Coronavirusinfektion hos kat (FIP)

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Coronavirusinfektion

- Coronavirus giver i meget sjældne tilfælde FIP, som nok er den mest frygtede infektion blandt racekatte.
- Hvorfor?
  - Rammer spontant-sporadiske tilfælde
    - Risikofaktorer – populationstæthed, smittetryk?, stress?
  - Diagnose kan være vanskelig at stille
  - Oftest unge dyr der lige er kommet fra opdrætter
  - Der findes ingen effektiv kur-aflivning!

Coronavirusinfektion

- Coronavirus (FCoV):
- Harmløst tarmvirus
- Giver forbipasserende diarré, feber, øvre luftvejsinfektionstegn i nogle tilfælde
  - Smitter via kattebakken
  - Smitter katte i alle aldre
    - 85-90% renser sig umiddelbart, men kan reinficeres
    - 10-15% renser sig langsommere enkelte kan blive permanent inficerede
    - Under 1% vil udvikle FIP – killinger!

Coronavirusinfektion

- Forekomst i Danmark (antistoffer) :

Type af kat	Antal undersøgt	%positive
Vildtlevende katte	104	22.0
Hus/have katte	229	9.1
Lejlighedskatte	118	18.1
Katterikatte	96	73.0
Ukendt	28	39.0

Coronavirusinfektion

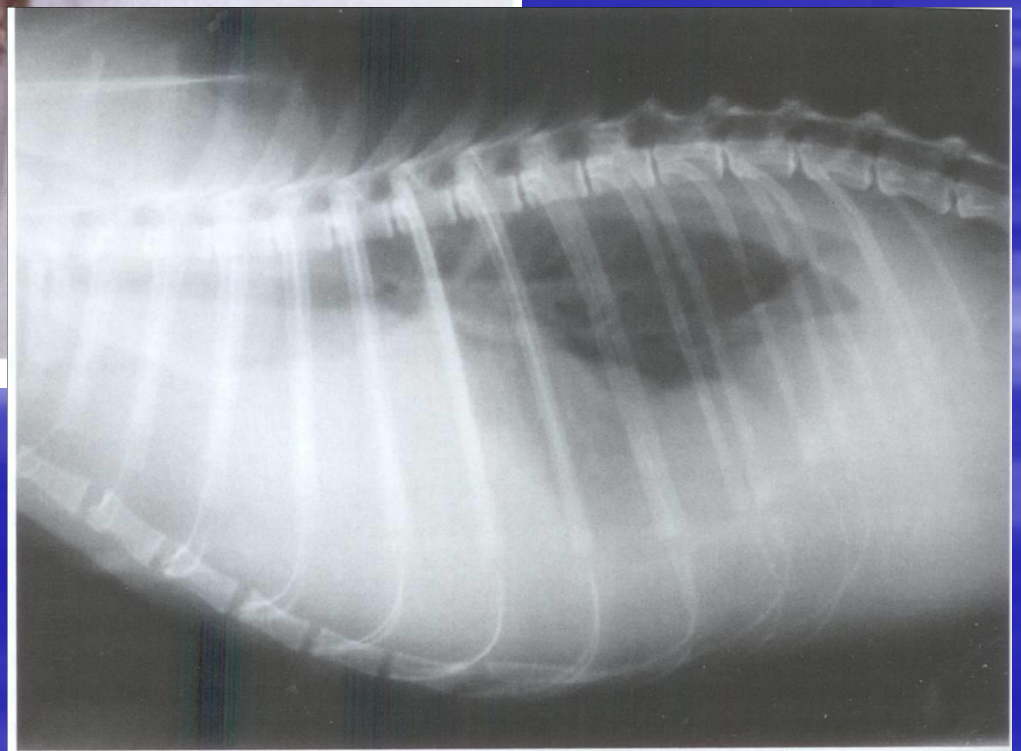
- Smitte:
  - Udskilles af permanent smittebærer
  - Smitter via afføring
  - Kattebakker!
  - Størrelsen af kattegruppen afgørende for smitte
    - Max. 5-6 katte pr. gruppe
  - Nogle typer grus mindsker smitte?
    - www.dr-addie.com/preventionS
  - Modtagelighed aldersrelateret

Coronavirusinfektion

- Udvikling af sygdom:
  - FCoV muterer i tarmen, og får evnen til at inficere andre celler (makrofager).
  - Dermed kan virus spredes til alle væv
  - Sygdom skyldes dannelse af betændelsesreaktioner i væv (pyogranulomer)
  - Den våde form skyldes karbetændelse (vasculitis) (karrene bliver utætte)

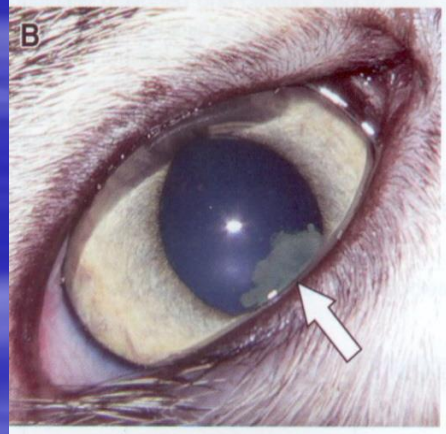
Coronavirusinfektion

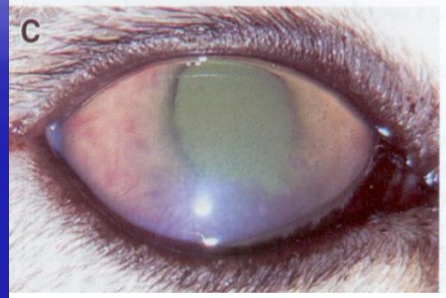
- Genetisk prædisponering?
  - Racedisponering?
    - Hellig Birma
    - Perser
- Forskellige stammer
  - Hot strains???



