Schiffmann et al. The Journal of Basic and Applied Zoology (2020) 81:20
https://doi.org/10.1186/s41936-020-00162-2

The Journal of Basic and Applied Zoology

REVIEW Open Access

Extrahepatic biliary tract pathologies in mammalian species of zoo animals and wildlife: a review

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Abstract

Mammalian species express a broad variety in the shape of their extrahepatic biliary tract. While a gall bladder is present in many species, others are lacking this organ. Evolutionary driving forces for these differences have not been determined yet, and organ-specific pathologies might present potentially influencing factors. We reviewed the literature regarding extrahepatic biliary tract pathologies reported in mammalian species of zoo animals and wildlife. Specific pathologies have been reported in the taxonomic orders *Proboscidea*, *Chiroptera*, *Carnivora*, *Artiodactyla*, *Primates*, *Rodentia*, and *Lagomorpha* with variable frequencies of etiological categories. While metabolic disorders with cholelith formation have been reported mainly in captive populations, parasitological infestation was found particularly in free-ranging animals. Based on the available data, we hypothesize *Proboscidea*, *Primates,* and *Rodentia* species to be prone to cholelithiasis. Species belonging to the *Artiodactyla* seem to be more susceptible to parasitological infestation while in representatives of the *Carnivora* infectious, metabolic, neoplastic, and parasitological disorders have been reported nearly equally. Extending our knowledge on extrahepatic biliary tract pathologies in exotic pets and wildlife will support the work of veterinary practitioners as well as scientists in evolutionary biology, making further research in this area strongly recommendable.

Keywords: Biliary tract pathologies, Zoo animals, Wildlife

Introduction

In mammalian species, a fascinating variability regarding anatomical and physiological features of the extrahepatic biliary tract does exist. Although comparative descriptions have been published centuries ago [Boyden, 1937; Crisp, 1862; Cuvier, 1835; Flower, 1872; Gorham & Ivy, 1937; Illingworth, 1936; Mann, 1924; Mann et al., 1920; Mentzer, 1929; Thomson, 1938], underlying causes for obvious inter-species differences such as the presence/absence of the gall bladder have not been determined yet [Gorham & Ivy, 1938; Higashiyama et al., 2018]. According to phylogenetic knowledge, the loss of the gall bladder is assumed in certain clades, and the presence of the organ considered the original state [Gorham & Ivy, 1938; Housset et al., 2016]. When discussing potentially driving forces for the evolutionary loss of an organ, it is common practice to consider the advantages respectively disadvantages of possessing this specific structure [Turumin et al., 2013]. Potential pathologies present an unambiguously disadvantageous aspect. As an example, cholecystolithiasis or cholecystitis will only occur in species possessing a gall bladder. Considering the fact that in human medicine, cholecystectomies are one of the most frequent surgeries conducted in the modern times [Jones & Deppen, 2018], it can be hypothesized whether it would be advantageous for the human species to live without this organ. Additionally, knowledge of occurring species-specific pathologies is important for veterinarians, as well as researchers working with exotic pet and wildlife species. Especially when taking into account the very often unspecific clinical signs (e.g., inappetence and

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weight loss) of extrahepatic biliary tract alterations, awareness of potentially occurring disorders of this organ system is critical for practitioners working with exotic pet and wildlife species. Nevertheless, to date, no comprehensive compilation on the pathologies of the extrahepatic biliary tract in these mammalian species is available. It is the aim of this report to review the available literature on biliary tract pathologies in exotic pet and wildlife species and compile the corresponding data in a concise manner. This data collection will support the work of veterinary practitioners as well as research in the evolutionary development of the extrahepatic biliary tract in mammals.

