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CASOS CLÍNICOS INCOMUNS E PERFIL DO USO DE ANTIBIÓTICOS EM PEQUENOS ANIMAIS: ESTUDO RETROSPECTIVO (2015-2019)

DISSERTAÇÃO DE MESTRADO

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Dissertação apresentada ao programa de Pós-graduação Stricto sensu em Ciência Animal da Universidade Federal do Pampa, como requisito parcial para obtenção do Título de Mestre em Ciência Animal.

Orientador: Diego Vilibaldo Beckmann

Coorientadora: Marília Teresa de Oliveira

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Dedico esta dissertação a Ilza Irnea Primaz (*in memorian*) e Cacildo Primaz (*in memorian*).

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RESUMO

O objetivo dessa dissertação foi realizar um estudo retrospectivo dos casos clínicos e cirúrgicos realizados em pequenos animais em um hospital universitário no período entre 1º de janeiro de 2015 e 31 de dezembro de 2019. Para a realização deste estudo foram revisados 3869 fichas de atendimentos clínicos e procedimentos cirúrgicos realizados em cães e gatos. Em uma primeira etapa, foi realizada a busca e identificação de casos passiveis de publicação cientifica, a qual resultou em dois manuscritos intitulados "Severe serotonin syndrome induced for the association of selegiline and sertraline in a dog" e "Intra-abdominal torsion of a non-neoplastic cryptorchid testis in a adult dog". Na segunda etapa, foram identificados 1227 arquivos de clinica cirúrgica de pequenos animais e realizada uma análise quantitativa dos antibióticos utilizados em 1053 cães e gatos submetidos a procedimentos cirúrgicos. Este estudo resultou em um manuscrito intitulado "Estudo retrospectivo da utilização de antibióticos em cirurgia de pequenos animais (2015-2019)". Os dois primeiros manuscritos contribuem para formação acadêmica e pesquisa na medicina veterinária. O estudo do uso de antibióticos na medicina veterinária é de grande importância para saúde única, pois seu uso indiscriminado está diretamente relacionada com o aparecimento do crescente número de bactérias resistentes aos antibióticos. Portanto, conhecer a magnitude da administração de antibióticos em um Hospital Veterinário é fundamental para alertar os profissionais sobre cuidados necessários para sua utilização de maneira racional e otimização do seu uso.

Palavras-chave: Antibiótico; Cirurgia; Síndrome Serotonina; Torção Testicular.

ABSTRACT

The aim of this dissertation was to perform a retrospective study of clinical cases and surgery procedures performed in dogs and cats in university hospital between January 1, 2015 and December 31, 2019. In order to carry out this long study, 3869 clinical and surgical care records were carried out in dogs and cats. In a first step, was carried out the search and identification of passive cases of scientific publication, which resulted in two manuscripts entitled “Severe serotonin syndrome induced for the association of selegiline and sertraline in a dog” and “Intra-abdominal torsion of a non-neoplastic cryptorchid testis in an adult dog”. In the second stage, 1227 small animal surgical clinic files were identified and a quantitative analysis of the antibiotics used in 1053 dogs and cats undergoing surgical procedures was performed. This study was developed in a manuscript “Retrospective study of the use of antibiotics in small animal surgery (2015-2019)”.The first two manuscripts contribute to academic training and research in veterinary medicine. The study of the use of antibiotics in veterinary medicine is of great importance for unique health, as it is directly related to the increase in the number of antibiotic-resistant bacteria. Therefore, knowing the magnitude of antibiotic administration in a Veterinary Hospital is essential to alert professionals about care for their rational use and optimization of their use.

Keywords: Antibiotic; Surgery; Serotonin Syndrome; Testicular torsion.

SUMÁRIO

1 INTRODUÇÃO

A presente dissertação demonstrará em forma de três artigos, os resultados obtidos através de um estudo retrospectivo realizado em pequenos animais no Hospital Veterinário da Universidade Federal do Pampa. O estudo foi dividido em duas etapas, a primeira compreendeu a identificação de relatos de casos passiveis de publicação cientifica, e resultou em dois manuscritos intitulados "Severe serotonin syndrome induced for the association of selegiline and sertraline in a dog", "Intra-abdominal testicular torsion without neoplasia in a adult dog". A segunda etapa, compreendeu a identificação e análise de antibióticos utilizados em pequenos animais no período entre 1º de janeiro de 2015 e 31 de dezembro de 2019, que resultou em um manuscrito intitulado "Estudo retrospectivo da utilização de antibióticos em cirurgia de pequenos animais".

Os manuscritos estão estruturados de acordo com as normas das revistas para as quais serão submetidos. Portanto, o manuscrito 2 (Severe serotonin syndrome induced for the association of selegiline and sertraline in a dog) está de acordo com as normas da revista Research in Veterinary Science; os manuscritos 1 (Intra-abdominal torsion of a non-neoplastic cryptorchid testis in a adult dog) e 3 (Profile and quantification of antibiotic prescriptions in small animal surgery [2015-2021 retrospective]) estão estruturados de acordo com as normas da revista Ciência Rural. Além disso, para cada manuscrito foi realizada uma revisão de literatura referente ao tema abordado.

A pesquisa referente a este trabalho foi executada no Hospital Veterinário Universitário da Universidade Federal do Pampa, sob a coordenação do professor Dr. Diego Vilibaldo Beckmann.

2 REVISÃO DE LITERATURA

2.1 Torção Testicular Intra-abdominal em Cães

A torção testicular intra-abdominal (ITI) ocorre quando o testículo retido na cavidade abdominal gira em torno do seu próprio eixo (HECHT et al. 2004; QUARTUCCIO, et al. 2012; CARR et al. 2015; KHAN et al. 2018). Testículos podem encontrar-se localizados na cavidade abdominal devido a uma afecção congênita comum em cães denominada criptorquidismo (VERONESI et al., 2009; FERANTI et al., 2015; FONSECA, 2009; BOOTHE, 2003). O criptorquidismo é caracterizado pela falha na descida do testículo para o escroto (MELO, 2018; BALLABEN et al., 2016). Comumente ocorre unilateralmente e acomete o testículo direito principalmente de cães de pequeno porte (MELO, 2018; CRUZ, 2015; CORRIA et al. 2003). A origem desta alteração ainda é desconhecida, entretanto, acredita-se que fatores hereditários e hormonais interfiram no processo de migração testicular (MELO, 2018; BALLABEN et al., 2016).

A ITT ocorre devida uma frouxidão do gubernáculo de testículos retidos, os quais tendem a rotar sobre seu eixo mais facilmente (HECHT et al. 2004; QUARTUCCIO, et al. 2012; CARR et al. 2015; KHAN et al. 2018). Além da frouxidão do gubernáculo de testículos retidos, outro fator que pode contribuir e predispor a ITT é a presença de neoplasia testicular. Nestes casos, o peso da neoplasia predispõe a rotação do testículo sobre seu eixo (HECHT et al. 2004; QUARTUCCIO, et al. 2012; CARR et al. 2015; KHAN et al. 2018). O desenvolvimento de neoplasia testicular possui maior probabilidade de acometer testículos ectópicos de cães idosos (BERTOLDI et al., 2015; DE SOUSA ALEIXO et al. 2015). Assim, a ITT possui apresentação mais frequente em cães senis associadas a neoplasias e ao criptorquidismo (GRADIL et al., 2006; HECHT S et al., 2004; QUEIROZ et., al., 2004).

Os sinais clínicos da torção testicular intra-abdominal culminam com dor abdominal aguda e intensa, e sinais clínicos gastrointestinais de ocorrência comum em outras afecções como vômito e diarreia (VILIOTTI et al., 2018; LOPES; VOLPATO, 2015). O quadro de dor aguda abdominal caracterizada como síndrome do abdômen agudo é considerada uma emergência médica, e determinar a sua causa é fundamental para estabelecer o diagnóstico correto e tratamento (CRUZ-ARÁMBULO; ABDELLATIF et al., 2017; MAZZEI, et al., 2013). Casos de abdômen agudo são comuns na rotina clínica e cirúrgica de pequenos animais, e por sua vez exigem uma abordagem sistemática envolvendo o exame clínico com ênfase criteriosa na palpação abdominal e exames complementares (YOOL, 2012; DYE, 2003; HEEREN, 2004). Os exames complementares como ultrassonografia e Doppler podem auxiliar nos diagnósticos diferenciais de dor abdominal aguda, sendo essencial a realização da ultrassonografia abdominal total (JOHNSTON et al., 2001; FELDMAN E NELSON,2004).

O diagnóstico da ITT é realizado através da ultrassonografia abdominal e Doppler (JOHNSTON et al., 2001; FELDMAN E NELSON, 2004). A confirmação de presença ou ausência de neoplasia pode ser realizada por exame histopatológico do testículo (VERONESI et al., 2009; AGNEW& MACLACHLAN, 2017). O tratamento da ITT consiste na realização da orquiectomia, e a prevenção da ITT e neoplasias testiculares estão associada à castração de cães jovens (CRIVELLENTI et al., 2013; FONSECA, 2009; MAYHEW P., 2009; LOPES; VOLPATO, 2015).

2.1 Síndrome Serotoninérgica

A Síndrome Serotoninérgica (SS) é induzida por drogas que causam hiperatividade serotoninérgica nas sinapses do sistema nervoso central e periférico (ABOUKARR; GIUDICE, 2018; BALDO, 2018; BUCKLEY et al., 2014). Frequentemente resulta da associação de drogas seratoninérgicas, embora uma overdose medicamentosa também pode resultar em um excesso de serotonina nas sinapses cerebrais e desencadear a SS (DELPHINE et al., (2015, FOONG et al., 2018, RICHARD, 1997). Na Medicina Veterinária, a SS já foi relatada pela utilização de diferentes drogas serotoninérgicas (CHANG et al., 2014; GWALTNEY-BRANT et al., 2000; INDRAWIRAWAN; MCALEES, 2014). Entre as drogas capazes de causar a SS, pode-se citar a selegilina, que é um inibidor irreversível da monoamina oxidase (IMAO) e a sertralina que é um inibidor seletivo da receptação da serotonina (IRSS) (MAZUMDER et al., 2018; KALÁSZ et al., 2014; THANACOODY, 2016; GRANT, 2019).

A sertralina e selegilina são utilizadas como mono terapias para tratamento de distúrbios comportamentais emocionais de pequenos animais (BSAVA, 2014; BOWEN E HEATH, 2005; HORWITZ; MILLS, 2010). Entretanto, interações resultantes da coadministrações das mesmas, podem levar a casos de SS com presença de graves sinais clínicos (DELPHINE et al., 2015, FOONG et al., 2018, RICHARD, 1997). Portanto, em caso de necessidade de coadministração das drogas, a selegilina deve ser mantida na extremidade inferior da faixa terapêutica (ABOUKARR et al., 2018).

A SS é caracterizada como uma tríade de sinais clínicos clássicos que resultam em alterações neuromusculares, autonômicas e estadas mental (FITZGERALD; BRONSTEIN, 2013; MOHAMED et al., 2008; THOMAS et al., 2012; GWALTNEY-BRANT; ALBRETSEN, 2000). Os sinais clínicos frequentemente são observados uma a seis horas após exposição aos medicamentos desencadeadores, sendo o diagnóstico clínico (BOYER et al., 2005; BUCKLEY et al., 2014). Para realização do diagnóstico da SS em humanos, critérios baseados nos sinais clínicos como de Sternbach, Radomski e Hunter já foram descritos (STERNBACH, 1991, RADOMSKI ET AL., 2000, DUNCKEY et al., 2003). Entretanto, na Medicina Veterinária, esses critérios ainda não foram estabelecidos, e o diagnóstico consiste no histórico de ingestão de droga serotoninérgica e sinais clínicos relacionados a alterações neuromusculares, autonômicas e estadas mental SS (CHANG et al., 2014;FITZGERALD & BRONSTEIN, 2013; GWALTNEY-BRANT et al., 2000; INDRAWIRALAWAN & MCALEES, 2014; ORTOLAN et al., 2018; THOMAS et al., 2012).

Para confirmar o diagnóstico através de critérios de Sternbach é necessário a apresentação de pelo menos três dos sinais clínicos: Alterações do estado mental (confusão, hipomania) agitação, mioclonia, diaforese, tremor, diarreia, incoordenação e febre. Já os critérios de Radomski utilizam-se a apresentação de sinais clínicos divididos em critérios maiores e menores, sendo o maior: consciência prejudicada, humor elevado, Semicoma/coma, mioclonia, tremor, rigidez hiperreflexia, febre; Menor: inquietação, insônia, incoordenação, pupilas dilatadas, acatisia, taquicardia, taquipneia, dispneia, diarreia hipertensão e hipotensão. Os critérios de Hunter são os mais atuais e compreendem a apresentação de pelo menos dois destes sinais clínicos clônus espontâneo, clônus induzível, clônus ocular, agitação, sudorese, tremor e hiperreflexia (STERNBACH, 1991, RADOMSKI ET AL., 2000, DUNCKEY et al., 2003).

