Problems in the management of canine leishmaniasis

(Relevant questions, evidences and their application back to different patients

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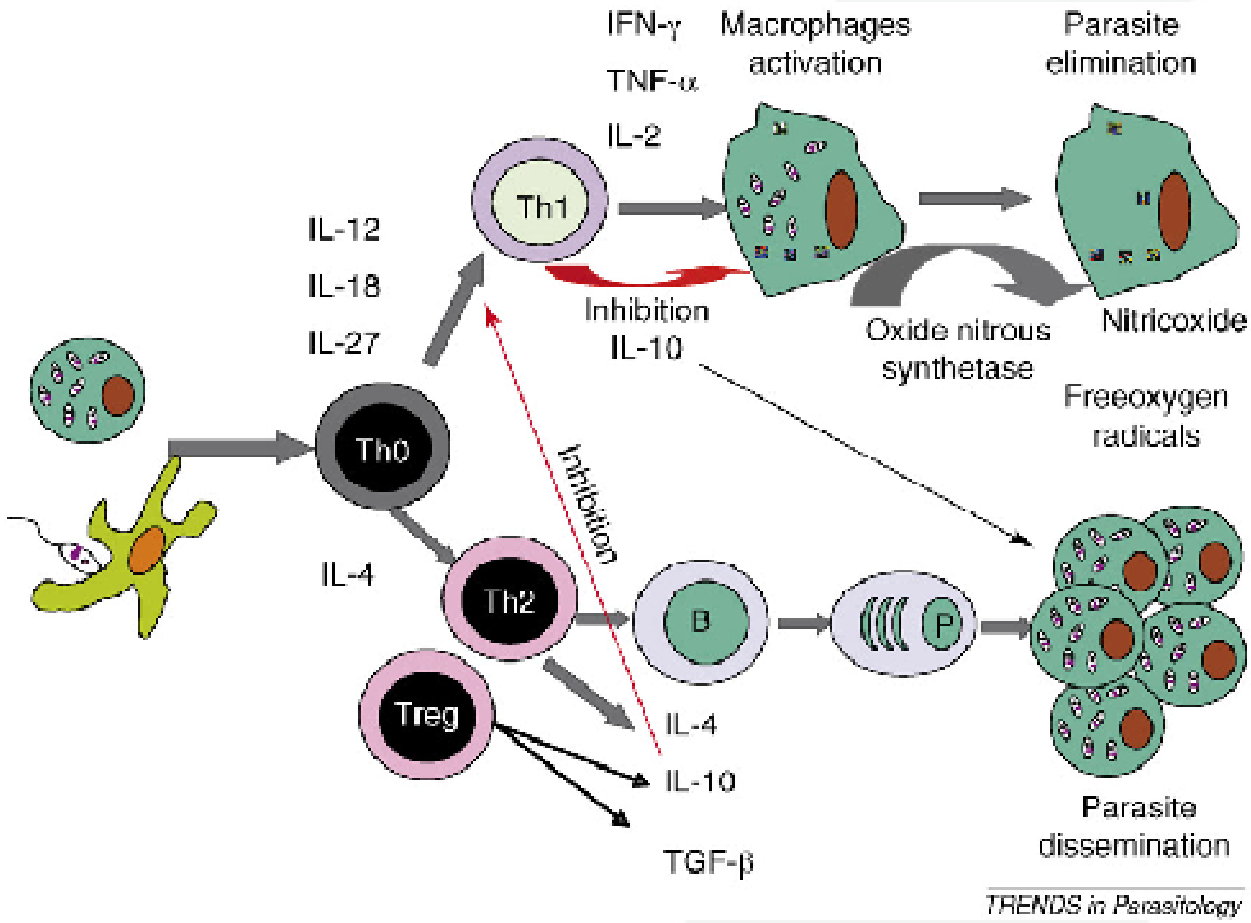
CANINE LEISHMANIOSIS

- Probably the most important canine disease in the Mediterranean
- A lot of research going on in many centers and institutions: >150 papers published in 2008
- However, the translation of basic research to clinical practice is lacking, as also are lacking good controlled, randomized clinical trials
- Furthermore, many trials have been done in dog populations different from dogs attending the veterinary clinics: stray dogs, dogs in shelters, dogs included in epidemiological surveys,…

Example: Immune response



Example 1. Immune response (2)