Coronavirusinfektion

- Kliniske tegn
  - 2 sygdomsbilleder med samme patologi
  - Våd form udgør 80 - 90%:
    - Ophobning af væske i bughule og/eller brysthule
      - Strågult, pusflager, koagulerer ved henstand,
      - højt indhold af protein, lavt celleindhold
    - Svingende feber (antibiotika uvirksomt)
    - Nedsat til ophørt ædelyst/vægttab udtalt
    - Nedstemthed
    - Besværet vejrtrækning
    - Blege/gullige/smudsige slimhinder
    - Udvikler sig hurtigt





Coronavirusinfektion

- Tør form udgør mellem 10 og 20% (?):
  - Almene tegn
    - Svingende feber (antibiotika uvirksomt)
    - Nedsat ædelyst
    - Nedstemthed
  - Organspecifikke tegn
    - Lever – gullige slimhinder, opkastninger, vægttab, etc.
    - CNS – nedstemthed, depressiv, kramper
    - Øje – udfældninger i øjenkamre
    - Tarmsystem – varierende, ofte almene, som våd
    - Brysthuleorganer - vejrtrækningsproblemer

Coronavirusinfektion

- Kliniske tegn ved tør og våd FIP:

Våd FIP, kliniske tegn fra:	Antal katte
Bughulen	62
Bughulen og brysthulen	24
Brysthulen	12
Bughulen og øjne	3
Bughulen og CNS	2
Bughulen, brysthulen og CNS	1
Bughulen, brysthulen og øjne	1
Bughule, CNS og øjne	1
Total	107

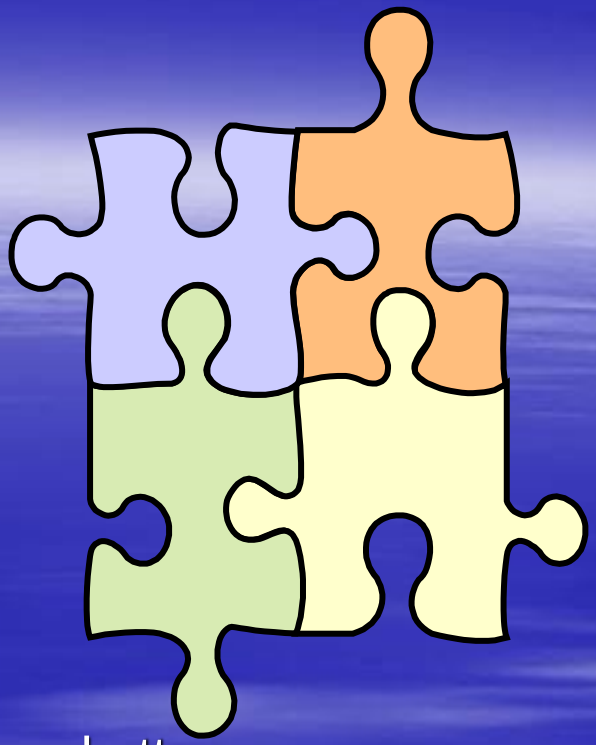
Coronavirusinfektion

Tør FIP, kliniske tegn fra:	Antal katte
Bughulen	30
CNS	22
Øjne	14
CNS og øjne	8
Bughule og øjne	7
Bughule og brysthule	4
Bughule, brysthule og CNS	3
Bughule, brysthule og øjne	2
Bughule, CNS og øjne	2
Brysthulen	1
Brysthulen, CNS og øjne	1
Total	94

Felin infektiøs peritonitis (FIP)

- Smitsom bughindebetændelse
- Diagnosen skal stilles (en af dyrlægens udfordringer):
  - 100% diagnose kun på 2 måder:
    - 1. Karakteristiske histopatologiske forandringer i væv.
    - 2. Påvisning af FCoV/FeCV i celler (makrofager) i væske fra bug eller brysthule.

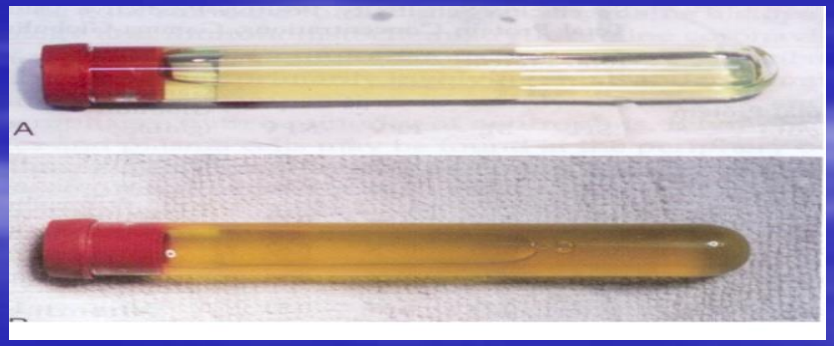
FIP



- Diagnosen er et ”puslespil”:
  - Værdien af parametre varierer!
    - Anamnese – ”den rigtige kat”
      - Alder: 6 måneder til 2 år
      - Fra katteri eller andet sted med mange katte
    - Kliniske tegn

FIP

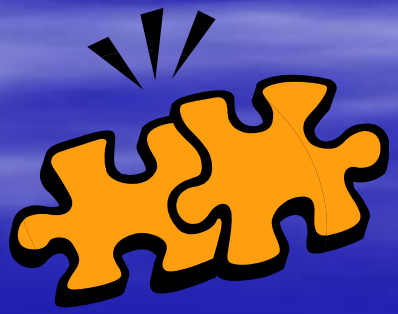
- Undersøgelse af væske (effusioner) vigtigst:
  - Karakteristisk strågult med udfældninger (fibrin)
  - Sterilt
  - Celler der tyder på en ikke specifik betændelsestilstand
    - Neutrofile, lymfocytter i mindre antal.
  - Immuncytologi – påvisning af FCoV/FeCV i celler
    - Stærkt indikativ ved positiv test, negativ test?
  - PCR test
  - Højt proteinindhold
  - Rivaltas test



www.youtube.com/watch?v=XmOk2veunqA

FIP

- Hvor mange brikker har vi fået lagt?
  - Tør form - ingen?
    - Blodundersøgelser:
      - Tilstedeværelse af betændelsesceller (neutrofile) i forhøjet antal
      - Andre celler i nedsat antal (lymfocytter)
      - Forhøjet globulin, især gamma-globuliner, lavt albumin
      - Albumin/globulin ratio under 0.7
      - Ikke regenerativ anæmi
      - Forhøjede levertal (ALT, bilirubin)

