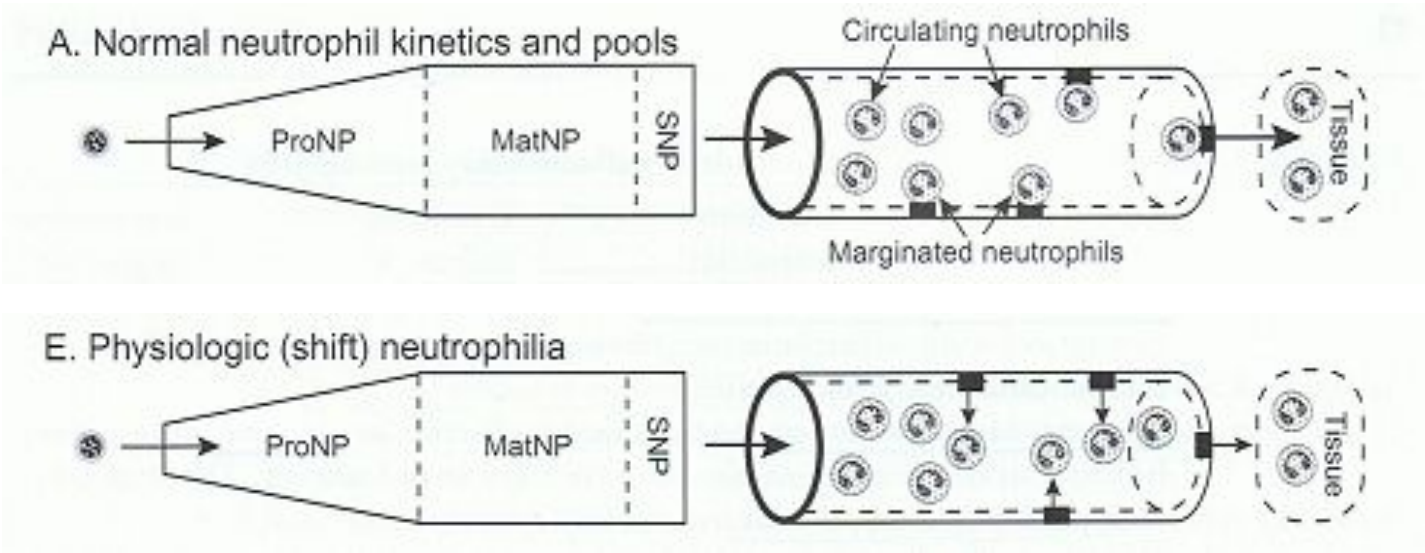
- <u>Biologische factoren</u>
  - Normaalwaarden afhankelijk van testmethode
    - Gebruik referentiewaarden van het labo!!!
  - Geen invloed van leeftijd bij gezonde dieren
    - volwassen sterkere stijging
  - Beperkte invloed van ras
  - Geen invloed van geslacht
    - stijging tijdens de dracht
  - Geen circadisch ritme, geen dag-dag variatie
  - Corticoïden
    - CRP SAA : geen invloed
    - Haptoglobin : stijging

2. Acute Phase Proteïns APP

- **Vergelijking APP-WBC**
  - Stijgen vroeger dan WBC!!!
  - APP 6* sensitiever
    - Stijgen zelfs als WBC normaal blijven
  - Stijgen ook indien problemen met beenmerg
  - Dalen sneller : monitoring mogelijk
  - Stijging altijd significant: specifiek
    - !!subklinische aandoeningen!!!
  - Geen invloed van corticoïden
  - Langere stabiliteit voor analyse

2. Acute Phase Proteïns APP

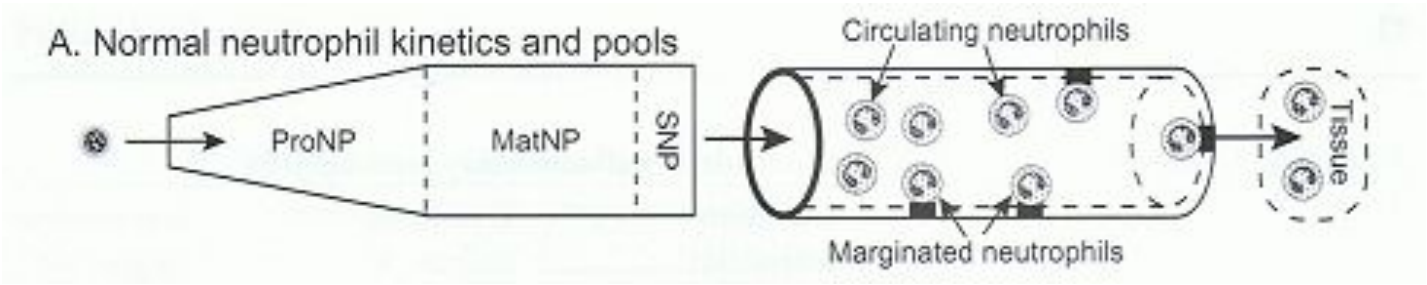
- **<u>Vergelijking APP-WBC</u>**
  - Stijging altijd significant: specifiek
  - Geen invloed van corticoïden
- Neutrofilie
  - Fysiologische neutrofilie (adrenaline) K>H

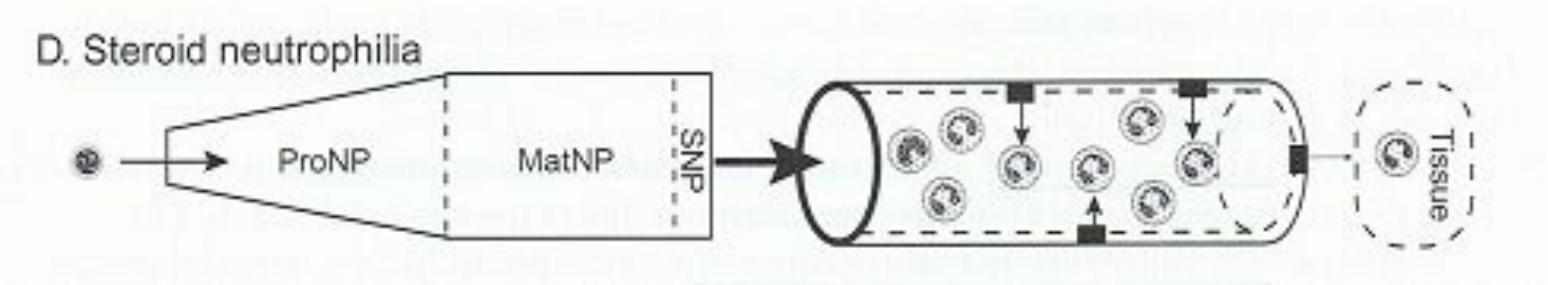


2. Acute Phase Proteïns APP

❖ Vergelijking APP-WBC

- ➢ Neutrofilie
- ➢ Steroïd geïnduceerde neutrofilie H>K (Haptoglobine!!)
  - ■ endogeen
  - ■ exogeen