Material and methods

In the course of a comprehensive research on visceral organ morphology of the class *Mammalia*, we addressed the question of why there exists an enormous interspecies variability in the anatomy and physiology of the extrahepatic biliary tract. The corresponding findings are in the process for publication. When investigating the existing literature for information regarding the presence/absence of the gall bladder, we additionally reviewed the reports concerning pathologies of the extrahepatic biliary tract in mammalian species of exotic pets and wildlife. In doing so, we defined exotic pets as pet species that are not-native to a region and/or non-domesticated [Warwick et al., 2018]. We searched the existing literature for relevant reports by using specific search terms (bile, gallstone, cholelithiasis, biliary neoplasia, gall bladder parasites, biliary tract) in online resources (GoogleScholar—https://scholar.google.de/, PubMed—https://www.ncbi.nlm.nih.gov/pubmed/). Further, we checked cited reports from peer-reviewed journals as well as the grey literature. Subsequently, we categorized reported pathologies into the four etiological categories: "infectious," "metabolic (exclusively cholelithiasis)," "neoplastic," and "parasitological." We summarized collected data in a table and sorted them according to the etiological category and taxonomic order of the species concerned. Additionally, we extracted information from each report regarding pathologic alterations if indicated as well as the living condition (free-ranging vs. captive) of the investigated animals. Due to their nature, we analyzed data exclusively in a descriptive manner regarding represented taxonomic groups and discuss corresponding salience. We ascertained taxonomic orders according to O´Leary et al. (2013).

Results

Our literature research revealed reports on pathologies of the extrahepatic biliary tract in mammalian species belonging to the orders *Proboscidea*, *Chiroptera*, *Carnivora*, *Artiodactyla*, *Primates*, *Rodentia*, and *Lagomorpha* (Table 1). In the order *Primates* as well as *Carnivora,* the cases we found cover 17 different species. In *Artiodactyla*, 12 different species were affected and in *Rodentia* four. In *Chiroptera*, *Lagomorpha* and *Proboscidea* cases are reported in only two different species (Table 1). When looking at the presumed/determined etiological categories, all of them are reported in *Carnivora* while we did not find any report of the "parasitological" category in *Primates*. In contrast, the latter is predominantly reported in *Artiodactyla* and as a single category in *Chiroptera* as well as *Lagomorpha*. In *Proboscidea* and *Rodentia*, the majority of the reports belong to the "metabolic" category with the occurrence of choleliths (Table 1). The majority (27/34 = 79.41%) of reported metabolic pathologies originate from individuals living in captivity. In contrast, parasitological infestations were reported mainly (19/24 = 79.17%) in free-ranging populations. Infectious and neoplastic pathologies were reported exclusively in captive populations.

Discussion

Although we restricted our investigation strictly to pathologies of the extrahepatic biliary tract, this differentiation was not always clear (e.g., cholangiocarcinoma in liver tissue [Cho et al., 2017]). We are aware of the fact that the domestic ferret (*Mustela putorius furo*) may not completely fulfill our definition of an exotic pet in dependence of the geographic region. Nevertheless, we consider it to belong to this category here.

With respect to the nature of our data, the compilation does not allow any calculation of prevalence or comparisons of such parameters between taxonomic orders. For instance, the number of reports in a taxonomic order might indicate the prevalence of specific pathologies or just the intensity of research conducted in species belonging to this order. Nevertheless, distinct differences between the orders are obvious. The latter is expressed in the number and in the amount of reports representing the different etiological categories. Our research did not detect any report of extrahepatic biliary tract pathologies in mammals belonging to the order *Xenarthra*, *Hyracoidea*, *Macroscelidea*, *Sirenia*, *Lipotyphla*, *Perissodactyla*, *Pholidota*, *Dermoptera*, and *Scandentia*. If this finding is due to a lack of corresponding reports or a lower prevalence of the specific pathology in these orders, cannot be concluded from the available data. While we expect at least cholelithiasis to occur in wild species of *Perissodactyla* as described for the domestic horse [Peek & Divers, 2000], similar assumptions for further orders would be highly hypothetical. Independent of any taxonomic affiliations, metabolic disorders with the conformation of choleliths represent the most frequently reported pathologies. Although their amount is overwhelming in contrast to the further etiological categories, this does not implicitly mean that they represent

Table 1 Reported pathologies of the extrahepatic biliary tract in mammalian exotic pets and wildlife species

