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Review Article

What is known about *Tritrichomonas foetus* infection in cats?

O que sabemos sobre a infecção por *Tritrichomonas foetus* em gatos?

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Abstract

Tritrichomonas foetus is a parasite that has been definitively identified as an agent of trichomonosis, a disease characterized by chronic diarrhea. *T. foetus* colonizes portions of the feline large intestine, and manifests as chronic and recurrent diarrhea with mucus and fresh blood, which is often unresponsive to common drugs. Diagnosis of a trichomonad infection is made by either the demonstration of the trophozoite on a direct fecal smear, fecal culture and subsequent microscopic examination of the parasite, or extraction of DNA in feces and amplification by the use of molecular tools. *T. foetus* is commonly misidentified as other flagellate protozoa such as *Giardia duodenalis* and *Pentatrichomonas hominis*. Without proper treatment, the diarrhea may resolve spontaneously in months to years, but cats can remain carriers of the parasite. This paper intends to serve as a source of information for investigators and veterinarians, reviewing the most important aspects of feline trichomonosis, such as trichomonad history, biology, clinical manifestations, pathogenesis, world distribution, risk factors, diagnosis, and treatment.

Keywords: Trichomonosis, domestic cat, diarrhea, endoparasites.

Resumo

Tritrichomonas foetus é um parasito que foi identificado definitivamente como agente de tricomoníase, caracterizada por diarreia crônica. *T. foetus* coloniza porções do intestino grosso dos felinos e se manifesta como uma diarreia crônica e recorrente, com muco e sangue, geralmente irresponsiva às drogas comumente usadas no tratamento. O diagnóstico da infecção por tricomonadídeos é feito pela demonstração de trofozoítos no exame direto de fezes frescas, cultura fecal e subsequente exame microscópico ou extração do DNA do parasito na amostra fecal e amplificação, utilizando-se técnicas moleculares. *T. foetus* é comumente confundido com outros protozoários flagelados, como *Giardia duodenalis* e *Pentatrichomonas hominis*. Sem tratamento adequado, a diarreia pode cessar espontaneamente em meses ou anos, porém os gatos podem permanecer portadores do parasito. Esse artigo pretende servir como fonte de informação para pesquisadores e veterinários, revisando os mais importantes aspectos da tricomoníase felina, como histórico, biologia, manifestações clínicas, patogênese, distribuição mundial, fatores de risco, diagnóstico e tratamento.

Palavras-chave: Trichomoníase, gato doméstico, diarreia, endoparasitos.

Introduction

Tritrichomonas foetus is a trichomonad that was first described as a bovine venereal pathogen, causing infertility, abortion, and endometritis (FELLEISEN, 1999; STOCKDALE et al., 2006). More than a decade ago, *T. foetus* was also identified in the feces of domestic cats with chronic diarrhea (GOOKIN et al., 1999; LEVY et al., 2003). Trichomonads had been observed in cats with and without diarrhea (DA CUNHA & MUNIZ, 1922; JORDAN, 1956), but was considered to be commensal and opportunistic (DIMSKI, 1989; BARR, 1998). For a long time, *T. foetus* may have been confused with *Pentatrichomonas* sp. or *Giardia* sp. under microscopic analysis (GOOKIN et al., 1999); however, with genetic identification through molecular tools, *T. foetus* was considered the causal agent of feline trichomonosis in 2003 (LEVY et al., 2003).

Since feline trichomonosis has been identified as an emerging gastrointestinal disease, researchers have turned their interest to understanding its etiology, epidemiology, and pathogenesis, as well as diagnosis and treatment (GOOKIN et al., 1999, 2006, 2010; GRAY et al., 2010).

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Taxonomy

Trichomonads of the species *Tritrichomonas foetus* are anaerobic protozoan parasites placed in the phylum Parabasalia, order Trichomonadida, and family Trichomonadidae (BRUGEROLLE & LEE, 2000). A new rank system classifies trichomonads as [Excavata: Parabasalia: Trichomonadida] (ADL et al., 2005).

History

Trichomonosis was first described in a cat in Brazil by Da Cunha & Muniz (1922), who named the agent *Trichomonas felis*. Years later, Brumpt (1925) found trichomonads with three to five anterior flagella in dogs and cats in France, adopting the name *Trichomonas felis* for the parasite present in both animals. One year later, Tanabe identified *Pentatrichomonas* sp. in a cat, naming the parasite *Pentatrichomonas felis* (TANABE, 1926).

Kessel (1928) observed natural and experimental trichomonosis in nine kittens. These animals presented with diarrhea that progressed to dysentery, and they died within 10 days of infection.