2. Acute Phase Proteïns APP

- **Vergelijking APP-WBC**
  - Stijging altijd significant: specifiek
  - Geen invloed van corticoïden
- Neutrofilie
  - Fysiologische neutrofilie (adrenaline) K>H
  - Steroïd geïnduceerde neutrofilie H>K
    - endogeen
    - exogeen
  - Reactieve neutrofilie
  - Paraneoplastische neutrofilie
  - Leukemie
  - CLAD en TNS

A canine model of Cohen syndrome: Trapped Neutrophil Syndrome

Jeremy R Shearman[1,2] and Alan N Wilton[1,3*]

Leukocyte Adhesion Deficiency in Children and Irish Setter Dogs

THOMAS R. BAUER, JR., YU-CHEN GU, KATE E. CREEVY, LAURA M. TUSCHONG, LISA EMBREE, STEVEN M. HOLLAND, ROBERT A. SOKOLIC, AND DENNIS D. HICKSTEIN

2. Acute Phase Proteïns APP

- **Toepassingen**
  - Diagnose van inflammatoire aandoeningen
  - Diff. Diagnose
  - Monitoring van de evolutie
  - Prognose?
- Hond>Kat

2. APP: CRP

FULL PAPER *Clinical Pathology*

C-Reactive Protein Concentration in Dogs with Various Diseases

Masaaki NAKAMURA[1)], Masashi TAKAHASHI[1)], Koichi OHNO[1)*], Akiko KOSHINO[1)], Ko NAKASHIMA[1)], Asuka SETOGUCHI[1)], Yasuhito FUJINO[1)] and Hajime TSUJIMOTO[1)]

[1)]*Department of Veterinary Internal Medicine, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1–1–1 Yayoi, Bunkyo-ku, Tokyo 113–8657, Japan*

(Received 29 March 2007/Accepted 26 September 2007)

- **Chirurgie**
  - Snelle stijging (binnen de 24u)
  - Stijging afhankelijk van operatie trauma (bv. Orthopedie)
  - Meestal zeer sterke daling bij verwijderen hechtingen
    - Op dat moment WBC nog sterk gestegen!!

2. APP: CRP

- **GI-stelsel**
  - Gastritis, ulcus (o.a. Door NSAID)
    - !! GEEN STIJGING

C-reactive protein as a prognostic indicator in dogs with acute abdomen syndrome

Angelica M. Galezowski, Elisabeth C. R. Snead, Beverly A. Kidney, Marion L. Jackson[1]

Table 1. Diagnosis and serum C-reactive protein (CRP) concentrations at presentation (0 hr) and at 48–72 hr in 32 dogs with acute abdomen syndrome.*

Dog no.	Diagnosis	CRP (mg/l) 0 hr	CRP (mg/l) 48–72 hr
1	Parvoviral enteritis†	74	22.4
2	Parvoviral enteritis	19.2	21
3	Parvoviral enteritis	34.1	9.8
4	Parvoviral enteritis	41.4	30.1
5	Parvoviral enteritis	58	19.6
6	Parvoviral enteritis	83	15.1
7	Parvoviral enteritis	63	9
8	Acute pancreatitis	4.7	13.6
9	Acute pancreatitis	146	50.2
10	Acute pancreatitis	51.3	42.1
11	Acute pancreatitis	25.2	37
12	Acute pancreatitis and peritonitis†	32.8	NA
13	Acute pancreatitis and pancreatic carcinoma†	202.5	91
14	Hemorrhagic gastroenteritis	29.3	14.5
15	Hemorrhagic gastroenteritis	18.5	12.8
16	Acute gastroenteritis	0.2	3.7
17	Acute gastroenteritis	2.3	0
18	Jejunal foreign body†	37.4	NA
19	Linear foreign body	2.2	17.8
20	Suspect gastric ulceration	0	0.9
21	Gastric ulceration	0	0
22	Gastric dilatation and volvulus	0	6.8
23	Splenic hemangiosarcoma‡	16.6	NA
24	Pyometra	72.5	17.9
25	Pyometra	86	33.2
26	Urinary tract rupture with septic peritonitis	16.9	13.9
27	Uroabdomen with septic peritonitis†	25.5	NA
28	Urolithiasis and urethral obstruction	0	0
29	Possible urinary obstruction	0.9	9.4
30	Immune-mediated hemolytic anemia†	140	47.6
31	Chocolate toxicosis	0.4	0.2
32	Heatstroke	6	5.9

* CRP reference interval: 0–9 mg/l. NA = not available.
† Euthanized.
‡ Died.

2. APP: CRP

- **GI-stelsel**
  - Gastritis (o.a. Door NSAID)
  - IBD: beperkte stijging 10-15 microgr/mL
    - Afhankelijk van de ergheid
    - Monitoring mogelijk!!
    - NB AGP en Haptoglobulin niet bruikbaar
- Enteritis, obstructie : sterke stijging
  - Geen invloed van niet inflammatoire aandoeningen
    - EPI, SIBO, andere

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  - Geen invloed van niet inflammatoire aandoeningen
    - EPI, SIBO, andere
- Pancreatitis
  - Monitoring!!!

2. APP: CRP

Table 1. Representative diseases with significantly high plasma CRP levels

Diseases*	(n)	CRP (mg/dl)			Number of dogs	
		Median**	Min.	Max.	≥1 mg/dl (%)	≥10 mg/dl (%)
Pyometra	7	20.0	3.5	>20	7 (100%)	5 (71%)
Sterile nodular panniculitis	7	20.0	10.0	>20	7 (100%)	5 (100%)
Acute pancreatitis	5	15.0	6.1	>20	5 (100%)	3 (60%)
Idiopathic polyarthritis	31	13.0	1.7	>20	31 (100%)	21 (67%)
Hemangiosarcoma	5	7.6	3.1	16	5 (100%)	2 (40%)
Nasal adenocarcinoma	5	6.7	0.1	9	4 (80%)	0 (0%)
Immune-mediated hemolytic anemia	35	6.5	0	>20	30 (86%)	9 (26%)
Cholangiocellular carcinoma	7	6.3	0.1	19	6 (86%)	2 (29%)
Acute lymphoblastic leukemia	6	4.5	0.1	>20	5 (83%)	1 (17%)
Malignant histiocytosis	16	4.3	0.3	>20	11 (69%)	4 (25%)
Lymphoma	127	3.5	0	>20	91 (72%)	26 (21%)
Bronchopneumonia/Pneumonia	16	3.3	0.2	11	12 (75%)	1 (6%)
Malignant mesothelioma	7	2.7	0.7	15	5 (71%)	1 (14%)
Demodicosis	7	2.6	0	7.1	5 (71%)	0 (0%)
Chronic hepatitis	7	1.6	0	9.7	4 (57%)	0 (0%)
Cardiac tamponade	6	1.5	0.7	6.7	3 (50%)	0 (0%)
Myelodysplastic syndrome	5	1.3	0	14	3 (60%)	1 (20%)
Intestinal adenocarcinoma	13	1.0	0	14	8 (62%)	3 (23%)
Immune-mediated thrombocytopenia	7	1.0	0	12	4 (57%)	1 (14%)

* Diseases (n≥5) in which the median of the CRP concentration exceeded the reference range (≥1 mg/dl) were shown.
** CRP values higher than the measurement limit (>20 mg/dl) were statistically analyzed as 20 mg/dl.