Category	Underlying cause	Described pathological alterations	Species concerned	Reference
Order *Proboscidea*				
Metabolic (cholelithiasis)	Bacterial infection of biliary tract with *Salmonella London*	Around 1 liter of faceted gall stones in hepatic duct (up to 2 cm in diameter); thickened and dilated bile ducts	Asian elephant (*Elephas maximus*) *c*	Decker and Krohn (1973)
Metabolic (cholelithiasis)	Undetermined, diet?, bacterial infection of biliary tract?	One single cholelith (4.0 kg) composed mainly out of bile alcohols and a small amount of bilirubin	African elephant (*Loxodonta africana*) *f*	Agnew et al. (2005)
Metabolic (cholelithiasis)	Undetermined	Many choleliths (diameter of 1–6 cm) in severly dilated and mildly inflamed bile duct	African elephant (*Loxodonta africana*) *c*	Pagan et al. (1999)
Metabolic (cholelithiasis)	Undetermined, diet?, bacterial infection of biliary tract?	Several gallstones in bile ducts (diameter of around 8 cm)	Asian elephant (*Elephas maximus*) *c*	Jarofke (2007)
Parasitological	*Fasciola jacksoni*	Parasites in bile ducts	Asian elephant (*Elephas maximus*) *c,f*	Caple et al. (1978); Evans (1910); Perera and Rajapakse (2009)
Order *Chiroptera*				
Metabolic (cholelithiasis)	Undetermined	Conformation of choleliths in gall bladder or bile duct	Flying fox (*Pteropus sp.*) *ns*	Farina and Lankton (2018)
Neoplastic	Secondary to hepatic heochromatosis?	Cholangiocarcinoma	Egyptian fruit bat (*Rousettus aegyptiacus*)	Leone et al. (2016)
Parasitological	*Toxocara pteropodis*	Parasite in gall bladder	Spectacled flying-fox (*Pteropus conspicillatus*) *c*	Prociv (1990)
Order *Carnivora*				
Infectious	*Pseudomonas aeruginosa*	Cholecystitis with subsequent rupture of the gall bladder	Domestic ferret (*Mustela putorius furo*) *c*	Huynh et al. (2014)
Infectious	Undetermined	Cholangiohepatitis, bile duct hyperplasia	Domestic ferret (*Mustela putorius furo*) *c*	García et al. (2002)
Infectious	*Isospora sp.*	Neoplastic-like thickening of the common bile duct	American mink (*Neovison vison*) *c*	Davis et al. (1953)
Infectious	*Streptococcus sp., Escherichia coli*	Cholecystitis	Kinkajou (*Potos flavus*) *c*	Potier and Reineau (2015)
Metabolic (cholelithiasis)	Calcium carbonate, phosphate, bile pigments	Conformation of choleliths in bile duct	Polar bear (*Ursus maritimus*) *ns*	Illingworth (1936)
Metabolic (cholelithiasis)	Undetermined	A solitary green and orange cholelith with a diameter of 2 cm in the gall bladder	Grizzly bear (*Ursus arctos horribilis*) *c*	Moulton (1961)
Metabolic (cholelithiasis)	Undetermined	Conformation of choleliths (70% palmitic calcium, 30% proteins)	Kinkajou (*Potos flavus*) *c*	Potier and Reineau (2015)
Metabolic (cholelithiasis)	Undetermined, parasitic infection (ascariasis)?	Single cholelith and cholecystitis	Asiatic cheetah (*Acinonyx jubatus venaticus*) *c*	Vali et al. (2016)
Neoplastic	Undetermined, age?	Gall bladder adenocarcinoma, biliary cystadenoma	African lion (*Panthera leo*) *c*	Chu et al. (2012); Sakai et al. (2003)
Neoplastic	Undetermined	Bile duct carcinoma	Black panther (*Panthera pardus*) *c*	Hubbard et al. (1983)
Neoplastic	Undetermined	Biliary cystadenoma	Striped skunk (*Mephitis mephitis*) *c*	Chu et al. (2012)
Neoplastic	Undetermined, secondary to intrahepatic biliary cysts?	Biliary cystadenoma and cystadenocarcinoma	Black-footed ferret (*Mustela nigripes*) *c*	Lair et al. (2002)
Neoplastic	Undetermined	Adenocarcinoma of the gall bladder	Sloth bear (*Melursus ursinus*) *c*	Dorn (1964); Montali et al. (1981)
Neoplastic	Undetermined	Biliary carcinoma	Malayan sun bear	Montali et al. (1981)