In 1956, a young cat presenting with chronic diarrhea was diagnosed with trichomonosis, described as an infection caused by *Trichomonas* sp. (JORDAN, 1956).

From 1956 to 1996, there was a lack of reports about feline trichomonosis, presumably because of the assumption that the trichomonads were non-pathogenic commensal species and only existed when there was a pre-existing enteric disease (DIMSKI, 1989; BARR, 1998; GOOKIN et al., 1999). In 1996, based on the microscopic examination of fecal smears, Romatowski (1996, 2000) identified the trichomonads as *Pentatrichomonas hominis*, and causing a mucoid diarrhea in kittens and adult cats.

In 2001, after a molecular assay to analyze the gene 18S rRNA present in trichomonad isolates, the identity of the agent as *Tritrichomonas foetus* was revealed, with 99.9% similarity (LEVY et al., 2003).

Tritrichomonas foetus has also been identified in the reproductive tract of a cat with pyometra in Norway, although the cause of the uterine infection was attributed to the bacteria *Streptococcus* sp., which was present in the genital secretion (DAHLGREN et al., 2007).

Gray et al. (2010) examined the reproductive tracts of 15 cats previously diagnosed with intestinal infection caused by *T. foetus*. They used light microscopy, immunohistochemical analysis, and PCR assay, and found no evidence of the parasite in the reproductive tracts.

Molecular Approach

Several studies have investigated the agent present in cattle and the possibility that this was the source of the feline infection. An epidemiological study of cats found no association between *T. foetus* infection and proximity to cattle (GOOKIN et al., 2004). Studies involving cross-transmission conducted by Stockdale et al. (2007, 2008) indicated phenotypic differences related to infectivity and pathogenicity among the feline and bovine isolates. The molecular characterization of feline isolates compared to cattle showed genetic differences. Thus, Slapeta et al. (2010) suggested a species-specific distinction of *T. foetus* between the cattle and cat genotypes. Other researchers have also observed few but consistent genetic differences between cattle and feline isolates. Sun et al. (2012) reported differences in the nucleotides and amino acids of cysteine protease 8 from bovine and feline isolates, elucidating a possible adaptation to their preferred host.

A new name, *Tritrichomonas blagburni*, was proposed for the feline parasite in order to differentiate it from the bovine parasite (WALDEN et al., 2013). According to the authors, the host specificity, as well as morphological and genetic information, must be considered in any taxonomic evaluation. This is still scientifically controversial, since data obtained from comparative analyzes of the two transcriptomes have failed to confirm that they are two distinct species (MORIN-ADELINE et al., 2014).

In addition, studies suggested that *T. suis*, a trichomonad of the domestic pig, is morphologically indistinguishable from *T. foetus*. Sequencing of a variable DNA fragment and comparison of gene sequences did not reveal differences between *T. suis* and *T. foetus* bovine isolates. Thus, researchers concluded that *T. foetus* and *T. suis* belong to the same species, proposing that they are synonyms (TACHEZY et al., 2002; LUN et al., 2005).

Morphology

The parasites *T. foetus* only have a trophozoite stage. They are small flagellates, ranging in size from 10–25 μm in length and 3–15 μm in width (GOOKIN et al., 2006). They have a pear-shaped body, one nucleus, three anterior flagella, and a posterior flagellum (WARTONA & HONIGBERG, 1979). The posterior flagellum travels along the body of the parasite, forming the undulating membrane (GOOKIN et al., 2006). The axostyle, a rigid organelle, extends through the body length of the parasite (LEVINE, 1985), and protrudes from the posterior extremity (GOOKIN et al., 2006).

Life Cycle

The life cycle is a simple asexual cycle, where the trophozoite multiplies by longitudinal binary division, and transmission occurs directly between hosts via ingestion of trophozoites (GOOKIN et al., 2017).

There is no true cyst stage, but some authors describe that in conditions of environmental stress, such as nutrient scarcity, drug action, or abrupt temperature changes, there may be pseudo-cyst formation. In this case, the flagella are internalized, but the cell is not surrounded by a cyst wall (PEREIRA-NEVES et al., 2003; PEREIRA-NEVES & BENCHIMOL, 2009; ROSA et al., 2015).