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2. APP: CRP

ORIGINAL RESEARCH

C-reactive protein concentration in dogs with primary immune-mediated hemolytic anemia

Christine Griebsch[1], Gisela Arndt[2], Jens Raila[3], Florian J. Schweigert[3], Barbara Kohn[1]

[1]Faculty of Veterinary Medicine, Clinic of Small Animals and [2]Institute for Biometrics and Data Processing, Free University of Berlin, Berlin, Germany; and [3]Institute of Nutritional Science, University of Potsdam, Potsdam, Germany

- **Auto-immune aandoeningen**
  - Rheumatoïde arthritis, Polyarthritis
    - Tijdens niet actieve fase van de aandoening : CRP normaal
  - IMHA
    - Significante stijging bij **alle** aangetaste dieren op dag 0
    - Sterke daling door immunosuppressieve behandeling op dag8 en normalisatie op dag14
    - Geen verschil tussen wel en niet overlevenden (DIC) op dag8

		C-reactive protein (µg/mL)			
Group	Parameter	Day 0	Day 3	Day 8	Day 14
1 (survival time ≥14 days)	Median (range)	242 (40–576)	69 (16–183)*	35 (0–217)*	2 (0–50)*
	n	24	18	16	10
2 (survival time < 14 days)	Median (range)	194 (69–438)	119 (24–187)	41	—
	n	6	5	1	0

2. APP: CRP

ORIGINAL RESEARCH

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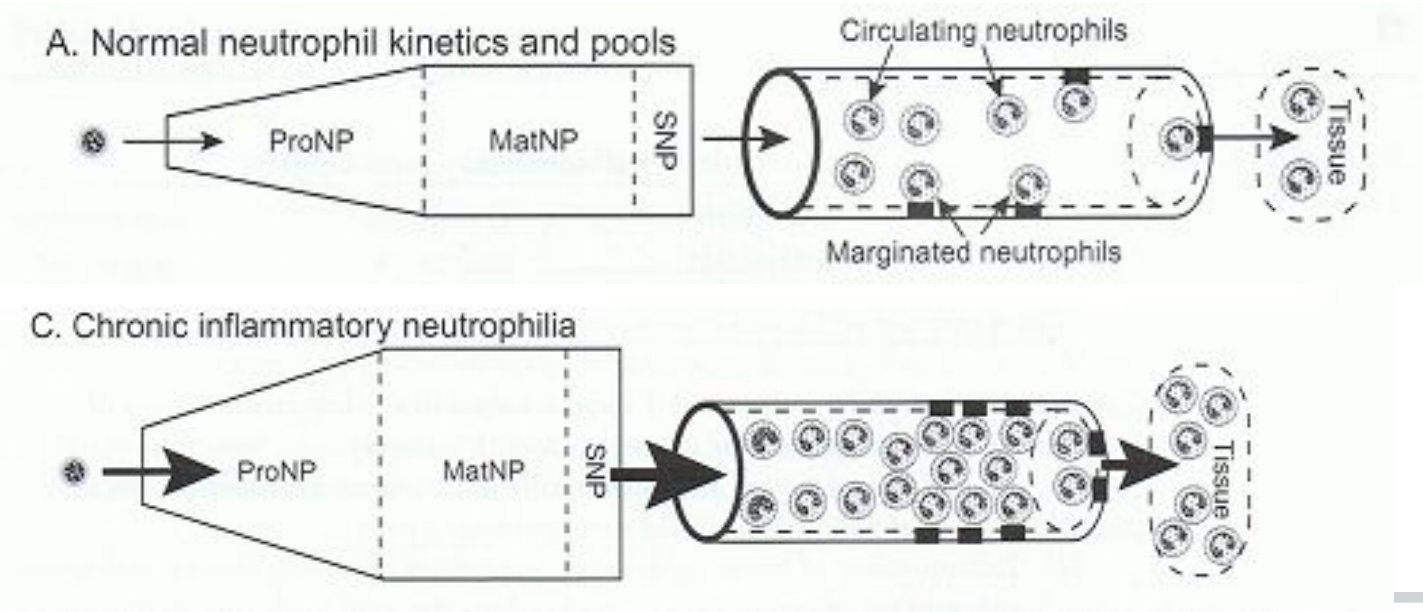
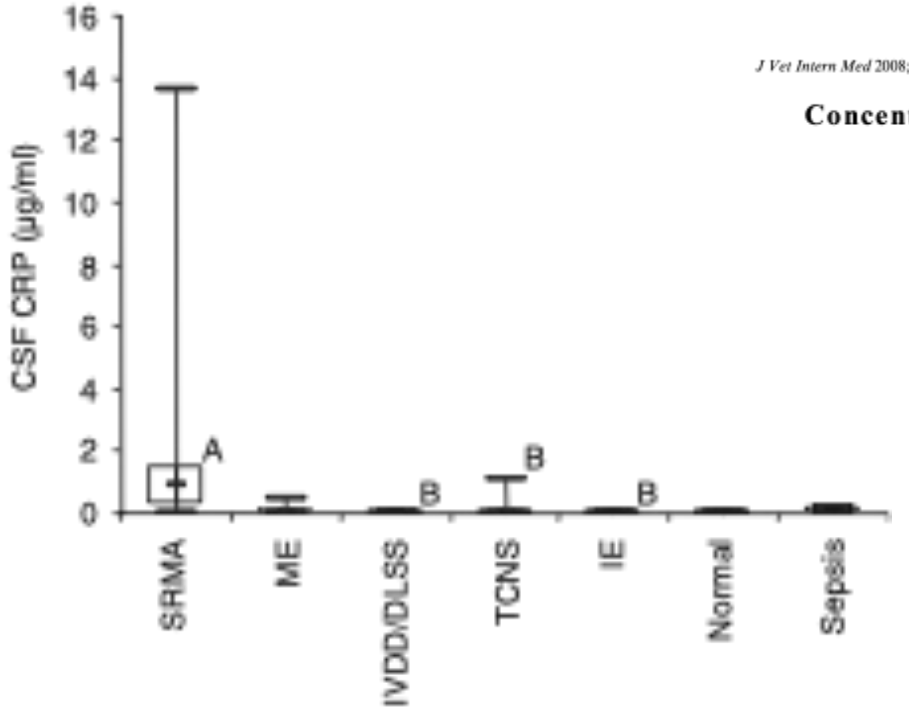
- **Auto-immune aandoeningen**
  - IMHA
    - 1 dier constante verhoging : miltnecrose
    - WBC blijven hoog
      - Corticoïden
      - minder verbruik



2. APP: CRP

- **Auto-immune aandoeningen :** Steroid-responsive meningitis-arteritis
  - CRP stijgt bij alle patiënten
  - niet bij andere neurologische aandoeningen



J Vet Intern Med 2008;22:1149–1156

Concentrations of Acute-Phase Proteins in Dogs with Steroid Responsive Meningitis-Arteritis

