Arch Med Vet **47, 1-6 (2015)**

REVIEW ARTICLE

Is cryptosporidiosis an underestimated disease in cats?[#]

¿La cryptosporidiosis es una enfermedad subestimada en los gatos?

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RESUMEN

Estudios científicos acerca de la presencia de *Cryptosporidium* spp. en los gatos son escasos. En esta revisión bibliográfica se tratan los aspectos epidemiológicos y clínicos, así como los métodos de diagnóstico, la conducta terapéutica, y las medidas de control y prevención de la cryptosporidiosis en el gato doméstico, con el objetivo de establecer si se trata de una enfermedad subestimada en la rutina de laboratorio y en la clínica de pequeños animales.

Palabras clave: *Cryptosporidium,* gato doméstico, zoonosis, epidemiología.

SUMMARY

Studies on the occurrence of *Cryptosporidium* spp. in cats are still scarce. In this literature review, we address epidemiological and clinical aspects, as well as diagnostic methods, therapeutic behavoiur, and control and prevention measures for this disease in cats, with the aim of investigating if cryptosporidiosis is an underestimated disease in the laboratory routine and in small animal medical clinics.

Key words: *Cryptosporidium,* feline, zoonoses, epidemiology.

INTRODUCTION

The genus *Cryptosporidium* is represented by obligate intracellular protozoa that parasitize particularly the epithelial surface of the gastrointestinal tract of their hosts (Fayer *et al* 2000, Xiao *et al* 2004). In 1907, this coccidian was first found on the gastric mucosa of a rat and was then named *Cryptosporidium muris* (from Latin, *Crypto*: absent, hidden; *Sporidium*: spore) for not showing sporocysts, but only sporozoites (Tyzzer 1907).

The first cases of cryptosporidiosis were reported for humans in 1976 (Meisel *et al* 1976, Nime *et al* 1976). Bird y Smith (1980) noted that six out of seven cryptosporidiosis patients were immunosuppressed, which led them to define this disease as opportunistic. However, in 1984, it was stated that this disease would particularly affect immunodeficient patients, becoming chronic and frequently fatal, even though it could also affect immunocompetent individuals, who would develop acute gastroenteritis (Navin y Juranek 1984).

Accepted: 03.07.2014.

[#] Fundação de Amparo à Pesquisa do Estado de São Paulo (proc. 2010/51111-9).

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Waterborne *Cryptosporidium* outbreaks in 1989 affected 5,000 people in the cities of Swindon and Oxfordshire, United Kingdom (Richardson *et al* 1991) and > 403,000 individuals in Milwaukee, United States, in 1993 (Mackenzie *et al* 1994). These facts implied that contaminated water, although treated, was the main form of transmission of this disease (Tzipori y Widmer 2008).

Only in 2004, cryptosporidiosis was included in the Neglected Diseases Initiative of the World Health Organization due to its close association with poor sanitation and low purchasing power (Savioli *et al* 2006). Since then, a considerable amount of research on this disease has been carried out for several production animals: sheep (Barker y Carbonell 1974), goats (Mason *et al* 1981), horses (Inácio *et al* 2012), buffaloes (Amer *et al* 2013). In pets, there are still few studies involving cats (Coelho *et al* 2009) but studies with dogs are worthy of note (Bresciani *et al* 2008).

Published papers about the occurrence of intestinal parasites are more frequently related to dogs than to feline hosts, probably because the canine population is larger than the feline population, also the faecal collection is easier with dogs since cats normally bury their excrement.

The aim of the present study is to show the clinical and epidemiological relevance of cryptosporidiosis for

domestic cats, making this disease closer to the routine of veterinary clinicians and sanitarians by means of a scientific literature review addressing the following subjects: taxonomy, epidemiology, clinical signs, diagnosis, treatment, and control and prevention.

CRYPTOSPORIDIUM

The taxonomy is not well defined, and still requiring improved genetic and biochemical parameters (Plutzer y Karanis 2009). *Cryptosporidium* has been classified as a separate group belonging to Superphylum Alveolata, Phylum Apicomplexa, and Class Conoidasida (Adl *et al* 2012).

