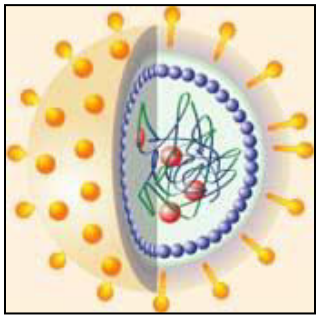
CORONAVIRUS FELINI
E
PERITONITE INFETTIVA

PERITONITE INFETTIVA FELINA

MALATTIA PROGRESSIVA SISTEMICA

FIPV ⇒ **FCoV VIRULENTO**



ESITO LETALE

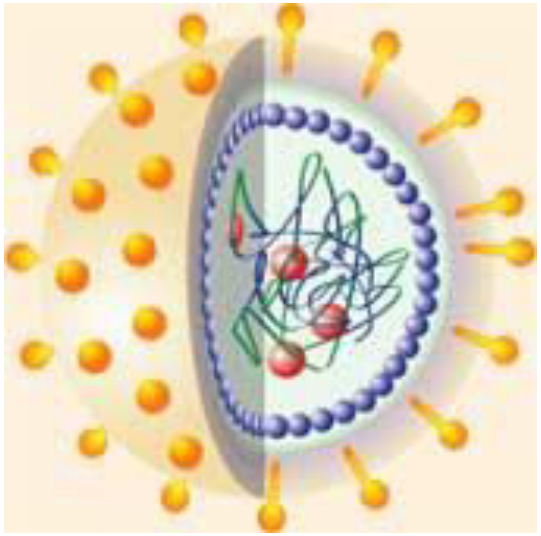
ESITO LETALE

- **VERSAMENTI IN CAVITÀ SIEROSE**
- **LESIONI PIOGRANULAMOTOSE DIFFUSE**

FCoV

Famiglia: *Coronaviridae*

RNA/1+ (27-32kb), envelope

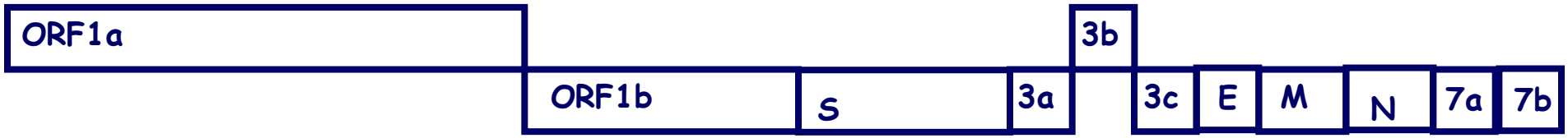


Sensibile disinfettanti ma sopravvive per 7 sett in ambiente secco

Trasmissione diretta e indiretta

GENOMA FCoV

29.000 nt – 11 ORFs



ORF 1a/ 1b

REPLICASI VIRALE

3' END ORFs

PROTEINE STRUTTURALI
E NON STRUTTURALI

The first two-thirds of the genome consists of two partially overlapping ORFs, ORF1a and ORF1b. These ORFs are translated into a polyprotein which is the precursor both of the viral RNA-dependent RNA polymerase and of proteases.

The one-third in the 3'end of the genome contains ORFs encoding for the major structural proteins, spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins. These ORFs are interspersed with several ORFs encoding for different non-structural proteins, most of which are of unknown function

PROTEINE VIRALI

PROTEINA S
(1451-1454 aa)

N-terminus — **RECETTORI (f-APN)**

C-terminus — **ATTIVITÀ FUSOGENA**

Abs NEUTRALIZZANTI?

PROTEINA M
(262-264 aa)

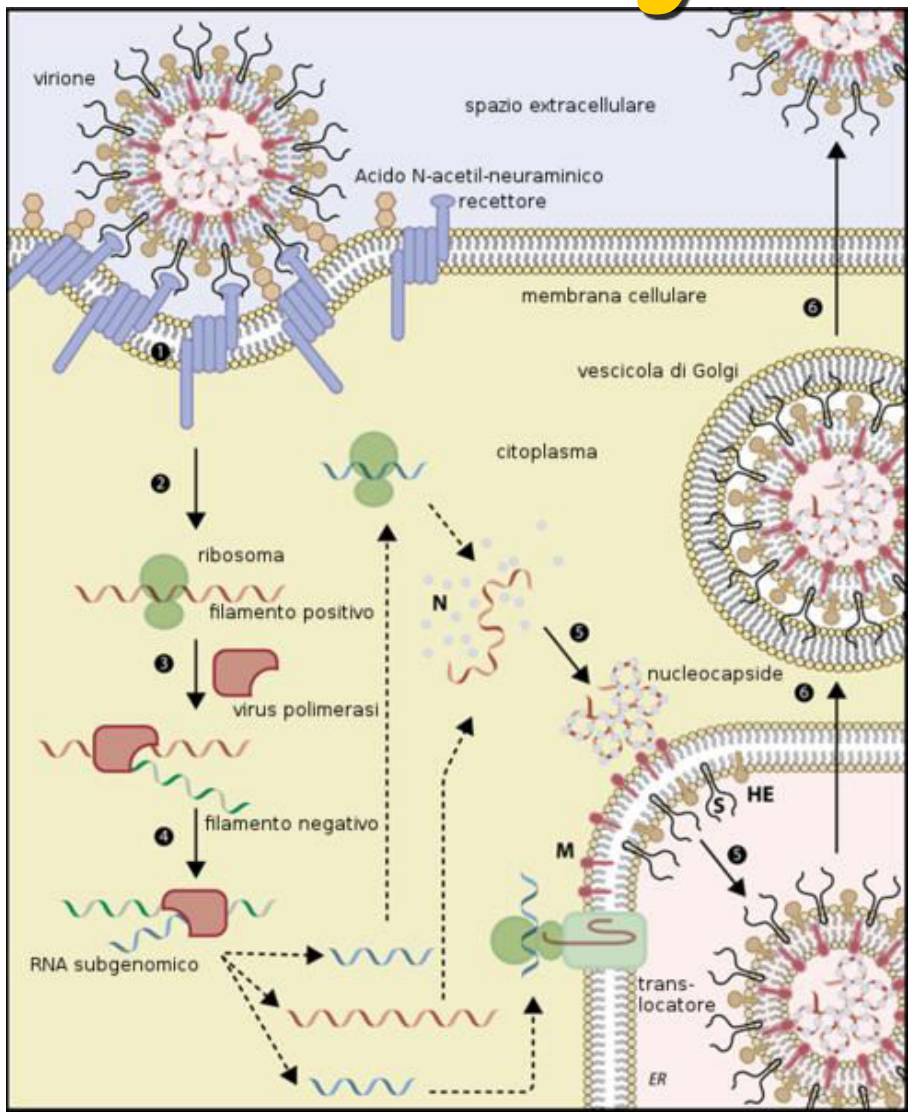
PROTEINA DI MEMBRANA

PROTEINA N
(381-382 aa)

ASSOCIATA A RNA VIRALE

REPLICATION

Nested sub-genomic mRNA strategy



Error rate: 1/10.000 nt

Large RNA encodes <u>ns protein</u> to minimize errors

RNA is relatively stable in absence of host and enviromental selection pressures Phillips et al., 2013