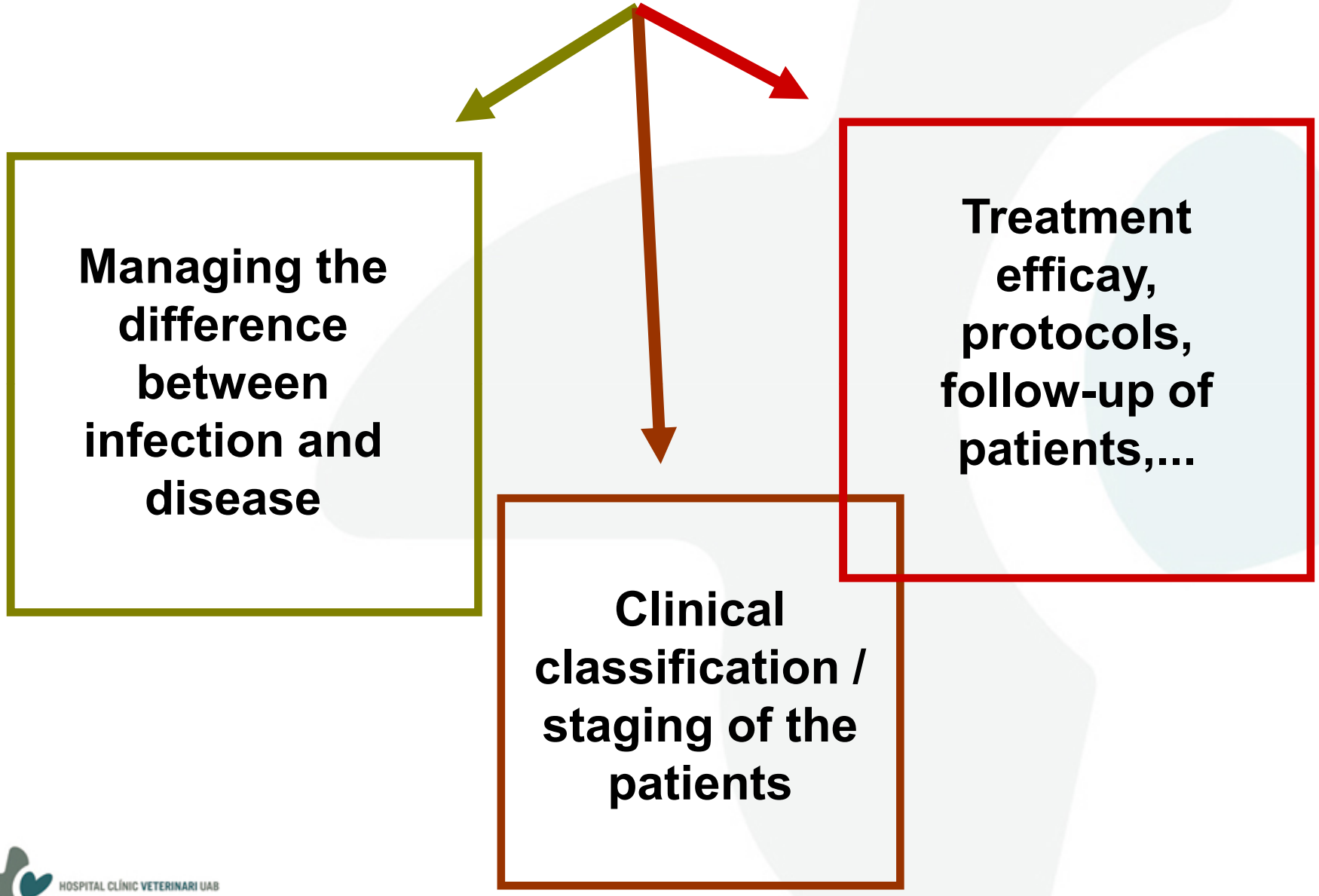
However…

1. **There are not validated tests to evaluate the immune status in dogs**

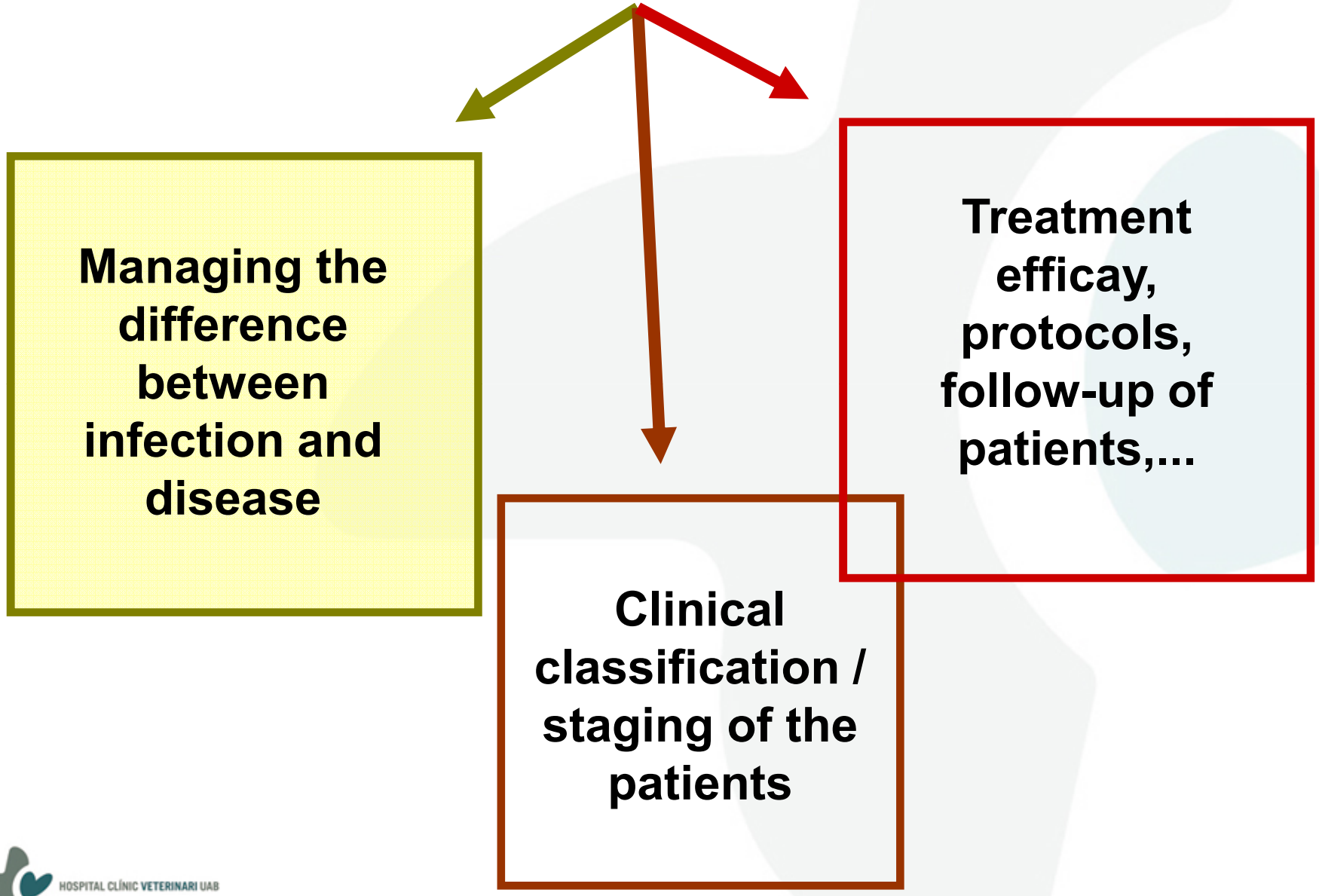
2. **There is not a single immune potentiating