Table 1 Reported pathologies of the extrahepatic biliary tract in mammalian exotic pets and wildlife species *(Continued)*

Category	Underlying cause	Described pathological alterations	Species concerned	Reference
			(*Helarctos malayanus*) *c*	
Neoplastic	Undetermined	Biliary cystadenoma	Asiatic black bear (*Ursus thibetanus*) *c*	Chu et al. (2012)
Neoplastic	Undetermined	Cholangiocarcinoma, bile duct adenocarcinoma	Margay cat (*Felis wiedii*) *c*	Hubbard et al. (1983); McClure et al. (1977)
Neoplastic	Age?, undetermined	Leiomyosarcoma of the gall bladder	Giant otter (*Pteronura brasiliensis*) *c*	Peters et al. (2007)
Parasitological	*Eimeria sp.*	Gall bladder wall thickened, bile ducts enlarged and firm	Domestic ferret (*Mustela putorius furo*) *c*	Williams et al. (1996)
Parasitological	*Pseudamphistomum truncatum*	Significant alterations of gall bladder walls, thickened shrunken gall bladder	American mink (*Neovison vison*) *f*	Hawkins et al. (2010); Simpson et al. (2005)
Parasitological	*Pseudamphistomum truncatum*	Significant alterations of gall bladder walls, thickened shrunken gall bladder	Eurasian otter (*Lutra lutra*) *f*	Hawkins et al. (2010); Simpson et al. (2005)
Parasitological	*Pseudamphistomum truncatum*	Cholangiohepatitis, hepatic fibrosis	Gray seal (*Halichoerus grypus*) *f*	Neimanis et al. (2016)
Order *Artiodactyla*				
Neoplastic	Undetermined	Gall bladder adenocarcinoma	Alpaca (*Vicugna pacos*) *c*	Lombard and Witte (1959)
Parasitological	*Fasciola gigantica*	Bile duct calcification	Uganda kob (*Kobus kob*) *f*	Bindernagel (1972)
Parasitological	*Fasciola gigantica*	Bile duct calcification	Hartebeest (*Alcelaphus buselaphus*) *f*	Bindernagel (1972)
Parasitological	*Fasciola gigantica*	Bile duct calcification	African buffalo (*Syncerus caffer*) *f*	Bindernagel (1972)
Parasitological	*Dicrocoelium dendriticum*	Bile duct thickening	Mouflon (*Ovis orientalis*) *f*	reviewed in Bindernagel (1972); Duchácek and Lamka (2003)
parasitological	*Dicrocoelium dendriticum*	Bile duct thickening	Fallow deer (*Dama dama*) *f*	reviewed in Bindernagel (1972); Duchácek and Lamka (2003)
Parasitological	*Dicrocoelium dendriticum*	Bile duct thickening	Chamois (*Rupicapra rupicapra*) *f*	reviewed in Bindernagel (1972); Duchácek and Lamka (2003)
Parasitological	*Dicrocoelium dendriticum*	Bile duct thickening	Roe deer (*Capreolus capreolus*) *f*	reviewed in Bindernagel (1972); Duchácek and Lamka (2003)
Parasitological	*Dicrocoelium dendriticum*	Bile duct thickening	Red deer (*Cervus elaphus*) *f*	reviewed in Bindernagel (1972); Duchácek and Lamka (2003)
Parasitological	*Dicrocoelium dendriticum*	Bile duct thickening	White-tailed deer (*Odocoileus virginianus*) *f*	reviewed in Bindernagel (1972); Duchácek and Lamka (2003)
Parasitological	*Cooperioides hepaticae*	Cholangitis, bile duct thickening, gall bladder dilatation	Impala (*Aepyceros melampus*) *f*	Gallivan et al. (1996)
Parasitological	*Stilesia hepatica*	Thickening and distention of main bile duct	Impala (*Aepyceros melampus*) *f*	Gallivan et al. (1996)
Parasitological	*Fasciola gigantica*	Thickening main bile duct	Impala (*Aepyceros melampus*) *f*	Gallivan et al. (1996)
Parasitological	*Dicrocoelium dendriticum*	Parasites in bile ducts	Alpaca (*Vicugna pacos*) *c*	Kaufmann et al. (2007)
Parasitological	*Fasciola gigantica*	Cholecystitis, gall bladder hyperplasia	Philippine brown deer (*Cervus mariannus*) *f*	Portugaliza et al. (2015)
Order *Primates*				
Infectious?	Undetermined	Cholecystitis	Common marmoset	Chalmers et al. (1983);