CORONAVIRUS FELINI

FCoV 2 GENOTIPI

FCoV I
FCoV II

FCoV tipo I

Predominante in Europa e America

70-90% INFEZIONI

DIFFICILE ISOLAMENTO *IN VITRO*

FCoV tipo II

Predominante in Asia

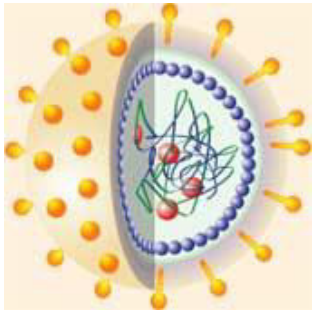
Ricombinazione tra
FCoV tipo I e CCoV

10-30% INFEZIONI

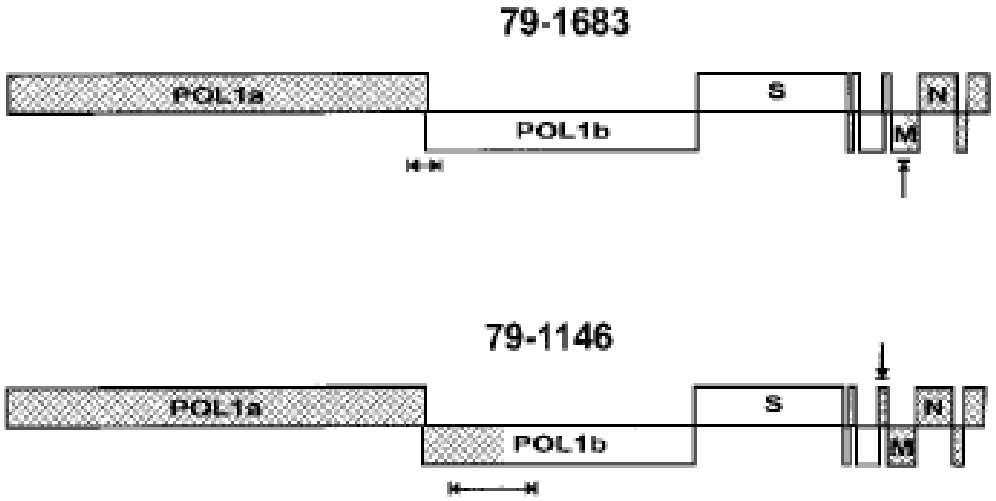
FACILE ISOLAMENTO *IN VITRO*

CORONAVIRUS FELINI

FCoV tipo II ➡ **RICOMBINAZIONE TRA FCoV TIPO I E CCoV tipo II**



ORF1b e geni S, 3a, 3b, 3c, E di CCoV



Herrewegh et al., J. Virol., 1998

CORONAVIRUS FELINI e CANINI

…PRIMA DEL 2003

FCoV **2 GENOTIPI** **FCoV I** **FCoV II**

CCoV **1 GENOTIPO**

CLASSICI CCoV

CORRELATI A FCoV TIPO II

CORONAVIRUS DEL CANE

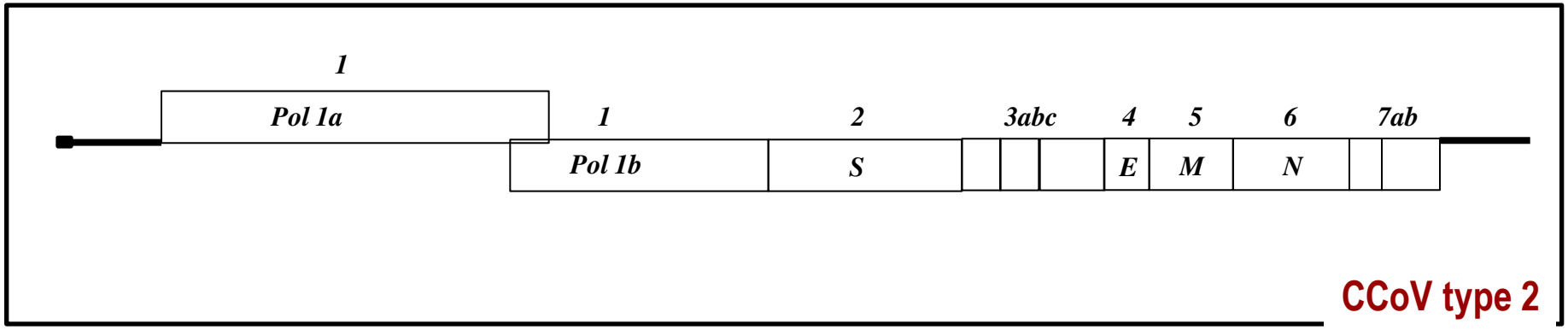
…DOPO IL 2003

2 GENOTIPI CCoV

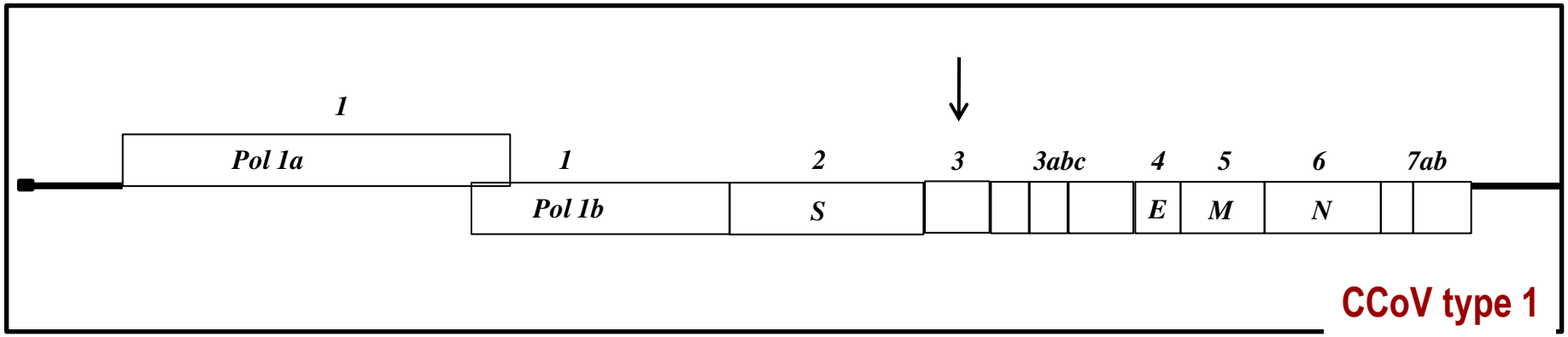
CLASSICI CCoV	NUOVI CCoV
CORRELATI A FCoV II	CORRELATI A FCoV I