drug of use in dogs. Many non-evidence based therapies are used by veterinarians:**

   - Levamisol
   - Cimetidine
   - Domperidone

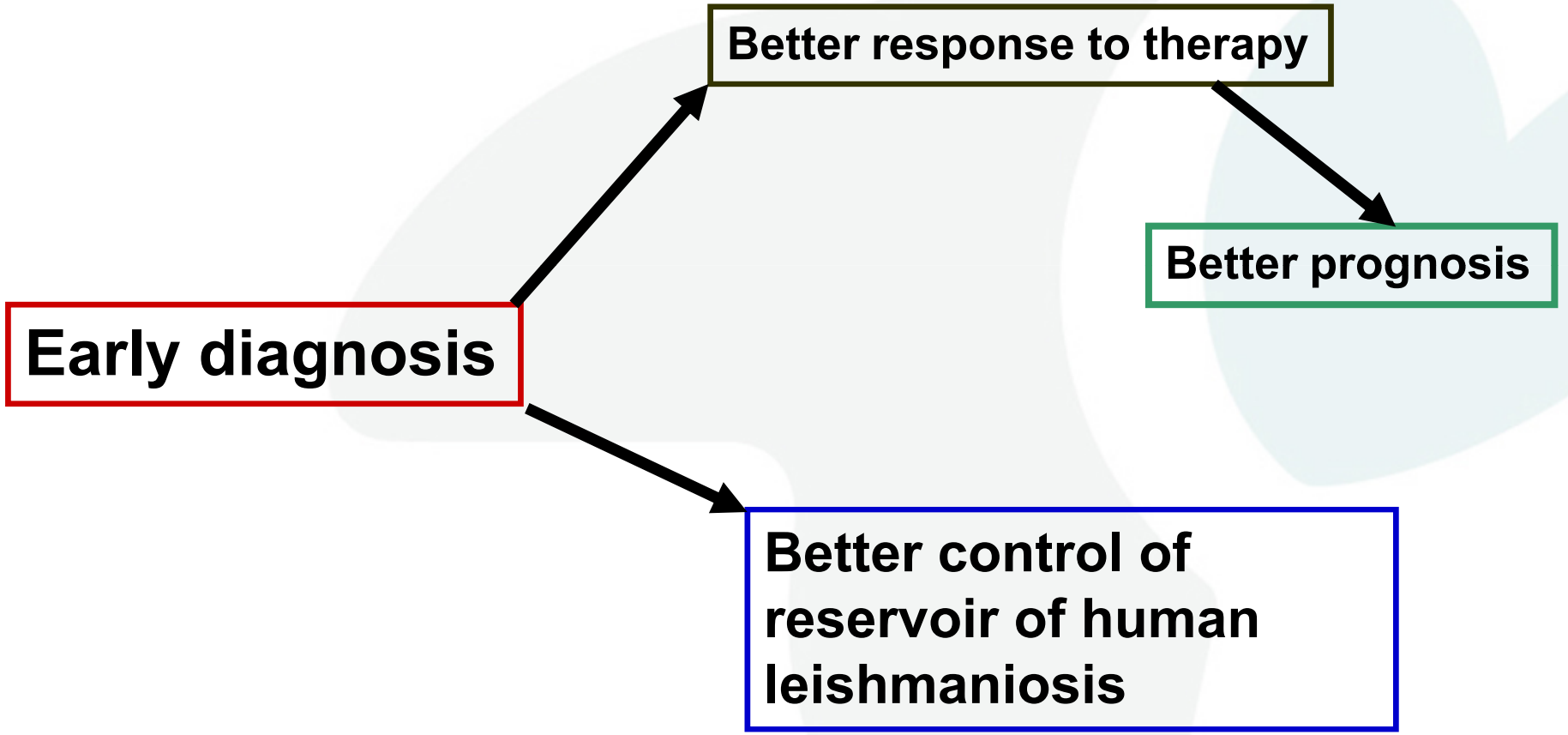
10 relevant questions from 3 areas...