A SS pode ser de rápida evolução e fatal, sendo indispensável o diagnóstico rápido e preciso para a sobrevida do paciente (BALDO BA; ROSE MA, 2019; BEAKLEY BD, et al., 2015). Contudo, é autolimitada, podendo ser resolvida em até 72 horas após a descontinuação do ou dos medicamentos causadores (ASUSTA HB, et al. 2019; JUREK L, et al., 2019).

2.1 Antibióticos

2.1.1 Características dos Antibióticos

Os antibióticos são drogas produzidas através de material sintético, natural ou derivadas semisintéticas (ABRAHAM, 2005; NELSON; COUTO, 2015, PATRICK, 2005; PUPO, 2006) capazes de inibir (bactericida) ou destruir (bacteriostático) o crescimento microbiano (FOSSUM, 2021; MACHADO et al., 2006; WALSH, 2003). Classificados de acordo com o grupo químico podem ser do tipo aminoácidos, açúcares, acetatos/propionatos ou quimioterápicos (MADING, 2016; QUINN, 2005; WALSH, 2003). Quanto ao mecanismo de ação, os antibióticos são classificados nos quais alteram ou destroem a parede celular da bactéria, inibidores da síntese da proteína ou do ácido desoxirribonucleico (DUNNING, 2007; FOSSUM, 2021). Ainda, são caracterizados pelo seu espectro de ação como de amplo espectro quando eficazes contra bactérias gram-positivas, gram-negativas, aeróbias ou anaeróbias ou de pequeno espectro de ação quando eficazes contra alguns tipos de bactérias (MADING, 2016; QUINN, 2005; WALSH, 2003).

A sua absorção e distribuição ocorre por via sistêmica através da difusão passiva ou facilitada após a administração da droga por via oral, injetável ou tópica. Alguns fatores como via de administração, composição, peso molecular podem influenciar na absorção do fármaco (DUNNING, 2007; SANTOS, 2010). No geral, a excreção ocorre pela filtragem renal sendo eliminado na urina, entretanto, também podem ser excretados nas fezes, saliva e suor (KILYE et al., 2017; MCEWEN; FEDORKA-CRAY, 2017). Outrora, é importante pontuar que os antibióticos possuem ação residual em tecidos e podem ser excretados no leite e permanecer na carne e ovos (MENDES et al., 2021). Por esta razão, é de suma importância que a carência do uso de antibióticos em animais de produção seja respeitada (ZHAO et al., 2021).

A descoberta da penicilina por Alexander Fleming e seu uso a partir de 1940 representou uma grande revolução para a prevenção e tratamento de doenças humanas e animal (LIU; MIHAI, 2009; HUGHES et al., 2015; FLEMING, 1945). Com o advento da penicilina e de diversos outros antibióticos, estes passaram a ser comercializados e administrados de maneira irracional resultando no desenvolvimento da resistência bacteriana (RAM) a maioria dos antibióticos existentes (GALLEGO, et al., 2019). Na medicina veterinária as ações e pesquisas sobre a utilização de antibióticos estão mais direcionadas a animais de produção (WHITE et al., 2002; ANGULO et al., 2009; MCEWEN; FEDORKA-CRAY, 2017). Entretanto, uma gama de antibióticos também é utilizada diariamente na cirurgia de pequenos animais (FOSSUM et al., 2021).

2.1.2 Antibióticos na Cirurgia de Pequenos Animais

Os antibióticos são utilizados rotineiramente nos procedimentos cirúrgicos de pequenos animais para prevenir ou tratar infecções, podendo ser administrado tanto no pré, trans e pós-operatório (FOSSUM, 2021; COSTA et al., 2016; SCHENEPF et al., 2021). A administração profilática de antibióticos é considerada uma medida de controle de infecção do sítio cirúrgico e essencial para reduzir os riscos associados à cirurgia e resistência quando empregada corretamente (JOHNSON, 2002; HEDLUND, 2005; DUNNING, 2007). De maneira geral, a antibioticoprofilaxia deve ser realizada quando existe um risco significativo de infecção como tempo cirúrgico superior a 90 minutos, implantação de prótese e ferida contaminadas ou traumatizada (LEVIN, 2002; FOSSUM, 2021; ALEIXO et al., 2009). No que diz respeito à antibioticoterapia, esta deve ser realizada para tratar infecções existentes em todos os procedimentos cirúrgicos contaminados (FOSSUM, 2021).

A escolha da antibioticoprofilaxia e antibioticoterapia, idealmente, deve-se basear nos resultados da cultura e antibiograma (GOULD, 2002; NELSON; COUTO, 2015). Porém, estes exames não são do tipo tempo real, requerendo dias de espera para obtenção de resultados (MCEWEN E FEDORKA-CRAY, 2017). Desta forma, a seleção da maioria dos antibióticos é realizada de forma empírica, baseada na flora bacteriana esperada no tecido-alvo (FOSSUM, 2021; COSTA et al., 2016). O antibiótico utilizado deve ser modificado se necessário de acordo com a resposta clínica ou após resultado da cultura e antibiograma (BICHARD; STEPHEN, 2008; DUNNING, 2007).

Diretrizes para prescrição de antimicrobianos na clínica cirúrgica de pequenos de animais já foram desenvolvidos e podem ser uma ferramenta para auxiliar o médico veterinário na escolha do medicamento adequado (ALERTON et al., 2021). Além disso, sistemas de vigilância de RAM, controle e registro médico dos antibióticos administrados em uma determinada população, podem auxiliar no desenvolvimento de um guia local para o uso adequado dos antibióticos em cirurgias (SINGLETON et al., 2017; WERNER et al., 2018). Ainda, a quantificação dos antibióticos utilizados nas cirurgias de pequenos animais em diversas áreas geográficas pode auxiliar a determinar um padrão de resistência e assim resultar em uma escolha adequada para cada paciente (SCHNEPF et al., 2021; CLEVEN et al., 2017; MCEWEN et al., 2018).

Estudo tem mostrado que, antibióticos classificados como criticamente importantes pela organização mundial de saúde tem sido utilizados com frequência nas práticas cirúrgicas veterinárias (SCHNEPF et al., 2021; SINGLETON et al., 2018). Com a crescente preocupação dos proprietários com a saúde de seus pets, bem como a longevidade a procura por procedimentos cirúrgicos vem aumentando, o que consequentemente resulta em um maior número de administrações de antibióticos e possivelmente em novos casos de RAM (BROCHADO et al., 2018; POMBA et al., 2017). Outro fator importante na disseminação da RAM é o contato próximo entre animal e humano, o qual pode facilitar a transferência recíproca entre espécies de bactérias resistentes com genes idênticos (POMBA et al., 2017; GUARDABASSI et al., 2014).

2.1.3 Resistência Bacteriana aos Antibióticos

Uma bactéria é considerada sensível a um antibiótico quando sofre sua ação, porém quando o medicamento não exerce efeito sobre a bactéria, esta é considerada resistente (CONCEIÇÃO et al., 2020; HOIBY, 2010). A bactéria torna-se resistente através mecanismos bioquímicos e genéticos que variam de patógeno para patógeno, alterando o seu material genético, mutando o DNA ou introduzindo genes de resistência (DEL FIO, 2000; AMATO et al., 2000). Os mecanismos de resistência bacteriana envolvem alteração da permeabilidade da membrana celular, alteração do sitio de ação do antimicrobiano, bomba de efluxo ativa e enzimático que degrada o antibiótico através de enzimas (ADAMS, 2003; AMATO et al., 2000). Além disso, as bactérias possuem a capacidade de rápida multiplicação, adaptação a diversos fatores como a exposição a agentes químicos potentes e podem trocar material genético entre linhagens (MADIGAN et al., 2016; QUINN, 2005).

A caracterização dos genes responsáveis pela resistência e o desenvolvimento de novos antibióticos, diminuição do tempo de internação podem auxiliar na prevenção da geração de novos microrganismos resistentes (FERNANDES, 2006; DEL FIO, 2000). Assim, a prescrição adequada e a diminuição do uso indiscriminado deste fármaco para humanos e animais é um fator chave na resolução deste problema de saúde única (GIGUÈRE et al., 2010; WERNER et al., 2018). Para que exista uma escolha mais racional dos antibióticos, a escolha deve ser baseada em guias de uso de antimicrobianos atualizados, e uma alternativa é a individualização da terapia antibiótica guiada por biomarcadores (AULIN et al., 2021).

O aumento de casos que envolvem bactérias resistentes tem sido associado ao uso inadequado de antibiótico sem hospitais, tempo prolongado de internação, aumento de pacientes imunocomprometidos e a demora no diagnóstico das infecções bacterianas (BICHARD; STEPHEN, 2008; FOSSUM, 2021). Na Medicina Veterinária mecanismos de controle e ações estão mais voltados a animais de produção alimentar (QEKWANA et al., 2017; AWOSILE et al., 2018). No entanto, pequenos animais são considerados um potencial reservatório, vetor e importante contribuinte para o desenvolvimento da RAM (CHOMEL et al., 2011). Embora, pouca ênfase é colocada na vigilância da utilização de antibióticos pesquisas detalhadas demonstrando a relações entre o uso de antimicrobianos e a seleção e disseminação de bactérias resistentes é necessária (SCHNEPF et al., 2021; CLEVEN et al., 2017; MCEWEN et al., 2018).

Animais de companhia, principalmente cães e gatos, são considerados potenciais reservatórios e vetores na transmissão da RAM devido à utilização indiscriminada de antibióticos de amplo espectro e ao contato próximo com seres humanos (GUARDABASSI et al., 2004; LLOYD, 2007). Assim, a presença bactérias multirresistentes em animais de companhia (AWOSILE et al., 2018; PANTOSTI et al., 2012; QEKWANA et al., 2017) aumentam o risco de falha no tratamento antimicrobiano de animais e consequentemente de seres humanos (AWOSILE et al., 2018; DELGADO et al., 2007; JACKSON et al., 2009). Entretanto, os casos de RAM em pequenos animais não são totalmente monitorados o que acarreta em poucos dados da RAM relacionados a cães e gatos (UKUHOR, 2021; SCHNEPF et al., 2021; DE-LAS-CASAS-CÁMARA et al., 2022).

Estudos apontam que o patógeno oportunistas do tegumento e mucosas como o *Staphylococcus spp.* são frequentemente isolados em pequenos animais e são responsáveis por causar complicações pós-cirúrgicas (LEMSADDEK et al. 2016; QEKWANA et al., 2017; AWOSILE ET AL., 2018; PORTILHO, 2020). A colonização de *S. pseudintermedius e S. aureus*nesses animais pode agravar a RAM uma vez que estudos têm demonstrado a ocorrência de transmissão de *Staphylococcusspp* de cães para humanos (PANTOSTI, 2012; DOS SANTOS et al., 2016). Além disso, a presença de *Enterococcusspp* que é resistente a clindamicina, penicilina G e cefalotina já foram isolados em estudos envolvendo identificação de RAM em pequenos animais (DELGADO et al., 2007; JACKSON et al, 2009; AWOSILE et al., 2018).

Em vista de mitigar a RAM, a Organização Mundial da Saúde classificou cinco classes de antimicrobianos de importância crítica de maior prioridade (HP-CIAs), alta prioridade (HP-CIAs), altamente importante e importante (WHO, 2018). Essa classificação foi realizada com base em sua importância clínica na medicina humana e no risco de transferência de resistência de animais e utilizam cinco fatores de priorização para classificas os grupos de antibióticos (WHO, 2018). Os fatores de priorização são divididos em C1, C2, P1, P2 e P3. O fator C1 corresponde à única, ou uma das terapias disponíveis, para tratar infecções bacterianas graves em pessoas; C2: bactéria que podem ser transmitidas aos seres humanos de fontes não humanas e que podem adquirir RAM de fontes não humanas; P1: infecções graves em grande número de pessoas, e com N de ANTB limitados; P2: alta frequência de uso do antimicrobiano, indicado para grupo de risco; P3: Infecções em pessoas para as quais já existem extensas evidências de transmissão de bactérias resistentes (Tabela 1).

TABELA 1- Lista de antibióticos de importância crítica da OMS.