CCoV tipo II ***CCoV tipo I***

EZIOLOGIA

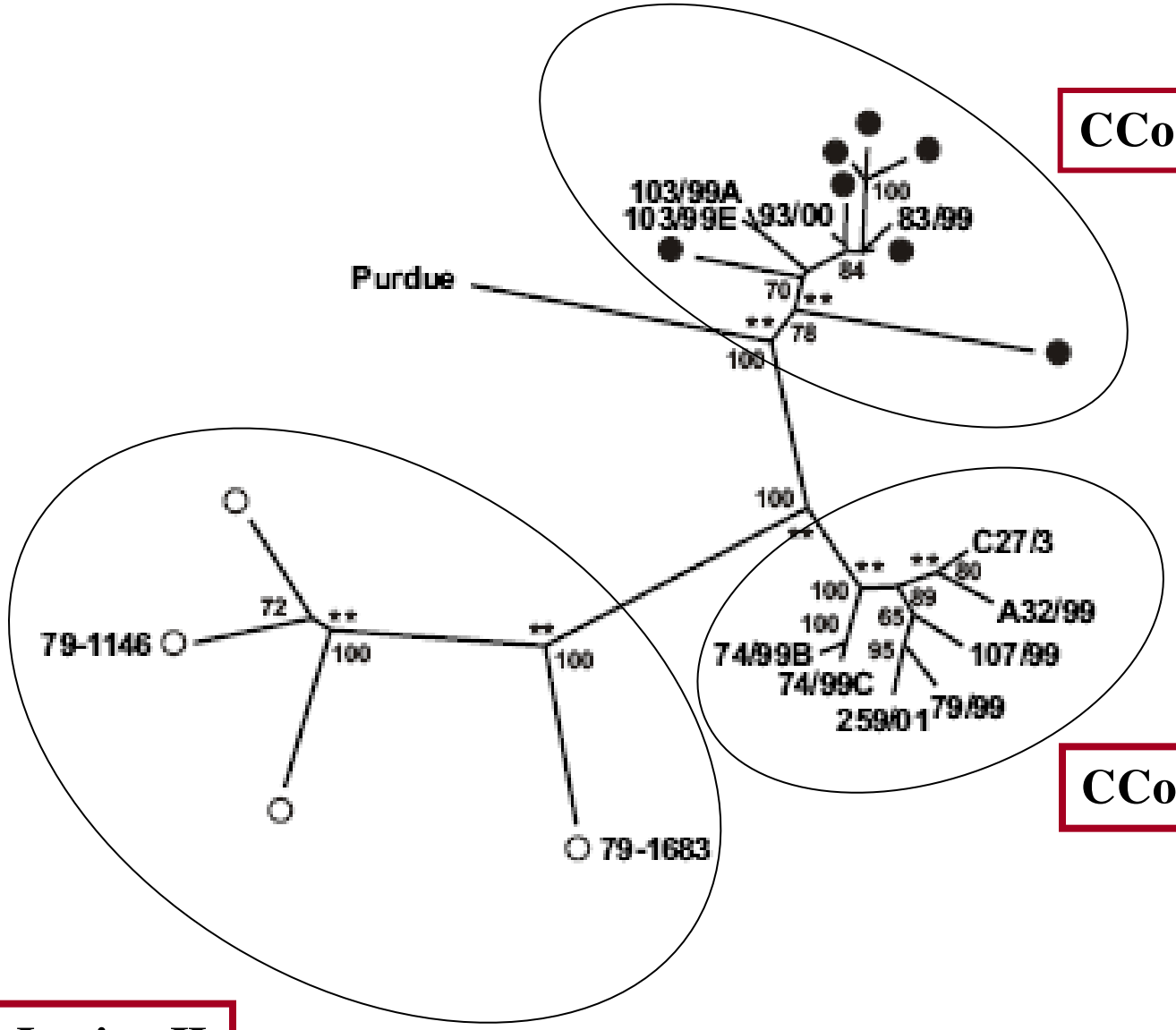


CCoV type 2

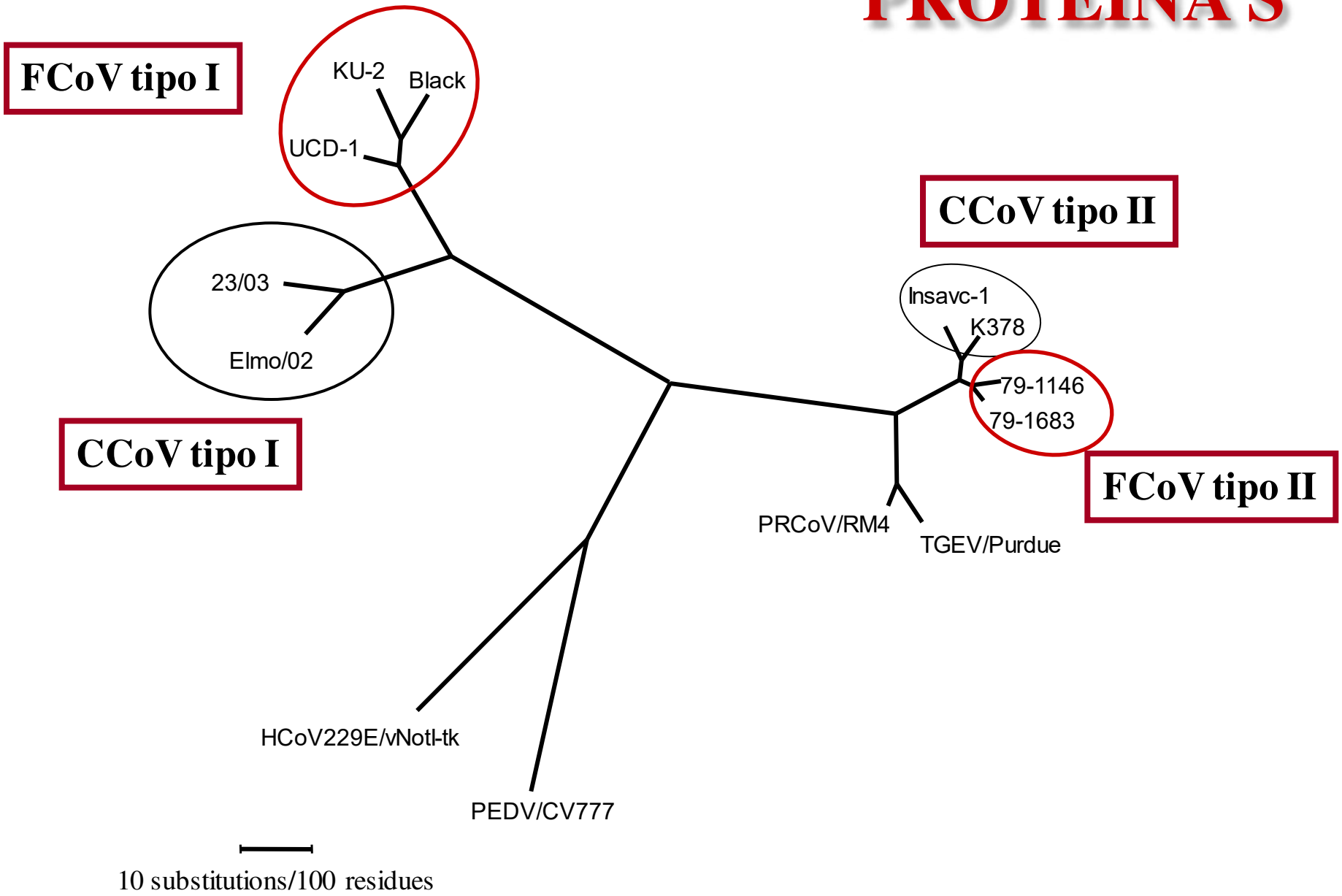


CCoV type 1

PROTEINA M


CCoV tipo II
103/99A
103/99E
93/00
83/99
100
84
Purdue
70
**
**
78
100
100
**
C27/3
**
**
80
100
89
A32/99
100
65
74/99B
95
107/99
74/99C
259/01
79/99
CCoV tipo I
72
**
79-1146
100
**
100
79-1683
FCoV tipo I e tipo II

PROTEINA S


FCoV tipo I
KU-2
Black
UCD-1
CCoV tipo II
23/03
Elmo/02
Insavc-1
K378
79-1146
79-1683
CCoV tipo I
FCoV tipo II
PRCoV/RM4
TGEV/Purdue
HCoV229E/vNotI-tk
PEDV/CV777
10 substitutions/100 residues

FELINE CORONAVIRUSES

FCoV ⇨ **2 BIOTYPES**

ENTERIC (FECV) ⇩ **MILD ENTERITIS**

VIRULENT (FIPV) ⇩ **INFECTIOUS PERITONITIS**

Since all FCoVs may induce systemic infection: these terms «biotypes» should be avoid

CORONAVIRUS FELINI

FECV

TROPISMO ENTERICO

Bassi titoli virali nel sangue!

- **SCARSO POTERE PATOGENO**
- **INFEZIONE PERSISTENTE (mesi)**

FIPV

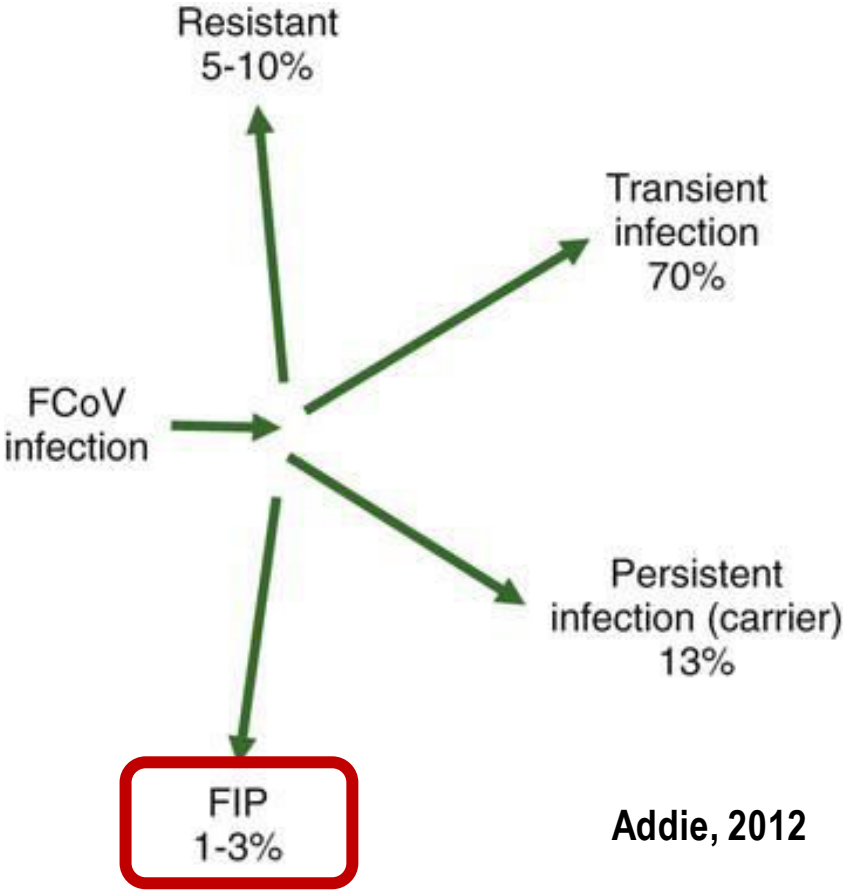
TROPISMO MONOCITI/MACROFAGI

- **ALTAMENTE PATOGENO**
- **DIFFUSIONE SISTEMICA**
- **MALATTIA** ⇨ **FIP**

5-10% CASI

EPIDEMIOLOGIA

FECV SI TRASMETTE MEDIANTE LE FECI



Addie, 2012

Feci: principale fonte infezione

Escrezione da 1 sett p.i. per mesi (lifelong: carriers)

Rara la trasmissione da gatti con FIP

FECV → ubiquitario

5-10% gatti FECV/+ sviluppano FIP

Fattori predisponenti:

- Razza (Bengala)
- Età (< 1 anno)
- Stress
- Co-infection (FeLV)

PATOGENESI

FECV → infezione asintomatica o lieve enterite

Sviluppo FIP per insorgenza mutanti dopo FECV

"burst replication"

In enterociti o
monociti/macrofagi

Sviluppo FIP: correlato a titolo virale e risposta immunitaria

PATOGENESIS

FIPV ORIGIN: the internal mutation theory

FIPV arises by internal mutation from FECV within each cat

Each mutation is the result of positive selection pressures

- **Initially for a switch from enterocyte to monocyte/macrophage tropism**
- **Ultimately for infection, replication and survival in peritoneal macrophages**

Three different genes have been associated with FECV→FIPV mutation

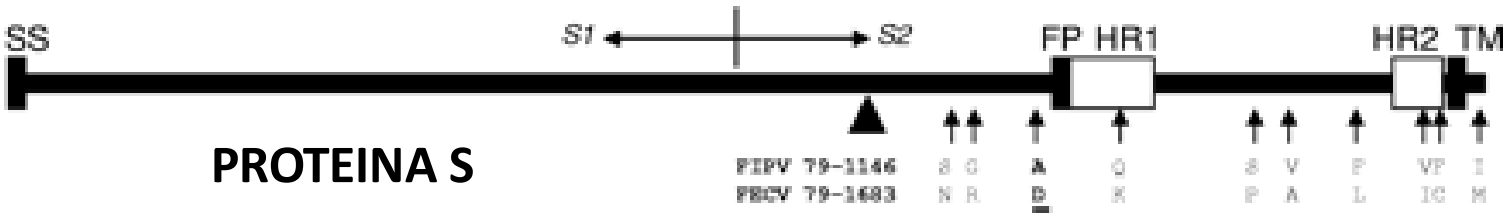
PATOGENESI

FIPV **DERIVA DA** **FECV**

MECCANISMI MOLECOLARI NON COMPLETAMENTE NOTI

DELEZIONI/MUTAZIONI PUNTIFORMI

- **ORFs 3c** ⇨ Vennema et al., 1998
- **ORF 7a** ⇨ Kennedy et al., 2001
- **3' end gene S** ⇨ Rottier et al., 2005



PROTEINA S

1. Mutations in the ORF 3c accessory gene

2/3 of FIPVs have ORF 3c mutations that lead to truncated protein

1/3 with no truncating mutations, have increased number of nt changes

Only truncating mutations have effect on host cell tropism

FIPVs with truncating ORF 3c mutations do not replicate in the gut epithelium, but efficiently replicate in macrophages

2. Mutations in the 7a/7b ORF

- Deletion in the 7a ORF has been associated to changes in virulence ultimately resulting in FIP

- The 7b ORF, the 3' most gene, has been speculated to have a role in virulence, as deletions in this region lead to decreased virulence

(Herrewegh et al., 1995; Vennema et al., 1998)

Deletions in ORF 7b gene can occur naturally in both FECVs and FIPVs

ORF 7 is crucial for FIPV replication in monocyes/macrophages, but ORF 7 mutation is not involved in FECV-to-FIPV transformation

3. Mutations in the S gene

Mutations in the S gene are strongly associated with FIP

nt mutations caused minor changes in single aa (1058-met→leu; 1060-ser→ala)

Even minor changes in aa might be responsible for increase macrophages tropism

These mutations were only observed in FIPVs diseased tissue and not in virus feces

These mutations occur in monocytes/macrophages

Their role in causing disease in unknown,
but they are more likely to be involved in macrophage infectivity than in subsequent host-virus immune interactions

PATOGENESI

Sviluppo FIP: correlato a titolo virale e risposta immunitaria

FIP

EFFUSIVA:
polisierosite, vasculite

SECCA: granulomi

In base a intensità della risposta immunitaria cellulare

PATOGENESI

FIPV → **INFEZIONE MACROFAGI**

FECV perde tropismo per enterociti e lo acquista vs macrofagi

↳ Dove avviene???