10 relevant questions from 3 areas...



Managing the difference between infection and disease (I): the non proven paradigma



Managing the difference between infection and disease (II): the situation

Screening of numerous healthy dogs with PCR, serology of both

Numerous clinically healthy dogs IFA + or PCR +

Different clinicians give diverse interpretations to these results

Treatment is also very variable: from scientific neglect to long-term polytherapy

Managing the difference between infection and disease (III)

(1) Should clinically healthy dogs be screened for carrying *Leishmania* DNA?

(2) Should clinically healthy dogs be screened for *Leishmania*-specific antibodies?

(3) How should a clinically healthy seropositive dog be managed?

Managing the difference between infection and disease (III)

(1) Should clinically healthy dogs be screened for carrying *Leishmania* DNA?

NO

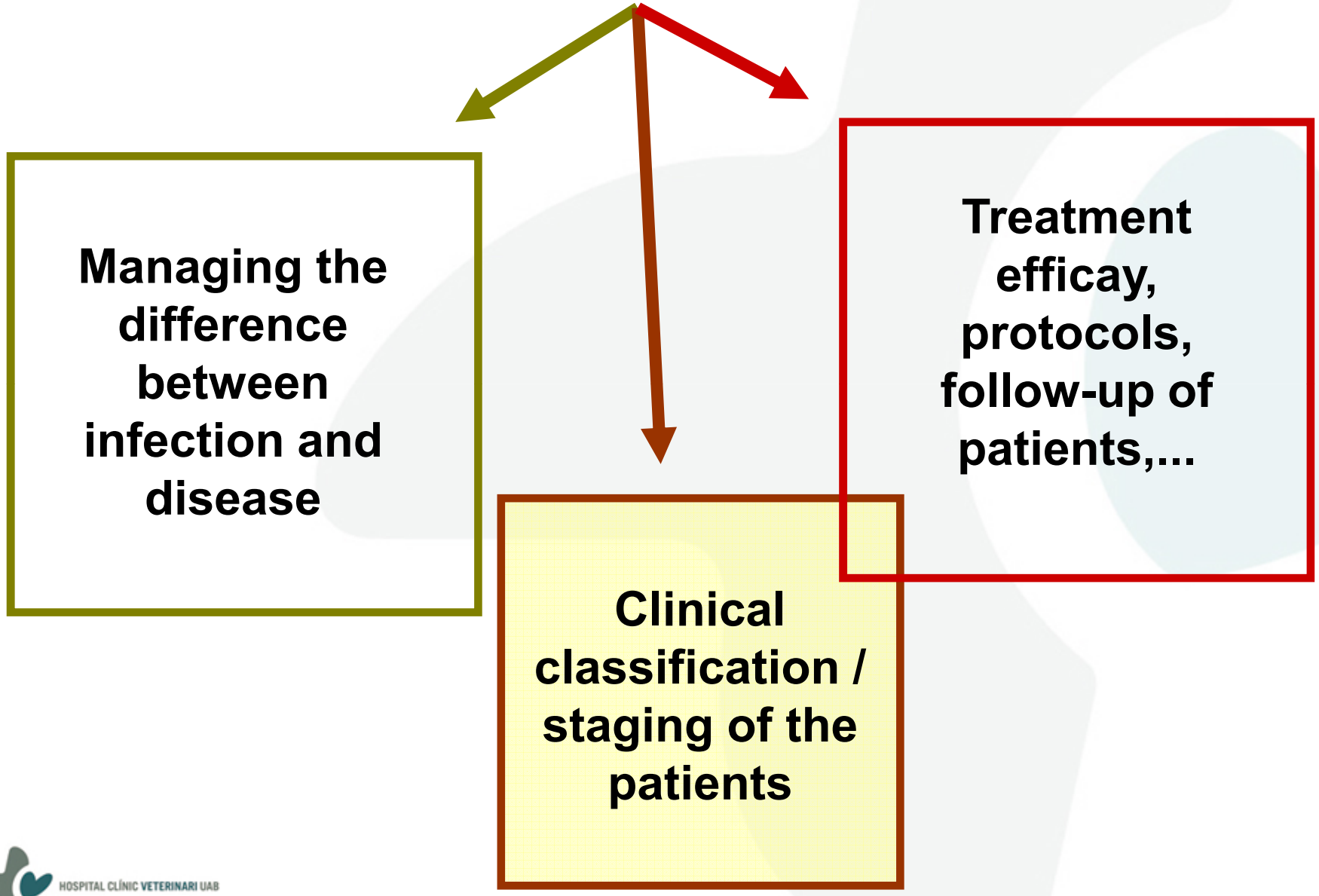
(2) Should clinically healthy dogs be screened for *Leishmania*-specific antibodies?