Transmission

The transmission of *T. foetus* among cats occurs via the fecal–oral route (GOOKIN et al., 1999, 2001). Direct contact with contaminated fresh feces may be sufficient for the transmission of the parasite, since *T. foetus* does not release cysts into the

environment. However, Hale et al. (2009) showed that *T. foetus* trophozoites are more resistant to environmental conditions than previously thought, surviving in moist feces for seven days at room temperature (23-24°C). The ability of the parasite to survive outside the host may be an important factor in the epidemiology of the disease, especially in places with an overpopulation of cats. This survivability also suggests that self and mutual grooming by cats and fecal contamination of the environment are important factors in the epidemiology of the disease (HALE et al., 2009; VAN DER SAAG et al., 2010).

Although the experimental transmission of *T. foetus* between cattle and felines is possible, direct transmission from bovines to cats is not the primary source of infection (STOCKDALE et al., 2008). Gookin et al. (2004) found no association between feline infection and proximity to cattle.

Risk Factors

Tritrichomonas foetus is predominantly identified in young cats. Most studies have shown an average age of 12 months or less, ranging in age from 4 weeks to 16 years (GOOKIN et al., 1999, 2004; BURGENER et al., 2009; FREY et al., 2009).

In many studies, infected cats were 1 year old or younger (FOSTER et al., 2004; GOOKIN et al., 2004; YAEGER & GOOKIN, 2005; STOCKDALE et al., 2009; ARRANZ-SOLÍS et al., 2016). Holliday et al. (2009) found infected cats in a colony with a predominant age of over 1 year. The probable explanation for this discrepancy is that the infection may have entered the population for the first time, and the lack of protection by the immune system allowed older cats as well as young cats to develop clinical signs (HOLLIDAY et al., 2009). Cats, especially those more than 3 years old, may be asymptomatically infected, and can become an important source of parasitic infection for other felines (XENOULIS et al., 2010).

A predisposition to gender among cats infected with *T. foetus* has not been observed in any study (GOOKIN et al., 2004; GUNN-MOORE et al., 2007; BURGENER et al., 2009; STOCKDALE et al., 2009). In most studies, purebred cats are more affected (GUNN-MOORE et al., 2007; BURGENER et al., 2009; FREY et al., 2009; STOCKDALE et al., 2009; BELL et al., 2010; KLEIN et al., 2010). Conversely, two studies have shown that the infection is also common in mixed-breed cats (GOOKIN et al., 1999; HOLLIDAY et al., 2009). Since feline infection by *T. foetus* is more frequent in catteries and shelters (GOOKIN et al., 1999; FOSTER et al., 2004), it is not known whether infection is more frequent in purebred cats because of a genetic predisposition or because these cats usually live in places with an agglomeration of *T. foetus* (HOLLIDAY et al., 2009).

The role of overpopulation and management in contrast to genetic predisposition may be the answer to the higher prevalence of infection in purebred cats. This explanation is supported by the high prevalence of infection in a group of mixed-breed cat residents in a shelter with poor sanitary conditions (HOLLIDAY et al., 2009).

Although Gookin et al. (2004) did not find a significant association between *T. foetus* infection and litter boxes, the importance of feline population density is associated with the facility of transmission through boxes (GOOKIN et al., 2007).

It is not known whether the animal's immune status influences the pathogenesis of *T. foetus* infection. On the other hand, the high prevalence of infection in young cats may indicate a susceptibility to infection in the case of an immature immune system (GOOKIN et al., 1999). However, an experimental study did not observe a worsening of the diarrhea when an immunosuppressive dose of prednisolone was administered (GOOKIN et al., 2001). In addition, there seems to be no association between *T. foetus* infection and immunosuppressive diseases, such as those caused by feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) (GOOKIN et al., 1999; ROSADO et al., 2007).

Coinfections with other enteropathogens are often observed in cats with *T. foetus* (GOOKIN et al., 2004). Some authors question whether *T. foetus* is an isolated cause of diarrhea or if concomitant infections lead cats to be more vulnerable to the parasite (STOCKDALE et al., 2009).

Several studies suggest that coinfection with *Giardia* sp. is common. Risk and associated factors common to trichomonosis and giardiasis include diarrhea, high population density, and young age (GOOKIN et al., 2004). Gookin et al. (2004) found a coinfection of *T. foetus* and *Giardia* sp. in 12% of the cats, but this association was not significant. Steiner et al. (2007) observed that most cats infected in their study were also positive for *Giardia* sp., and Bissett et al. (2008) reported that 66% of cats studied were coinfected.

Coinfection with coccidia is also frequently reported (STOCKDALE et al., 2009; GOOKIN et al., 2001, 2005; BISSETT et al., 2008). Gookin et al. (2001) experimentally inoculated eight cats with a feline *T. foetus* isolate, four of which were already infected with *Cryptosporidium* spp. After inoculation with the *T. foetus* isolate, cats infected with *Cryptosporidium* spp. developed earlier and more severe diarrhea and had a greater number of trophozoites in the direct exam than did cats without coccidia. On the other hand, there was no difference in the number of oocysts removed.