Table 1 Reported pathologies of the extrahepatic biliary tract in mammalian exotic pets and wildlife species *(Continued)*

Category	Underlying cause	Described pathological alterations	Species concerned	Reference
			(*Callithrix jacchus*) *c*	Tucker (1984)
Metabolic (cholelithiasis)	Septation gall bladder?	Conformation of choleliths (mainly composed of cystine and calcium oxalate)	Golden lion tamarin (*Leontopithecus rosalia*) *c*	Pissinatti et al. (1992)
Metabolic (cholelithiasis)	Septation gall bladder?	Conformation of choleliths (mainly composed of cystine and calcium oxalate)	Golden-headed lion tamarin (*Leontopithecus chrysomelas*) *c*	Pissinatti et al. (1992)
Metabolic (cholelithiasis)	Septation gall bladder?	Conformation of choleliths (mainly composed of cystine and calcium oxalate)	Black lion tamarin (*Leontopithecus chrysopygus*) *c*	Pissinatti et al. (1992)
Metabolic (cholelithiasis)	Septation gall bladder?	Conformation of choleliths (mainly composed of cystine and calcium oxalate)	Wied´s marmoset (*Callithrix kuhlii*) *c*	Pissinatti et al. (1992)
Metabolic (cholelithiasis)	Undetermined	Conformation of choleliths (100% composed of calcium bilirubinate), cholecystitis	Rhesus monkey (*Macaca mulatta*) *c*	Kessler (1982)
Metabolic (cholelithiasis)	Presumably caused by increased biliary cholesterol levels	Conformation of choleliths (11 stones measuring up to 4 mm), edematous gall bladder walls	Rhesus monkey (*Macaca mulatta*) *c*	Martin et al. (1973)
Metabolic (cholelithiasis)	Undetermined	Conformation of choleliths	Baboon (*Papio sp.*) *c*	McSherry et al. (1971)
Metabolic (cholelithiasis)	Cholesterol	Conformation of choleliths (100% cholesterol), gall bladder fibrosis	Slender loris (*Loris tardigradus*) *c*	Plesker et al. (2012)
Metabolic (cholelithiasis)	Undetermined	Conformation of choleliths	Galago (*Galago crassicaudatus*) *c*	Burkholder et al. (1971)
Metabolic (cholelithiasis)	Undetermined	One single cholelith	Common marmoset (*Callithrix jacchus*) *c*	Tucker (1984)
Metabolic (cholelithiasis)	Undetermined, diet?	Single gallstone (70x30 mm) obstructed the common bile duct	Chimpanzee (*Pan troglodytes*) *c*	Chatterton et al. (2011)
Metabolic (cholelithiasis)	Age?, bacterial infection of biliary tract?	Choleliths composed exclusively out of pigments	*Callithrix sp. c*	Chenet and Petit (2018)
Metabolic (cholelithiasis)	Age?, bacterial infection of biliary tract?	Choleliths composed exclusively out of pigments	*Leonthopithecus sp. c*	Chenet and Petit (2018)
Metabolic (cholelithiasis)	Undetermined	Dilated ductus choledochus containing biliary sludge with stenosis of the duodenal papilla	Sumatran orangutan (*Pongo pygmaeus abelii*) *c*	Schuele et al. (2018)
Metabolic (cholelithiasis)	Inflammatory ileal disease?, abnormal protein metabolism?	Cholelith in bile duct (95% cystine, 5% miscellaneous)	Black lion tamarin (*Leontopithecus chrysopygus*) *c*	Smith et al. (2006)
Metabolic (cholelithiasis)	Inflammatory ileal disease?, abnormal protein metabolism?	Choleliths in gall bladder and bile duct (5% cholesterol, 95% miscellaneous respectively 70% calcium phosphate, 30% miscellaneous)	Golden lion tamarin (*Leontopithecus rosalia*) *c*	Smith et al. (2006)
Metabolic (cholelithiasis)	Inflammatory ileal disease?, abnormal protein metabolism?	Cholelith in gall bladder (60% miscellaneous, 40% calcium carbonate respectively 80% cystine, 20% miscellaneous)	Golden lion tamarin (*Callithrix argentata*) *c*	Smith et al. (2006)
Metabolic (cholelithiasis)	Inflammatory ileal disease?, abnormal protein metabolism?	Cholelith in gall bladder	Wied´s marmoset (*Callithrix kuhlii*) *c*	Smith et al. (2006)
Metabolic (cholelithiasis)	cholesterol and proteins	Conformation of choleliths	African green monkey (*Chlorocebus aethiops*) *c*	Kleinlützum and Plesker (2017)
Metabolic (cholelithiasis)	Undetermined	Conformation of choleliths	Squirrel monkey (*Saimiri sciureus*) *c*	Lieberman et al. (2016)
Metabolic (cholelithiasis)	Undetermined	One single large cholelith (composed of cholesterol, bile salts and pigments) lead to gall bladder rupture and fatal peritonitis	Orangutan (*Pongo sp.*) *c*	Fox (1930)
Metabolic	Undetermined	Multiple (10-15) choleliths in gall bladder with a	Owl monkey (*Aotus*	Anver et al. (1972)