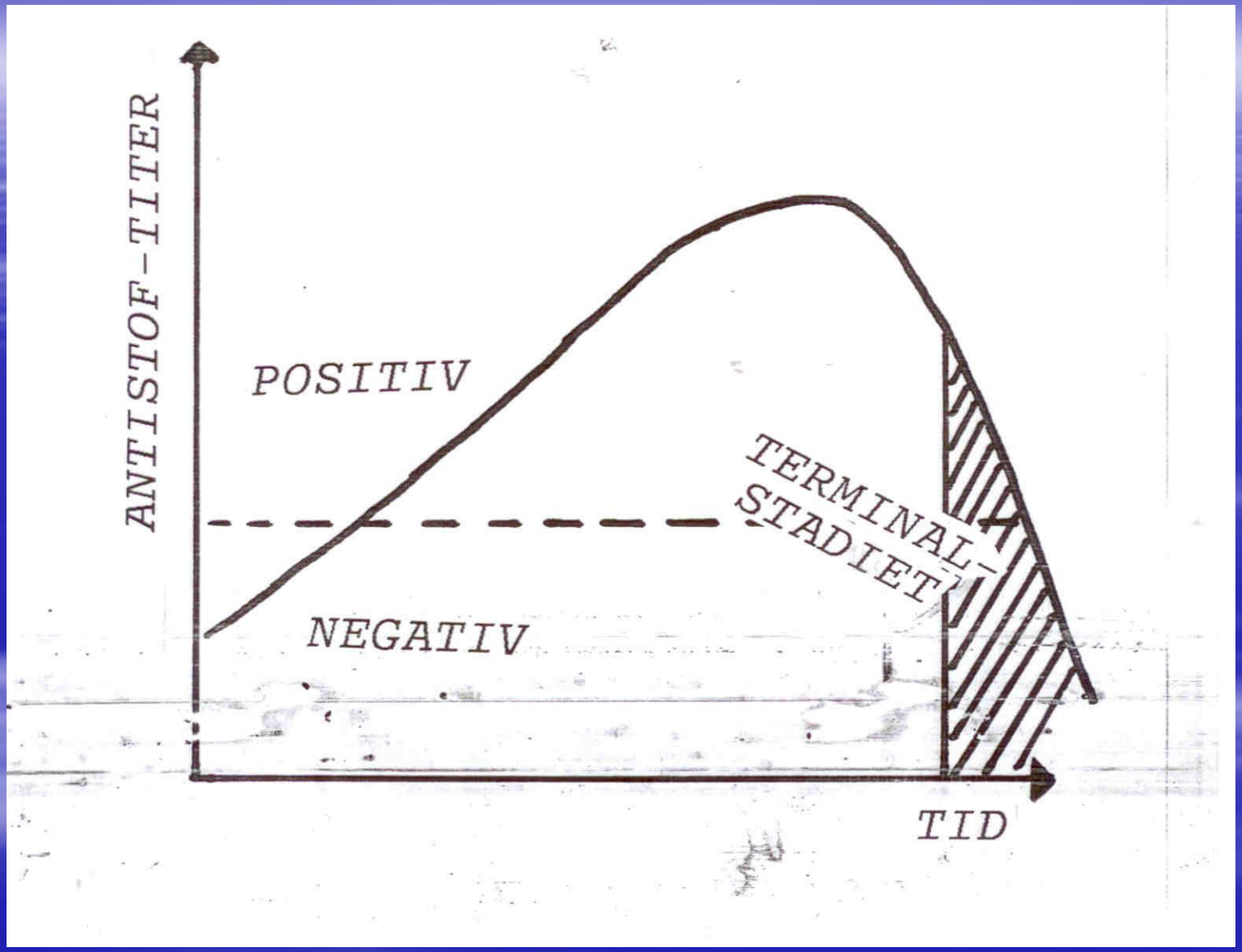


FIP

- PCR – væske, væv
  - mRNA RT-PCR- Påviser kun replikerende virus.
    - IDEXX
- Akutfase proteiner
    - SAA – værdi?

FIP

- Hvad med antistofbestemmelse?
  - Er en brik, men ikke en af de vigtige.
  - Antistofbestemmelse er for FCoV
  - Antistofniveau fortæller ikke noget om sygdom
  - Kan mangle ved klinisk FIP.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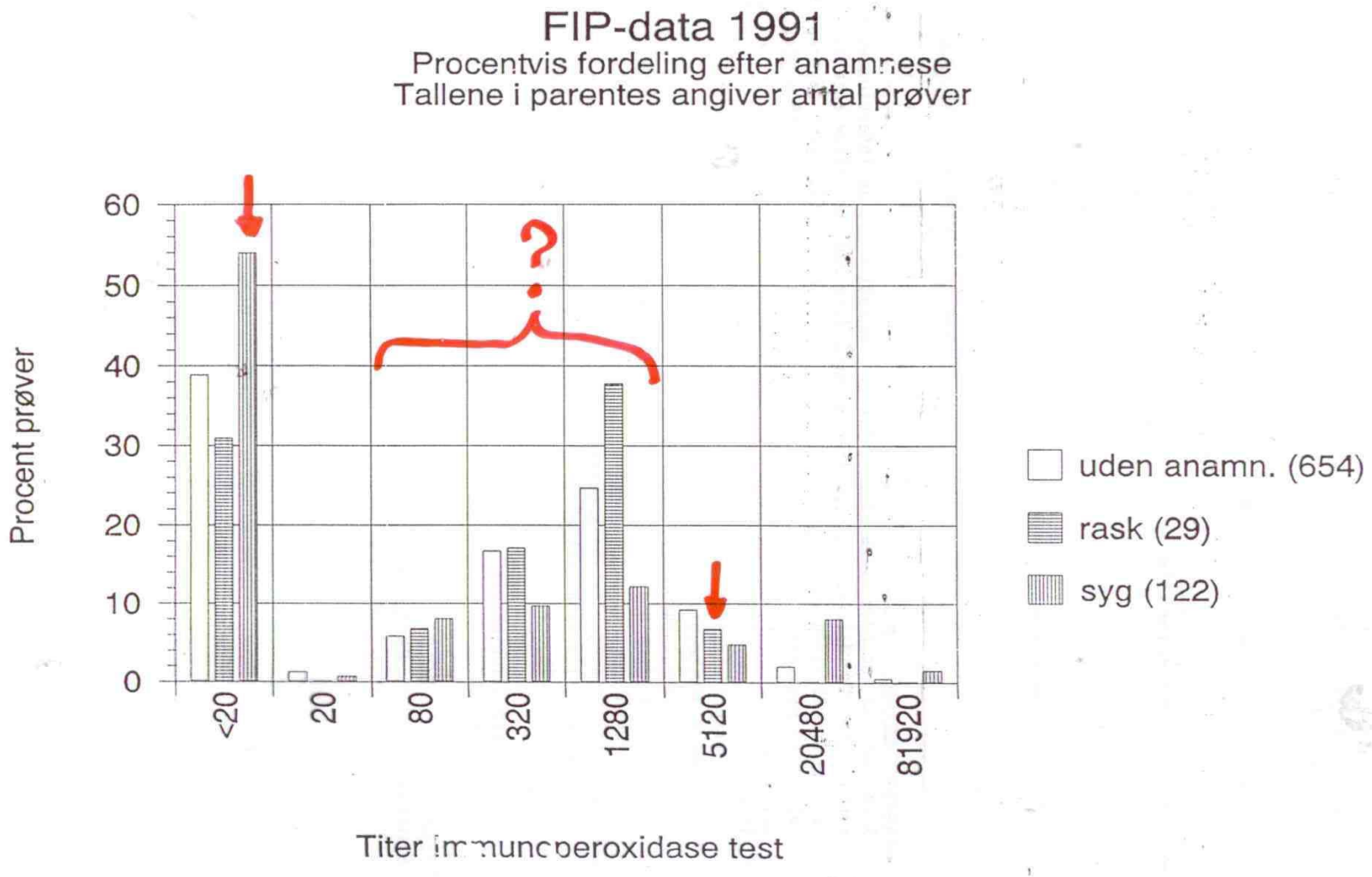
FIP-data 1991
Procentvis fordeling efter anamnese
Tallene i parentes angiver antal prøver
Procent prøver
60
50
40
30
20
10
0
<20
20
80
320
1280
5120
20480
81920
Titer immunoperoxidase test
?
uden anamn. (654)
rask (29)
syg (122)