Prevalence

Studies with feline trichomonosis in several countries have indicated that *T. foetus* is prevalent among domestic cats around the world (STEINER et al., 2007). In Brazil, there are only three reports of *T. foetus* infection in domestic cats. In Rio de Janeiro, Santos et al. (2015) found a prevalence of 5.2% of different-aged cats with diarrhea, using culture and PCR. In São Paulo, Hora et al. (2017) described a clinical case of *T. foetus* infection in a chronic diarrheic 7-month-old cat and Duarte et al. (2018) observed five infected cats (3.6%).

In summary, the global prevalence of *T. foetus* infection in domestic cats, with and without diarrhea, ranges from 0-81.8%, according to the number of samples analyzed, the diagnostic method used, geographical region, and lifestyle of the cat population (Table 1).

Table 1. Prevalence of *Tritrichomonas foetus* infection in domestic cats, according to the country, fecal sample source, and diagnostic method used.

Country	Fecal Sample/ Source	Diagnostic method	Case report	Prevalence (%)	Reference
Australia	Cats from clinic	Direct exam; fecal culture; PCR; sequencing	16	-	BISSETT et al., 2008
Australia	Cats from cattery (82) and shelters (52)	Fecal culture; PCR	-	0	BISSETT et al., 2009
Australia	Cats from clinic	Direct exam; PCR	13	-	BELL et al., 2010
Austria and Germany	Fecal samples (31)	PCR; sequencing	-	19.4	STEINER et al., 2007
Austria	Necropsy (96)	CISH; PCR; sequencing	-	2.9	MOSTEGL et al., 2012
Brazil	Cats without diarrhea	Fecal culture; PCR	-	5.2	SANTOS et al., 2015
Brazil	Cat with diarrhea	Direct exam; PCR	1	-	HORA et al., 2017
Brazil	Cats with and without diarrhea	Direct exam; PCR	-	3.9	DUARTE et al., 2018
Canada	Cats from clinic	PCR	1	-	PHAM, 2009
Canada	Cats from cat show	Fecal culture; PCR	-	23.6	HOSEIN et al., 2013
Canada	Cats from clinic	Fecal culture; PCR	-	0.7	HOSEIN et al., 2013
Canada	Cats from shelter	Fecal culture	-	0	RAAB et al., 2016
China	Cats with diarrhea	Direct exam; PCR	29	-	KÖSTER et al., 2015
Czech Republic	Cats with and without diarrhea	Fecal culture	-	0	CEPLECHA et al., 2017
France	Cats from cat show	Fecal culture	-	14.3	PROFIZI et al., 2013
Germany	Cats with diarrhea	Direct exam; PCR; sequencing	3	-	SCHREY et al., 2009
Germany	Cats with diarrhea	Direct exam; fecal culture	-	3.4	KLEIN et al., 2010
Germany	Cats from cat show	Fecal culture; PCR; sequencing	-	15.7	KUEHNER et al., 2011
Greece	Cats with and without diarrhea	PCR	-	31	BELL et al., 2010
Greece	Cats with and without diarrhea	PCR	-	20	XENOULIS et al., 2010
Italy	Cats from catteries	Direct exam; fecal culture; PCR	-	32.4	HOLLIDAY et al., 2009
Italy	Cats with and without diarrhea	Fecal culture	-	0	MUGNAINI et al., 2012
Italy	Cats without diarrhea	PCR	-	2.1	MANCIANTI et al., 2015
Italy	Cats with diarrhea	PCR	-	5.2	VERONESI et al., 2016
Japan	Cats with diarrhea	Fecal culture; PCR; sequencing	-	8.8	DOI et al., 2012
Korea	Cats from clinics	Direct exam; fecal culture; PCR	-	2	LIM et al., 2010
Netherlands	Cats with diarrhea	PCR	-	2	VAN DOORN et al., 2009
New Zealand	Cats from cat show	Fecal culture; PCR	-	81.8	KINGSBURY et al., 2010

PCR: Polymerase chain reaction, - Not studied.

Table 1. Continued...