Table 1 Reported pathologies of the extrahepatic biliary tract in mammalian exotic pets and wildlife species *(Continued)*

Category	Underlying cause	Described pathological alterations	Species concerned	Reference
(cholelithiasis)		diameter of 2-3 mm and composed almost completely of cholesterol	*trivirgatus*) *c*	
Neoplastic	Undetermined	Gall bladder adenocarcinoma	Guinea baboon (*Papio papio*) *c*	Lombard and Witte (1959)
Neoplastic	Undetermined	Cholangioma	Slow loris (*Nycticebus coucang*) *c*	Chu et al. (2012)
Neoplastic	Aflatoxin B_1 (experimentally induced)	Adenocarcinoma of gall bladder and/or bile ducts	Rhesus monkey (*Macaca mulatta*) *c*	Sieber et al. (1979)
Neoplastic	Aflatoxin B_1 (experimentally induced)	Adenocarcinoma of gall bladder and/or bile ducts	Cynomolgus monkey (*Macaca fascicularis*) *c*	Sieber et al. (1979)
Neoplastic	Age?, undetermined	Gall bladder adenoma	Chimpanzee (*Pan troglodytes*) *c*	Starost and Martino (2002)
Order *Rodentia*				
Infectious?	Undetermined	Chronic severe cholecystitis with greatly thickened walls	Viscacha (*Lagostomus maximus*) *c*	Hamerton (1932)
Metabolic (cholelithiasis)	Calcium carbonate, phosphate, bile pigments	Conformation of choleliths	Beaver (*Castor sp.*) *ns*	Illingworth (1936)
Metabolic (cholelithiasis)	Diet (fiber content), season	Conformation of choleliths (100% cholesterol)	Deer mouse (*Peromyscus maniculatus gambelii*) *f*	Ginnett et al. (2003); Schwab and Theis (1989)
Metabolic (cholelithiasis)	Diet (rich in cholesterol?)	Conformation of choleliths	Cottonrat (*Sigmodon hispidus*) *f*	Pence et al. (1978)
Order *Lagomorpha*				
Parasitological	*Dicrocoelium dendriticum*	Bile duct thickening	European hare (*Lepus europaeus*) *f*	reviewed in Bindernagel (1972); Duchácek and Lamka (2003)
Parasitological	*Dicrocoelium dendriticum*	Bile duct thickening	European rabbit (*Oryctolagus cuniculus*) *f*	reviewed in Bindernagel (1972); Duchácek and Lamka (2003)