A. Bathen-Noethen, R. Carlson, D. Menzel, R. Mischke, and A. Tipold

2. APP: CRP

- **Auto-immune aandoeningen :** Steroid-responsive meningitis-arteritis
  - CRP daalt bij succesvolle behandeling
  - volgt celgehalte CSF

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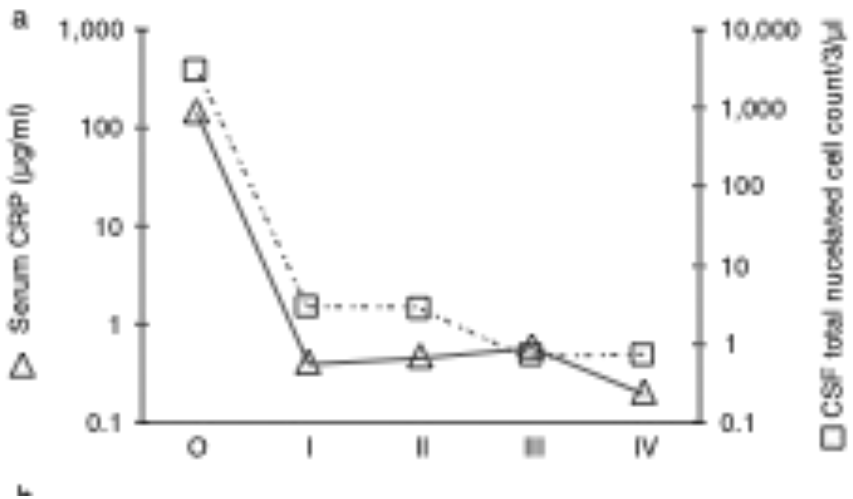

2. APP: CRP

- **Auto-immune aandoeningen :** Steroid-responsive meningitis-arteritis
  - daling en normalisering voorspelt kans op recidief niet
  - bij relapse nieuwe stijging

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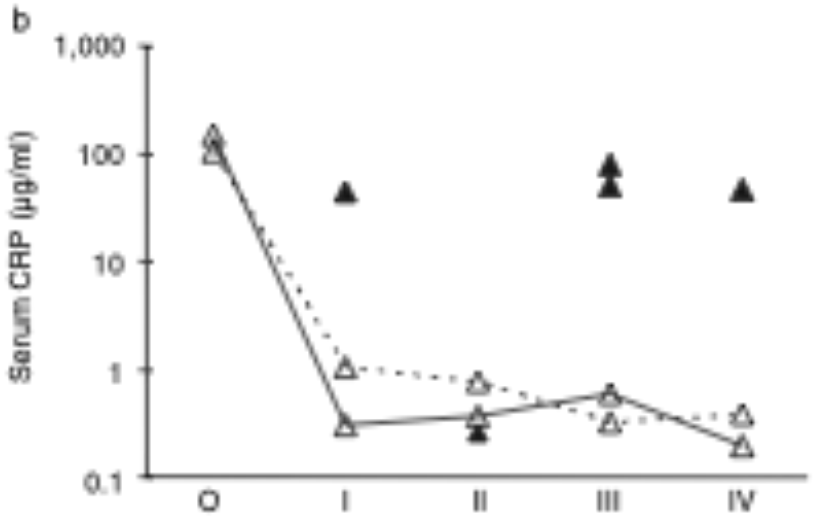
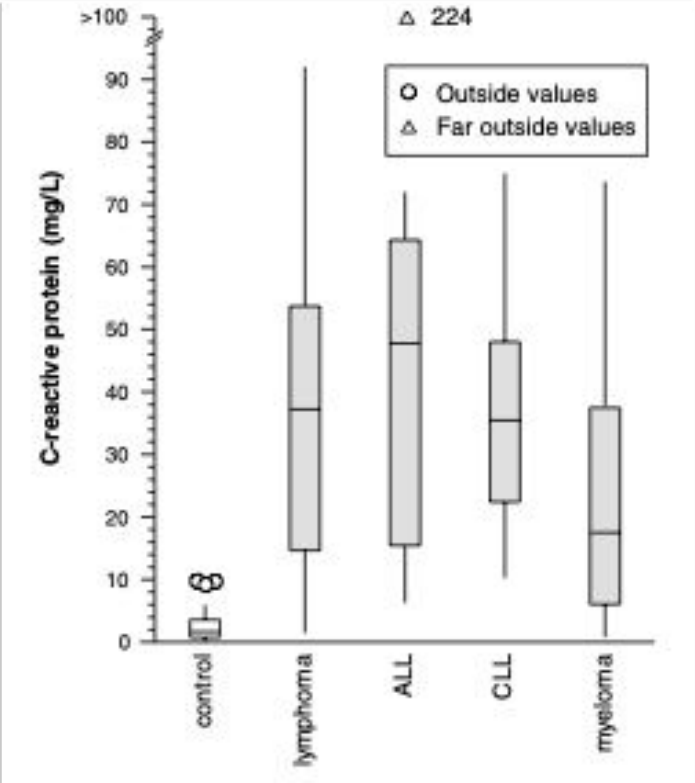


2. APP: CRP

- **Hematologische tumoren en lymfoom**
  - meeste hem. tumoren: uitgesproken stijging!!



Changes in C-reactive protein and haptoglobin in dogs with lymphatic neoplasia

R. Mischke [a,b,*], M. Waterston [b], P.D. Eckersall [b]

2. APP: CRP

- **Hematologische tumoren en lymfoom**
  - bij remissie: daling CRP
  - 68% verhoogd CRP (andere studies 100%)
  - remissie: 90% normaal CRP
  - partiële remissie: significant hoger dan remissie
  - Conclusie
    - CRP als marker voor remissie
    - best combineren met andere markers om progressie te volgen

J Vet Intern Med 2007;21:1231–1236

Serum C-Reactive Protein Concentration as an Indicator of Remission Status in Dogs with Multicentric Lymphoma

Lise Nielsen, Nils Toft, P. David Eckersall, Dominic J. Mellor, and Joanna S. Morris

2. APP: CRP

❖ Hematologische tumoren en lymfoom

Computational diagnosis and risk evaluation for canine lymphoma

E. M. Mirkes

Department of Mathematics, University of Leicester, Leicester, LE1 7RH, UK

I. Alexandrakis, K. Slater, R. Tuli

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Computational diagnosis of canine lymphoma

E M Mirkes[1], I Alexandrakis[2], K Slater[3], R Tuli[2] and A N Gorban[1]