Grupos	Classes Antimicrobianas	Critérios				
		C1	C2	P1	P2	P3
Maior prioridade	Cefalosporina 3°Geração	x	x	x	x	x
	Glicopeptideos	x	x	x	x	x
	Macrolideos	x	x	x	x	x
	Polimixina	x	x	x	x	x
	Quinolonas	x	x	x	x	x
Alta prioridade	Aminoglicosideo	x	x		x	x
	Ansamicina	x	x	x	x	
	Carbapenemos	x	x	x	x	
	Glicilciclinas	x	x	x		
	Lipoptideos	x	x	x		
	Monobactamas	x	x	x		
	Oxazolidinonas	x	x	x		
	Peinicilina (natural, aminopenicilina, antipseudomonas)	x	x		x	x
	Derivados de ácido fosfônico	x	x	x		
Altamente Importante	Amidinopenicilina		x			
	Amfenicois		x			
	Cefalosporina 1º e 2º Geração		x			
	Lincosaminas		x			
	Penicilina (anti-stafilococos)		x			
	Ácido Pseudomônicos		x			
	Riminofenazinas	x				
	Esteróide antibacteriano		x			
	Estreptograminas		x			
	Sulfonamidas		x			
	Sulfonas	x				
	Tetraciclina	x				
Importante	Aminociclitóis					
	Polipeptideos					
	Nitrofurano					
	Nitromidazólico					
	Pleuromutilinas					

Adaptado de WHO, 2018.

3 OBJETIVOS

3.1 Objetivo geral

Realizar estudo retrospectivo dos casos clínicos e cirúrgicos de pequenos animais do hospital veterinário desta instituição no período entre 01 de janeiro de 2015 e 30 de dezembro de 2019.

3.2 Objetivos Específicos

Quantificar e identificar como os antibióticos estão sendo utilizados na clínica cirúrgica de pequenos animais e acordo com a Classificação de Antibióticos Criticamente Importantes da Organização Mundial da Saúde.

Relatar um caso em formato de manuscrito intitulado: "Severe serotonin syndrome induced for the association of selegiline and sertraline in a dog".

Relatar um caso em formato de manuscrito intitulado: "Intra-abdominal testicular torsion without neoplasia in a adult dog".

4 MATERIAL E MÉTODOS

Os resultados desta dissertação estão apresentados sob a forma de manuscrito. As seções Introdução, Métodos, Resultados, Discussão, Conclusão e Referências Bibliográficas encontram-se nos manuscritos a seguir. Os manuscritos estão no formatado de acordo com as normas das respectivas revistas, os quais serão submetidos os trabalhos.

MANUSCRITO 1

O presente manuscrito está no formatado e de acordo com as normas da Revista Ciência Rural, o qual foi submetido para publicação.

Intra-abdominal torsion of a non-neoplastic cryptorchid testis in an adult dog

Intra-abdominal torsion of a non-neoplastic cryptorchid testis in an adult dog

Torção intra-abdominal de testículo criptorquideo sem neoplasia em cão adulto

ABSTRACT

Intra-abdominal or intrascrotal testicular torsion in dogs occurs due to spermatic cord rotation. Dogs with testicular torsion commonly present severe pain and require surgical intervention. Torsion of intra-abdominal retained testicles in cryptorchid adult dogs is often associated with the presence of testicular neoplasia**.** Here, we report the case of a 5-year-old male poodle with uncommon intra-abdominal testicular torsion (ITT) in the absence of neoplasia, which presented with acute abdominal pain in the hypogastric region and was referred to the veterinary hospital. Cryptorchidism and alterations compatible with testicular torsion were visualized during ultrasound examination. Intra-abdominal orchiectomy and histopathological analysis of the testes confirmed the diagnosis of ITT in the absence of neoplasia. The patient presented satisfactory clinical outcomes. This report shows that ITT can occur in adult dogs in the absence of testicular neoplasia and that it should be included as a differential diagnosis in cases of acute abdominal pain in cryptorchid dogs. Furthermore, ultrasound examination associated with pain in the hypogastric region was decisive for the diagnosis of ITT.

Keywords: Acute abdomen, cryptorchidism, ultrasound exam, surgery.

RESUMO

A torção testicular intra-abdominal ou intra-escrotal em cães ocorre devido à rotação do cordão espermático. Os cães com torção testicular comumente apresentam dor intensa e necessitam de intervenção cirúrgica. A torção dos testículos retidos no abdômen em cães adultos está geralmente associada à presença de neoplasia testicular. O objetivo deste relato é descrever um caso incomum de torção testicular intra-abdominal (ITT) sem neoplasia em um cão macho, de 5 anos de idade, da raça Poodle, encaminhado ao Hospital Veterinário com dor abdominal aguda em região hipogástrica. Durante o exame ultrassonográfico, foi possível confirmar o criptorquidismo e evidenciar alterações compatíveis com torção testicular. A orquiectomia intra-abdominal e posterior análise histopatológica confirmaram a ITT sem neoplasia associada. O paciente apresentou evolução clínica satisfatória. Este relato mostra que a ITT sem neoplasia pode ocorrer em cães adultos e que deve ser considerada como um possível diagnóstico em casos de dor abdominal aguda. Além disso, o exame ultrassonográfico associado à dor em região hipogástrica foi decisivo para o diagnóstico de ITT.

Palavras-chave: dor abdominal aguda, criptorquidismo, ultrassom, cirurgia.

Testicular torsion is uncommon in dogs and caused by the rotation of the intrascrotal testis (CRIVELLENTI et al., 2012; VILIOTTI et al., 2018) or intra-abdominal testis around its own axis (PEARSON & KELLY, 1975; QUARTUCCIO et al., 2012). Pain is the main clinical sign of spermatic cord torsion (HECHT et al., 2004; QUARTUCCIO et al., 2012; CARR et al., 2015), and this requires a surgical intervention (SCHNECK & BELLINGER, 2007; QUARTUCCIO et al., 2012). Ultrasound is a routine examination for testicular torsion diagnoses and other pathologies that cause abdominal pain (PINTO et al., 2001; HECHT et al., 2004; FELUMLEE, 2012).

Cryptorchidism is frequently associated with testicular neoplasia, such as Sertoli cell tumors and seminoma, in dogs of all ages (PEARSON & KELLY, 1975; QUARTUCCIO et al., 2012; KHAN et al., 2018; SANTOS & ALESSI, 2010; HAYES et al., 1985). The presence of testicular neoplasia results in a progressive enlargement of the gonads, which increases the possibility of torsion (PEARSON & KELLY, 1975; HAYES et al., 1985). In cryptorchid adult dogs, torsion of the testis in the absence of neoplasia has occasionally been reported(HECHTet al., 2004; CRHA et al., 2015; CARR et al., 2015).This report describes an uncommon case of intra-abdominal testicular torsion (ITT) without neoplasia in a dog presenting with acute abdominal pain in the hypogastric region.

A 5-year-old male poodle (weight: 2.8 kg) presented to the veterinary hospital with acute abdominal pain and a history of neutering performed 3 years prior. During clinical examination, the patient presented with intense pain on abdominal palpation of the right hypogastric region, mild dehydration, tachycardia, and tachypnea. The main differential diagnoses were urinary tract diseases, intestinal intussusceptions, and foreign bodies. Initially, neutering history disregarded testicular torsion and complications associated with cryptorchidism. The patient underwent an abdominal ultrasound examination to determine the diagnosis.

Abdominal ultrasound examination revealed an oval structure (5 × 3 × 2 cm) with a mixed echotexture in the right caudal abdominal quadrant, compatible with a testicle (Figure 1A and 1B). The patient presented with severe pain during the ultrasound examination, specifically during the intra-abdominal testicle evaluation, and was administered tramadol hydrochloride 3 mg/kg) intravenously (IV) and replacement fluid therapy (Ringer's lactate solution, 3mL.kg/h). Ultrasound findings associated with severe pain were suggestive of ITT. Ultrasound examination also revealed the presence of gallstones and splenic lesions. The hemogram and serum biochemistry values are shown in Table 1. Hemogram showed mild neutrophilia, moderate eosinophilia, and moderate monocytosis (TVEDTEN, 2010; NABITY& RAMAIAH, 2010). Moreover, serum biochemical analysis showed a marked increase in the levels of alanine aminotransferase (220 UI/L) and alkaline phosphatase (218 UI/L) (MALAKOUTI et al., 2017).

A median laparotomy was performed for intra-abdominal orchiectomy. During surgery, the testicle was localized in the right caudal abdominal quadrant and removed. The testicle presented with edema and congestion. The abdominal cavity was inspected during the surgical sequence, and gallstones were removed (cholecystectomy). Splenectomy was also performed to avoid complications. Microscopic sections of the testis showed ischemia, severe diffuse hemorrhage with moderate neutrophilic inflammation and necrosis suggestive of torsion, and parenchyma with normal architecture, without evidence of neoplasia (Figure 1C).The histopathology report confirmed the clinical diagnoses of ITT in the absence of neoplasia as well as splenic scar nodules.

The dog was hospitalized for 3days. During the first 2days, no postoperative pain was detected, and the patient was maintained on fluid therapy (2mL.kg/h) with Ringer's lactate. Treatment with cephalothin (30 mg/kg, IV) TID; Omeprazole (1 mg/kg, IV), SID; Meloxicam (0.1 mg/kg, SC), SID; Methadone (0.3 mg/kg, IM) TID was also implemented. On the 3day post-surgery, the patient was discharged with a prescription for oral cephalexin (30 mg/kg, PO) BID. Then, 10 days after surgery, the patient returned for evaluation and presented satisfactory clinical progress. Physical examination failed to reveal any abnormalities on abdominal palpation.

Testicular cord torsion in the absence of neoplasia is uncommon in adult cryptorchid dogs. Generally, the prevalence of testicular torsion in adult cryptorchid dogs is frequently associated with testicular neoplasia (QUARTUCCIO et al., 2012; PEARSON & KELLY, 1975; KHAN et al., 2018). Progressive enlargement of the gonad due to the presence of neoplasia predisposes the gonad to testicular rotation (PEARSON & KELLY, 1975; HAYES et al., 1985). ITT in the absence of neoplasia has only been reported in cryptorchid puppy dogs (HECHT et al., 2004; CARR et al., 2015). It is likely that the gubernaculum laxity of the testis retained in the abdominal cavity predisposes testicular rotation (BOOTHE, 2003; GRADIL et al., 2006). This report describes the clinical conduct, ultrasound and histopathological findings, and surgical treatment of a case of ITT without neoplasia.

Cryptorchidism is a common developmental defect in dogs, and it often occurs in small purebreds such as poodles (BOOTHE, 1998; VERONESI et al., 2009; MEMON, 2010). The right hypogastric region is the common location of retained testicles and, consequently, in the ITT (ROMAGNOLI, 1991; AMANN & VEERAMACHANENI, 2007). Complications of the intra-abdominal testicle such as infertility, increased risk of neoplasia, and testicular torsion can result in acute pain (HECHT et al., 2004; QUARTUCCIO et al., 2012; CARR et al., 2015; KHAN et al., 2018). Consequently, dogs with cryptorchidism should be neutered a younger age to avoid complications (BOSSCHERE & DEPREST, 2010; BUFALARI et al., 2015; STOKOWSKI et al., 2016; KHAN et al., 2018).The clinical diagnosis of cryptorchidism was possible due to pain in the right hypogastric region (AMANN & VEERAMACHANENI, 2007; HECHT et al., 2004; QUARTUCCIO et al., 2012) and ultrasound findings (HRICAK et al., 1983; HECHT et al., 2004).

The ultrasound examination was preponderant to reach the diagnosis of acute ITT as the dog was presumably spayed, corroborating with previous case reports (MIYABAYASHI et al., 1990; HECHT et al., 2004; CARR et al., 2018). Other diagnostic methods can support the diagnosis of ITT, such as color Doppler ultrasound (HECHT et al., 2004;ERDOĞAN et al., 2021), computed tomography (KLANG et al., 2017; STOKOWSKI et al., 2016), laparoscopy (FERANTI, 2015; CARR et al., 2015), and contrast-enhanced ultrasound scanning (METZGER-ROSE et al.,1997).

The enlargement of a retained testicle and the presence of mixed echogenicity are predominant findings of acute testicular torsion with or without neoplasia (HRICACK et al., 1983; PALTIEL, 2002; QUARTUCCIO et al., 2012; CARR et al., 2015). However, ultrasound examination did not disregard the presence of testicular neoplasia (HRICACK et al., 1983; HECHT, 2003). The absence of testicular neoplastic characteristics in the histopathological analysis confirmed the diagnosis of ITT in the absence of neoplasia

(VERONESI et al., 2009; AGNEW& MACLACHLAN, 2017).

Median laparotomy enables the visualization and removal of the altered testicle (QUARTUCCIO et al., 2012; CRIVELLENTI et al., 2013), in addition to performing splenectomy (FOSSUM et al., 2021) and cholecystectomy (AGUIRRE et al., 2007). The marked increase in alanine aminotransferase and alkaline phosphatase levels is probably related to the presence of gallstones, which is a determinant of cholecystectomy performance (AGUIRRE et al., 2007; NELSON & COUTO, 2010).Splenic scars and cholelithiasis may not cause pain. Such alterations would result in pain in the mesogastric region but not in the hypogastric region (CENTER, 2009; NELSON & COUTO, 2010; NYLAND et al., 2015). Consequently, meticulous abdominal palpation was used to determine the focus of pain and increased ITT diagnoses (DYE et al., 2003; ABDELLATIF et al., 2017).