Squilibrio risposta LT vs LB è responsabile di incapacità a resistere all'infezione da FIPV

Produzione Abs è controproducente:

potenziano uptake e replicazione FIPV in macrofagi e contribuiscono a vasculite da ipersensibilità III tipo

↓

FIP effusiva: Vigorosa risposta umorale, scarsa risposta cellulare

FIP secca: Risposta cellulare parzialmente efficace in contenimento FIPV in pochi macrofagi

PATOGENESI

FIP

RISPOSTA CELLULARE ASSENTE → FORMA UMIDA

RISPOSTA CELLULARE DEBOLE → FORMA SECCA

RISPOSTA CELLULARE FORTE → NO MALATTIA

FIP effusiva e secca sono a volte interscambiabili:

- Forma secca spesso segue a breve forma umida
- Stadi finali forma secca revertono in forma umida

PATOGENESI

FIPV → **INFEZIONE MACROFAGI**

DISREGOLAZIONE CITOCHINE:

- **AUMENTO** di IL-1β, IL-6, IL-10, **TNF-α**
- **DIMINUZIONE** di **IF-γ**, IL-12, IL-18

PATTERN DI TIPO Th2

APOPTOSI CELLULE T

CD4 e CD8

> RISPOSTA UMORALE

< RISPOSTA CELLULARE

AUMENTO PERMEABILITÀ VASALE e RICHIAMO MACROFAGI

EFFUSIONI CAVITARIE E FORMAZIONE DI GRANULOMI

PATOGENESI

FIPV → **INFEZIONE MACROFAGI**

DISREGOLAZIONE RISPOSTA IMMUNITARIA:

DEPLEZIONE NK e LTreg e
RIDUZIONE ATTIVITÀ CITOTOSSICA NK

Deplezione da sangue periferico, linfonodi mesenterici e milza

DIA DA ELIMINARE

PATOGENESI

INFEZIONE SPERIMENTALE

De Groot-Mijnes et al., J. Virol., 2005

5 GRUPPI

TEMPI DI SOPRAVVIVENZA

FASE ACUTA (7-8 gg) e TEMPORANEA REMISSIONE

- **RAPID PROGRESSORS**
- **INTERMEDIATE PROGRESSORS**
- **DELAYED PROGRESSORS**
- **PROLONGED SURVIVORS**
- **LONG-TERM SURVIVORS**

RECRUDESCENZA E MORTE IN 21, 28 E 35 gg P.I.

EPISODI FEBBRILI E MORTE IN 50-54 gg P.I.

CONTROLLO della MALATTIA

EVOLUZIONE IN FUNZIONE DELLA RISPOSTA CELLULARE

PATOGENESI

FIP umida → Piogranuloma
FIP secca → Granuloma

<u>Piogranuloma</u>:

- **accumulo di macrofagi, neutrofili, linfociti e plasmacellule intorno alle venule**

  Risultato di upregulation di molecole di adesione e dei recettori

- **accumulo di liquido in cavità**

  VEGF: fattore responsabile di versamento

  Ricco di proteine plasmatiche, fattori di coagulazione, proteine infiammatorie e prodotti di degradazione di Hb

SINTOMATOLOGIA

Quadri clinici estremamente variabili

FEBBRE CRONICA FLUTTUANTE, LETARGIA, ANORESSIA, PERDITA PESO

FORMA UMIDA

DECORSO RAPIDO (4-5 SETTIMANE)

FORMA SECCA

Più difficile da diagnosticare

DECORSO PROTRATTO (SETTIMANE-MESI)

FORMA UMIDA

VERSAMENTI IN ADDOME, TORACE, PERICARDIO, VASCULITE e LESIONI PIOGRANULOMATOSE

- PERITONITE (90%)
- PLEURITE (40%)

Aumento volume rene, ispessimento ileocecale e/o colon (diarrea cronica e vomito), linfoadenomegalia, dispnea per polmonite piogranulomatosa

SHOCK, MORTE

FORMA SECCA

FORME CLINICHE

LESIONI PIOGRANULOMATOSE DIFFUSE

- PERITONEO (50%)
- PLEURE (10%)
- OCCHIO/SNC (30%/10%)
- ORGANI ADDOMINALI: rene, linfonodi, fegato, milza, pancreas

Segni neurologici (10% dei casi)

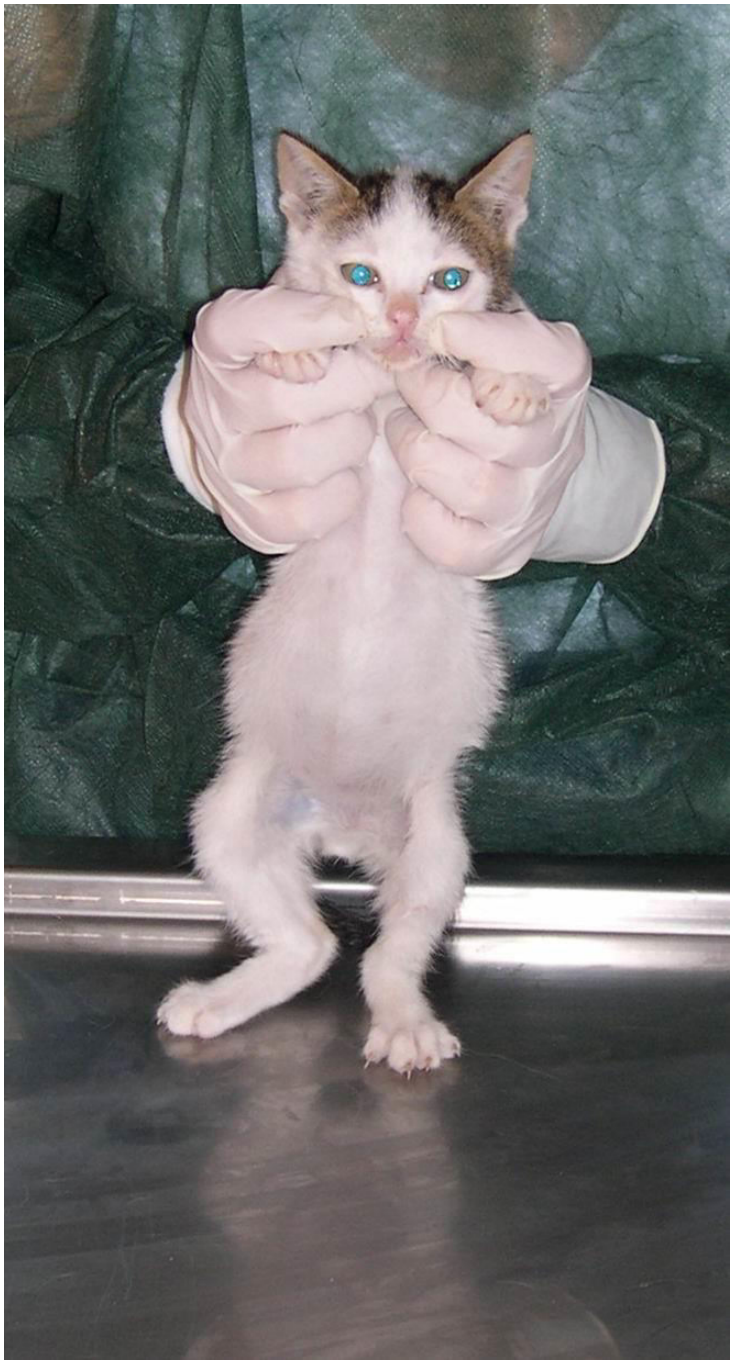
Paresi posteriore, incoordinazione, iperestesia, convulsioni, pedalage, paralisi n. sciatico, facciale, trigemino, brachiale, nistagmo

SEGNI OCULARI

Uveite e corioretinite, emorragie retiniche e distacco, cambio colore e gonfiore iride con lesioni nodulari

SEGNI CUTANEI

Lesioni multiple nodulari per flebite necrotica-piogranulomatosa e fragilità cutanea