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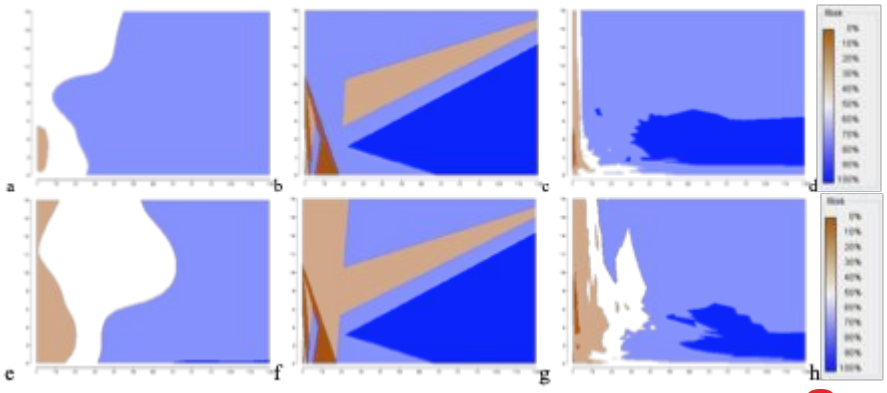
[2] Avacta Animal Health, Unit 706, Avenue E, Thorp Arch Estate Wetherby, LS23 7GA
[3] PetScreen Ltd, Biocity, Pennyfoot Street, Nottingham, NG1 1GF, UK

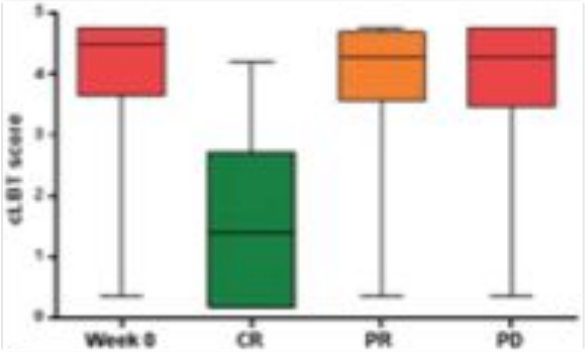
Table 1. Relative information gain for 'Lymphoma'

Tested feature	RIG	RIG under given Lymphadenopathy	
		Y	N
Lymphadenopathy	28.92%	-	-
CRP binned	24.38%	15.00%	23.52%
Hapt binned	7.02%	1.76%	14.32%
Age binned	6.07%	1.62%	9.39%
Sex	0.95%	3.79%	22.84%



2. APP: CRP

- **Hematologische tumoren en lymfoom**



Utility of a multiple serum biomarker test to monitor remission status and relapse in dogs with lymphoma undergoing treatment with chemotherapy

I. Alexandrakis[1], R. Tuli[1], S. C. Ractliffe[1], S. W. Tappin[2], R. D. Foale[2], A. Roos[3] and K. J. Slater[1]

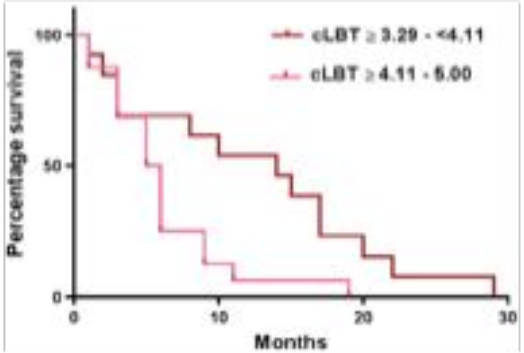
[1]Avacta Animal Health Unit 651, Thorp Arch Estate, Wetherby, LS23 7FZ, UK
[2]Dick White Referrals Station Farm, Cambridgeshire, CB8 0UH, United Kingdom
[3]Dierenkliniek Korte Akkeren, Gouda, Netherlands

Table 5. Optimal cLBT cut-offs to define the three different remission states as assessed by the clinicians showing the calculated values for sensitivity, specificity and 95% confidence intervals (CI)

cLBT cut-off	Sensitivity %	95% CI	Specificity %	95% CI
CR (Complete remission)				
0.83	71.0	61.5–79.4	100.0	96.7–100.0
1.93	38.3	29.1–48.2	100.0	96.7–100.0
PR (Partial remission)				
1.93	93.8	69.8–99.8	100.0	79.4–100.0
3.29	81.3	54.3–95.6	100.0	79.4–100.0
PD (Progressive disease)				
3.29	80.8	69.9–89.1	100.0	95.1–100.0
4.11	57.5	45.4–69.0	100.0	95.1–100.0

2. APP: CRP

❖ **Hematologische tumoren en lymfoom**



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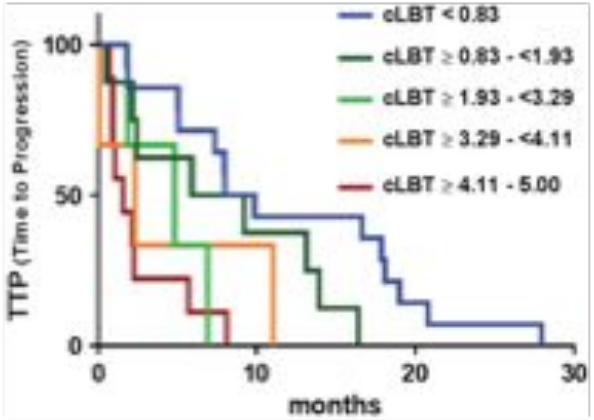

2. APP: CRP

- **Geen significante stijging**
  - Neurologische aand.
    - Epilepsie, discus hernia, necrotiserende meningoencephalitis
  - Endocriene aandoeningen
  - DM, Cushing, Hypothyreoïdie
  - Respiratoire aandoeningen
  - Bronchitis (allergisch, besmettelijk)

C-Reactive Protein Concentration in Dogs with Various Diseases

Masaaki NAKAMURA[1)], Masashi TAKAHASHI[1)], Koichi OHNO[1)]*, Akiko KOSHINO[1)], Ko NAKASHIMA[1)], Asuka SETOGUCHI[1)], Yasuhito FUJINO[1)] and Hajime TSUJIMOTO[1)]

Table 2. Representative diseases without increased CRP levels

Diseases*	(n)	CRP (mg/dl)			Number of dogs
		Median	Min.	Max.	≥1 mg/dl (%)
Epilepsy	33	0	0	0.7	0 (0%)
Atlantoaxial subluxation	5	0	0	0.4	0 (0%)
Hypothyroidism	5	0	0	0.5	0 (0%)
Urolithiasis	5	0	0	0.7	0 (0%)
Brain tumor	8	0	0	1.0	1 (13%)
Intervertebral disk protrusion	22	0.1	0	3.0	3 (14%)
Hyperadrenocorticism	11	0.1	0	1.5	1 (9%)
Tracheal collapse	11	0.1	0	0.7	0 (0%)
Rhinitis	8	0.1	0	0.7	0 (0%)
Mitral valve insufficiency	10	0.2	0	2.1	1 (10%)
Necrotizing meningoencephalitis	9	0.2	0	0.8	0 (0%)
Hypoadrenocorticism	7	0.2	0	7.2	1 (14%)
Portosystemic shunt	13	0.3	0	3.0	2 (15%)
Bronchitis	6	0.3	0	1.8	2 (33%)
Megaesophagus	5	0.3	0	0.6	0 (0%)
Hydrocephalus	10	0.3	0	1.1	1 (10%)
Allergic bronchitis	5	0.4	0.1	0.8	0 (0%)
Diabetes mellitus	5	0.4	0.2	0.5	0 (0%)
Leiomyosarcoma	6	0.4	0.2	2.7	1 (17%)

* Diseases (n≥5) in which the median of the CRP concentration did not exceed the reference range (<1 mg/dl) are shown.