It could make sense in territories where disese is endemic, but evidences have not been published

(3) How should a clinically healthy seropositive dog be managed?

It depends on the titre

Relevant questions from 3 areas...



Clinical classification / staging of the patients

- From clinical point of view, leishmaniosis is a extremely pleomorphic disease, including very mild cases and severe and fatal cases

- Most studies are difficult to evaluate due to the poor definition of the patients ("clinical signs + seropositivity"):

Dog with mild lymphadenopathy and 1:80 IFA

versus

Dog with severe renal disease and 1:2560 IFA

Clinical classification / staging of the patients (II)

Classification of patients in “asymptomatic”, “oligosymtomatic” and “polysymptomatic” is absolutely inadequate, and it has create a lot of misinformation and confusion

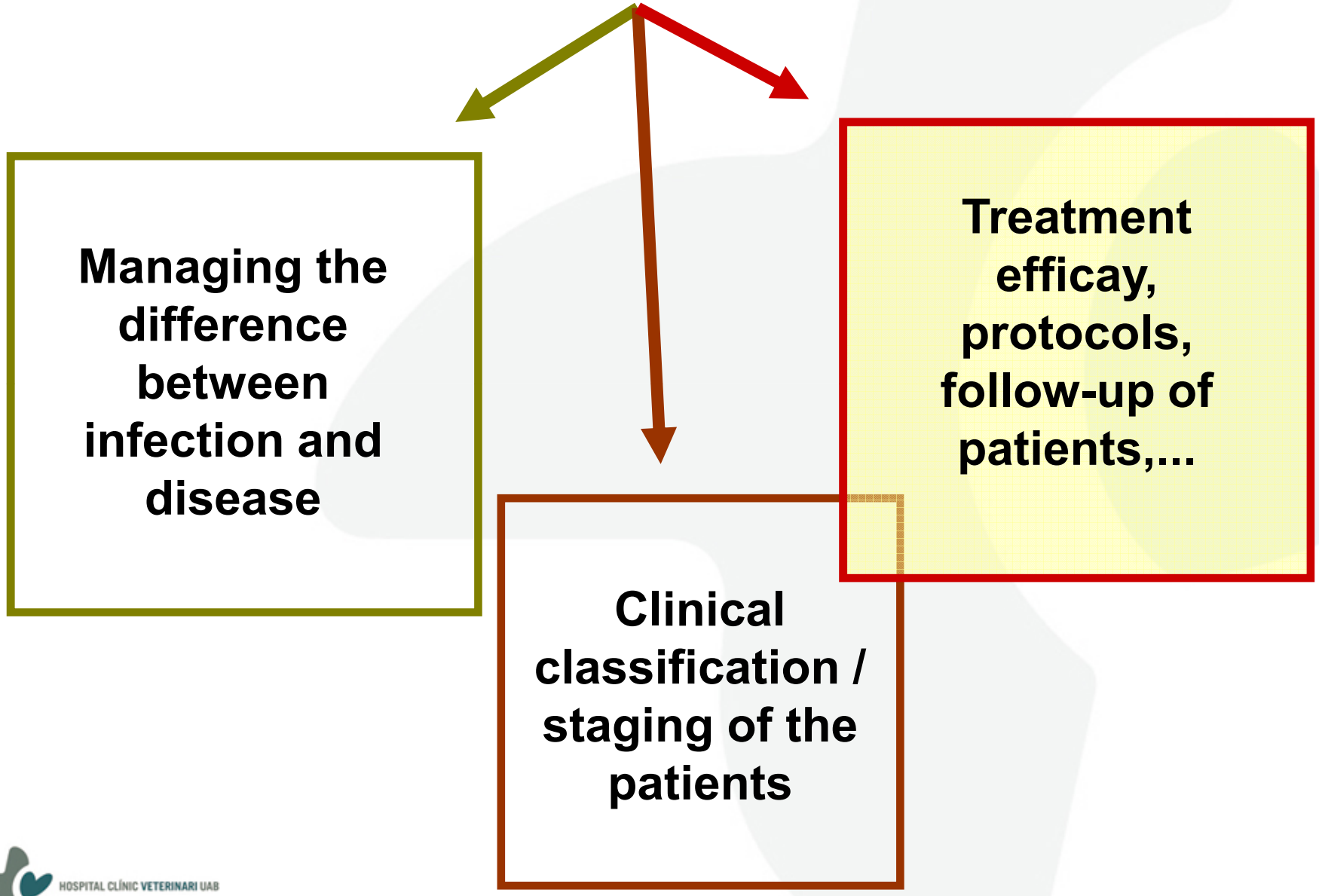
- **Animals do not have “symptoms”, only human beings can express to the physician the effects and perception of the disease. The correct term is “clinical signs”**
- **The three groups are poorly defined, in each paper the patients are classified in a different way**
- **Not all clinical signs have the same importance and severity: lymphadenopathy or asthenia *versus* epistaxis or renal disease**