Country	Fecal Sample/ Source	Diagnostic method	Case report	Prevalence (%)	Reference
Norway	Cats from clinics	Direct exam; PCR; sequencing	3	-	DAHLGREN et al., 2007
Norway	Cats from cat show	Fecal culture; PCR; sequencing	-	21.2	TYSNES et al., 2011
Poland	Cat with diarrhea	PCR	1	-	DĄBROWSKA et al., 2015
Spain	Cats without diarrhea	Direct exam; PCR	-	25	MIRÓ et al., 2011
Spain	Cats with diarrhea	Fecal culture; PCR	-	38.7	ARRANZ-SOLÍS et al., 2016
Switzerland	Cats with and without diarrhea	Fecal culture; PCR	-	25.7	BURGENER et al., 2009
Switzerland	Cats with diarrhea	Fecal culture; PCR	-	24.4	FREY et al., 2009
United Kingdom	Cats with diarrhea	PCR	-	18.8	PARIS et al., 2014
United Kingdom	Cat with diarrhea	Direct exam; PCR	1	-	MARDELL & SPARKES, 2006
United Kingdom	Cats with diarrhea	PCR	-	14.4	GUNN-MOORE et al., 2007
United Kingdom	Cats from clinic	PCR	-	20	GUNN-MOORE & TENNANT, 2007
USA	Cats with diarrhea	Direct exam; fecal culture	32	-	GOOKIN et al., 1999
USA	Cats with diarrhea	Direct exam; fecal culture; PCR	26	-	FOSTER et al., 2004
USA	Cats from cat show	Direct exam; fecal culture; PCR	-	30.8	GOOKIN et al., 2004
USA	Cats with diarrhea	Direct exam; fecal culture; PCR	7	-	YAEGER & GOOKIN, 2005
USA	Cat with diarrhea	Direct exam; fecal culture; PCR	1	-	GOOKIN et al., 2006
USA	Cats with diarrhea	Fecal culture; PCR	4	-	KATHER et al., 2007
USA	Cats with diarrhea	Fecal culture; PCR	4	-	ROSADO et al., 2007
USA	Fecal samples	Fecal culture; PCR	-	9.8	STOCKDALE et al., 2009
USA	Cats from catteries	Direct exam; PCR	-	24.6	GRAY et al., 2010
USA	Cats with diarrhea	Fecal culture; PCR	-	5.9	QUEEN et al., 2012
USA	Cats from clinic	Direct exam; fecal culture; PCR	104	-	XENOULIS et al., 2013
USA	Cats with diarrhea	PCR	-	39.7	POLAK et al., 2014
West Indies	Feral cats and owned outpatient cats	Fecal culture; PCR	-	0	YAO et al., 2018

PCR: Polymerase chain reaction, - Not studied.

Pathogenesis

Because it is a recently described parasite, the pathogenesis of *T. foetus* infection in cats is still not fully understood (TOLBERT & GOOKIN, 2016). There are hypotheses on whether the parasite alone could cause clinical signs, or whether feline trichomonosis could be a multifactorial disease, associated with enteric coinfections and host-related factors (GOOKIN et al., 2004).

T. foetus colonizes the ileum, cecum and colon of cats (GOOKIN et al., 2001; STOCKDALE et al., 2008). Experimental works demonstrated the cytotoxic and proteolytic activity of *T. foetus* to mammalian cells (BURGESS & MCDONALD, 1992). Infection is characterized by moderate lymphoplasmacytic and neutrophilic infiltration of the propria lamina (YAEGER & GOOKIN, 2005). A reduced colonic epithelium, cryptic hypertrophy, hyperplasia and increased mitotic activity, loss of goblet cells, and microabscesses in

crypts have been described (SCHREY et al., 2009). Eosinophilic inflammation can also occasionally be observed (YAEGER & GOOKIN, 2005; SCHREY et al., 2009).

Some factors suggest that bacteria present in the colon are an important part of the pathogenesis of diarrhea in cats infected with *T. foetus*. For example, diarrhea in these animals is usually slowed down with the administration of antibiotics (GOOKIN et al., 1999, 2001). If these antibiotics directly reduce the bacterial contribution in the pathogenesis of diarrhea or simply reduce the numbers of *T. foetus* by nutrient support depletion is unknown (TOLBERT & GOOKIN, 2016).

Chronically infected cats may show extensive periods of clinical remission, but relapsing episodes of diarrhea may be triggered by dietary changes or stressful events that could change the colonic microbiota (FOSTER et al., 2004).