2. APP: SAA

Changes in some acute phase protein and immunoglobulin concentrations in cats affected by feline infectious peritonitis or exposed to feline coronavirus infection

A. Giordano *, V. Spagnolo, A. Colombo, S. Paltrinieri

Dipartimento di Patologia Animale, Igiene e Sanità Pubblica Veterinaria, Sezione di Patologia Generale Veterinaria e Parassitologia – Università degli Studi di Milano Via Celoria 10, 20133, Milano, Italy

Accepted 22 February 2003

Table 2
Mean values (± SD) recorded in the three groups of cats

	Controls (C) ($n = 24$)	FCoV-exposed (FE) ($n = 11$)	FIP(F) ($n = 32$)	ANOVA
Total proteins (g/dL)	7.69 ± 0.83	7.86 ± 0.67	8.27 ± 1.49	n.s.
A/G ratio	1.03 ± 0.24	0.97 ± 0.32	0.47 ± 0.25	***
Albumins (g/dL)	3.83 ± 0.57	3.91 ± 0.99	2.43 ± 0.46	***
Globulins (g/dL)	3.86 ± 0.74	4.29 ± 1.21	5.85 ± 1.57	***
α_1-Globulins (g/dL)	0.55 ± 0.34	0.64 ± 0.26	0.53 ± 0.28	n.s.
α_2-Globulins (g/dL)	0.71 ± 0.33	0.54 ± 0.21	1.16 ± 0.43	***
β-Globulins (g/dL)	0.76 ± 0.18	0.82 ± 0.39	1.09 ± 0.51	**
γ-Globulins (g/dL)	1.84 ± 0.57	2.29 ± 0.87	3.07 ± 1.41	***
Serum amyloid A (μg/mL)	10.21 ± 8.32 ($n = 17$)	7.92 ± 7.12 ($n = 7$)	82.88 ± 50.23 ($n = 26$)	***
Haptoglobin (mg/mL)	1.30 ± 0.64	1.80 ± 0.83	2.13 ± 0.73	***
α_1-Acid glycoprotein (mg/mL)	1.20 ± 0.62 ($n = 22$)	1.19 ± 0.49 ($n = 11$)	2.72 ± 1.46 ($n = 29$)	***
Immunoglobulin G (g/dL)	1.73 ± 1.8 ($n = 7$)	n.d.	2.25 ± 3.09 ($n = 30$)	n.s.
Immunoglobulin M (g/dL)	0.63 ± 0.63 ($n = 7$)	n.d.	0.36 ± 0.31 ($n = 30$)	n.s.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; n.d. = not determined; n.s. = not significant.

2. APP: SAA

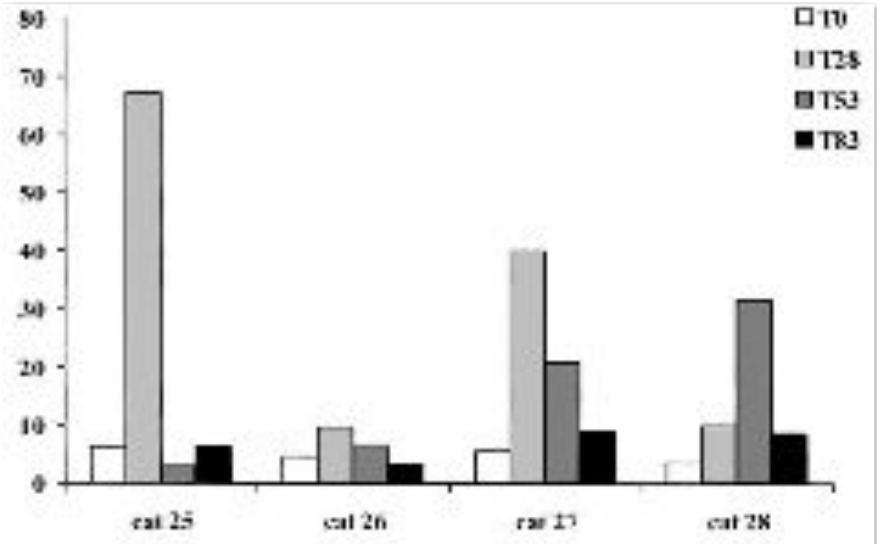

Fig. 1. Serum amyloid A concentrations (μg/mL) in the four samples from FCoV-exposed cats.

Bij Corona infectie transiënte stijging SAA

Bij <u>FIP permanente</u> stijging bij alle katten

2. APP: SAA

Veterinary Clinical Pathology ISSN 0275-6382

CASE REPORT

Time–course monitoring of serum amyloid A in a cat with pancreatitis

Takashi Tamamoto, Koichi Ohno, Aki Ohmi, Izumi Seki, Hajime Tsujimoto

Department of Veterinary Internal Medicine, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo, Japan

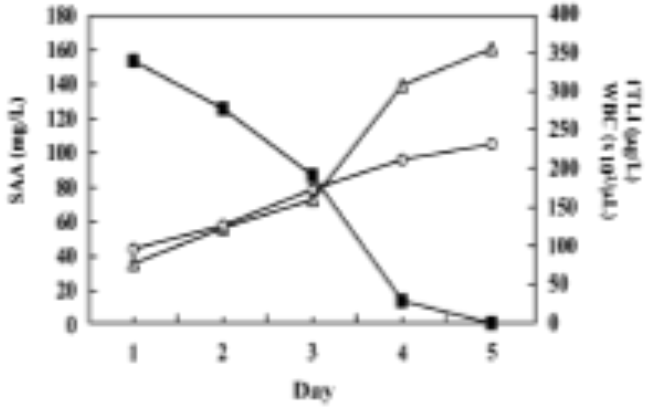

Figure 1. Time–course of changes in SAA concentration (■), WBC count (○), and fTLI concentration (△) in a cat presenting with pancreatitis on day 1 and during 5 days of treatment with plasma transfusion, intravenous fluids, prednisolone, and antibiotics.

Goede correlatie tussen optreden van de symptomen en stijging SAA

SAA gestegen in het begin van de aandoening

- WBC niet
- fTLI stijgt geleidelijk tijdens de eerste 5 dagen

2. APP: SAA

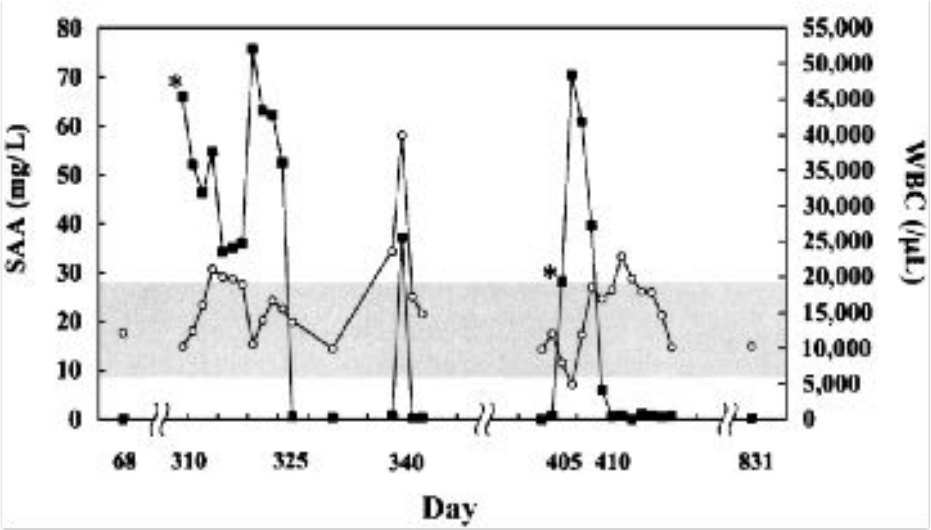

Figure 2. Time–course of changes in SAA concentration (■) and WBC count (○) in a cat with pancreatitis, from days 68 to 831 after initial presentation. The gray zone shows the reference interval for WBC count. The reference interval for SAA concentration is < 0.9 mg/L. *Indicates the time points when the cat showed clinical signs of recurrent pancreatitis, such as anorexia and vomiting.