Studies have revealed certain specificity of species and genotypes of this coccidian with its hosts (Xiao y Fayer 2008). Currently, 30 *Cryptosporidium* species have been described, of which 20 are found in mammals, while 61 genotypes have been determined according to the host and genetic analyses (Plutzer y Karanis 2009, Chalmers y Katzer 2013, Slapeta 2013).

Morphological analyses of oocysts or immunological tests are not capable of determining the species within *Cryptosporidium* genus, since oocysts are too small, show morphological variation or are identical among the different species, do not have sporocysts and usually are of difficult visualization. In addition, oocysts have conserved antigens, which do not allow differentiation between species by means of immunological tests (Fayer 2008).

Thus, the use of molecular tools in epidemiological studies has provided new perspectives on the diversity of *Cryptosporidium* spp. capable of infecting humans and animals (Xiao *et al* 2004), which has helped understand the zoonotic and anthroponotic role of this parasite (Bajer 2008).

EPIDEMIOLOGY OF CRYPTOSPORIDIOSIS IN CATS

The first report of cryptosporidiosis for cats was done by Iseki (1979), who named the species *Cryptosporidium felis*, mostly prevalent among cats. Subsequently, *Cryptosporidium muris* (Pavlasek y Ryan 2007) and *Cryptosporidium parvum* (Sargent *et al* 1998) were identified for this host, the latter showing high zoonotic potential. Infection by *Cryptosporidium* oocysts in cats occurs frequently, and prevalence may vary from 0 to 30% (Sargent *et al* 1998, McReynolds *et al* 1999, Fayer *et al* 2006, Huber *et al* 2007, Rambozzi *et al* 2007, Tzannes *et al* 2008, Ballweber *et al* 2009, Coelho *et al* 2009, Gow *et al* 2009, Paoletti *et al* 2011, Pereira *et al* 2011, Pereira y Ferreira 2012, Spada *et al* 2013).

Cats younger than one year had two-fold higher chance of becoming infected by *Cryptosporidium* when compared to cats older than one year in Turin, Italy (Rambozzi *et al* 2007). In the United States, McReynolds *et al* (1999) verified that cats older than 10 years had a four-fold higher chance of becoming infected by this protozoan when compared to kittens younger than one year. The association between infection by *Cryptosporidium* sp. and the age of the cats has already been noted (Ballweber *et al* 2009), but logistic regression was not performed to verify the participation of this significant difference among plots; visually, the prevalence of positive samples was higher among cats younger than one year but there was no occurrence among animals older than 10 years, which differs from the findings of McReynolds *et al* (1999). This could be related to a still immature or impaired immune system. This hypothesis is reinforced by Oliveira-Lemos *et al* (2012) who detected oocyst release for 8.3% faecal samples, of which 80% animals were positive to feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) according to serology.

Cats raised outside the house had five-fold higher chance of acquiring cryptosporidiosis when compared to cats raised only inside the house (McReynolds *et al* 1999); however, this issue remains controversial (Rambozzi *et al* 2007, Ballweber *et al* 2009). Such divergence could be justifiable since those studies were conducted at different times and sites. In addition, the risk factors of this infection may be multifactorial. Occurrence of clinical signs doubles the chance of infection by *Cryptosporidium* sp. (McReynolds *et al* 1999, Rambozzi *et al* 2007), while occurrence of other enteroparasites is associated with cryptosporidiosis in cats, tripling the risk of infection (Rambozzi *et al* 2007), since contaminated water and food constitute sources of infection by several gastrointestinal parasites. Cats fed homemade food had almost seven-fold higher chance of acquiring cryptosporidiosis compared to cats that only ingested animal food (Rambozzi *et al* 2007), confirming the importance of food in the epidemiology of this disease.