EMATOLOGIA

FORMA UMIDA/SECCA

- **Neutrofilia/Linfopenia** «Leucogramma da stress»
- **Anemia non rigenerativa (HCT<30%)**
- **> Proteine seriche (12gr/dl)**
- **Ipergammaglobulinemia e > α2-globuline**
- **Rapporto albumine/globuline (Ipoalbuminemia)**
- **Aumento glicoproteina acida α1 (AGP)**

dd con cardiomiopatie e tumori,
ma non con traumi ed infezioni batteriche

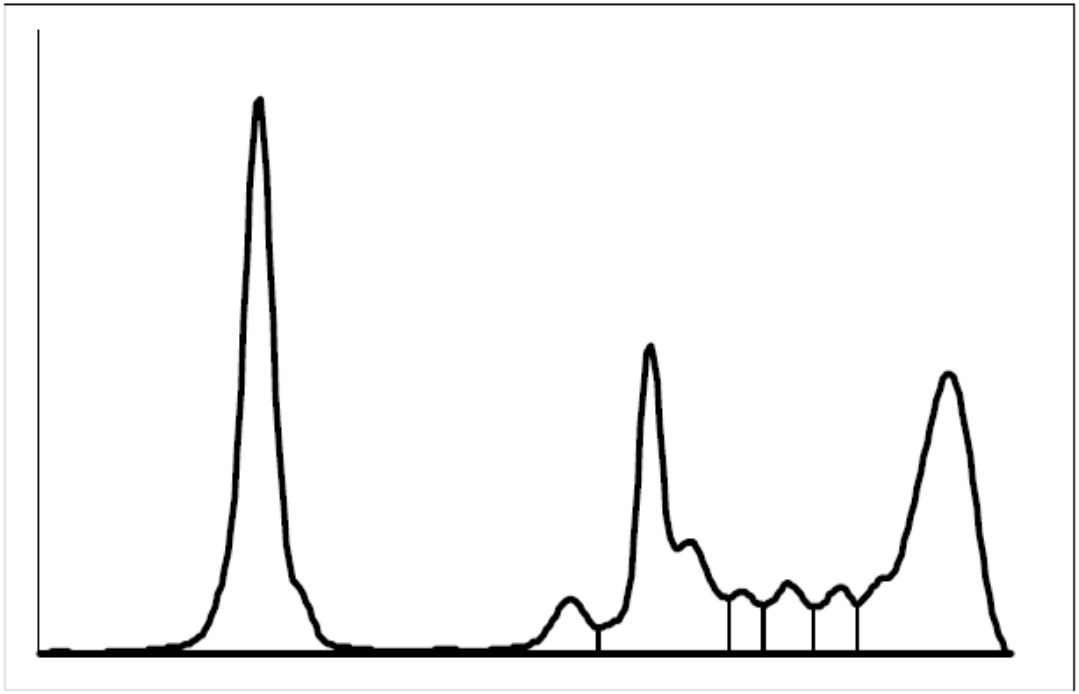
- **> enzimi epatici, urea, creatinina, bilirubina (ittero)**

22 ottobre 2010

Esami di laboratorio

specie: GATTO razza: EUROPEO DSH sesso: F età: 7 mesi

ELETTROFORESI



		Intervallo di riferimento	
		min	max
Albumina (%) :	34.8	39.4	54.8
Globuline ALFA (%) :	25.1	17.8	27.6
Globuline ALFA1 (%) :	3.6	0.8	1.6
Globuline ALFA2 (%) :	21.5	17.0	26.0
Globuline BETA (%) :	10.7	6.4	9.4
Globuline BETA1 (%) :	2.9		
Globuline BETA2 (%) :	4.1		
Globuline BETA3 (%) :	3.7		
Globuline GAMMA (%) :	29.4	16.2	28.2
Rapporto A/G:	0.53		

Esami di laboratorio

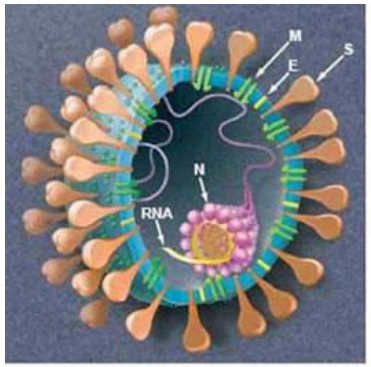
PROFILO BIOCHIMICO

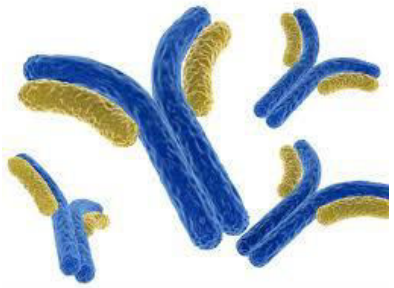
		Intervallo di riferimento	
		min	max
CPK (IU/L) :	144	90	320
AST (IU/L) :	26	15	35
ALT (IU/L) :	27	32	87
ALP (IU/L) :	46	19	70
GGT (IU/L) :	0.1	0.1	0.6
Colinesterasi (IU/L) :	2809	1955	3950
Bilirubina Totale (mg/dL) :	0.22	0.14	0.26
Proteine Totali (g/dL) :	8.1	6.3	7.8
Albumine (g/dL) :	2.4	3.0	4.0
Globuline (g/dL) :	5.7	3.0	4.5
Rapporto A/G:	0.42	0.72	1.25
Colesterolo (mg/dL) :	119	95	210
Trigliceridi (mg/dL) :	33	19	81
Urea (mg/dL) :	57	32	64
Creatinina (mg/dL) :	0.93	0.95	1.85
Glucosio (mg/dL) :	84	86	116
Calcio (mg/dL) :	9.8	9.3	11.2
Fosforo (mg/dL) :	6.6	3.5	6.6
Magnesio (mg/dL) :	0.86	0.81	1.05
Sodio (mEq/L) :	151	145	152
Potassio (mEq/L) :	4.4	3.5	4.7
Rapporto Na/K:	34.4	31	43
Cloro (mEq/L) :	119	112	119
Cloro corretto (mEq/L) :	123.2	112	119
Lattato (mmol/L) :	4.4	0.3	1.1
HCO-3 (mmol/L) :	13.2	12.0	22.5
Divario Anionico:	23.0	14.5	24.0
Osmol. sier. mis. (mOsm) :	305	303	313
Osmol. sier. calc. (mOsm) :	295	285	296
Div. Osmolale:	10	15	25
Ferro totale (µg/dL) :	24	50	118
UIBC (µg/dL) :	177	130	225
TIBC (µg/dL) :	201	175	303
Saturazione (%) :	11.9	19.5	42.5
SAA (µg/ml) :	149.4	0.1	0.5

Diagnosi

Cosa fare

VIRUS O PARTI DI ESSO
(antigeni, RNA)





ANTICORPI
No vaccini (USA)

NON È POSSIBILE DIFFERENZIARE FIPV DA FECV

"More cats die that are misdiagnosed based on vets taking the word for these tests as gospel or over inflating their value, than the number of cats who truly have FIP" – Niels Pedersen

DIAGNOSI

INTRA VITAM

ANAMNESI

SINTOMATOLOGIA

Gattili
Febbri ricorrenti

POST MORTEM

ESAME ANATOMO-ISTOPATOLOGICO

IMMUNOISTOCHIMICA

Macrofagi infetti

RT-PCR su ORGANI

DIAGNOSI

POST MORTEM

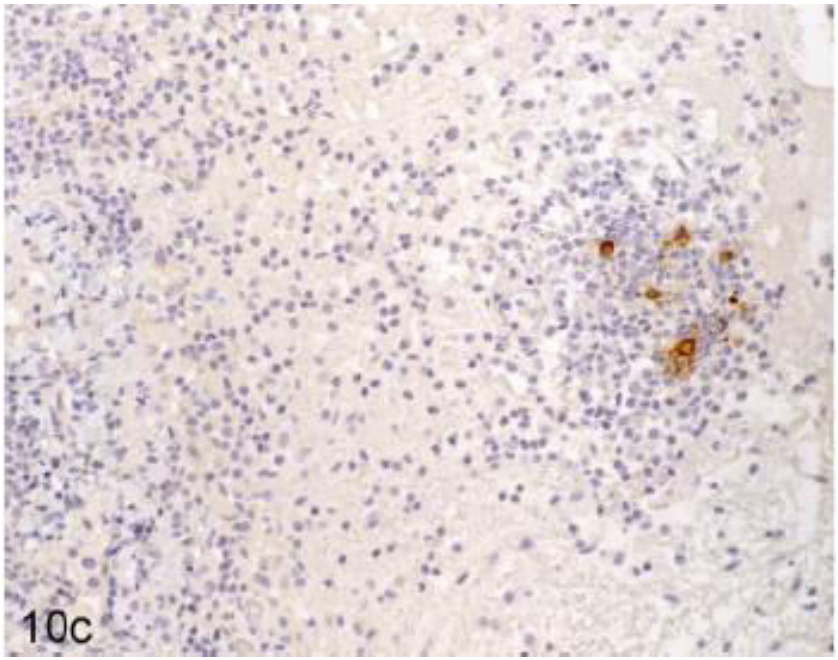
Quale test/campione per FIP?