SAA goed gecorreleerd aan optreden en verdwijnen symptomen

WBC niet

Goede marker voor respons behandeling

2. APP: SAA

FULL PAPER *Clinical Pathology*

Verification of Measurement of the Feline Serum Amyloid A (SAA) Concentration by Human SAA Turbidimetric Immunoassay and Its Clinical Application

Takashi TAMAMOTO[1)], Koichi OHNO[1)], Aki OHMI[1)], Yuko GOTO-KOSHINO[1)] and Hajime TSUJIMOTO[1)]

[1)]*Department of Veterinary Internal Medicine, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1–1–1 Yayoi, Bunkyo–ku, Tokyo 113–8657, Japan*

(Received 31 March 2008/Accepted 27 June 2008)

Table 1. Diseases (n≥3) in which the mean SAA concentration exceeded the reference range (≥ 0.82 mg/*l*)

Diseases	n	SAA concentration (mg/*l*) Mean	Min.	Max.	Number of cats ≥ 0.82 mg/*l* (%)
Acute pancreatitis	3	56.9	23.2	88.9	3 (100)
Feline infections peritonitis	8	29.4	0.2	88.3	6 (75)
Hyperthyroidism	4	16.5	0.1	64.2	2 (50)
Diabetes mellitus	8	14.9	0	80.6	3 (38)
Lymphoma	30	13.7	0	61.6	17 (57)
Cholangitis	11	11.9	0	79.3	4 (36)
Malignant mesothelioma	6	10.4	0.5	48.5	5 (83)
Chronic renal failure	11	8.7	0	40.7	5 (45)
Lang carcinoma	3	7.7	0.1	22.7	1 (33)
Squamous cell carcinoma	8	5.7	0	32.7	3 (38)
Polycystic kidney disease	4	5.5	0.5	14.9	2 (50)
Otitis media	7	5	0	33.9	1 (14)
Brain tumor	3	4.5	0.1	13.2	1 (33)
Nasal adenocarcinoma	6	4.1	0	24	1 (17)
Rhinitis	8	4	0.1	30.3	1 (13)
Gastroenteritis	14	2.4	0	29	3 (21)
Immune-mediated hemolytic anemia	5	1.5	0	4.5	2 (40)
Esophagostenosis	3	1.2	0	3.3	1 (33)
Bronchopneumonia	7	0.9	0	6.1	1 (14)

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2. APP: SAA

- SAA sterk gestegen bij ontstekingen
  - Infectieus/Niet infectieus
  - Pancreatitis : sensitiviteit **100%** !!!!
  - FIP : sensitiviteit **75%**

2. APP: SAA

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2. APP: SAA

- SAA sterk gestegen bij ontstekingen
- Stijgt bij neoplasieën
  - Vnl. Maligne tumoren
  - Lymfoom sterke stijging mogelijk

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- Gastro-enteritis
  - lage sensitiviteit
  - ddx!!! pancreatitis

2. APP: SAA

FULL PAPER *Clinical Pathology*

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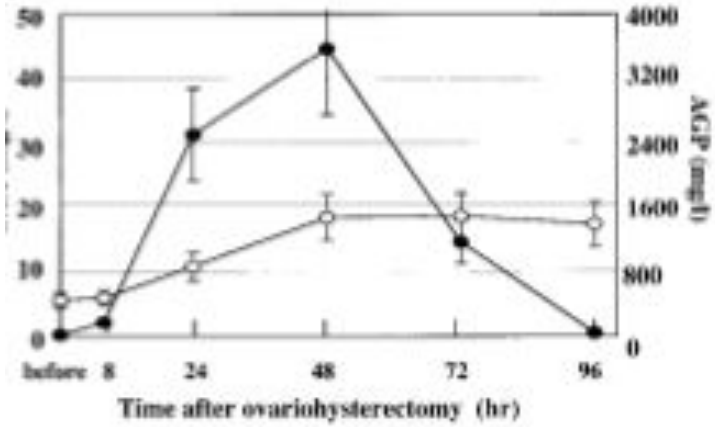
2. APP: SAA

- SAA sterk gestegen bij <u>ontstekingen</u>
- Stijgt bij <u>neoplasieën</u>
  - Vnl. Maligne tumoren
- Gastro-enteritis
  - lage sensitiviteit
- Stijgt ook bij endocriene aandoeningen (DM, T4)
- Stijgt ook bij niet inflammatoire nieraandoeningen
  - CNI PKD (PS. doe altijd BO)
- Respiratoire aandoeningen
  - lage sensitiviteit: ook als ontsteking!!!!!!
- IMHA !!

2. SAA en chirurgie



ig. 4. Time-course changes in the SAA (●) and AGP (○) concentrations in cats (n=3) before and after ovariohysterectomy. The SAA concentration was measured by a SAA-TIA kit, and the AGP concentration was measured by a feline-specific single radial immunodiffusion assay.