Testicular torsion is uncommon in dogs, and ITT is considered more predisposed in adult dogs with testicular neoplasia. This report of testicular torsion shows that ITT can occur in adult cryptorchid dogs without neoplasia. Neutering of dogs with cryptorchidism is necessary to avoid complications such as testicular torsion and, consequently, severe abdominal pain. The findings of the abdominal ultrasound examination associated with acute abdominal pain in the right hypogastric region are essential for ITT diagnosis. Therefore, ITT in the absence of neoplasia should be included as a clinical suspicion in cases of acute abdominal pain.

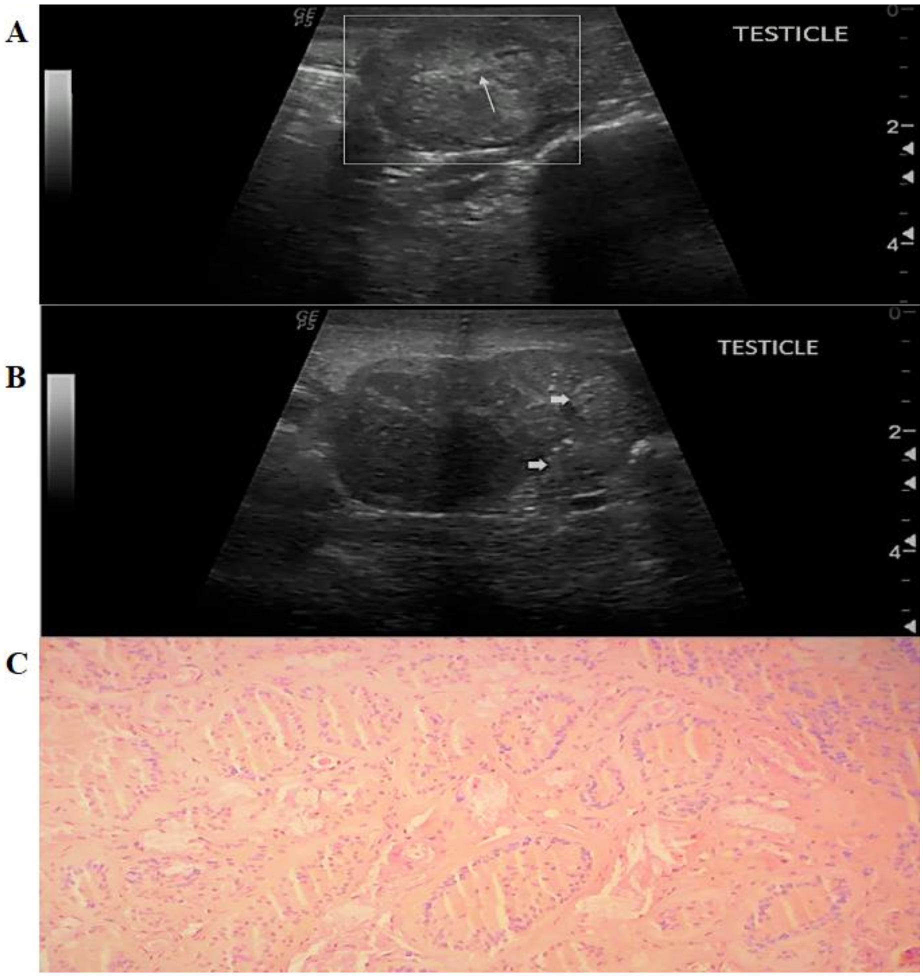

Figure 1 –Intra-abdominal testicular cord torsion in an adult poodle dog. (A) Sagittal ultrasonographic image of the intra-abdominal right testicle. The testicle appears oval with mixed echotexture. The hyperechoic linear structure (arrow) in the sagittal position represents the mediastinum testicle. (B) Sagittal ultrasonography image of the right testicle. A portion of the swollen spermatic cord is visualized (arrows). (C) Microscopic section of the twisted testicle (Hematoxylin and eosin, 10X; H-E). Necrosis is present in multiple seminiferous tubules, and there is severe diffuse hemorrhage.

Table 1 – Hematology and serum biochemistry of an adult dog with intra-abdominal torsion of a non-neoplastic cryptorchid testis.

Parameter	**Values**	**Reference Interval**
Erythrocytes (×10^6/µL)	5.5	5.5–8.5
Hemoglobin (g/dL)	13.2	12–18
Hematocrit (%)	36.0	37–50
Platelets (×10^3/µL)	441	200–500
Leucocytes (×10^3/µL)	16.4	6–17
Neutrophil (/µL)	11.8	3–11.5
Eosinophil (/µL)	2.1	0.1–1.25
Monocytes (/µL)	1.8	0.15–1.35
Lymphocytes (/µL)	2.1	1–4.8
Plasma proteins (g/dL)	7.0	5.5–7.5
Fibrinogen (g/dL)	0.6	0.1–0.5
Total Protein (g/dL)	6.3	5.4–7.1
Albumin (g/dL)	3.2	2.6–3.3
Globulin (g/dL)	3.0	2.5–4.1
Creatinine (mg/dL)	0.8	0.5–1.5
Urea (mg/dL)	27.0	20–60
ALT (UI/L)	220	21–102
ALP (UI/L)	218	20–156
AST (UI/L)	33.0	23–66

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase.

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BIOETHICS AND BIOSECURITY COMMITTEE APPROVAL

The report was performed with an animal routinely treated by the HUVET-UNIPAMPA and was not part of any project; it was simply a clinical case report.

DECLARATION OF CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

The authors contributed equally to the manuscript.

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MANUSCRITO 2

O presente manuscrito está de acordo com formato e normas da Revista Research in Veterinary Science, o qual será submetido para publicação.

Severe serotonin syndrome induced by association of selegiline and sertraline in a dog

Severe serotonin syndrome induced by association of selegiline and sertraline in a dog

HIGHLIGHTS

- Serotonin syndrome induced by selegiline and sertraline association in a dog
- Antidepressants association has the potential to induce severe serotonin syndrome
- Antidepressants has been prescribed to small animals
- Coma in dog by serotonin toxicity

ABSTRACT

Serotonin syndrome (SS) is a disorder induced by ingestion of an overdose or by combination of serotonin medications such as selective serotonin reuptake inhibitors (SSRis) and monoamine oxidase inhibitors (MAOis). A 15-year-old-7kg female poodle, 1-hour post ingestion of sertraline (SSRis) and selegiline (MAOis) presented anxiety, agitation, hyper salivation, walk incoordinated, vocalization, followed by coma. Physical exam revealed modified Glasgow Coma Scale of 5, tachycardia, normal respiratory rate and temperature, mild dehydration, empty urinary bladder with urinary incontinence. Gradual recovery with absence of neurological clinical signs post 109-hour of medications ingestion without specific treatment was observed. The clinical manifestation of SS and history of sertraline and selegilne co-administration was essential for veterinary recognize to the diagnosis. This report showed that severe SS in the dog could occur by sertraline and selegiline combination.

Keywords: SSRis; MAOis; antidepressants; serotonin toxicity

Serotonin syndrome (SS) or serotonin toxicity is a potentially life-threatening adverse drug reaction resulting from increased serotonin in the brain synapses (Aboukarr and Giudice, 2018; Baldo, 2018; Buckley et al., 2014; Thanacoody, 2016). The clinical manifestation has been relationship as dose- and drug-dependent, ranging from mild (for example, diarrhea, salivation and lethargy) to severe (for example, coma and seizures) (Boyer and Shannon, 2005; Dunkley et al., 2003; Mohammad-Zadeh et al., 2008; Thomas et al., 2012). The SS diagnosis is supported by history of ingestion to serotonergic medications associated with clinical signs related to mental-status changes, autonomic hyperactivity, and neuromuscular abnormalities (Boyer, 2005; Fitzgerald and Bronstein, 2013; Gwaltney-Brant et al., 200; Haberzettl et al., 2013; Mohammad-Zadeh et al., 2008; Ortolan et al., 2018; Thomas et al., 2012).

The dogs SS has been reported by selective serotonin reuptake inhibitors (SSRis) medications (citalopram, escitalopram, paroxetine, fluoxetine, fluvoxamine, sertraline, 5-HT1B Inhibitor), supplement alimentary (5-Hydroxytryptophan), and in cats by SSRis (escitalopram, citalopram, fluoxetine, enlafaxine) and opioid (tramadol) (Chang et al., 2014;Fitzgerald and Bronstein, 2013; Gwaltney-Brant et al., 2000; Indrawiralawan and McAlees, 2014; Ortolan et al., 2018; Thomas et al., 2012). SS in companion animals is usually reported by accidental overdose of human medications (Gwaltney-Brant et al., 2000; Hopkins et al., 2017; Mohammad-Zadeh et al., 2008; Ortolan et al., 2018) whereas in humans the SS by co-administration of serotonergic medications is most commonly, such as SSRis and monoamine oxidase inhibitors (MAOis) association (Aboukarr and Giudice, 2018; Francescangeli, et al. 2019; Ibister et al., 2007). The sertraline (SSRis) and selegiline (MAOis) are safe monotherapy for the treatment of emotional behavioral disorders in dogs and humans (Karagiannis et al., 2015; Waston et al., 2018; Aboukarr and Giudice). The combined use of these drugs induced the SS in humans (Aboukarr and Giudice, 2018; Richard et al., 1997); however, there is limited information of SS induced by sertraline and selegiline in dogs. Thus, reports an uncommon case of severe SS induced by co-administration of sertraline and selegiline in an old dog, from the moment of drug ingestion to complete recovery.

A 15-year-old-7kg female poodle in a coma was referred to the University Veterinary Teaching Hospital approximately 20-hours post oral ingestion of sertraline (2mg/kg) and selegiline (1mg/kg). According to the owner, these drugs were prescribed to treat an episode of incoordination and tremor which lasted about one-minute. One-hour post these drugs ingestion, the dog showing anxiety, agitation, hypersalivation, walk incoordinated, vocalization, followed by laterally recumbent without responses to stimuli performed by the owner. On neurological examination, the patient presented laterally recumbent, absent deep pain perception, and mGCS of 5 suggesting a grave prognosis (Dewey and DaCosta, 2017; Platt et al., 2001).The clinical course of this case and the Small Animal Modified Glasgow Coma Score (mGCS) evaluation are depicts in a timeline (Figure-1).

In the physical examination was identified tachycardia (160 bpm), normal respiratory rate (34 breaths per minute), 38.2°C of temperature, mild dehydration, empty urinary bladder with urinary incontinence. Moreover, hemogram and biochemistry examination were realized and the values were within reference ranges (Table 1). The dog was diagnosis with severe SS from the history of two serotonergic medications co-administration associated with the clinical manifestation. The patient was hospitalized, monitored every hour by mGCS and underwent fluid therapy (Ringer's lactate, 50mg/kg/24h), nutrition by nasogastric tube, urinary monitoring output, and change of recumbent.

The patient showed no changes in mGCS evaluation until the 48-hour post sertraline and selegiline co-administration (PSS).On evaluation in 49 hours PSS the dog presenting laterally recumbent with inability to hold the head up, limb movement, responsive to auditory stimuli and perception of smell(mGCS score 11). In the 50-hours PSS the dog presented sternal recumbence with ability to hold the head up. In this moment, the nasogastric tube was removed and the dog starting ingesting water and wet food gradually and limitedly on his own. The urinary catheter was removed in 51-hours PSS owing to urinary output has remained within reference values. The 53-hours PSS, the dog urinated in-stream confirming control of the urinary sphincter, and started walk in circles and incoordenated (mGCS score 16).

The dog showed gradually and spontaneously recovery during the hospitalization. In the 89-hours PSS, the dog presented only episodes of paresis and a normal level of consciousness. On the next day (109-hours PSS), the dog presented complete neurological recovery and it was suggested a new clinical evaluation to investigate the tremor and incoordination episode. However, the owner did not return to the hospital with the dog. Therefore, determining the cause of this episode was not possible. In recent telephone contact, the owner informed that the dog did not present more episodes of incoordination and tremors, and died 1.5 years post SS of unknown cause.