Clinical classification / staging of the patients (III)

(4) **There is an urgent need of a clinical staging of the patients:**

- Probably a system of 4 stages (I, II, III, IV)
- Based on clinical signs, clinicopathologic abnormalities and antibody titre
- Each stage must have different treatment and prognosis
- The system must be validated

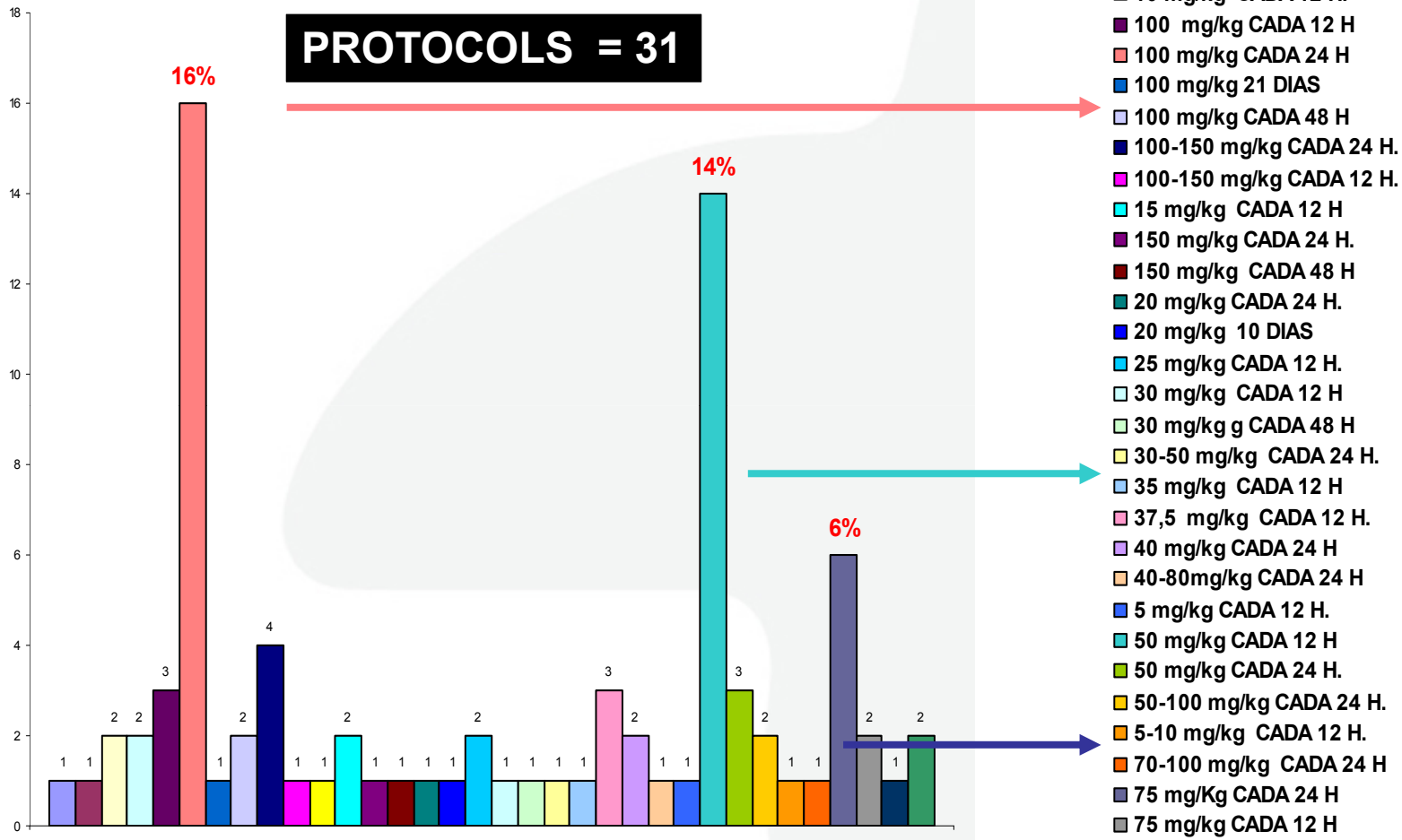
Relevant questions from 3 areas...