Dogs and cats seem to pose a minimal risk of infection to humans since they are more frequently infected by *Cryptosporidium canis* and *C. felis*, respectively, which are not usually found among humans who generally become infected by *C. parvum* and *Cryptosporidium hominis*. The absent or low association reported in the scientific literature between occurrence of cryptosporidiosis and the contact with a pet reinforces this hypothesis (Lucio-Forster *et al* 2010). However, it has been reported an association between cryptosporidiosis in the elderly and their domiciled cats (Pereira y Ferreira 2012).

Cryptosporidium genus tends to a specie-specificity, and accidental infection in other hosts can occur. Humans are usually infected by *Cryptosporidium hominis* and *Cryptosporidium parvum*, but infections by *Cryptosporidium meleagridis*, *C. canis*, *C. felis*, *Cryptosporidium suis*, *C. muris* and *Cryptosporidium andersoni* have already been identified, as well as the genotypes deer, monkey, opossum, rabbit, and squirrel (Feng *et al* 2009, Smith y Nichols, 2010).

CLINICAL SIGNS

In general, infected cats are asymptomatic (Mtambo *et al* 1991, Nash *et al* 1993, Fayer *et al* 2006). Nevertheless, immunosuppressed animals are more susceptible to developing clinical signs (Monticello *et al* 1987).

Rambozzi *et al* (2007) verified the association between infection by *Cryptosporidium* spp. and occurrence of diarrhea in cats; on the other hand, that same study showed association between this coccidiosis and co-infection by other enteroparasites such as *Toxascaris leonina*, *Toxocara cati*, *Cystoisospora* spp., *Aelurostrongylus abstrusus* and *Dipylidium caninum* (Rambozzi *et al* 2007), which makes it difficult to determine the basal cause of clinical signs. The presence of asymptomatic carriers may influence environmental contamination and promote active infection among immunosuppressed individuals.

In active infection, *Cryptosporidium* spp. may induce enterocyte microvilli atrophy and fusion, as well as local inflammation, reducing the absorption surface (Koudela y Jirí 1997). There is evidence that such interaction induces enterocyte apoptosis in the host (Buret *et al* 2003, Mele *et al* 2004) and this pathogenesis leads to unbalanced nutrient transport (Thompson *et al* 2008, Vadlamudi *et al* 2013).

DIAGNOSIS

Diagnostic methods have been widely employed in microscopy. Oocysts can be visualized under a phase contrast microscope by following Sheather's flotation method (Teixeira *et al* 2011) or several staining techniques, including: Ziehl-Neelsen modified (Henriksen y Pohlenz 1981), kinyoun (Ma y Soave 1983) and malachite green (Elliot *et al* 1999). Even though these techniques are relatively simple and low cost, none of them is capable of differentiating between species within *Cryptosporidium* spp. Furthermore, a good microscopist is required to detect the oocysts in case of low shedding (Quílez *et al* 1996, Morgan *et al* 1998, Clark 1999).

Several immunodiagnostic methods, such as direct immunofluorescence, can be used since they show high sensitivity (98.5-100%) and specificity (96-100%) and are capable of recognizing epitopes on the surface of oocysts of *Cryptosporidium* spp. (Sterling y Arrowood 1986, McLauchlin *et al* 1987, Grigoriew *et al* 1994, Garcia y Shimizu 1997).

Antigens present in oocysts may also be detected by the techniques ELISA and immunochromatography showing specificity between 98 and 100% (Garcia y Shimizu 1997, Johnston *et al* 2003), but the sensitivity of these methods remains controversial (Johnston *et al* 2003).

Several molecular techniques based on polymerase chain reaction (PCR) may also be employed in the diagnosis of this disease. These techniques allow molecular characterization and help study the epidemiology and the ecology of this disease, constituting therefore the most used techniques in scientific research (Thompson *et al* 1998, Fayer *et al* 2000)

TREATMENT

There are few reports on the treatment of *Cryptosporidium* spp. for cats since the drugs available so far have reduced efficacy and the clinical signs, when present, are generally self-limiting for immunocompetent patients.