An old dog with severe SS induced by sertraline (SSRis) and selegiline (MAOis) presented gradually and spontaneously recovery, without specific treatment. The presentation of the severe clinical signs such as coma could lead the dog to die as already reported in humans SS (Boyer and Shannon, 2005; Dunkley et al., 2003; Mohammad-Zadeh et al., 2008;Thomas et al., 2012). SS associated with serotoninergic medications co-administration is uncommon in dogs and the most cases have been associated with accidental overdose of serotoninergic medications such as SSRis (Mohammad-Zadeh et al., 2008; Thomas et al., 2012). Altoug there is limited information of SS induced by sertraline and selegiline in dogs, the clinical signs already reported in others animals SS (Chang et al., 2014;Fitzgerald and Bronstein, 2013; Gwaltney-Brant et al., 2000; Indrawiralawan and McAlees, 2014; Ortolan et al., 2018; Thomas et al., 2012). Specific criteria based in the signs were development to identify this syndrome in human medicine, however these criteria are not established to veterinary (Dunkley et al., 2003; Radomski et al., 2000; Sternbach, 1991).

The clinical manifestation was attributed to serotonin toxicity caused by excess of serotonin owing the sertraline and selegiline co-administration (Foong et al., 2018; Francescangeli, et al. 2019; Ibister et al. 2005; Baldo, 2018, Volpi-Abadie et al. 2013). The excess of serotonin also resulted in release of noradrenaline, dopamine, and glutamate in the anterior hypothalamus (Isbster and Buckley, 2005; Shioda et al., 2004; De Souza et al., 1986). Thus, many other pathways that involving theses neurotransmitters may have been recruited lead to several clinical signs relationship to hyperactivity and hypo activity (Ibster and Buckley, 2005; Guyton, 2019). Moreover, the clinical signs of hyperactivity (agitated, hypersalivation, vocalization) one-hour PSS, hypo activity (coma, laterally recumbent) and findings in clinical evaluation (dehydration, tachycardia, normothermia) are consistent with previous reports of SS in small animals (Chang et al., 2014; Fitzgerald and Bronstein, 2013; Gwaltney-Brant et al., 2000; Indrawiralawan and McAlees, 2014; Ortolan et al., 2018; Thomas et al., 2012).

Selegiline is an irreversible selective MAO-B inhibitor with potential for induce the SS by overdose or combination with others serotoninergic medications such as SRRis (Aboukarr and Giudice, 2018; Baldo, 2018). However, the combination of SSRI and MAOi-B inhibitor (selegilina) is well tolerated in humans, provided that their recommended doses are not exceeded and the SSRI dose is kept at the lower end of the therapeutic range (Abouark and Giudice, 2018). In this case, the doses of sertraline and selegiline given were within the prescribed range (Viana, 2019) witch lead to increase of serotonin and consequently to the SS (Ibister eat al. 2005, Foong et al., 2018; Magyar et al. 1967). Possibly, the sertraline (SSRis) resulted in inhibition of serotonin uptake (Fitzgerald et al. 2013) and Cytochrome P450

Microsomal Oxidases (Francescangeli, et al. 2019), and the selegiline in inhibitions of the serotonin metabolism (Ibister et al. 2005, Foong et al., 2018; Magyar et al. 1967).

The SS in dogs frequently is resolved between 24 and 72-hours with discontinuation of serotonergic medications and institution of supportive care (Mohammad-Zadeh et al., 2008; Thomas et al., 2012).In this case, the prolonged clinical signs can be justified by a possible longer half-life owing interaction of sertraline and selegiline. The delayed institution of fluid therapy in the patient may have decreased the rate of sertraline and selegiline absorption slowed the elimination of these drugs (Murdoch and McTavish, 1992; Schatzberg and Nemeroff, 2017). Moreover, pharmacokinetic drug interactions are also implicated through the cytochrome P450 pathway, a pathway that sertraline inhibits and the selegiline metabolism is dependent (Mitchell, 1997; Scotton et al, 2019; Yoshida et al., 1986). This interaction lead to potentially toxic levels of serotonergic drugs and may be a vicious cycle of progressive SSRI accumulation (Francescangeli, et al., 2019).

The drugs discontinuation, fluid therapy and intensive monitoring were fundamental to the patient recovery (Asusta, et al. 2019; Jurek, et al., 2019; Rusyniak, 2018). Fluid therapy replaced the hydration and facilitated the excretion of drugs, mainly selegiline that has renal excretion (Schatzberg and Nemeroff, 2017) different from sertraline that has only 0.2% excreted in the urine (Murdoch and McTavish, 1992). Cyproheptadine drug (5-HT2 receptor antagonist) could have been used as antidotes (Indrawirawan, 2014; Mohammad-Zadeh et al., 2008; Pugh, 2013). However, this drug was not administrated due the interactions and incompatibility with the sertraline (Viana, 2019).

The first episode of tremor and incoordination reported for the owner was not evaluated. A possible diagnosis is epileptic seizures, however is not possible to confirm only with owner report (Dewey; Costa, 2017; Carneiro et al., 2017). In addition, is necessary related that the antidepressants not correspond to the treatment of epilepsy or epileptic seizure

(Charalambous et al., 2014; Waston et al., 2018). However, in cases of epilepsy associated with anxiety disorders, sertraline can be included in the treatment (Waston et al., 2018).

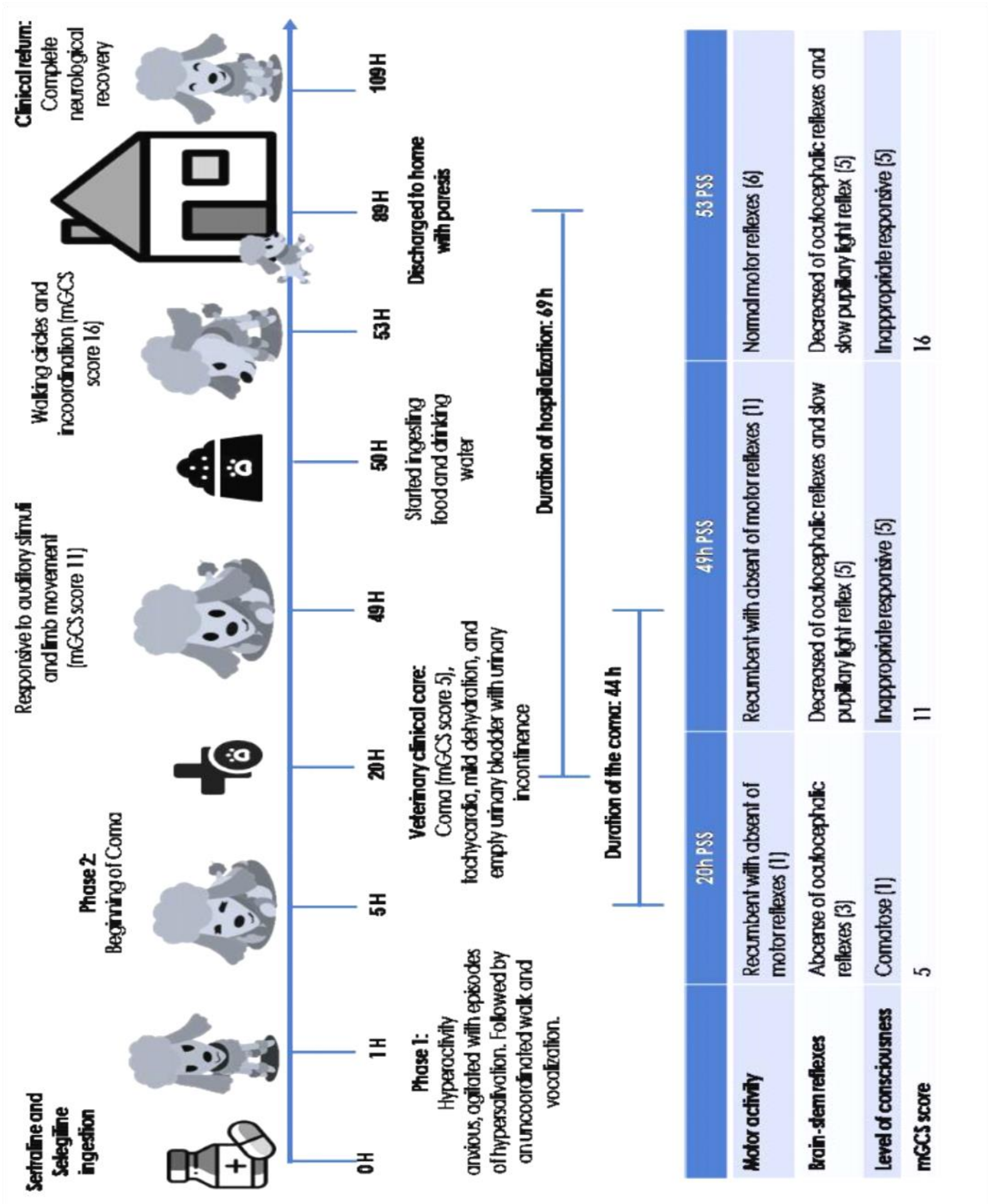
This report showed that the SS may occur in dogs post combined ingestionof sertraline and selegiline and consequently cause severe clinical signs such as coma. The prolonged clinical signs description from the moment of drug ingestion to complete recovery could assist in the identification of new cases. Furthermore, suggest further investigations of dogs SS and the establishing diagnostic criteria.

Table 1 – Hematology and serum biochemistry of a dog with severe SS

Parameter	Values	Reference Interval
Erythrocytes ($\times10^6$/µL)	7.5	5.5–8.5
Hemoglobin (g/dL)	13.8	12–18
Hematocrit (%)	38.0	37–50
Platelets ($\times10^3$/µL)	421	200–500
Leucocytes ($\times10^3$/µL)	14.4	6–17
Neutrophil (/µL)	7.8	3–11.5
Eosinophil (/µL)	1.1	0.1–1.25
Monocytes (/µL)	0.9	0.15–1.35
Lymphocytes (/µL)	2.1	1–4.8
Plasma proteins (g/dL)	7.0	5.5–7.5
Fibrinogen (g/dL)	0.3	0.1–0.5
Total Protein (g/dL)	6.1	5.4–7.1
Albumin (g/dL)	3.0	2.6–3.3
Globulin (g/dL)	3.2	2.5–4.1
Creatinine (mg/dL)	0.8	0.5–1.5
Urea (mg/dL)	27.0	20–60
ALT (UI/L)	98	21–102
ALP (UI/L)	110	20–156
AST (UI/L)	33.0	23–66

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase.

Figure 1 - Clinical course timeline of the case and the Small Animal Modified Glasgow Coma Score.



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BIOETHICS AND BIOSECURITY COMMITTEE APPROVAL

The report was performed with an animal routinely treated by the HUVET-UNIPAMPA and was not part of any project; it was simply a clinical case report.

DECLARATION OF CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

The authors contributed equally to the manuscript.

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MANUSCRITO 3

O presente manuscrito está no formatado e de acordo com as normas da Revista Ciência Rural, o qual será submetido para publicação.

Profile and quantification of antibiotic prescriptions in small animal surgery (2015-2021 retrospective)

Profile and quantification of antibiotic prescriptions in small animal surgery (2015-2021 retrospective)

Perfil e quantificação das prescrições de antibióticos em cirurgias de pequenos animais (retrospectivo 2015-2019)

ABSTRACT

Excessive and irrational prescribing of antibiotics is a common practice in the small animal surgical clinic and contributes to the unique global health problem that is antimicrobial resistance (AMR). Animals such as dogs and cats can be facilitators of the transmission of resistant bacteria, so the study of the use of antibiotics in this population is necessary to discuss and plan actions to reduce AMR. Thus, the objective of this research is to provide results of the use of antimicrobials in the surgeries of dogs and cats in a university veterinary hospital. To carry out this retrospective study, 1227 medical records of the small animal surgical clinic were identified and reviewed and quantitative analysis of the antibiotics used in 1053 dogs and cats undergoing surgical procedures was performed. An amount of 2.73kg of antibiotics, 16107 administrations, and 2302 antibiotic prescriptions in five years were identified. The most used antibiotics were Cephalosporins (59.1%), Penicillin (15.9%), and Ansamycin (7.4%). An important result of this study was the identification of the increase in the prescription of critically important antibiotics by the World Health Organization in the last two years. Therefore, it is suggested that control measures such as continuous monitoring of the antimicrobials use in small animals should be implemented so that these rates do not increase further.

Keywords: Surgery; Antimicrobial Resistance (RAM); dog and cat; Critically Important Antibiotics.