Table 2
Accuracy of various diagnostic tests for FIP

Category	Test Type	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence (%)	Ref.
Protein analysis	Total protein ≥8 g/dl	57	64	76	43	67	138,143,a
	Gamma-globulin ≥2.5 g/dl	70	86	90	61	65	143
	A:G ratio						
	≤0.8	80	82	92	61	72	143
	<0.45	25	98	64	90	13	139
	Protein electrophoresis	38	50	60	29	67	144
	α_1-Acid glycoprotein levels >1.5	85	100	100	75	70	192
Effusion analysis	Total protein >3.5 g/dl	87	60	77	71	72	142
	Gamma-globulin ≥1.0 g/dl	82	83	84	80	53	143
	A:G ratio						
	≤0.9	86	74	79	82	53	143
	≤0.5	62	89	86	68	53	143
	Rivalta test	98	80	84	97	51	143
	Presence of antibodies	86	85	86	85	51	143
	Cytology suggestive of FIP	90	71	89	73	72	142
	Antigen staining in macrophages	72	100	100	68	62	142,143,193,a
Serology	IFA (any titer)	85	57	44	90	28	143
	IFA (titer >1,600)	67	98	94	88	28	143
	ELISA	100	93	94	100	53	155,187,a
	Antigen–antibody complex	48	91	67	84	26	143
Viral nucleic acid detection	Nested RT-PCR						
	Serum	55	88	90	48	67	143,163,a
	Effusion	96	92	96	92	63	143,162,163,a
	mRNA RT-PCR						
	Blood	94	92	67	92	15	168–170,a

Abbreviations: A:G ratio, albumin to globulin ratio; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescent antibody assay; mRNA, messenger RNA NPV, negative predictive value; PPV, positive predictive value; RT-PCR, reverse transcriptase polymerase chain reaction.
[a] Calculated based on concatenated data from original studies

FIP Virus RealPCR™ Test
- On peritoneal, pleural or CSF fluid
- On tissue biopsy or aspirate

Step 4. Confirmatory testing

Wet FIP suspect

Nonseptic exudate
- Yellow, viscous, clear
- High protein
- Low cellularity

Dry FIP suspect
- Pyogranulomatous inflammation

Step 3. Supportive fluid analysis or biopsy findings

CBC
- Mild anemia
- Neutrophilia
- Lymphopenia

Biochemistry
- Increased globulin
- Low albumin to globulin ratio
- Elevated liver enzymes
- Elevated bilirubin
- Azotemia

Retrovirus
- FeLV positive or negative
- FIV positive or negative
- FCoV antibody titer positive with higher titers more suspicious

Step 2. Suggestive minimum database findings

Signalment
- Young (<2 years)
- Elderly
- Purebreed more than mixed-breed

Presenting complaint
- Lethargy
- Failure to thrive or poor growth
- Decreased appetite, weight loss
- With or without distended abdomen, dyspnea
- With or without seizures, ocular disease

History
- Multicat household, shelter
- Stressful event (e.g., new home, spay/neuter, concurrent infections)

Physical examination
- Mild fever
- Effusion
- Abdominal mass, organ enlargement
- Central nervous system abnormalities, ocular disease

Step 1. Consistent clinical presentation

- Endelige brik er kun histopatologi!

FIP

- Behandling:
  - Ingen! Kun lindrende. Udsætter blot aflivning!
    - Immunsuppression
      - Prednisolon
      - Cyclofosfamid
    - Felint interferon
      - Meget blandede resultater
        - Kan uden tvivl forlænge liv
        - Skal vi det?
      - Kræver yderligere undersøgelser