Clinical Signals

The clinical signals vary from subclinical to severe cases of intestinal disease (FOSTER et al., 2004). Experimentally, the signs appeared 2-7 days after oral ingestion (GOOKIN et al., 2001). Clinical signs include chronic or intermittent diarrhea, yellowish-green and malodorous stools, characteristics of colitis, which may include the presence of live blood, mucus, fecal incontinence, tenesmus, and/or flatulence (GOOKIN et al., 2001; XENOULIS et al., 2013). Fecal consistency usually ranges from semi-formed to liquid (SCHREY et al., 2009; XENOULIS et al., 2010). More severe cases may include marked inflammation in the anal region and rectal prolapse (FOSTER et al., 2004; BURGENER et al., 2009).

As expected in a disease that usually affects the large intestine, most infected cats have good body conditions, with no systemic signs (GOOKIN et al., 1999, 2001; TOLBERT & GOOKIN 2009), although one-fifth of infected cats can show systemic signs, such as anorexia, depression, weight loss, vomiting, and fever (STOCKDALE et al., 2007).

Clinical signs last from 5-24 months, averaging 9 months after diagnosis (FOSTER et al., 2004). The severity of clinical signs varies, ranging from asymptomatic cases to intractable diarrhea (FOSTER et al., 2004; GRAY et al., 2010; XENOULIS et al., 2010).

Diagnostic Tools

Once the parasite only has the trophozoite phase, it cannot be identified in routine coproparasitological techniques and does not survive refrigeration. Therefore, the diagnosis of *T. foetus* infection requires more specific procedures (GOOKIN et al., 1999).

Diagnosis can be made by direct examination of fresh feces smear (GOOKIN et al., 1999), fecal culture using specific media (GOOKIN et al., 2003), or PCR amplification (GOOKIN et al., 2002), which is the most widely used method in the literature. In addition, the parasite can be identified via histopathologic analysis of intestinal biopsies (GOOKIN et al., 2001; YAEGER & GOOKIN, 2005).

Suitable fecal samples include either a freshly voided stool or collected by manual extraction with the aid of a fecal loop or by a colon flush technique, in which approximately 10 ml of sterile saline is injected through a catheter into the colon and then aspirated (TOLBERT & GOOKIN, 2009; YAO & KOSTER, 2015).

Fecal samples should be fresh, free of contaminating litter, and kept unrefrigerated before testing (TOLBERT & GOOKIN, 2009). To maximize the sensitivity of the direct examination and culture, feces should be analyzed within a 6-hour period after collection (HALE et al., 2009).

Diagnostic methods require the presence of parasite trophozoites in the feces. Fluctuations in the release of trophozoites are characteristic of venereal trichomonosis in cattle (SKIRROW et al., 1985). Similarly, in cats, the elimination of trophozoites in feces is probably intermittent (GOOKIN et al., 2001; STOCKDALE et al., 2008; HALE et al., 2009), and can be reduced by recent antibiotic therapy (GOOKIN et al., 1999; FOSTER et al., 2004; TOLBERT & GOOKIN, 2009).

Direct fecal exam

The identification of motile trophozoites present in a fecal sample diluted with saline by direct examination using 200× or 400× optical microscopy is a simple and inexpensive means to detect *T. foetus* in feline feces. However, this test has low specificity and sensitivity (HALE et al., 2009).

The sensitivity of the technique is low because it depends on the presence of a large number of viable trophozoites in the fecal sample (HALE et al., 2009), and was below 2% in experimentally infected cats (GOOKIN et al., 2001, 2003) and 4% in naturally infected cats (GOOKIN et al., 2003, 2004). Detection can be optimized by using fresh, non-refrigerated, and diarrheal stools and performing multiple test analyses (GOOKIN et al., 2001, 2004).

The specificity of the exam depends on the professional, who must be trained to differentiate *T. foetus* from other protozoan trophozoites, such as *Giardia* sp. (GOOKIN et al., 2003). The trophozoites of *T. foetus* are pear shaped and have three anterior flagella, one nucleus, and an undulating membrane. The trophozoites of *Giardia* sp. have no undulating membrane, two nuclei, and one ventral disc. Trophozoites of *T. foetus* and *Giardia* sp. have the same size but move differently. The trophozoites of *Giardia* sp. have a falling leaf-like motility, while those of *T. foetus* move progressively (GOOKIN et al., 2004).

T. foetus and *P. hominis* cannot be easily distinguished morphologically from each another by examining living specimens. *P. hominis* has five anterior flagella, but these flagella are difficult to enumerate in a moving trophozoite (LEVY et al., 2003). Gookin et al. (2007) argue that *P. hominis* infection does not appear to contribute to the failure to diagnose trichomonosis, since *P. hominis* infection would always be accompanied by *T. foetus*, but the reverse is not true. Ceplecha et al. (2013) disagreed, and affirmed that the survival of *P. hominis* in fecal stools is a factor to be considered. According to them, confirmation of the true agent by molecular techniques is important to avoid the unnecessary use of ronidazole, the treatment of choice for feline trichomonosis, which has neurotoxic potential.