Therapy and follow up of the patients

- Huge diversity of therapeutical protocols
- Most of them based on “personal experience” or on non.validated sources
- Also diversity of folllow-up protocols (serology, RT-PCR,…)
- Very few controlled/randomized studies

2005 Spanish Survey (106 clinics)
Glucantime® protocols



Unanswered = 17 clínics

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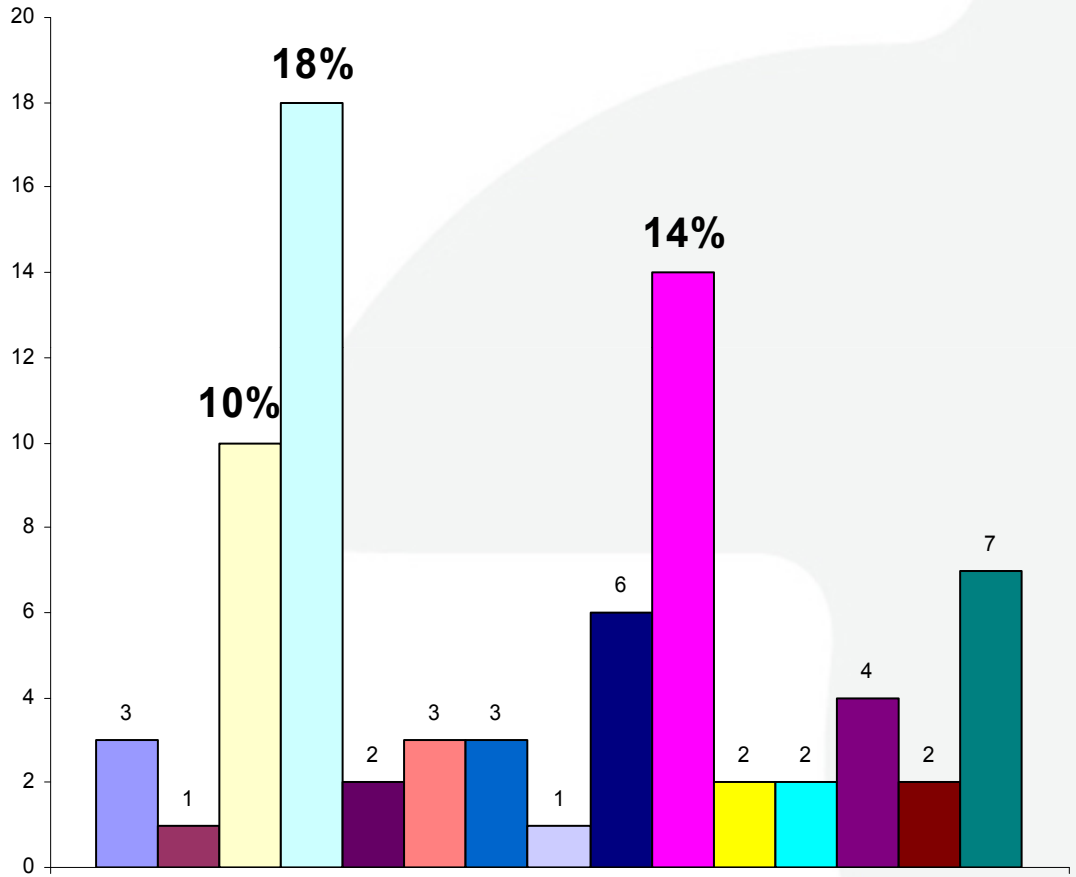
2005 Spanish survey (106 clinics)
Allopurinol protocols

PROTOCOLS = 15



- 20/30mg/kg CADA 12 H.
- 20-30 mg/kg CADA 24 H.
- 10 mg/kg CADA 24 H.
- 10 mg/kg CADA 12 H.
- 100 mg/kg CADA 12 H
- 10-20 mg/kg CADA 24 H
- 10-20 mg/kg CADA 12 H
- 10-30 mg/kg CADA 48 H.
- 20 mg/kg CADA 24 H.
- 20 mg/kg CADA 12H
- 25 mg/kg CADA 12 H.
- 30 mg/kg CADA 12 H
- 30 mg/kg g CADA 24 H
- 40 mg/kg CADA 12 H
- 5 mg/kg CADA 12 H.