RESUMO

A prescrição excessiva e irracional de antibióticos é uma prática comum na clínica cirúrgica de pequenos animais e contribui para o problema grave de saúde única mundial que é a resistência aos antimicrobianos (RAM). Animais como cães e gatos podem ser facilitadores da transmissão de bactérias resistentes, portanto o estudo do uso de antibióticos nesta população se faz necessário para discutir e planejar ações para redução da RAM. Assim, o objetivo desta pesquisa é fornecer resultados do uso de antimicrobianos em cirurgias de cães e gatos em um hospital veterinário universitário. Para a realização deste estudo retrospectivo, foram identificados e revisados 1227 prontuários da clínica cirúrgica de pequenos animais e realizada uma análise quantitativa dos antibióticos utilizados em 1053 para cães e gatos submetidos a procedimentos cirúrgicos. Foram identificados um montante de 2,73kg de antibióticos, 16107 administrações e 2302 prescrições de antibióticos em cinco anos. Os antibióticos mais utilizados foram Cefalosporinas (59,1%), Penicilina (15,9%) e Ansamicina (7,4%). Um resultado importante deste estudo foi à identificação do aumento da prescrição de antibióticos criticamente importantes da Organização Mundial da Saúde nos últimos 2 anos. Portanto, sugere-se que medidas de controle como o monitoramento contínuo do uso de antimicrobianos em pequenos animais sejam implementadas para que esses índices não aumentem ainda mais.

Palavras-chave: cirurgia; resistência antimicrobiana (RAM); cão e gato; antibióticos criticamente importantes.

INTRODUCTION

The indiscriminate use of antibiotics has favored antimicrobial resistance (AMR), which makes it difficult to treat infections, increasing costs and the risk of mortality (BROCHADO et al., 2018; HAKANENET et al., 2017; SCOTTISH, 2014; POMBA et al., 2017; HAY et al., 2018). AMR is a current worldwide unique health problem, so multiple health professionals must search alternatives to mitigate the AMR (DE-LAS-CASAS-CÁMARA et al., 2022; MCEWEN et al., 2018; SCHNEPF et al., 2021; UKUHOR, 2021). In this perspective, several researches relationship with the use of antibiotics in animals and humans are being carried out to design, provide and discuss actions to control AMR (DE-LAS-CASAS-CÁMARA et al., 2022; MULANI et al., 2021; GUARDABASSI et al., 2014; SCHNEPF et al., 2021; UKUHOR, 2021; WERNER et al., 2018).

An important aspect to highlight is the favor for the transfer of resistant bacteria between humans and company animals such as cats and dogs owing to the increasingly close contact (CAIM, 2013; GUARDABASSI et al., 2014; HUGHES et al., 2012; PRESCOTT 2008; REGULA 2009; SCHNEPF et al., 2021). A growing concern is the daily and increasing use of antibiotics identical to those used in human medicine in clinical and surgery routine of small animals to treat and prevent infections (FOSSUM, et al., 2021; GBERINDYER et al., 2017; KIFLE & TADESSE et al., 2014; NWIYI, 2014; MOUICHE et al., 2021; SCHNEPF et al., 2021). For this reason, monitoring the use of antibiotics in these animals is essential for adopting measures to mitigate AMR (SINGLETON et al., 2019; SCHNEPF et al., 2021 WERNER et al., 2028). However, monitoring the use of antibiotics in small animals in some countries such as Brazil is still limited (HATA et al., 2016; ITAI et al., 2017; KHAN et al., 2017).

Particularly with regard to preserving the possibilities of antibiotic use, the World

Health Organization has established a classification for antibiotics of critical importance (CIA) for human health (WHO, 2018). In addition, to preservation of the possibilities of using antibiotics, the documentation of the use of antibiotics must be considered a necessity (SCHNEPF et al., 2021). Consequently, the quantification of antibiotic prescriptions in small animal surgery could contribute in the elaboration of alternatives to mitigate AMR (HARDEFELDT et al., 2017; MATEUS et al., 2011; MURPHY et al., 2012; PLEYDELL et al., 2012; SINGLETON et al., 2012; WERNER et al., 2018). Therefore, the aim of this study is to identify, quantify and evaluate the use of antibiotics in small animal surgical procedures.

MATERIALS AND METHODS

Data collection

The records of surgical procedures in small animals from a University Veterinary Hospital were reviewed in order to identify the use of antibiotics in small animal surgery between January 2015 and December 2021. Records with partial information or without information of the antibiotic used in the surgical procedure were excluded from this study.

Data collection included information about the antibiotic (dose, frequency, route, days and date of administration, culture and antibiogram), surgical procedures (surgical technique), and general animal data (race, sex, age, and weight). The collected data were distributed according to the antibiotics used in surgical procedures. First, the information was grouped according to the surgical procedures that used or did not use antibiotics. Afterward, to determinate the profile and quantify antibiotics used in small animal surgery, the data were classified according to the year of antibiotic use and organ system according to surgical procedures realized. In addition, antibiotics were grouped according to classification for antibiotics of critical importance to verify the CIA used (WHO, 2018).

Quantify and profile of antibiotics

The amount in kg of antibiotics used annually was determined by calculating the amount (adapted from Schenepf et al., 2021; Werner et al., 2018). The number of antibiotic administrations performed in the hospital or prescribed for home use was verified by calculating the number of administrations (adapted from Schenepf et al., 2021; Werner et al., 2018). To determine the profile of antibiotic use, the number of antibiotic prescriptions was calculated annually and for each organ system (adapted from Werner et al., 2018). In addition, was determined the diversity of antibiotic prescriptions (variety and frequency of antibiotic prescription) according to the organic system (Singleton et al., 2018). To analyze of data a descriptive statistical was performed.

RESULTS

In this study, 1227 records of surgical procedures in dogs and cats were identified and analyzed. However, only 1053 forms met the inclusion criteria. Among these, 920 files referred to surgical procedures performed on dogs (642 females [70.08%] and 278 [29.82%] males) and 133 in cats (88 females [64.29%] and 45 males [54.29%]). As for breed, 471 dogs (50.32%) and 18 cats (12.86%) were pure breeds, and 465 dogs (49.68%) and 122 cats (87.14%) were of undefined breeds. Mean age and weight for dogs were respectively 11.4 years (3 months – 16 years) and 4.8 kg (0.7 – 52 kg), and for cats, 11.4 years (3 months – 16 years) and 3.3 kg (1.1 – 7 kg). Information of the antibiotic use in surgery procedures in years of 2020 and 2021 was not found. During this period the hospital was closed owing to the Covid-19 pandemic.

The total amount of 2.73 kg of antibiotics was identified in this study (Table-1). Regarding the period of antibiotic use, the highest amount identified comprises the year 2016 for both dogs (0.083kg) and cats (0.019kg). The cephalosporins (79.2%) followed by penicillins (13.2%) were identified with the highest amount for dogs and cats. The amount in kg and percentage for the antibiotic group and the active ingredient are documented in table 1.

Overall, 13 groups of antibiotics were administered and 25 active ingredients were used for dogs while for cats only 13. The administrations number of antibiotic identified was of 16,101 (Table-2). The oral route (45%) was the most used for the administration of antibiotics, followed by the topical route (28%) and the injectable route (27%). The highest result of the number of administrations identified was cephalosporins (42.9%), followed by ansamycins (17.9%) and penicillins (14.2%). Regarding the number of administrations of antibiotics with CAOMS, the highly important group (48.68%) was identified with the highest number of administrations, followed by highly priority (34.70 %), highest priority (9.19%) and important (7.43%). The number of antibiotic administrations for each antibiotic group and active ingredient are documented in number and percentage in Table 2. Moreover, an important aspect to highlight in table 2 is the increase in the number of administrations of critically important antibiotics in the last 2 years.

The antibiotics identified as the most prescribed were cephalosporins (59.1%), penicillins (15.9%) and ansamycin (7.4%) respectively. First-generation cephalosporins were identified with the highest number of prescriptions (58.82%), followed by ampicillin (9.04%), and topical rifamycin (7.30%). The number of antibiotic prescription for each antibiotic group and active ingredient are documented annually in number and percentage in Table 3. The numbers of antibiotic prescription for each organic system group are documented in number and percentage in Table 4. According with organic system group, the antibiotics of highest priority were more prescription for surgery procedures of digestive system. Furthermore, more an important aspect to highlight is the increase in the number of prescription of critically important antibiotics in the last 2 years (Figure- 1).

The PD closest to 0 was from the ophthalmic system (0.19) and the reproductive system 1A was identified as the closest to 1 (0.40). The number of surgery procedures according with the organic system, use of antibiotic, frequency of infection and PD are documented in Table 5. Only 30 (2.8%) surgical procedures (elective surgical of the reproductive system) were performed without the use of antibiotics. Of these, 11 had surgical wound infection, and the surgical wound infection comprised a total of 8%.

Other important aspect to highlight is the identification of no more than 3 culture and antibiogram examination. In these examination were identified growth for coagulase positive *Staphylococcus* with resistance to Ampicillin/Sulbactam Amoxicillin/Clavulanic Acid, Azithromycin, Cephalothin, Cefotaxime, Cefazolin, Cefoxitin, Ciprofloxacin, Clindamycin, Erythromycin, Gentamycin, Levofloxacin, Norfloxacin, Rifampicin; and, Coagulase-negative *Staphylococcus* with resistance to Sulfametazol/Trimethoprim and Penicillin.

DISCUSSION

In this retrospective study, we identified the profile of antibiotics use in small animals surgery in the teaching veterinary hospital through of quantify the administration and prescription of antibiotics. Although the results of this study are not representative of the use of antibiotics for the whole of Brazil, they can serve as a basis for discussion of the rational use of antibiotics in small animal surgery (HARDEFELDT et al., 2017; MURPHY et al., 2012; SINGLETON et al., 2012; WERNER et al., 2018). In addition, it encourages the development of mechanisms to monitor the acquisition of veterinary antibiotics as occurs in some countries (MCEWEN et al., 2018; SCHNEPF et al., 2021).

Small animals live in closer and closer contact with humans, being considered members of the family. However, these animals are also potential vectors for the dissemination of resistant bacteria (CHOMEL et al., 2011; FEDORKA-CRAY, 2017; GUARDABASSI ET AL., 2004; LLOYD, 2007; MCEWEN; POMBA et al., 2017; ZHANG et al. ., 2016). Therefore, this very close contact associated with the indiscriminate use of antibiotics can further aggravate the unique global health problem that is AMR (DE-LAS-CASAS-CÁMARA et al., 2022; MULANI et al., 2021; SCHNEPF et al., 2021; UKUHOR, 2021). Thus, quantify and identify how the antibiotics used in these animals can contribute to research and alternatives to mitigate AMR (HARDEFELDT et al., 2017; MATEUS et al., 2011; MURPHY et al., 2012; SINGLETON et al., 2012; WERNER et al., 2018).

There are currently a few publications with several results relationship to antibiotic use in small animals (HARDEFELDT et al., 2018; MOUICHE et al., 2021; SCHNEPF et al., 2021). In this study, the most commonly antimicrobials used during the study period were cephalosporins, followed of penicillin and ansamycin. The penicillin already was identify as the most commonly antibiotic used in studies realized in Nigeria, Ethiopa and Germany (KIFLE & TADESSE et al., 2014; GBERINDYER et al., 2017; NWIYI, 2014; MOUICHE et al., 2021; SCHNEPF et al., 2021) and the cephalosporin were documented in other studies (HUR et al., 2021; SINGLETON et al., 2017). The differences may be explained by the absence of a common sense for antibiotic prescriptions, reduced cost of antibiotic between countries, treatment for differential disease (HARDEFELDT et al., 2017; MOUICHE et al., 2021).

Although this study showed a slight decrease in the proportion of drug administration in compactions with Australia, Italy, United Kingdom, and Germany (ESCHER et al., 2011; HUR et al., 2021; SINGLETON et al., 2017; SCHNEPF et al., 2021), is necessary emphasize that administration number of antibiotics of critical importance presented an increase in the last 3 year. The factors that contributed to this increase was not possible to determinate, however it is assumed that it is related to the significant number of cases of antimicrobial resistance in small animals or even with the veterinarian negligence in prescribing these drugs (AWOSILE et al., 2018; PANTOSTI et al., 2012; QEKWANA et al., 2017). Previous research has associated the high number of critically important antibiotics used with the large number of critical cases and emergencies within the researched population (WERNER et al., 2018; SINGLETON et al., 2012). However, this is not a reality of this study, because elective surgical procedures represent the largest number in this study.

In particular, there is great worldwide concern when the administration of 3rd generation cephalosporins, macrolides and quinolones (MCEWEN; FEDORKA-CRAY, 2017; POMBA et al., 2017; ZHANG et al., 2016; SCHEPNEF et al., 2021; WHO, 2018). These drugs are considered of critical importance and should ideally be prioritized for human use (WHO, 2018; SCHEPNEF et al., 2021). In this study was observed increase in the use of macrolides and quinolones, and although the 3rd generation cephalosporins were rarely prescribed, studies have already shown that 3rd generation cephalosporins have been commonly prescribed for cats (SINGLETON et al. 2017; BUCKLAND et al., 2016; BURCKE et al., 2017). Thus, these results corroborate that control measures for the acquisition and prescription antibiotics to small animals should be instituted to the control the AMR (WERNER et al., 2018).