Fecal culture

Fecal culture is a sensitive and specific method for the diagnosis of *T. foetus* infection in cats (GOOKIN et al., 2003). Two culture media are most commonly used and validated for parasite growth. The 'In Pouch™ TF – Feline' culture pouch system (Biomed Diagnostics, White City, Oregon, USA) is an easy-to-use commercial test that can be performed within veterinary clinics because of its practicality. This pouch can be incubated at 37 °C or room temperature (23-24 °C), but the trichomonads multiply quickly at 37 °C (GOOKIN et al., 2004). In Pouch culture systems inoculated with more than 0.1 g of cat feces, led to overgrowth of gas-producing bacteria or yeast within 24 hours, which inhibited its usefulness for diagnosis (GOOKIN et al., 2003). The other medium is modified Diamond's medium that is enriched with nutrients and antibiotics, which requires sterilization and incubation at 37 °C (GOOKIN et al., 2004). The culture is examined under optical microscopy from days 2-12 after incubation, to identify mobile trophozoites. It may take up to 7 days for the organism to become detectable (GOOKIN et al., 2003).

Gookin et al. (2004) found no significant difference between the two culture media, while Hale et al. (2009) determined a sensitivity of 83% and 100% for the InPouch™ commercial test and the modified Diamond's medium methods, respectively. The limitation of this diagnostic method is that it requires viable trophozoites. At low temperatures and desiccation, *T. foetus* may die. Researchers have shown that feces maintained at room temperature for up to 6 h represent a suitable material for diagnostic investigation through fecal culture (HALE et al., 2009). The addition of saline solution to the fecal is recommended if the sample is transported or stocked prior to culturing. In addition, the fecal sample should be free of sand, which could desiccate the sample and kill the parasite (GOOKIN et al., 2003).

Polymerase Chain Reaction (PCR)

The PCR method is considered a specific and more sensitive detection method for *T. foetus*, since it does not require viable trophozoites (GOOKIN et al., 2002; VERMEULEN, 2009). The solution of the fecal sample or culture can be sedimented in a centrifuge and submitted for PCR analysis (TOLBERT & GOOKIN., 2009). A study by Gookin et al. (2004) found a sensitivity of 94.4% (34/36). On the other hand, the high cost of the exam may be a prohibitive factor in many cases (GOOKIN et al., 2004).

A large variety of molecular protocols were developed for the detection of *T. foetus* in cattle and felines (HO et al., 1994; FELLEISEN et al., 1998; GOOKIN et al., 2002; BONDURANT et al., 2003; GRAHN et al., 2005). Many tests rely on amplification of the 5.8S rRNA gene sequences using ITS1 and ITS2, which are more conserved regions among isolates (FELLEISEN, 1997). The most-used technique is the nested PCR, where two primer pairs are used, TFR3 and TFR4 and TFITS-F and TFITS-R (GOOKIN et al., 2002). Several studies have shown that the rRNA gene sequence is highly conserved among *T. foetus* isolates, and is reliably different from those of other trichomonads (GOOKIN et al., 2002). Therefore, primers TFR3 and TFR4 were specially designed to amplify the 347 bp fragment of *T. foetus* DNA (GOOKIN et al., 2002). The second primer pair (TFITS-F and TFITS-R) amplifies a 208 bp fragment of the rRNA gene, which binds to the sequence amplified by the primer pair as previously described (GOOKIN et al., 2003). The combined use of these pairs of primers (TFR3 and TFR4 with TFITS-F and TFITS-R) results in the detection of 50 parasites per gram of feces 90% of the time, and 500 parasites per gram of feces 100% of the time (GOOKIN et al., 2002). One such study showed that nested PCR (single tube) did not amplify the genomic DNA of feline isolates of *Giardia* sp. or *P. hominis*.

The reduced sensitivity of PCR for the detection of *T. foetus* in feces is due to the presence of inhibitors in feces, which are not found in other substances, such as blood. The composition of feces is biologically complex, dependent on the intestinal flora, diet, and concomitant diseases (KATHER et al., 2007). Fecal components, such as polysaccharide complexes, bile salts, hemoglobin degradation products, phenolic compounds, and heavy metals are generally co-extracted with the pathogen DNA and may interfere with the PCR (GOOKIN et al., 2002; STAUFFER et al., 2008). Presence of bacteria also interfere with *T. foetus* identification by PCR, as well as in the fecal culture (CLOTHIER et al., 2015).