TABLE 1 Drugs that have been suggested for use in FIP cases

Drug	Comments	ABCD recommendation [EBM grade*]
ANTIVIRALS		
Ribavirin	Works in vitro but toxic in cats	Not recommended [II]
Vidarabine	Works in vitro but toxic in cats	Likely ineffective [IV]
Human interferon-alpha – SC high dose	Although human interferon-alpha has in vitro effects on FCoV, SC treatment did not work in an experimental trial	Ineffective [II]
Human interferon-alpha – PO low dose	No trials Only acts as immune stimulant if given orally Immune stimulation should be avoided in cats with FIP	Contraindicated [IV]
Feline interferon-omega	One placebo-controlled study of naturally occurring cases and one uncontrolled study	No benefit was observed [grade I study]; may require further studies in view of anecdotal clinical evidence [IV]
IMMUNOSUPPRESSANTS		
Prednisolone/dexamethasone – immunosuppressive doses	No controlled studies. Some cats have improved during treatment and survived for several months, but does not cure FIP	Currently supportive treatment of choice [III] If effusion is present, dexamethasone IT or IP may help
Pentoxyfylline	Aimed at treating the vasculitis Some veterinarians in practice have tried this treatment, but there are no published studies or case reports	Requires studies [IV]
Ozagrel hydrochloride	Thromboxane synthesis inhibitor aimed at treating the inflammatory response. Only used in two cases with beneficial effect	Controlled studies needed [III]
Ciclosporin A	Aimed to immunosuppress (lower the corticosteroid dose). No published studies	Not recommended because directed more at cellular immunity than humoral (lack of data) [IV]
Cyclophosphamide	Aimed to immunosuppress (lower the corticosteroid dose). No published studies	Might be considered in combination with glucocorticoids [IV]
Chlorambucil	Aimed to immunosuppress (lower the corticosteroid dose). No published studies	Might be considered in combination with glucocorticoids [IV]
Azathioprine	Toxic in cats (!) Aimed to immunosuppress (lower the corticosteroid dose). No published studies	Not recommended [IV]
Salicylic acid (aspirin) – platelet inhibitory dosage	Aimed at treating the inflammatory response as well as the vasculitis. No published studies	May have some beneficial effect, but side effects possible if used in combination with high steroid doses

*For explanation of EBM grades, see box on page 595. SC = subcutaneous, PO = oral, IP = intraperitoneal, IT = intrathoracic

Ny behandling af FIP

- Mulig behandling med ”3C-like protease inhibitor GC376”
  - Antiviral medicin (HIV, hepatitis C)
  - 19/20 behandlede katte nogen effekt
  - 6/20 katte lever længere end 12 måneder
  - Eneste type katte uden effekt er gruppen med neurologiske tegn.
  - P.t. kun en eksperimentel behandling.

FCoV

- Forebyggelse:
  - Tidlig fravænning og isolation
    - Isolation af hunkat 3 uger inden fødsel
      - Udskillelse fra hunkat mindskes/ophører
      - Udsættes ikke for reinfektion
    - Killinger fravænnes ved 4-6 uger
      - Moderens antistoffer holder til 6-7 uger
      - Isoleres helt efter fravænning
      - Meget vanskeligt projekt
      - Etik og moral?

FCoV

- Forebyggelse (fortsat):
  - Antal katte i huset/gruppen
    - 5-6 maksimum
    - ”vandtætte skodder” mellem grupperne
  - Kattebakkerne:
    - Antal. 1 pr. kat!
    - Hyppige skift
    - Rigtige grus – viruseffektivt, uden ”spor”
    - Væk fra foder
    - Rensning af bakker med chlorprodukter

FCoV

- Forebyggelse (fortsat):
  - Nye katte ind i katteriet (hvis fri for FCoV):
    - Antistof negativ
    - Isolation i 3-4 uger
    - Retest om mistanke om problemer
  - Parring ind og ud kun til FCoV negative katte
  - Ingen udstillinger
  - Frihed for FCoV i længere tid mulig?????

FIP

- Vaccination
  - Felocell FIP, intranasal vaccine
    - Ikke tilgængelig i DK
    - Effekt omdiskuteret
    - Mistænkt for at give sygdom

There is a small chance your cat gets FIP –

If it does there is no chance

Reklameslogan for FIP vaccinen i USA

Cases

- Iris:
  - 5 mdr. gammel british shorthair. Blevet mere stille over et par måneder. Ædelyst gået ned. Vil ikke lege med andre katte. Sover det meste af dagen. Undersøgt ved egen dyrlæge. Stor blodprofil udtaget. Ingen fund. Behandlet i 2 omgange med antibiotika.

- Undersøgelse
  - meget mager kat, temp: 40.3 (er stadig i ab-beh.)
  - slimhinder smudsige, moderat dehydreret, vejrtrækning anstrengt
  - Ved undersøgelse af bughulen føles mindre fortætninger/knuder.
  - Mistanke om tør FIP

Owner
Animal **Cat Iris-SF**

Order ID **90877008**
Laboratory No. **VM739233/28.06.2007**

Test	Result	Sign	Reference value	Unit	Remark
Large Check-up					1)
Kidney:					
Urea (BUN)	**3.2**		1.7 - 5.5	mmol/l	
Creatinine	**65**		< 177	umol/l	
Sodium	**151**		146 - 165	mmol/l	
Potassium	**3.4**		3.0 - 5.0	mmol/l	
Inorganic Phosphate	**1.9**		1.42 - 2.77	mmol/l	
Liver:					
Bilirubin	**9.4**	+	< 5.1	umol/l	
ALT (GPT)	**41.8**		< 175	U/l	
Reference range in oriental breed cats up to 375					
Alkaline phosphatase	**6**		< 149	U/l	
GGT	**<1**		< 5	U/l	
AST (GOT)	**71.4**		< 120	U/l	
GLDH	**2**		< 9	U/l	
Total protein	**85**		57 - 94	g/l	
Albumin	**25**	-	26 - 56	g/l	
Globulin	**60**			g/l	
Albumin-Globulin ratio	**0.42**	--	> 0.76		
Pancreas:					
Glucose	**4.8**		3.0 - 5.6	mmol/l	
Cholesterol	**4.9**	+	1.8 - 3.9	mmol/l	
Fructosamine	**350**		< 390	umol/l	
Muscle:					
CPK	**499**	+	< 475	U/l	
LDH	**517**	+	< 260	U/l	
Calcium	**2.29**	-	2.3 - 3.0	mmol/l	
Magnesium	**0.91**		0.6 - 2.0	mmol/l	
Triglycerides	**0.4**	-	0.6 - 1.1	mmol/l	
Haemogram					
Leukocytes	**20.3**	++	6 - 11	G/l	
In stressed cats up to 18					
Erythrocytes	**5.56**		5 - 10	T/l	
Haemoglobin	**8.0**	-	9 - 15	g/dl	
Packed cell volume (PCV)	**26**	-	28 - 45	%	
MCV	**47**		40 - 55	fl	
HbE	**14**		13 - 17	pg	