The antibiotics of critical importance represented 43.2% of the total antibiotics used in this study. The irrational use of this antibiotics results in increase of AMR and consequently in antimicrobial treatment failure for animals and humans (POMBA et al., 2017; BROCHADO et al., 2018; HAY et al., 2018). The AMR and the risk of transmission of resistant bacteria between species has resulted in the banning of certain antibiotics for small animals in some countries, which reduces the possibility of treatment for diseases (MCEWEN; FEDORKA-CRAY, 2017; POMBA et al., 2017; ZHANG et al., 2016). The lack of control of AMR can result in further reductions of antibiotics for veterinary use, which associated with resistant bacteria will possibly make the treatment of serious infections impossible (BROCHADO et al., 2018; HAY et al., 2018; POMBA et al., 2017).

An important aspect to highlight is the expressive use of topic rifamicin (ansamycin). The ansamycin is considerate an antibiotics of critical importance and utilized to treat mycobacteria, including tuberculosis in humans (SURETTE et al., 2021; WHO, 208). The wide use of this drug can result in bacterial resistance, reducing the treatment options for infections caused by mycobacterium (WHO, 208). For this reason, the use of ansamycin must be decreased. In addition, there is no evidence in the literature to support routine use of topical or local antimicrobial agents on surgical wounds (BENNET-GUERRO et al., 2010; BAND et al., 2016). However, in cases where the use of topical antimicrobials is indicated for wound treatment, the use of antiseptics is suggested (BOUCHER et al., 2018; ECHOLS et al., 2015; FOSSUM, 2021), although these can also increase the risk of resistance to some antibiotics (KAMPF, 2016).

The first-generation cephalosporins such as in others researches were the most commonly used antibiotics (ESCHER et al. 2011; SINGLETON et al. 2012; SCHMITT et al. 2019). The drug is utilized in surgical prophylaxis, it is recommended to avoid its use to treat clinical infections in hospitals, in order to reduce bacteria resistant to this drug in surgical patients (HOWE; BOOTHE, 2015). Metronidazole compared to other studies was not frequently prescribed (SINGLETON et al. 2017; HUR et al., 2020) which can be justified by the fact that the drug can cause serious side effects in dogs and cats (SINGLETON et al. 2020; WAYNE et al., 2011).

Develop programs for rational antibiotic prescribing that is accessible for veterinary surgeons is of paramount importance to assist researchers and AMR control. A control measure that can help control ARM is monitoring the prescription diversity (SINGLETON et al. 2012). In human hospitals that the monitoring prescription diversity were implemented, revealed a decrease in the prevalence of resistant bacteria associated with increase in the number of prescription diversity (SANDIUMENGE et al., 2006; TAKESUE et al., 2010). In this study was not possible determinate the relation with PD and AMR owing the decrease number of antibiogram and culture examination.

The 8% of surgical wound infections corroborates with studies that demonstrate that infections can affect from 0.5% to 18.1% of surgical procedures in small animals (WEESE, 2008). Overall, surgical infections are often associated with failure of the basic surgical asepsis principles (BOUCHER et al., 2018; MARCHI et al., 2018) and may be also associated with AMR (FOSSUM et al., 2021; MULANI et al., 2021). Therefore, suggest future investigation bacterial resistant in the hospital associate to control of antibiotics prescription.

CONCLUSION

In this study, we showed an increase of critically antibiotic prescription in the last two years. In general, the results of this researcher could be used as a baseline for future study of profile of antibiotic use in Brazil. Furthermore, suggest prospective research will be compared with this baseline and control measures such as continuous monitoring of antimicrobial use in small animals are implemented.

TABLE 1 - Amount of antimicrobial active ingredients used in the surgery of dogs and cats in 2015 at 2019 in a teaching Hospital.

WHO classification	Antimicrobial group and Active ingredient	2015	Total documented (kg) 2016	2017	2018	2019	Total	(%)
CIA*–highest priority	**Cephalosporins (3rd generation)**	**0**	**0,0136**	**0,0124**	**0,0034**	**0,0117**	**0,0411**	**1,48%**
	Cefovecin	0	0	0,0007	0,0002	0	0,0009	**0,03%**
	Ceftiofur	0	0	0,0002	0	0,0034	0,0036	**0,13%**
	Ceftriaxone	0	0,0136	0,0115	0,0032	0,0083	0,0366	**1,32%**
	Quinolones	**0,0411**	**0,028435**	**0,0124**	**0,0034**	**0,0117**	**0,097035**	**3,50%**
	Enrofloxacin	0,0009	0,000324 9	0,0007	0,0002	0	0,002124 9	**0,08%**
	Levofloxacin	0,0036	0,001299 5	0,0002	0	0,0034	0,008499 5	**0,31%**
	Macrolides	**0,0002**	**0,0004**	**0,0006**	**0,0004**	**0,0002**	**0,0018**	**0,06%**
	Spiramycin	0,0002	0,0004	0,0006	0,0004	0,0002	0,0018	**0,06%**
	Total	**0,0413**	**0,042435**	**0,0254**	**0,0072**	**0,0236**	**0,139935**	**5,05%**
CIA*–high priority	**Aminoglycosides**	**0**	**0**	**0**	**0,0044**	**0**	**0,0044**	**0,16%**
	Amikacina	0	0	0	0,0044	0	0,0044	**0,16%**
	Penicilin	**0,0506**	**0,0593**	**0,0494**	**0,1135**	**0,0812**	**0,354**	**12,78%**
	Amoxicillin	0,0289	0,0535	0,0358	0,0796	0,0499	0,2477	**8,94%**
	Ampicillin	0,0217	0,0058	0,0136	0,0339	0,0313	0,1063	**3,84%**
	Ansamycins	**0**	**0**	**0**	**0**	**0,0141**	0,0141	**0,51%**
	Rifampicin	0	0	0	0	0,0141	0,0141	**0,51%**
	Total	**0,0506**	**0,0593**	**0,0494**	**0,1179**	**0,0953**	**0,3725**	**13,45%**
Highly important	**Penicilin**	**0,0002**	**0,0002**	**0,0001**	**0,0006**	**0,0053**	**0,0064**	**0,23%**
	Benzilpeniciline	0,0002	0,0002	0,0001	0,0006	0,0053	0,0064	**0,23%**
	Sulfonamides	**0,0002**	**0,002**	**0,001**	**0,0004**	**0,0008**	**0,0044**	**0,16%**
	Sulfadiazine	0,0002	0,002	0,001	0,0004	0,0008	0,0044	**0,16%**
	Cephalosporins (1rd generation)	**0,3522**	**0,7231**	**0,4928**	**0,3735**	**0,182**	**2,1236**	**76,65%**
	Cefalexin	0,2892	0,3837	0,2712	0,2346	0,1435	1,3222	**47,73%**
	Cefazolin	0	0	0	0,0017	0	0,0017	**0,06%**
	Cefalotin	0,063	0,3394	0,2216	0,1372	0,0385	0,7997	**28,87%**
	Tetracyclines	**0**	**0**	**0,0065**	**0,0022**	**0**	**0,0086**	**0,31%**
	Doxycycline	0	0	0,0065	0,0022	0	0,0086	**0,31%**
	Total	**0,3526**	**0,7253**	**0,5004**	**0,3767**	**0,1881**	**2,1431**	**77,36%**
Important	**Trimethopim**	**0**	**0,0018**	**0**	**0,0004**	**0,0008**	0,0030	**0,11%**
	Trimethoprim	0	0,0003	0	0	0,0001	0,0004	**0,01%**
	Nitromidazole	**0,0098**	**0,0365**	**0,033**	**0,0195**	**0,0131**	0,1119	**4,04%**
	Metronidazole	0,0098	0,0365	0,033	0,0195	0,0131	0,1119	**4,04%**
	Total	**0,0098**	**0,0383**	**0,033**	**0,0199**	**0,0139**	**0,1149**	**4,15%**
	Total	0,4543	0,865335	0,6082	0,5217	0,3209	2,7704	**100,00%**

*CIA: critically important antibiotics.2.66 kg was documented for dogs and 0.063 kg for cats.

TABLE 2 - Antimicrobial active ingredients administered in the surgery of dogs and cats in 2015 at 2019 in a teaching Hospital.

WHO classification	Antimicrobial group and Active ingredient	Total documented						
		2015	2016	2017	2018	2019	Total	(%)
CIA*–highest priority	**Cephalosporins (3rd generation)**	**0**	**56**	**46**	**34**	**50**	**186**	**1,15%**
	Cefovecin	0	0	2	1	0	3	**0,02%**
	Ceftiofur	0	0	8	0	22	30	**0,19%**
	Ceftriaxone	0	56	36	33	28	153	**0,95%**
	Quinolones	**140**	**218**	**70**	**154**	**430**	**1012**	**6,28%**
	Enrofloxacin	93	218	59	134	286	790	**4,90%**
	Ciprofloxacin**	47	0	0	0	144	191	**1,19%**
	Levofloxacin	0	0	11	20	0	31	**0,19%**
	Macrolides	**46**	**79**	**56**	**57**	**45**	**283**	**1,76%**
	Spiramycin	46	79	26	57	45	253	**1,57%**
	Total	**186**	**353**	**172**	**245**	**525**	**1481**	**9,19%**
CIA*–high priority	**Aminoglycosides**	**119**	**30**	**72**	**54**	**174**	**449**	**2,79%**
	Gentamicin**	0	0	0	20	0	20	**0,12%**
	Neomicin**	0	0	14	0	106	120	**0,75%**
	Tobramicin**	15	0	28	6	14	63	**0,39%**
	Amikacina	104	30	30	28	54	246	**1,53%**
	Penicilin	**335**	**512**	**275**	**476**	**653**	**2251**	**13,98%**
	Amoxicillin	40	161	26	48	175	450	**2,79%**
	Amoxicillin + acid. clavulanic	172	273	156	303	272	1176	**7,30%**
	Ampicillin	123	78	93	125	206	625	**3,88%**
	Ansamycins	**311**	**865**	**941**	**558**	**214**	**2889**	**17,94%**
	Rifamicin**	311	865	941	558	154	2829	**17,56%**
	Rifampicin	0	28	0	0	60	88	**0,55%**
	Total	**765**	**1407**	**1288**	**1088**	**1041**	**5589**	**34,70%**
Highly important	**Penicilin**	**35**	**1**	**6**	**2**	**23**	**67**	**0,42%**
	Benzilpeniciline	35	1	6	2	23	**67**	**0,42%**
	Sulfonamides	**4**	**34**	**8**	**134**	**310**	**490**	**3,04%**
	Sulfadiazine	4	34	8	4	20	**70**	**0,43%**
	Sulfadiazine**	0	0	0	130	289	**419**	**2,60%**
	Cephalosporins (1rd generation)	**1114**	**2236**	**1569**	**1123**	**683**	**6725**	**41,75%**
	Cefalexin	932	1230	830	661	587	**4240**	**26,32%**
	Cefazolin	0	0	0	2	0	**2**	**0,01%**
	Cefalotin	182	1006	739	460	96	**2483**	**15,42%**
	Tetracyclines	**0**	**0**	**32**	**39**	**0**	**71**	**0,44%**
	Doxycycline	0	0	32	39	0	**71**	**0,44%**
	Amphenicol	**62**	**34**	**93**	**40**	**259**	**488**	**3,03%**
	Chloramphenicol**	62	34	93	40	259	**488**	**3,03%**
	Total	**1215**	**2305**	**1708**	**1338**	**1275**	**7841**	**48,68%**
Important	**Trimethopim**	**0**	**32**	**0**	**4**	**20**	**56**	**0,35%**

Trimethoprim	0	12	0	4	20	**36**	**0,22%**
Nitromidazole	**144**	**329**	**194**	**212**	**195**	**1074**	**6,67%**
Metronidazole	144	329	194	212	195	**1074**	**6,67%**
Nitrofuran	**38**	**28**	**0**	**0**	**0**	**66**	**0,41%**
Nitrofuran**	38	28	0	0	0	**66**	**0,41%**
Total	**182**	**389**	**194**	**216**	**215**	**1196**	**7,43%**
Total	**2348**	**4454**	**3362**	**2887**	**3056**	**16107**	**100,00%**

*CIA: critically important antibiotics; * Topical antibiotic.

TABLE 3 - Antimicrobial active ingredients prescription in the surgery of dogs and cats in 2015 at 2019 in a teaching Hospital.