A DNA sample can be tested for the presence of inhibitors through a separate reaction, where bacterial 16S rRNA genes are amplified. If these genes cannot be amplified, PCR inhibitors are present in the fecal sample (GOOKIN et al., 2006). To minimize the false-negative results caused by the presence of inhibitors, there are techniques that optimize fecal material extraction, using proteinase K and temperature optimization, and the use of an additional washing step prior to DNA elution (GOOKIN et al., 2002).

Histopathology

The trophozoites of *T. foetus* can also be detected in the large intestine by histopathology, but their preservation in the biopsy specimens is difficult, because of its fragility. Yaeger and Gookin (2005) observed parasites in formalin-fixed colon tissues. Immunohistochemistry, fluorescence, and chromogenic *in situ* hybridization are techniques developed to localize and identify the parasite in tissue samples maintained in formalin, but are not commercially available (GOOKIN et al., 2010).

Treatment

The search for an effective and safe treatment for feline *T. foetus* infection is ongoing. The parasite demonstrated a poor sensitivity to several antimicrobial drugs, including metronidazole and tinidazole, drugs commonly used to treat intestinal protozoa and human vaginal trichomonosis (GOOKIN et al., 1999; ROMATOWSKI, 2000; GOOKIN et al., 2001; KATHER et al., 2007).

Ronidazole is currently the drug of choice for treatment (GOOKIN et al., 2006). The drug is rapidly absorbed into the proximal small intestine, metabolized, and eliminated by the liver and kidneys (ROSADO et al., 2007; LEVINE et al., 2011).

The current recommended dose is 30 mg/kg once daily for a period of 14 days (LEVINE et al., 2011). High doses of ronidazole are associated with signs of neurotoxicity in cats, with changes occurring at least three days after treatment and ceasing within one to four weeks after discontinuation (ROSADO et al., 2007). The neurotoxic effects are dose-dependent and can be attributed to the long half-life of the drug. Cats with neurotoxicity may exhibit loss of appetite, mental changes, lethargy, ataxia, facial tremors, hyperesthesia, weakness in the pelvic limbs, and occasionally convulsions (LEVINE et al. 2011). These cats may require intensive veterinary support until the side effects resolve (ROSADO et al., 2007).

After administration of the drug, the consistency of the feces of the infected cats generally improves rapidly in days and normalizes after the treatment of two weeks (GOOKIN et al., 2006; BURGENER et al., 2009; HOLLIDAY et al., 2009; BELL et al., 2010). In some cases of infected cats, diarrhea may not resolve for weeks after treatment due to severe colitis (TOLBERT & GOOKIN, 2009). Symptoms may return after treatment, since complete elimination of the parasite does not always occur (BURGENER et al., 2009; GOOKIN et al., 2010). Infection usually resolves after repeated treatment (GOOKIN et al., 2006). Studies have shown that treatment with other drugs such as fenbendazole, paromomycin, tinidazole, metronidazole, and furazolidone improved the consistency of feces during the treatment period, but the parasite was not eradicated, so diarrhea returned when the medications ceased (KATHER et al., 2007).

Prognosis

The prognosis for feline *T. foetus* infection is good. After infection, many cats maintain themselves with normal physical condition. In 88% of cats with diarrhea, fecal consistency returns to normal spontaneously after 2 years of infection (FOSTER et al., 2004).

The mean duration of diarrhea is 135 days (XENOULIS et al., 2010). However, the spontaneous elimination of *T. foetus* is rare. Recurrent diarrhea associated with stress or changes in the intestinal flora are common (FOSTER et al., 2004). In addition, studies reveal that chronic infection may predispose cats to develop inflammatory bowel disease (GOOKIN et al., 2001).

Prevention

Kittens or young animals raised in environments with agglomerations are more susceptible to infection due to stress or immune immaturity. Thus, minimizing stress and avoiding overpopulation would be important to reduce the chance of exposure to the agent and development of trichomonosis. As previously mentioned, the parasite is stable and viable in the environment for several days, which emphasizes the need for adequate disinfection of beds, transport boxes, litterboxes, and fomites (HALE et al., 2009).

Conclusion

Feline trichomonosis is a recent concern in veterinary medicine, caused by the parasite *T. foetus*. Infected cats can be asymptomatic or can present with chronic diarrhea. The diagnosis may be challenging as it demands more specific tests, such as fecal culture and PCR. Unfortunately, testing is still not routine in most veterinary clinics. Knowledge of this new emerging disease is important for the adequate parasite detection and treatment.

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