16-11-2007

MCHC	**30**	-	31 - 35	g/dl	
Thrombocytes	**46**	-	150 - 550	G/l	
Differential blood count					2)
Basophils	**0**		0 - 1	%	
Eosinophils	**0**		0 - 6	%	
Band neutrophils	**4**	+	0 - 3	%	
Segmented neutrophils	**82**	+	50 - 75	%	
Lymphocytes	**14**	-	15 - 50	%	
Monocytes	**0**		0 - 4	%	
Basophils (absolute)	**0**			/ul	3)
Eosinophils (absolute)	**0**		0 - 600	/ul	
Band neutrophils (absolute)	**813**	++	0 - 300	/ul	
Segmented neutrophils (abs)	**16671**	++	3000 - 11000	/ul	
Lymphocytes (absolute)	**2846**		1000 - 6000	/ul	
Monocytes (absolute)	**0**		0 - 500	/ul	
Atypical cells	**0**		negative		
Anisocytosis	+		negative		
Polychromasia	+		negative		
Your additional order:					
FeLV (antigen) Feline leukaemia virus	**negative**		negativ		4)
FIV (antibodies) Feline immunodeficiency virus	**negative**		negativ		5)
FIP/Coronavirus (antibodies) Feline infectious peritonitis	**1:400**			titre	6),7)
Electrophoresis					
A/G	**0.5**	--	> 0.76		
Albumin	**32.80**	--	45 - 60	%	
alpha-1 globulin	**4.8**		4 - 14	%	
alpha-2 globulin	**15.2**	+	7 - 12	%	
beta-globulin	**9.5**	--	16 - 31	%	
gamma-globulin	**37.7**	++	10 - 28	%	

Interpretation:

4) Presently the cat is not viraemic. Please note: the test result can also be negative in the very early stage of infection or in latently infected animals.

5) Antibodies against the feline immunodeficiency virus (FIV) could not be detected. Not all of the infected animals possess antibodies. Therefore it is recommended to perform a control examination in clinical suspicious animals using either PCR for detection of the progenome or repeating the antibody test in 6 - 8 weeks.

6) A coronavirus antibody titre of >= 1:100 is suggestive for an infection with coronavirus. The differentiation between antibodies against feline enteral coronavirus and FIP-inducing coronavirus is not possible. The following changed laboratory parameters can indicate FIP infection in conjunction with suggestive clinical signs: 1) Serum proteins: a) hyperproteinaemia b) hypoalbuminaemia c) hypergammaglobulinaemia
-> reduced albumin-globulin ratio (< 0.6 is suspicious for FIP) 2) Blood count: a) hypo- or aregenerative anaemia b) neutrophilia with left shift c) lymphopenia 3) Liver: a) hyperbilirubinaemia b) raised ALT

7) The serum was haemolytic. Results should be interpreted with caution.

Note:

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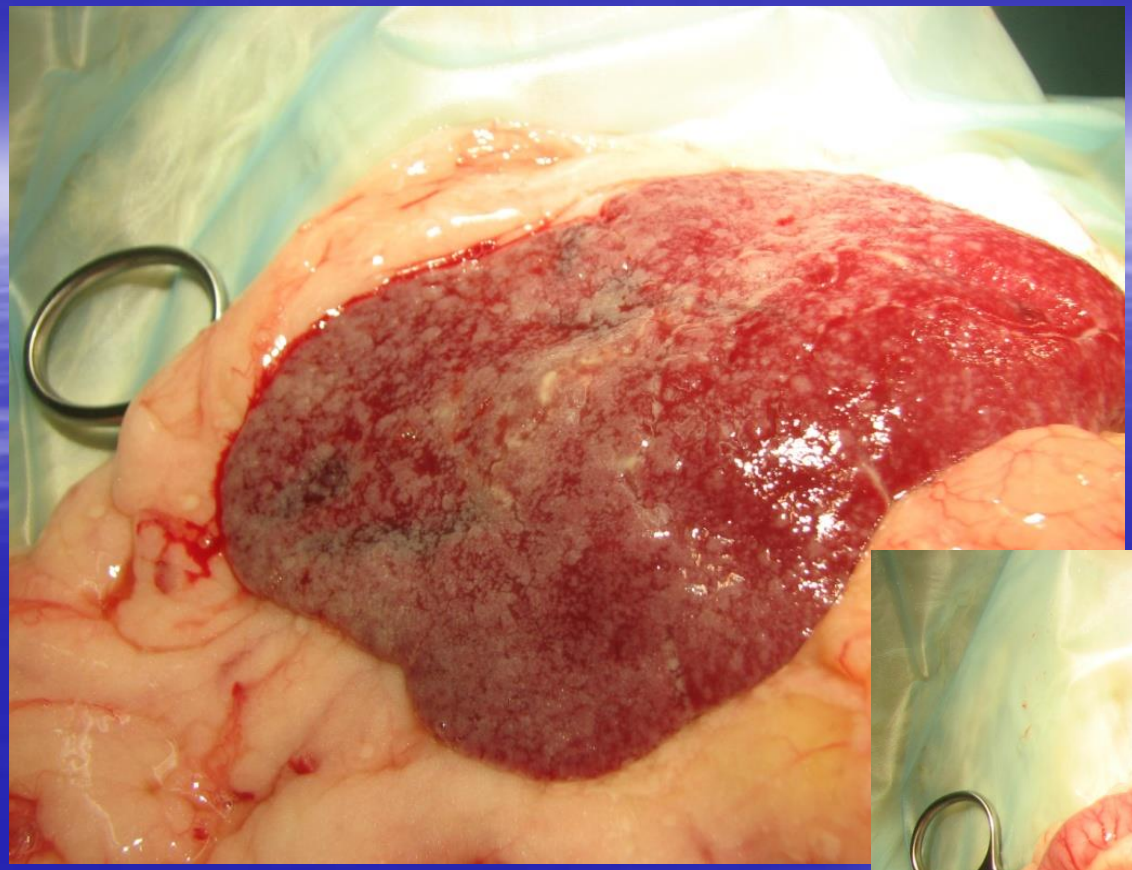