IMMUNOISTOCHIMICA (IHC)

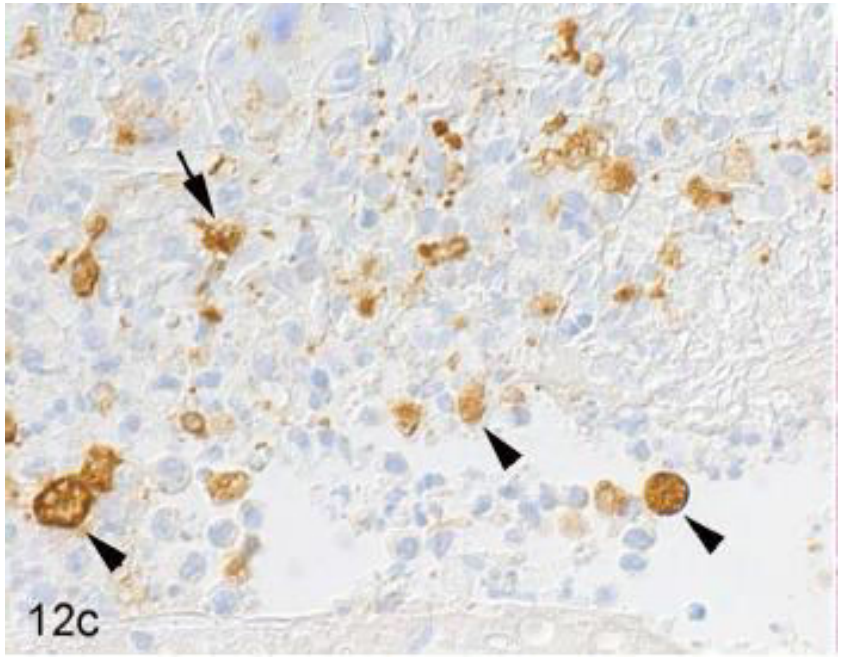
AG VIRALI IN TESSUTI INFETTI (MACROFAGI)

GOLD STANDARD

Pleura



Corteccia renale (vena)



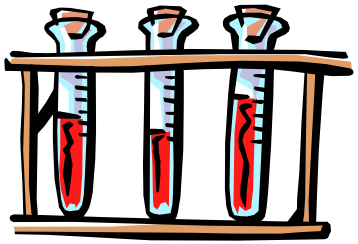
Kipar e Meli, 2014

DIAGNOSI

Quale test/campione per FIP?

INTRA VITAM

- ESAMI EMATOLOGICI



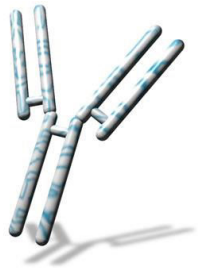
⇨

- ❖ Neutrofilia/linfopenia
- ❖ Ipergammaglobulinemia
- ❖ Albumina/globulina ratio
- ❖ Ipoalbuminemia
- ❖ Anemia
- ❖ Aumento AGP

- BIOPSIA ⇨ **Chirurgica**
  Non invasiva

- ANALISI EFFUSIONI ⇨ **Elevato contenuto proteico**

- SIEROLOGIA ⇨ **Non attendibile!**



DIAGNOSI

Quale test/campione per FIP?

INTRA VITAM

PROVA DI RIVALTA:

DIFFERENZIA ESSUDATO DA TRASUDATO

ESSUDATO:

- giallo, torbido, viscoso
- ricco proteine
- macrofagi, neutrofili e linfociti (500-5000µl)
- emorragico (+/-)
- no purulento

FORMA UMIDA

Courtesy Diane Addie, Feline Institute, Pyrenees, France.
Greene: Infectious Diseases of the Dog and Cat, 4th Edition

DIAGNOSI

INTRA VITAM

Quale test/campione per FIP?

SIEROLOGIA

Abs PER FCoV IN SIERO

FORMA UMIDA
FORMA SECCA

- IFI
- SN
- Test rapidi (RIM, ICGA)

NON È POSSIBILE DIFFERENZIARE Ab PER FIPV DA Ab PER FECV

TITOLI Ab > 1:800 ALTAMENTE INDICATIVI DI FIP

Healthy cats with titers < 1:100: infrequently shed FCEV
Cats with titers > 1:400: usually shed FECV

Low Abs titers in confirmed FIP: virus binds Abs

↓

Necessaria conferma con Real time PCR

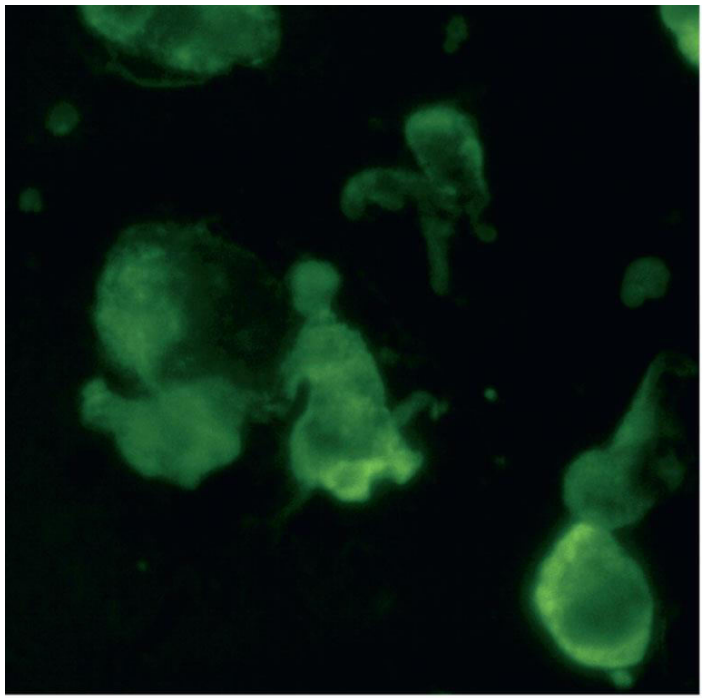
DIAGNOSI

INTRA VITAM

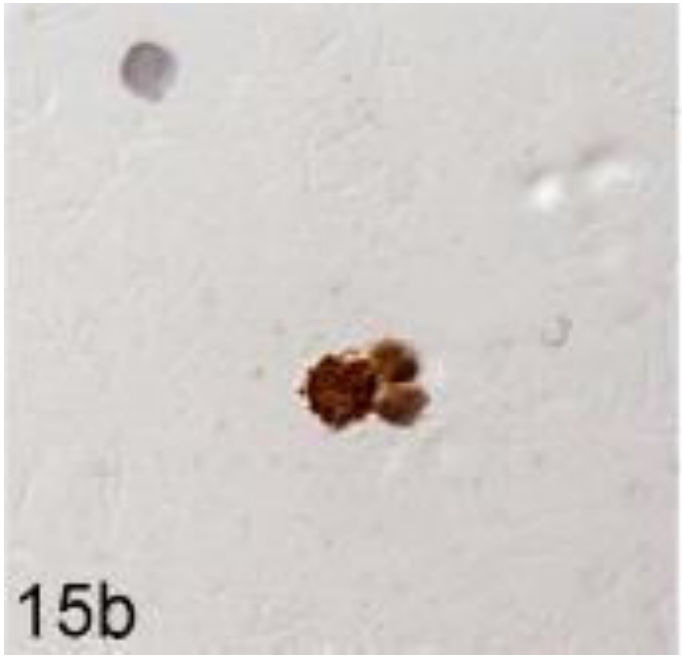
Quale test/campione per FIP?

IMMUNOFLUORESCENZA/IHC *FORMA UMIDA*

AG VIRALI IN MACROFAGI EFFUSIONI



Addie, 2012



Kipar e Meli, 2014

RT-PCR

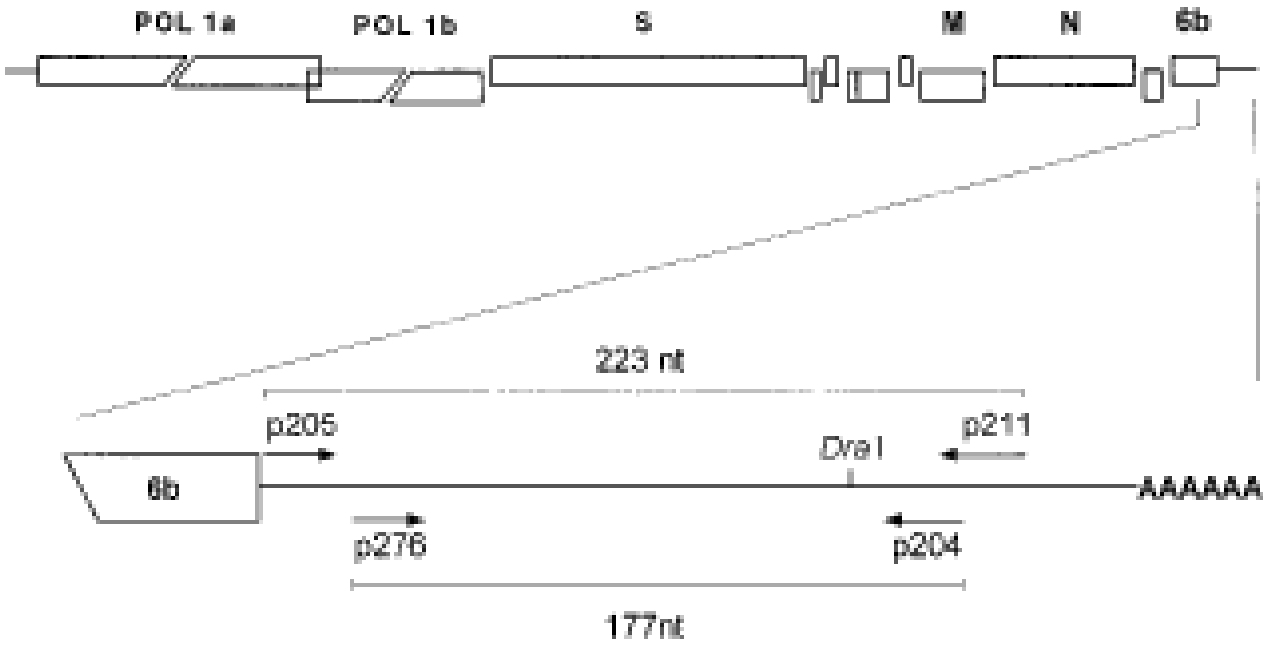
Test molecolari per FIP

JOURNAL OF CLINICAL MICROBIOLOGY, Mar. 1995, p. 684–689
0095-1137/95/$04.00+0

Vol. 33, No. 3

Detection of Feline Coronavirus RNA in Feces, Tissues, and Body Fluids of Naturally Infected Cats by Reverse Transcriptase PCR