Unanswered = 24 clínics

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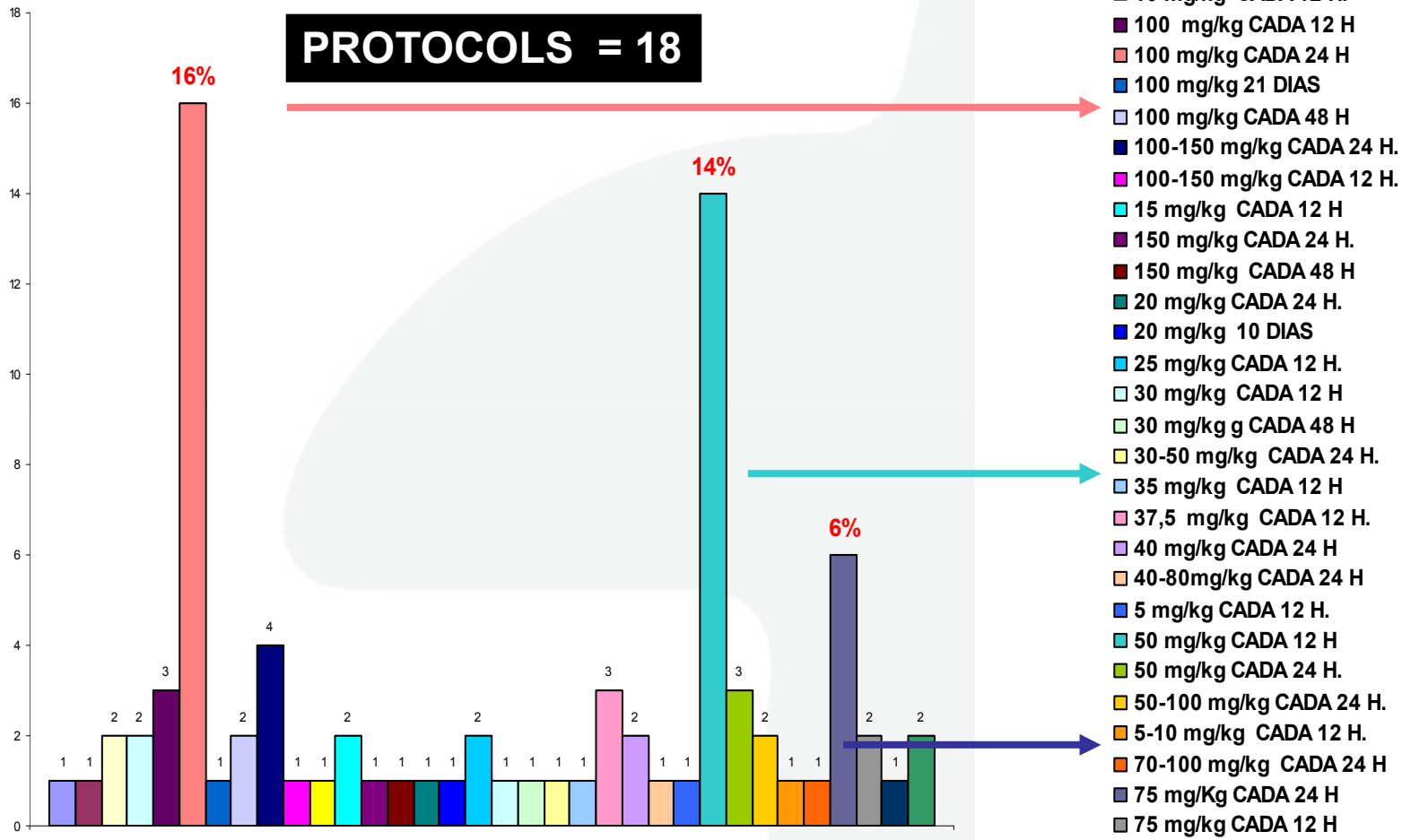
2007 Spanish Survey (n= 483 clinics)
Glucantime® + Allopurinol



Unanswered = ?? clínics

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Therapy and follow up of the patients (II)

In the last years a few publications have brought some useful information:

- Noli & Auxilia (2005). Treatment of canine leishmaniosis: EB review
- Few recent studies comparing miltefosine+ allopurinol to N-methyl-glucamine + allopurinol

  (Miró, 2008; Manna et al, 2008)

Therapy and follow up of the patients (III)

(5) Which is the most effective treatment for canine leishmaniosis?

(6) What is the expected clinical response to this treatment? What is the prognosis?

(7) Which clinicopathologic parameters should be monitored during the treatment of canine lesihmaniosis?

(8) What are the most common side effects of this treatment?

Therapy and follow up of the patients (IV)

(9) What are the evidences for the development of resistance to the anti-*Leishmania* drugs in dogs? What are the recommendations regarding this point?

No good evidences have been published, however, due to the importance of the topic, extrapolating from other disease we:

- Try to avoid treatment when possible
- Try to use allopurinol (not used in humans) as much as possible
- Reduce the time of using antimonies as much as possible
- Use adequate dosage of antimonies

Therapy and follow up of the patients (VI)

10. Remain dogs infected for life after therapy?

Apparently, yes. We think so because…

- Relapses are relatively common
- PCR detects Leishmania DNA years after diagnosis
- Dogs have developed leishmaniosis years after living in non-endemic countries

Therapy and follow up of the patients (VI)

10. Remain dogs infected for life after therapy? What is the importance of this fact for their health and for the public health?

- Clinical leishmaniosis can appear later on (Which are the triggers?), but …
- Probably the latent infection also helps to maintain an effective immune response and to control the infection…
- For public health, the importance of these dogs is unknown. Few indirect studies suggest that these dogs play a minor role in the epidemiology