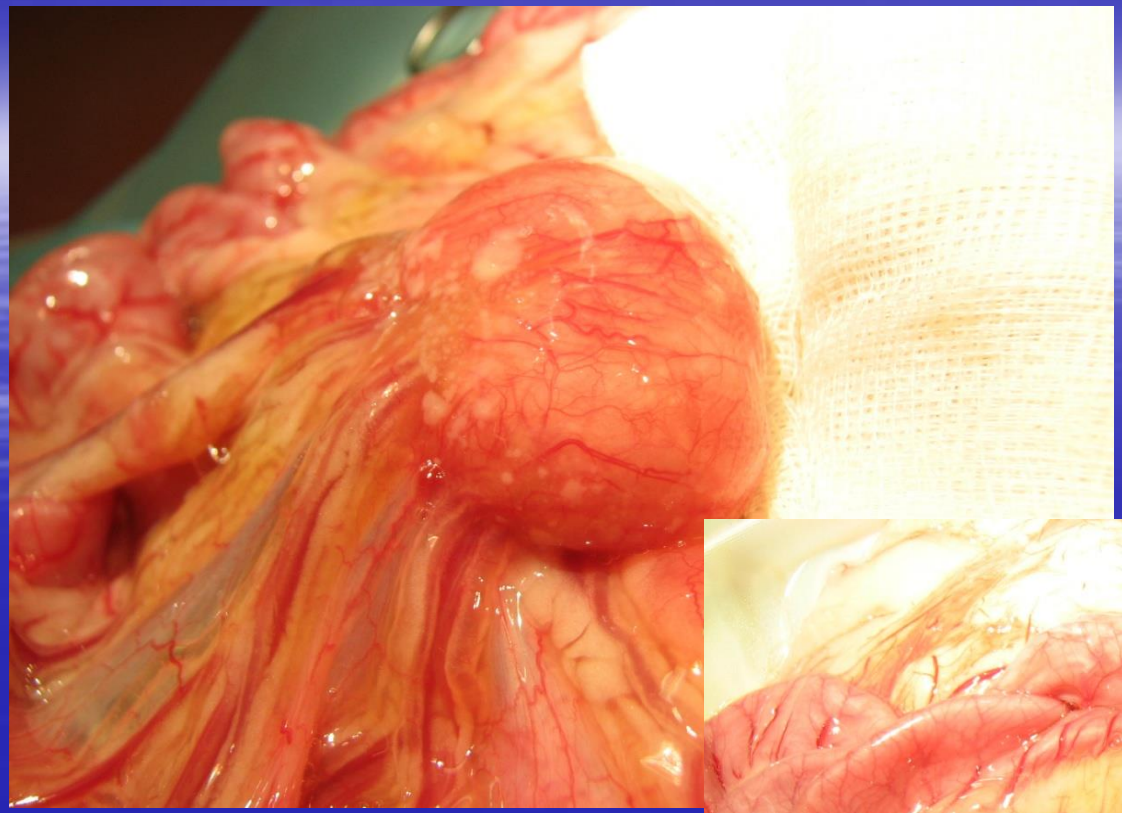

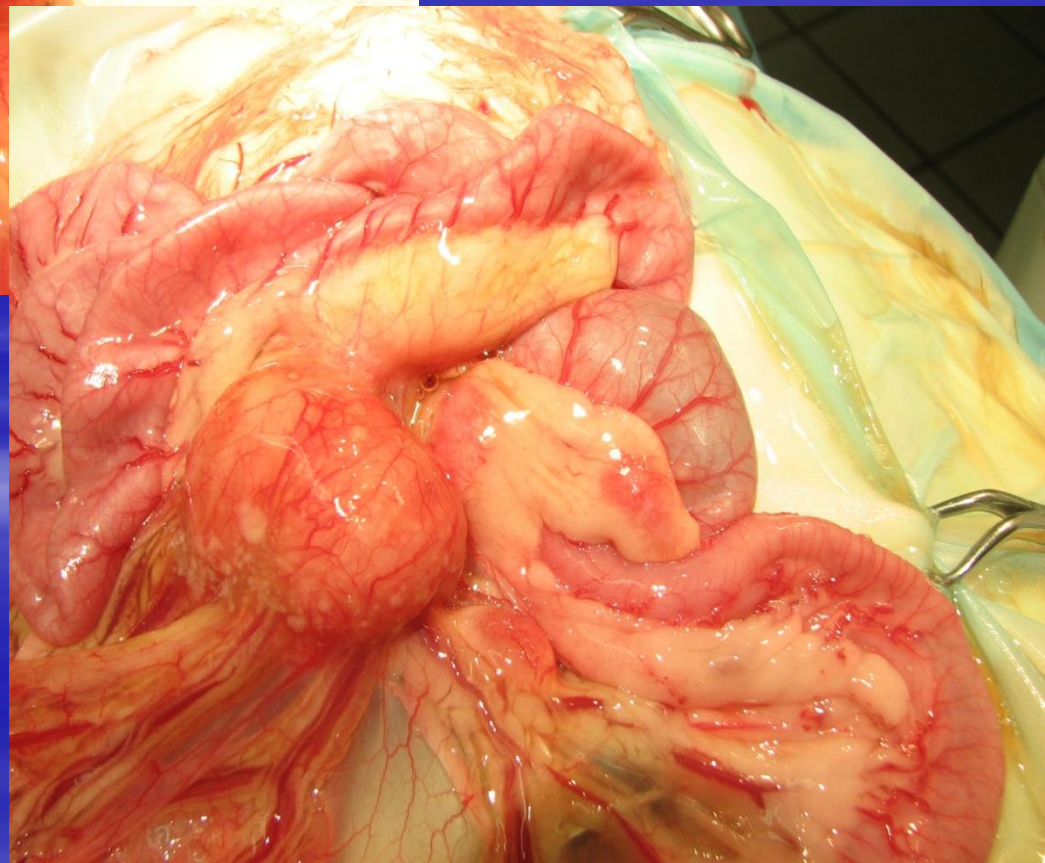

Case

- Zarina
  - 1 år gammel Maine Coon. Intakt hunkat. Parret 2 gange uden held. Sidste uger blevet tiltagende besværet, bughule stor og tung. Sover hele tiden
  - Feber 40.1, gullige slimhinder, ikterus, stor pendulerende abdomen.
  - Strågul, uklar væske kan udtages.