Tylosin was administered at 11 mg/kg twice a day during 28 days orally for cats infected by *Cryptosporidium* spp., and there was a remission of clinical signs in the first week of treatment (Lappin *et al* 1997). Tylosin is a macrolide with effects that are also immunomodulatory (Baba *et al* 1998). Since the animal had chronic diarrhea, the possibility of spontaneous healing is lower and tylosin efficacy, in this case, seems to be the most plausible hypothesis.

Paromomycin by oral route, at 165 mg/kg twice a day during five days, and the drug was capable of reducing oocyst release to undetectable levels; however, it was not possible to determine if the infection was completely eliminated (Barr *et al* 1994). In case of hematochezia, this drug is not recommended since it can be absorbed, developing nephrotoxic and ototoxic action (Gookin *et al* 1999).

Nitazoxanide was already used in the treatment of co-infection between *Giardia* spp. and *Cryptosporidium* spp., by the oral route, at 25 mg/kg twice a day during at least five days (Scorza y Lappin 2007). On the other hand, this drug can cause vomit and gastrointestinal irritation (Scorza y Tangtrongsup 2010).

So far, paromomycin has been the drug of choice to treat cryptosporidiosis (Shahiduzzaman y Daugschies 2012).

CONTROL AND PREVENTION

Good hygiene and basic sanitation conditions are key aspects to reduce not only the risk of oocyst ingestion but also environmental contamination, because cryptosporidiosis has a faecal-oral transmission.

Cryptosporidium spp. is sensitive to desiccation and ultraviolet rays (Rochelle *et al* 2005). Cat faeces must be daily removed with the aid of gloves. Subsequently, cleaning of the sand box with detergent and exposure to sunlight are effective measures.

Resistance of *C. parvum* to several environmental conditions was assessed. After one month of freezing, only 1.8% oocysts remained viable. The maximal resistance period of oocysts to desiccation was four hours, after which 100% of them were inactivated; however, they remained viable for more than six months while contained in the faeces. Flocculation with aluminum sulfate, similarly to what was done in water treatment stations, was not effective to eliminate the protozoan (Robertson *et al* 1992).

Filtration methods commonly used by water treatment stations are known to remove most oocysts contained in the water; however, *Cryptosporidium* spp. were found in

3.8-40% assessed water samples at a concentration of up to 0.5 oocysts per liter (Rose *et al* 1997). Thus, tap water supply is not indicated for humans and animals. On the other hand, oocysts present in small quantities of water can be inactivated when subjected to at least six hours of sunlight exposure (Méndez-Hermida *et al* 2007). This can be done before the cat has access to the water; however, this animal species prefers fresh water. Another form of inactivating oocysts is to boil the water for more than one minute (CDC 1999).

In addition, it is recommended that the access of animals to the streets be prevented and that only high-quality commercial animal food is supplied to cats; these are good alternatives to prevent the infection (McReynolds *et al* 1999, Rambozzi *et al* 2007).

Oocysts are not inactivated by most of the used disinfectants, such as hypochlorite, peracetic acid, ortho-phthalaldehyde, ethyl alcohol, glutaraldehyde, phenol, povidone iodine, quaternary ammonium and hydrogen peroxide, at concentrations inferior to 6%. *Cryptosporidium* spp. is sensitive to 6-7.5% hydrogen peroxide at 20ºC for 20 minutes. Material sterilization by means of autoclave and ethylene oxide is effective (Barbee *et al* 1999).

FINAL CONSIDERATIONS

Detection of *Cryptosporidium* oocysts in cat faeces is common, especially in kittens. Until now, treatments available have reduced efficacy; thus, the adopted preventive measures should be stricter. Preventing the access of cats to contaminated water, to the streets and to homemade food seems to be the most effective prevention form of this disease.

CONCLUSION

Microscopy, a simple and inexpensive technique, could be used in the diagnosis of cryptosporidiosis in faecal samples from cats in veterinary clinical medicine routine. Immunoassay techniques are recommended for laboratorial routine, monitoring in order to diagnose a large population scale. These actions could increase the diagnosis of this disease. Finally, investigations based on molecular characterisation of *Cryptosporidium* infection in cats are needed to clarify the real importance of this host in public health.

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