ARNOLD A. P. M. HERREWEGH,[1]* RAOUL J. DE GROOT,[1] ARNOST CEPICA,[2]
HERMAN F. EGBERINK,[1] MARIAN C. HORZINEK,[1]



NO DISCRIMINAZIONE TRA FIPV E FECV

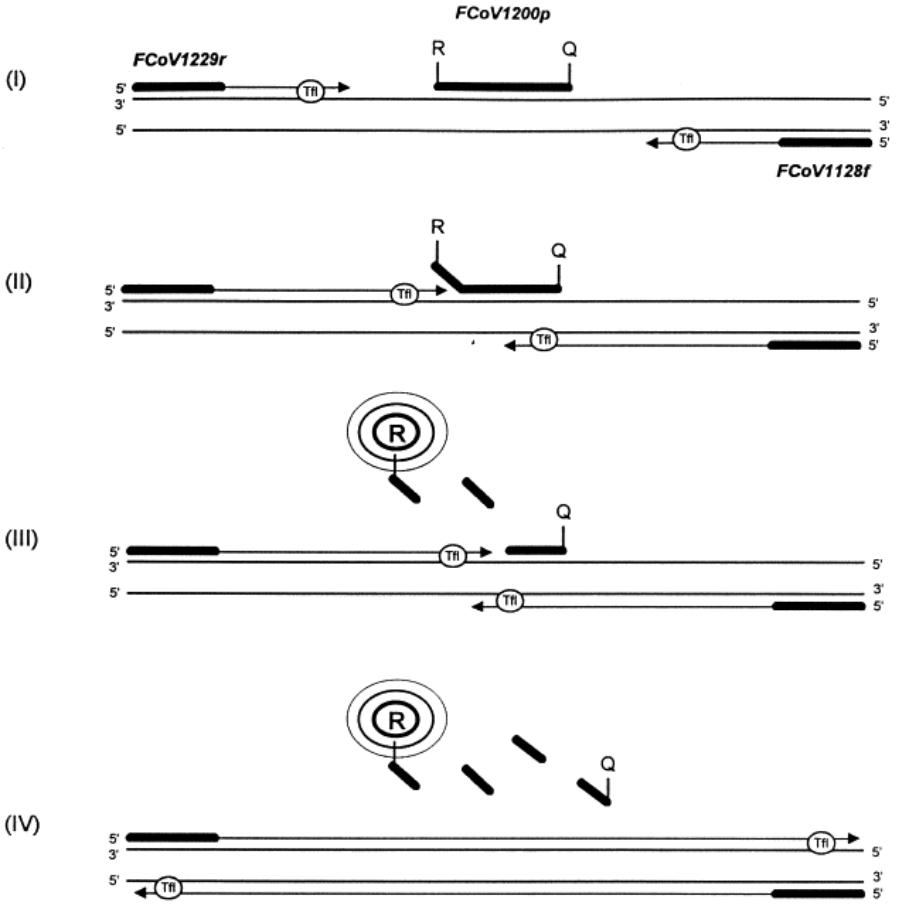
REAL-TIME RT-PCR

Test molecolari per FIP

Journal of Virological Methods 77 (1999) 37–46

One-tube fluorogenic reverse transcription-polymerase chain reaction for the quantitation of feline coronaviruses

Marco Gut [a,*,1], Christian M. Leutenegger [a,1], Jon B. Huder [b], Niels C. Pedersen [c], Hans Lutz [a]



NO DISCRIMINAZIONE TRA FIPV E FECV

mRNA RT-PCR

Ricerca specifica FIPV

Journal of Virological Methods 124 (2005) 111–116

A mRNA PCR for the diagnosis of feline infectious peritonitis

Fermin A. Simons[a,*], Harry Vennema[c], Jaime E. Rofina[b], Jan M. Pol[d], Marian C. Horzinek[e], Peter J.M. Rottier[a], Herman F. Egberink[a]

PRIMER For CONTIENE SEQUENZA LEADER (solo mRNA)

Results of FCoV mRNA RT-PCR in cats with clinical symptoms consistent with FIP and in healthy cats

Cats ($n = 1075$)	mRNA positive	mRNA negative
Cats with clinical symptoms indicative of FIP ($n = 651$)	301/651 (46%)	350/651 (54%)
Cats without clinical symptoms ($n = 424$)	23/424 (5%)	401/424 (95%)

Table 4
Results of FCoV mRNA RT-PCR of cats examined post-mortem

Cats ($n = 98$)	mRNA positive	mRNA negative
Cats with proven FIP ($n = 81$)	75/81 (93%)	6/81 (7%)
Cats with other diseases ($n = 17$)	0/17 (0%)	17/17 (100%)

RT-PCR PER mRNA SU SANGUE: POCO SENSIBILE

mRNA RT-PCR

Ricerca specifica FIPV

Journal of Feline Medicine and Surgery (2007) 9, 369–372

The detection of feline coronaviruses in blood samples from cats by mRNA RT-PCR

Kezban Can-Şahna DVM, PhD[1], **Veysel Soydal Ataseven** DVM, PhD[2], **Dilek Pınar** Res Ass[2], **Tuba Çiğdem Oğuzoğlu** Dr MedVet[3*]

Table 1. Distribution of FCoV infection in cats according to age and sex

Age	Tested cat (*n*)	Number of FCoV detected (%)	Sex		Remarks	
			Tested ♀:♂	FCoV detected ♀:♂	Indoor	Outdoor
6 months–1 year	7	5 (71%)	4:3	3:2	1*	6
2 years	6	3 (50%)	4:2	3:0	–	6
3 years	7	2 (29%)	4:3	1:1	–	7
5 years	1	1 (100%)	1:0	1:0	–	1
6 years	1	1 (100%)	1:0	1:0	1†	–
7 years	1	1 (100%)	0:1	0:1	1†	–
13 years	1	1 (100%)	1:0	1:0	1†	–
Unknown (>6 months old)	2	0 (0%)	1:1	0:0	–	2
Total	26	14 (54%)	16:10	10:4	4	22

*Cat with clinical signs of FIP.
†Three pedigree cats from same household.

ANCHE FECV REPLICA NEL SANGUE

RT-PCR PER mRNA SU SANGUE: POCO SPECIFICA

DIAGNOSI

- **RT-PCR SU SANGUE ED EFFUSIONI**

ANCHE FECV PUÒ ESSERE PRESENTE IN SANGUE ED EFFUSIONI!!!

RT-PCR SU mRNA GENE M (sequenza leader) ⇨ Simons et al., J. Virol. Methods, 2005

SOLO VIRUS IN ATTIVA REPLICAZIONE

REAL-TIME RT-PCR

Quale campione per FIP?

Feline coronavirus quantitative reverse transcriptase polymerase chain reaction on effusion samples in cats with and without feline infectious peritonitis

J. Feline Med. Surg. 2017 Feb;19(2):240-245.
doi: 10.1177/1098612X15606957

Louise Longstaff[1*], Emily Porter[2*], Victoria J Crossley[1],
Sophie E Hayhow[2], Christopher R Helps[3] and Séverine Tasker[1,3]

Table 2 Sensitivity, specificity, and positive and negative predictive values (PPV and NPV, respectively) of effusion reverse transcriptase quantitative PCR for the diagnosis of feline infectious peritonitis (FIP)

	Percentage	95% CI
Sensitivity	85.0	65.1–96.8
Specificity	100.0	85.2–100.0
PPV	100.0	80.5–100.0
NPV	88.5	69.9–97.6
Prevalence of FIP	46.5	31.5–62.2

ELEVATA SPECIFICITÀ, SENSIBILITÀ DISCRETA

REAL-TIME RT-PCR

Quale campione per FIP?