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VETERINARY DIAGNOSTIC SERVICES
Vet·Med·Lab

Vet.Med.Lab. ApS Frøhaven 24 DK-2630 Taastrup

90

Skovlunde Dyreklinik
Kristensen, Feldballe

Skovlunde Byvej 53

DK-2740 Skovlunde

Lab report

Owner/Animal
Cat Zarina 01 months
Your ID
05651761
Lab No.
VM865401 26.04.2005
Material
whole blood EDTA blood smear

Test	Result	Reference range	Unit	Note
FIP screening test				
FIP/Coronavirus (antibodies)	1:100		titre	1)
Feline infectious peritonitis				
Electrophoresis				
Total protein	56	57 - 94	g/l	
A/G	0.4	> 0.76		
Albumin	28.80	45 - 60	%	
alpha-1 globulin	5.4	4 - 14	%	
alpha-2 globulin	15.2	7 - 12	%	
beta-globulin	13.8	16 - 31	%	
gamma-globulin	36.8	10 - 28	%	
Total Bilirubin	1.34	< 0.3	mg/dl	
ALT (GPT)	33	< 175	U/l	
Reference range in oriental breed cats		up to 375		
Haemogram				
Leukocytes	20.5	6 - 11	G/l	
In stressed cats		up to 18		
Erythrocytes	5.71	5 - 10	T/l	
Haemoglobin	6.17	9 - 15	g/dl	
Packed cell volume (PCV)	22	28 - 45	%	
MCV	38	40 - 55	fl	
HbE	11	13 - 17	pg	
MCHC	29	31 - 35	g/dl	
Thrombocytes	305	150 - 550	G/l	
Differential blood count				
Basophils	0	0 - 1	%	
Eosinophils	0	0 - 6	%	
Band neutrophils	3	0 - 3	%	
Segmented neutrophils	82	50 - 75	%	
Lymphocytes	7	15 - 50	%	
Monocytes	7	0 - 4	%	
Basophils (absolute)	0		/ul	2)
Eosinophils (absolute)	0	0 - 600	/ul	
Band neutrophils (absolute)	615	0 - 300	/ul	
Segmented neutrophils (abs.	16810	3000 - 11000	/ul	
Lymphocytes (absolute)	1435	1000 - 6000	/ul	
Monocytes (absolute)	1435	0 - 500	/ul	
Atypical cells	0	negative		
Anisocytosis	+	negative		
Polychromasia	0	negative		

Further results see next page

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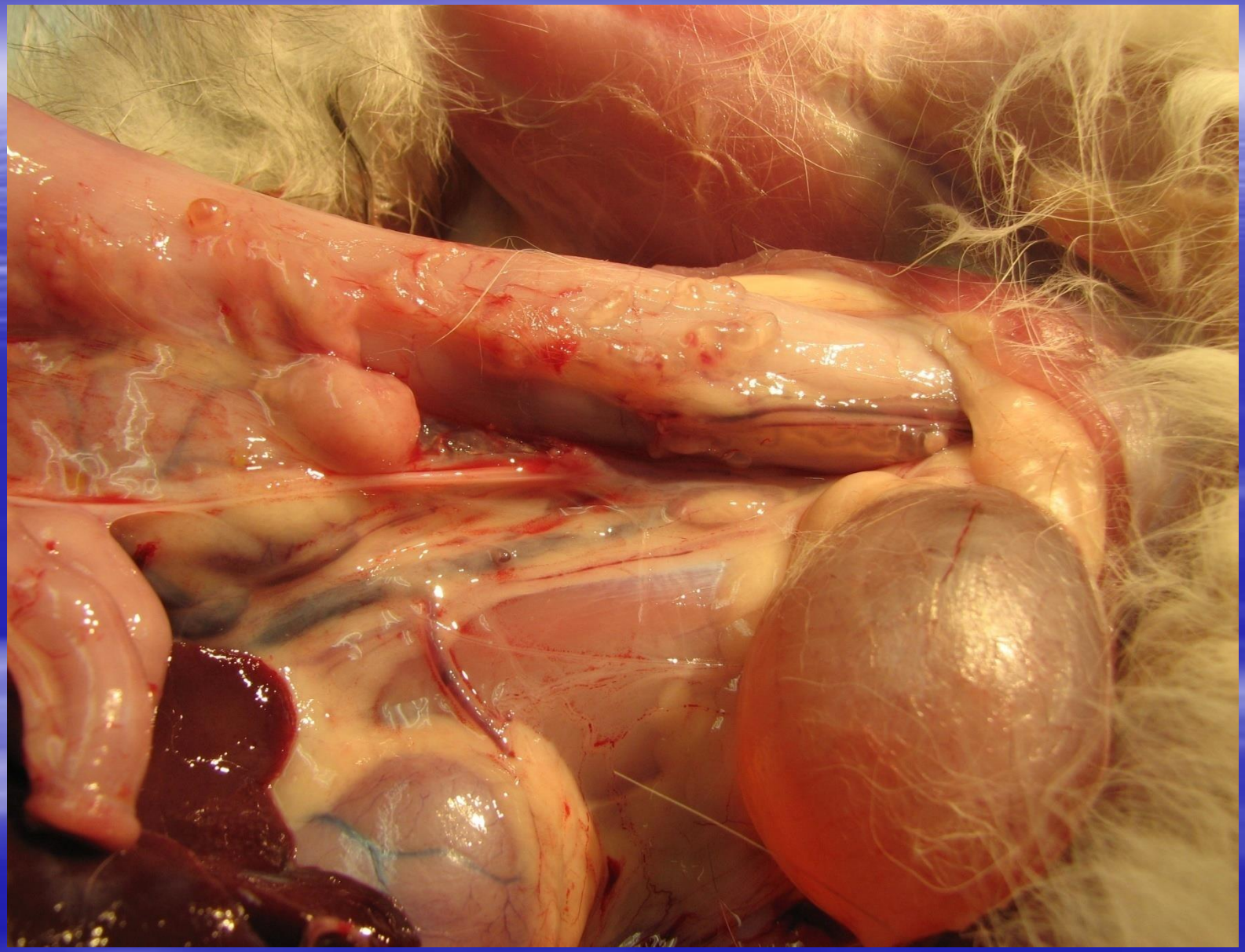
Interpretation:

1) A coronavirus antibody titre of >= 1:100 is suggestive for an infection with coronavirus. The differentiation between antibodies against feline enteral coronavirus and FIP-inducing coronavirus is not possible. The following changed laboratory parameters can indicate FIP infection in conjunction with suggestive clinical signs:
   1) Serum proteins:
      a) hyperproteinaemia
      b) hypoalbuminaemia
      c) hypergammaglobulinaemia
      -> reduced albumin-globulin ratio (< 0.6 is suspicious for FIP)
   2) Blood count:
      a) hypo- or aregenerative anaemia
      b) neutrophilia with left shift
      c) lymphopenia
   3) Liver:
      a) hyperbilirubinaemia
      b) raised ALT

Final report 26.04.05 15:23
Sincerely Dr. Bergermann
(Veterinarian)

Notes:

2) Basophils up to 200/ul are considered normal in the literature.