- Snelle stijging EN daling
- OHE normalisatie na 4 dagen

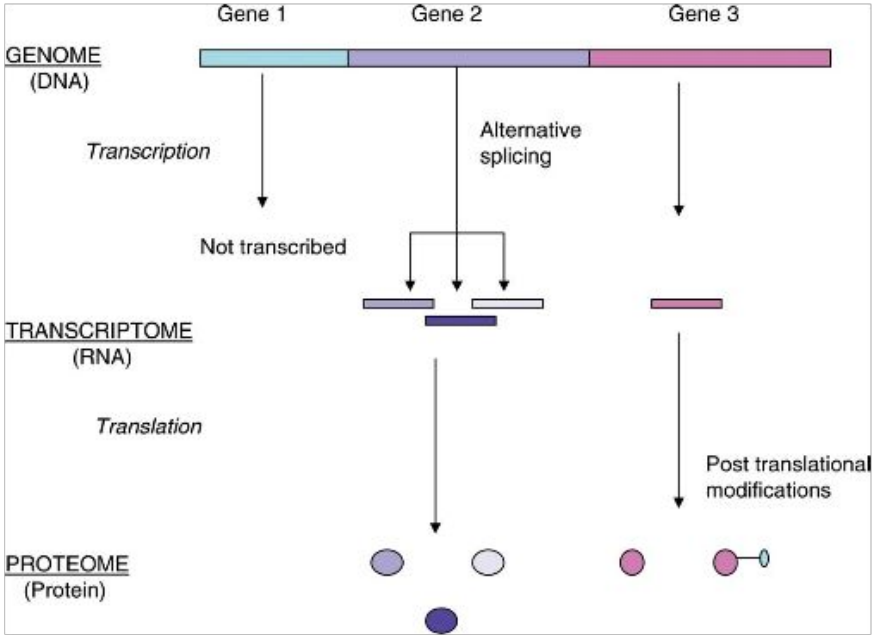
3. Proteomics

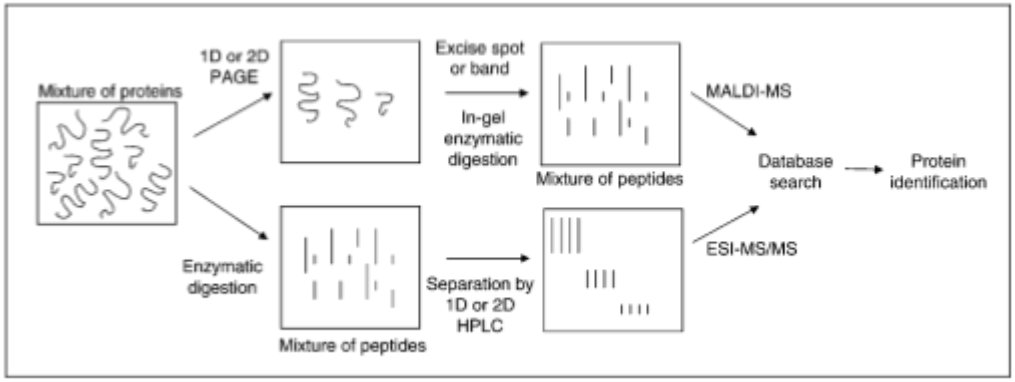
- Doel: aantonen van veranderingen in eiwitexpressie
- Gebruik:
  - diagnostische BIOMARKERS
  - monitoring (nieuwe) behandelingen
  - pathofysiologie van belangrijke aandoeningen

Proteomics

- Proteoom
  - Totaal aan eiwitten geproduceerd door een cel of een weefsel op een gegeven ogenblik of in een welbepaalde omgeving
  - “Snapshot” van de functie van de cel
- Proteomics: studie van het proteoom
- Na analyse wordt het proteoom vergeleken met een database van “referentie-proteomen”

Proteomics

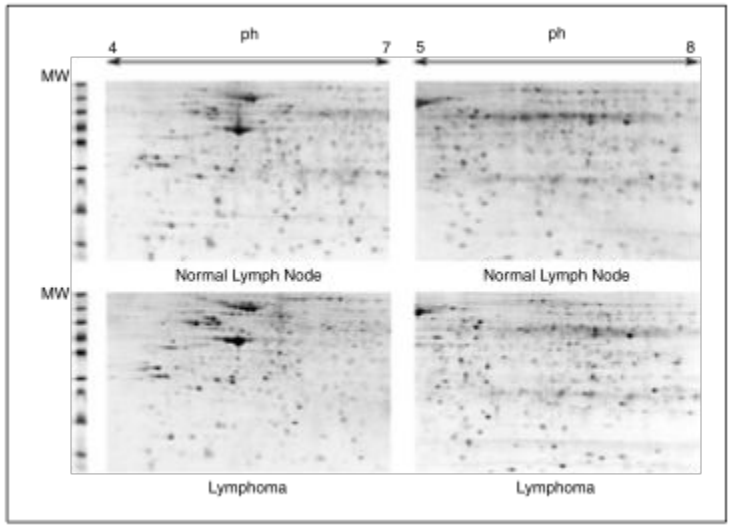

Gene 1
Gene 2
Gene 3
GENOME
(DNA)
Transcription
Alternative
splicing
Not transcribed
TRANSCRIPTOME
(RNA)
Translation
Post translational
modifications
PROTEOME
(Protein)


Mixture of proteins
1D or 2D
PAGE
Excise spot
or band
In-gel
enzymatic
digestion
Mixture of peptides
MALDI-MS
Database
search
Protein
identification
Enzymatic
digestion
Mixture of peptides
Separation by
1D or 2D
HPLC
ESI-MS/MS

3. Proteomics

Proteomics of Canine Lymphoma Identifies Potential Cancer-Specific Protein Markers

Dudley L. McCaw,[1] Arvan S. Chan,[2] Andrew L. Stegner,[2] Brian Mooney,[3] Jeffrey N. Bryan,[1] Susan E. Turnquist,[4] Carolyn J. Henry,[1,5] Hannah Alexander,[2] and Stephen Alexander[2]



- 2D-electroforese

3. Proteomics

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Table 1. Summary of two-dimensional electrophoretic analysis of proteins from noncancerous and lymphoma lymph nodes

Sample/ gel	Protein spot no.																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	C
N	*	*	*					*										*
N	*	*							*	*						*		
N				*				*										
N										*				*				*
N																		
N	*	*						*								*		
N							*											
N					*	*			*									
N			*	*			*			*								
N							*			*								
N	*	*	*				*											
N					*	*												*
N																		
L														*	*			*
L									*				*	*	*			
L													*					
L															*			
L	*				*	*												*
L	*	*		*										*				
L											*	*	*	*			*	
L						*			*				*	*				
L						*										*	*	*
L								*										
L	*	*																*

NOTE: pI at pH 5 to 8. Shaded boxes indicate the presence of a protein spot. *, spot excised for MALDI time-of-flight analysis. Abbreviations: N, noncancerous; L, lymphoma; C, control.

Proteomics
B-cel lymfoom

Proteomics of Canine Lymphoma Identifies Potential Cancer-Specific Protein Markers

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Clin Cancer Res 2007;13(8) April 15, 2007

Table 4. Identification of differentially regulated proteins

Protein name	Synonyms	Gene name	Accession no.	Molecular weight (kDa)	% Coverage	Mowse score	Normal samples	Lymphoma samples
Triosephosphate isomerase	Phosphotriose isomerase; triose phosphoisomerase; triosephosphate isomerase; triosephosphate mutase	TIM	P54714	26.7	72	74	9 of 13	1 of 11
Xaa-Pro dipeptidase	γ-Peptidase; iminopeptidase; peptidase D; proline peptidase; X-Pro dipeptidase; EC 3.4.13.9	PEPD human	P12955	54.5	32	67	8 of 13	0 of 11
Macrophage capping protein	Actin-regulatory protein CAPG	LOC483082; CAPG human; MCP	P40121	38.5	49	121	3 of 13 (0 of 13 in second group)	6 of 11 (5 of 11 in second group)
GST-P	GST7-7; EC 2.5.1.18	GST7-7	XP_532423	23.4	30	66	11 of 13	3 of 11

Conclusions: These proteins represent potential markers for the diagnosis of lymphoma and should be further investigated in human samples for validation of their utility as diagnostic markers.

zoolyx

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