Detection of feline coronavirus in cerebrospinal fluid for diagnosis of feline infectious peritonitis in cats with and without neurological signs

Journal of Feline Medicine and Surgery
1–6

Stephanie J Doenges[1], Karin Weber[1], Roswitha Dorsch[1], Robert Fux[2], Andrea Fischer[1], Lara A Matiasek[1], Kaspar Matiasek[3] and Katrin Hartmann[1]

Table 1 Cats with feline infectious peritonitis (FIP), clinical signs, method of confirmation of the diagnosis of FIP, presence of neurological and/or ocular signs, and threshold cycle (Ct) values of the tested cerebrospinal fluid (CSF) sample

Cat	Signs for inclusion	Diagnosis	Confirmation	Method of confirmation	Neurological and/or ocular signs	Ct values CSF
1	Thoracic effusion, icterus	FIP	Post mortem	Histopathology	Seizures	No Ct
2	Thoracic effusion, fever	FIP	Post mortem	Histopathology	–	36.1 (positive)
3	Thoracic effusion	FIP	Post mortem	Histopathology	–	No Ct
4	Ascites, icterus, neurological signs	FIP	Post mortem	Histopathology	Seizures	32.1 (positive)
5	Ascites, icterus	FIP	Post mortem	Histopathology	–	No Ct
6	Thoracic effusion	FIP	Post mortem	Histopathology	–	No Ct
7	Ascites	FIP	Post mortem	Histopathology	–	No Ct
8	Thoracic and pericardial effusions	FIP	Post mortem	Histopathology	–	31.7 (positive)
9	Ascites, neurological signs	FIP	Post mortem	Histopathology	Paresis, ataxia, anisocoria, inability to control urination and defecation	32.6 (positive)
10	Ascites, fever, icterus, neurological and ocular signs	FIP	Post mortem	Histopathology	Paresis, uveitis	32.0 (positive)
11	Ascites, icterus	FIP	Post mortem	Histopathology	–	No Ct
12	Ascites, icterus	FIP	Post mortem	Histopathology	–	No Ct
13	Ascites, icterus	FIP	Post mortem	Histopathology	–	No Ct
14	Thoracic effusion and ascites, fever	FIP	Post mortem	Histopathology	–	No Ct
15	Fever, icterus, neurological signs	FIP	Post mortem	Histopathology	Ataxia	26.5 (positive)
16	Fever, ocular signs	FIP	Post mortem	Histopathology	Uveitis	32.0 (positive)
17	Thoracic effusion, fever, ocular signs	FIP	Post mortem	Histopathology	Uveitis	29.9 (positive)
18	Thoracic effusion and ascites, fever	FIP	Post mortem	Histopathology	–	No Ct
19	Ascites, fever, icterus	FIP	Post mortem	Histopathology	–	No Ct

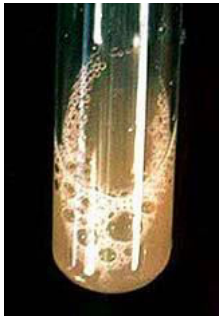
CSF:
BUONA SENSIBILITÀ
IN GATTI CON SEGNI NEUROLOGICI E/O OCULARI

DIAGNOSI INTRA-VITAM FIP SECCA

DIAGNOSI FIP

Cosa facciamo?

FORMA UMIDA — ***REAL-TIME RT-PCR*** / ***SIEROLOGIA***



RNA VIRALE

TITOLO Ab

FORMA SECCA — ***FORME NERVOSE/OCULARI*** / ***REAL-TIME RT-PCR***

RNA VIRALE

ALTRE MANIFESTAZIONI

SIEROLOGIA

TITOLO Ab

REAL-TIME RT-PCR

RNA VIRALE

ISTOLOGIA/IHC

QUADRO ISTOLOGICO/Ag VIRALI

Biologia molecolare

Risanamento colonie

Vet Clin Small Anim 41 (2011) 1133–1169
doi:10.1016/j.cvsm.2011.08.004

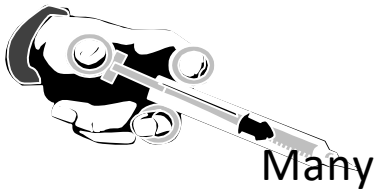
Feline Coronavirus in Multicat Environments

Yvonne Drechsler, PhD[1], Ana Alcaraz, DVM, PhD,
Frank J. Bossong, DVM, Ellen W. Collisson, PhD,
Pedro Paulo V.P. Diniz, DVM, PhD*,[1]

Table 3
Common methods to prevent FCoV infection and control feline infectious peritonitis outbreaks in multicat environments

Grouping by shedding status	Effective	Prevents reinfection of cats Increases socialization	Requires frequent serology or fecal PCR testing to determine shedding status	Only 1/3 of the seropositive cats shed the virus. Repeated fecal PCR test are required to document shedding. Expenses of lab tests may be a limiting factor.
Isolation and removal of chronic shedders from facility	Partially effective	Decreases risk of FIP by reducing frequent re-exposure to FCoV	May require depopulation if chronic shedders are not adoptable. May increase risk of FIP in other cats at the adopters environment	Shedding decreases once the cat is isolated. Chronic shedders should be adopted only to single-cat households.

- **IDENTIFICAZIONE GATTI INFETTI**
- **IDENTIFICAZIONE HIGH/CHRONIC SHEDDERS**



APPROCCI VACCINALI

Many attempts have been made to develop vaccines against FIP.
Unfortunately most of these studies have failed, with ADE observed in several trials

NON ESISTONO VACCINI TOTALMENTE EFFICACI!

- VACCINI ETEROLOGHI

TGEV ⇨ Woods and Pedersen, Vet. Microbiol., 1979

CCoV ⇨ Barlough et al., Lab. An. Sci., 1984; Stoddart et al., Res. Vet. Sci., 1988

HCoV ⇨ Barlough et al., Can. J. Vet. Med., 1985

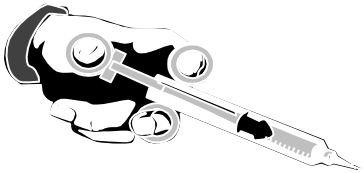
FECV ⇨ Pedersen et al., Am. J. Vet. Res., 1984

- VACCINI OMOLOGHI

FIPV avirulento ⇨ Pedersen and Black, Am. J. Vet. Res., 1983

APPROCCI VACCINALI

- VACCINI A SUBUNITÀ



⇒ **PROTEINA M**

PROTEINA N

⇒ Glansbeek et al., J. Gen. Virol., 2002

NON PROTETTIVI

- VACCINI RICOMBINANTI PROTEINA S

⇒ Vennema et al., J. Virol., 1990

ANTIBODY-DEPENDENT ENHANCEMENT (ADE)

L'ingresso del virus nei macrofagi è esaltato dalla presenza di Abs (RECETTORI PER Fc)

APPROCCI VACCINALI

European Advisory Board on Cat Diseases (ABCD)

At present, there is only one vaccine commercially available (Primucell©, Pfizer), in the USA and some European countries.

- FIPV TERMOSENSIBILE (in commercio) ⇒ Christianson et al., Arch. Virol., 1989

Primucell® contains a **temperature sensitive mutant of the type 2 FCo**V strain DF2. The vaccine is administered **intranasally** and aims at inducing **local mucosal immune responses** through the induction of IgA and cell-mediated immunity.

However, it does induce seroconversion, although rarely, and titers are generally low.

Also the **efficacy of this vaccine is in question** - it contains a type-2 strain, whereas type-1 coronaviruses are the prevalent ones in the field in most countries.

APPROCCI VACCINALI

European Advisory Board on Cat Diseases (ABCD)

Primucell® is ineffective in cats that have already experienced a FCoV field infection

Since Primucell® is licensed for use from 16 weeks of age and is not effective in younger cats, most kittens (especially those living in breeding colonies and multiple cat households) have already been infected and are seropositive.
This is an important limitation for its use.

The ADE that was a feature in some experimental vaccine trials has not been observed in field studies, suggesting that the vaccine can be considered safe

Primucell© RISULTATI CONTRASTANTI

Success rates between 0 and 75%

In a double-blind trial including 609 cats, no differences between the vaccinated and placebo group were found during the first 150 days after vaccination.
However, after 150 days, fewer FIP cases occurred in the vaccinated group compared to the placebo group (1 against 7)

APPROCCI VACCINALI

European Advisory Board on Cat Diseases (ABCD)

Primary vaccination course

A primary vaccination course consisting of **2 doses 3 weeks apart** from an **age of 16 weeks** onwards should be given.
Vaccination before 16 weeks was not shown to afford protection against infection.

Therefore there are **two particular problems in breeding catteries**:
-firstly most kittens are already seropositive at the age of vaccination and
-secondly FCoV infection occurs at a much younger age than 16 weeks

Booster vaccination

In cats of which the lifestyle has justified primary vaccination, **annual boosters** may be considered.
Although studies on the duration of immunity are lacking, it is thought to be short lived and **regular boosters may be required**

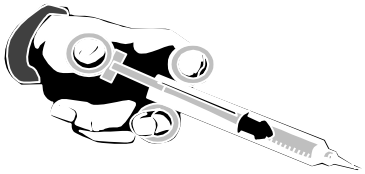
APPROCCI VACCINALI

- MLV FIPV deleti dei geni gruppo specifici

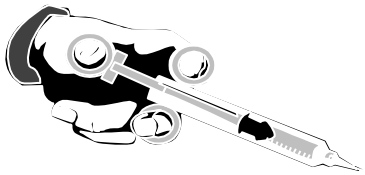
Δ3abc
Δ7ab

⇨ Hajiema et al., J. Virol., 2004

RISULTATI PROMETTENTI



SICURI
PROTETTIVI



APPROCCI TERAPEUTICI

1. **Impiego di farmaci che specificatamente <u>inibiscono la replicazione virale</u>**

2. **Impiego di farmaci in grado di <u>inibire la risposta infiammatoria</u>**

3. **Impiego di farmaci che <u>stimolino in modo non specifico il sistema immunitario</u>**

OBIETTIVI DI RICERCA

- BASI MOLECOLARI DELLA PATOGENICITÀ
- MECCANISMI PATOGENETICI
- VACCINI BIVALENTI (entrambi i sierotipi)

Prove effettuate quasi esclusivamente con FCoV tipo II

FCoV tipo I non facilmente coltivabile

Colonie FCoV-free


GRAZIE PER
L'ATTENZIONE!