WHO classification	Antimicrobial group and Active ingredient	Total documented						
		2015	2016	2017	2018	2019	Total	(%)
CIA*– highest priority	**Cephalosporins (3rd generation)**	**0**	**3**	**6**	**9**	**15**	**33**	**1,43%**
	Cefovecin	0	0	1	1	0	2	**0,09%**
	Ceftiofur	0	0	1	0	4	5	**0,22%**
	Ceftriaxone	0	3	4	8	11	26	**1,13%**
	Quinolones	**7**	**19**	**13**	**18**	**49**	**106**	**4,60%**
	Enrofloxacin	7	19	10	15	49	100	**4,34%**
	Ciprofloxacin**	0	0	2	1	0	3	**0,13%**
	Levofloxacin	0	0	1	2	0	3	**0,13%**
	Macrolides	**9**	**18**	**3**	**14**	**9**	**53**	**2,30%**
	Spiramycin	9	18	3	14	9	53	**2,30%**
	Total	**16**	**40**	**22**	**41**	**73**	**192**	**8,34%**
CIA*–high priority	**Aminoglycosides**	**2**	**1**	**4**	**5**	**5**	**17**	**0,74%**
	Amikacina	0	0	0	3	0	3	**0,13%**
	Gentamicin**	0	0	2	0	4	6	**0,26%**
	Neomicin**	1	0	1	1	1	4	**0,17%**
	Tobramicin**	1	1	1	1	0	4	**0,17%**
	Penicilin	**19**	**46**	**34**	**96**	**169**	**364**	**15,81%**
	Amoxicillin	2	19	11	5	14	51	**2,22%**
	Amoxicillin + acid. clavulanic	4	20	12	35	23	94	**4,08%**
	Ampicillin	13	7	11	56	132	219	**9,51%**
	Ansamycins	**26**	**70**	**49**	**49**	**8**	**202**	**8,77%**
	Rifamicin**	26	70	49	49	7	201	**8,73%**
	Rifampicin	0	0	0	0	1	1	**0,04%**
	Total	**47**	**117**	**87**	**150**	**182**	**583**	**25,33%**
Highly important	**Penicilin**	**4**	**2**	**2**	**1**	**23**	**32**	**1,39%**
	Benzilpeniciline	4	2	2	1	23	32	**1,39%**
	Sulfonamides	**2**	**4**	**3**	**15**	**11**	**35**	**1,52%**
	Sulfadiazine	2	4	2	1	0	9	**0,39%**
	Sulfadiazine**	0	0	1	14	11	26	**1,13%**
	Cephalosporins (1rd generation)	**191**	**408**	**326**	**259**	**87**	**1271**	**55,21%**
	Cefalexin	37	74	53	44	31	239	**10,38%**
	Cefazolin	0	0	0	1	0	1	**0,04%**
	Cefalotin	154	334	273	214	56	1031	**44,79%**
	Tetracyclines	**0**	**0**	**1**	**6**	**0**	**7**	**0,30%**
	Doxycycline	0	0	1	6	0	7	**0,30%**
	Amphenicol	**4**	**3**	**7**	**1**	**2**	**17**	**0,74%**
	Chloramphenicol**	4	3	7	1	2	17	**0,74%**

	Total	**201**	**417**	**339**	**282**	**123**	**1362**	**59,17%**
Important	**Trimethopim**	**0**	**0**	**1**	**0**	**1**	**2**	**0,09%**
	Trimethoprim	0	1	0	1	0	2	**0,09%**
	Nitromidazole	**14**	**63**	**22**	**34**	**24**	**157**	**6,82%**
	Metronidazole	14	63	22	34	24	157	**6,82%**
	Nitrofuran	**5**	**1**	**0**	**0**	**0**	**6**	**0,26%**
	Nitrofuran**	5	1	0	0	0	6	**0,26%**
	Total	**19**	**64**	**23**	**34**	**25**	**165**	**7,17%**
	Total	**283**	**638**	**471**	**507**	**403**	**2302**	**100,00%**

*CIA: critically important antibiotics; **Topical antibiotic.

TABLE 4 - Antimicrobial active ingredients prescription in the surgery of dogs and cats according organic system.

WHO classification	Antimicrobial group and Active ingredient	R1A*	R1B*	Total documented DG*	ON*	UR*	TM*	OF*	RP*	LF*	Total	(%)
CIA*–highest priority	**Cephalosporins (3rd generation)**	**0**	**9**	**6**	**13**	**1**	**4**	**0**	**0**	**0**	**33**	**1,4%**
	Cefovecin	0	0	0	2	0	0	0	0	0	2	0,1%
	Ceftiofur	0	0	2	3	0	0	0	0	0	5	0,2%
	Ceftriaxone	0	9	4	8	1	4	0	0	0	26	1,1%
	Quinolones	**19**	**43**	**5**	**8**	**11**	**13**	**0**	**2**	**5**	**106**	**4,6%**
	Enrofloxacin	19	43	5	5	11	10	0	2	5	100	4,3%
	Ciprofloxacin**	0	0	0	0	0	3	0	0	0	3	0,1%
	Levofloxacin	0	0	0	3	0	0	0	0	0	3	0,1%
	Macrolides	**1**	**0**	**42**	**7**	**0**	**3**	**0**	**0**	**0**	**53**	**2,3%**
	Spiramycin	1	0	42	7	0	3	0	0	0	53	2,3%
	Total	**20**	**52**	**53**	**28**	**12**	**20**	**0**	**2**	**5**	**192**	**8,3%**
CIA*–high priority	**Aminoglycosides**	**0**	**0**	**0**	**3**	**0**	**10**	**4**	**0**	**0**	**17**	**0,7%**
	Amikacina	0	0	0	3	0	0	0	0	0	3	0,1%
	Gentamicin**	0	0	0	0	0	6	0	0	0	6	0,3%
	Neomicin**	0	0	0	0	0	4	0	0	0	4	0,2%
	Tobramicin**	0	0	0	0	0	0	4	0	0	4	0,2%
	Penicilin	**131**	**71**	**48**	**64**	**16**	**26**	**3**	**4**	**1**	**364**	**15,8 %**
	Amoxicillin	3	15	18	7	2	5	1	0	0	51	2,2%
	Amoxicillin + acid. clavulanic	6	13	19	38	8	5	1	4	0	94	4,1%
	Ampicillin	122	43	11	19	6	16	1	0	1	219	9,5%
	Ansamycins	**40**	**76**	**15**	**42**	**3**	**22**	**2**	**1**	**1**	**202**	**8,8%**
	Rifamicin**	40	76	15	42	3	21	2	1	1	201	8,7%
	Rifampicin	0	0	0	0	0	1	0	0	0	1	0,0%
	Total	**171**	**147**	**63**	**109**	**19**	**58**	**9**	**5**	**2**	**583**	**25,3 %**
Highly important	**Penicilin**	**21**	**5**	**1**	**2**	**0**	**3**	**0**	**0**	**0**	**32**	**1,4%**
	Benzilpeniciline	21	5	1	2	0	3	0	0	0	32	1,4%
	Sulfonamides	**6**	**16**	**4**	**1**	**2**	**6**	**0**	**0**	**0**	**35**	**1,5%**
	Sulfadiazine	0	5	4	0	0	0	0	0	0	9	0,4%
	Sulfadiazine**	6	11	0	1	2	6	0	0	0	26	1,1%
	Cephalosporins (1rd generation)	**407**	**337**	**52**	**286**	**30**	**120**	**19**	**14**	**6**	**1271**	**55,2 %**
	Cefalexin	23	97	11	65	6	31	2	2	2	239	10,4 %
	Cefazolin	0	1	0	0	0	0	0	0	0	1	0,0%
	Cefalotin	384	239	41	221	24	89	17	12	4	1031	44,8 %
	Tetracyclines	**0**	**0**	**0**	**0**	**0**	**0**	**7**	**0**	**0**	**7**	**0,3%**

	Doxycycline	0	0	0	0	0	0	7	0	0	7	0,3%
	Amphenicol	**1**	**7**	**0**	**2**	**0**	**2**	**5**	**0**	**0**	**17**	**0,7%**
	Chloramphenicol**	1	7	0	2	0	2	5	0	0	17	0,7%
	Total	**435**	**365**	**57**	**291**	**32**	**131**	**31**	**14**	**6**	**1362**	**59,2%**
Important	**Trimethopim**	**0**	**0**	**2**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**0,1%**
	Trimethoprim	0	0	2	0	0	0	0	0	0	2	0,1%
	Nitromidazole	**4**	**55**	**50**	**35**	**3**	**7**	**1**	**2**	**0**	**157**	**6,8%**
	Metronidazole	4	55	50	35	3	7	1	2	0	157	6,8%
	Nitrofuran	**1**	**2**	**1**	**2**	**0**	**0**	**0**	**0**	**0**	**6**	**0,3%**
	Nitrofuran**	1	2	1	2	0	0	0	0	0	6	0,3%
	Total	**5**	**57**	**53**	**37**	**3**	**7**	**1**	**2**	**0**	**165**	**7,2%**
	Total	**631**	**621**	**226**	**465**	**66**	**216**	**41**	**23**	**13**	**2302**	**100,0%**

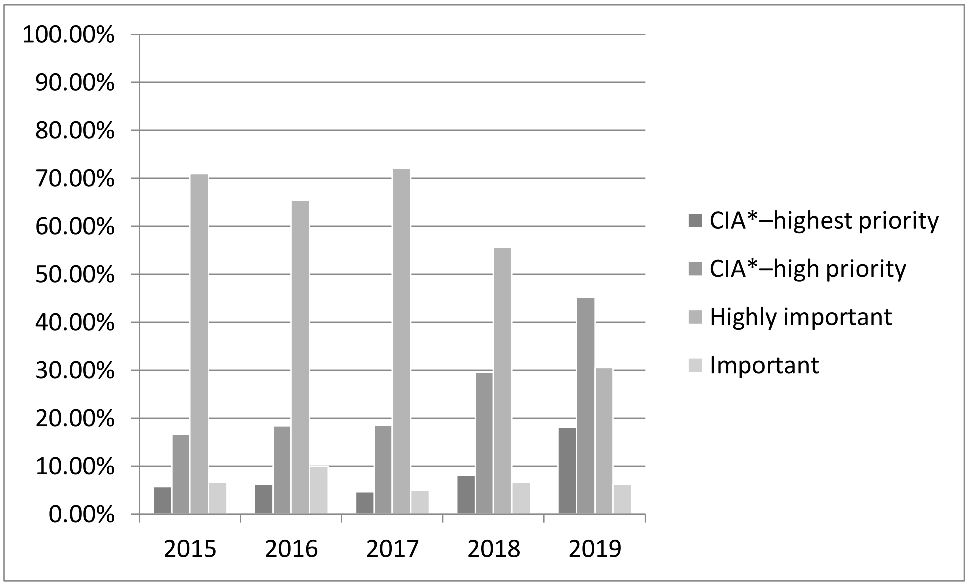
*CIA: critically important antibiotics; R1A: elective surgical procedures of reproductive system; R1B: therapeutic surgical procedures of reproductive system; DG: surgical procedures of digestive system; ON: surgical procedures of neurologic and orthopaedic system; UR: surgical procedures of urinary system; OF: surgical procedures ophthalmological system; RP: surgical procedures of respiratory system; LF: surgical procedures of lymphatic system;** Topical antibiotic.

TABLE 5 – Number of surgery procedures and antibiotic use according with the organic system, frequency of infection and PD.

Organic System	**Surgical procedure (N*)**	**Antibiotic Use**	**Surgical Infection**		**PD**
R1A*	498	468	29	3%	0,40
R1B*	203	203	16	2%	0,21
ON*	140	140	10	1%	0,20
DG*	78	78	1	0%	0,22
UR*	19	19	4	0%	0,25
TM*	89	89	19	2%	0,21
RP*	9	9	0	0%	0,27
OF*	13	13	0	0%	0,19
LF*	4	4	0	0%	0,24
Total	1053	1023	79	8%	0,21

*R1A: elective surgical procedures of reproductive system; R1B: therapeutic surgical procedures of reproductive system; DG: surgical procedures of digestive system; ON: surgical procedures of neurologic and orthopaedic system; UR: surgical procedures of urinary system; OF: surgical procedures ophthalmological system; RP: surgical procedures of respiratory system; LF: surgical procedures of lymphatic system.

FIGURE 1 –Prescription of Critically Important Antibiotics for dogs and cats over the 5 year study period.



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BIOETHICS AND BIOSECURITY COMMITTEE APPROVAL

The report was performed with an animal routinely treated by the HUVET-UNIPAMPA and was not part of any project; it was simply a clinical case report.

DECLARATION OF CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

The authors contributed equally to the manuscript.

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5 CONCLUSÃO

Pode-se concluir que o mestrado acadêmico em ciência animal possibilitou o desenvolvimento de pesquisa através de um formato diferente. Apesar da pandemia do COVID-19 limitar a realização de pesquisa em formato experimental, ainda assim, foi possível desenvolver um estudo retrospectivo e dois relatos de caso. Embora, o objetivo primário deste mestrado era realizar um estudo experimental, a realização deste estudo permitiu demonstrar a relevância de diferentes metodologias e proporcionar resultados importantes para a comunidade científica.

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