c captive, *f* free-ranging, *ns* not specified

the most prevalent extrahepatic biliary tract pathology in the species investigated here. Possibly, it is just their ease of macroscopic detection which led to the frequency of corresponding reports. As an example, according to Agnew et al. (2005), they were able to identify and analyze a cholelith in the lumbar region of an African elephant (*Loxdonta africana*) even though the animal had deceased months before dissection took place. In such a situation, it seems extremely unrealistic to determine an infectious, neoplastic, or parasitological pathology. Moreover, choleliths are usually detectable macroscopically without any further diagnostic tool which may be another explanation for the high frequency of reported choleliths. Apart from these confounding aspects, cholelith formation has been induced experimentally in many animal models using domestic (mouse, hamster, guinea pig, rabbit) [reviewed in Oldham-Ott & Gilloteaux, 1997] and even wildlife species (non-human primates) [Melchior et al., 1972] by feeding them a predisposing diet. Therefore, a correlation between dietary composition and gall stone formation seems very likely to be present in non-domestic species. Accordingly, most (27 out of 34 reports = 79.41%) of the reports on choleliths compiled here do originate from animals living under human care (Table 1), and it is highly probable that their diet is divergent from the one in the natural environment of the species. If this assumption should be correct, the dietary aspect of cholelith etiology might present a field for further improvements through zoo nutrition specialists. The latter might be of particular importance in primates and rodents. Preventative anti-parasitic treatment under conditions of captivity can explain why parasitological infestations have been reported mainly in free-ranging populations. In contrast, reports on infectious and neoplastic pathologies originate exclusively from animals living under human care. It can be hypothesized whether free-ranging individuals do rarely reach an age where neoplasia usually develops and whether the identification of infectious agents would require more sophisticated diagnostics than usually applied under field conditions. Further research would be needed to confirm or reject these assumptions in an evidence-based manner.

In *Proboscidea,* choleliths and infestation with liver flukes have been reported. In contrast to most other mammalian species, the bile of elephants is composed mainly of bile alcohols instead of bile acids [Hagey et al., 2010]. This physiological peculiarity has been hypothesized as a risk factor for the conformation of choleliths, especially if a bacterial infection of the biliary tract is present [Agnew et al., 2005; Decker & Krohn, 1973; Jarofke, 2007]. Recent research on gall stone formation in humans corroborates the potential correlation with the immune response on a bacterial infection [Munoz et al., 2019]. Furthermore, diet composition has been mentioned as a potential underlying cause for gall stone formations in elephants [Agnew et al., 2005; Jarofke, 2007]. Gall stone analysis might reveal more information regarding the impact of diet on cholelith formation and allow subsequent diet adaptations in captivity. Reports of infestation with liver flukes originate exclusively from elephant populations in Asian range countries [Caple et al., 1978; Evans, 1910; Perera & Rajapakse, 2009]. Nevertheless, the susceptibility of elephants to these trematodes should be kept in mind when caring for elephants under zoo conditions.

In *Chiroptera,* the single reported pathology was caused by a parasite, which completed an aberrant migration route in the gall bladder of his host [Prociv, 1990]. Further research is needed to determine whether *Chiroptera* species have a naturally low predisposition for extrahepatic biliary tract pathologies or if the absence of reports is due to a lack of investigation in this area. With respect to the limited size of many *Chiroptera* species, alterations of the gall bladder might be overlooked frequently during macroscopic examinations.

In *Carnivora*, pathologies of all categories investigated here have been reported repeatedly. While neoplasia has been documented exclusively in captive individuals, parasitological infestations occurred mainly in free-ranging individuals. Assuming an increased life expectancy and consequently elevated risk for neoplasia in captivity, this correlation does not seem surprising. Similarly, hygienic conditions and anti-parasitic treatment may decrease the risk for the parasitological infestation in individuals under human care. Again, cholelith composition analysis might reveal more information regarding the potential impact of diet on gall stone formation.

With the exception of one case of neoplasia, all reports in *Artiodactyla* describe parasitological infestations of the extrahepatic biliary tract mainly with trematode species. With respect to the comprehensive case numbers of hunted specimens and the lack of any report of choleliths in *Artiodactyla* species, we hypothesize a reduced susceptibility in representatives of this order. The same might be valid for infections of the extrahepatic biliary tract. In contrast, we consider *Artiodactyla* species to be prone to parasitological infestation and highlight the need for anti-parasitic monitoring and treatment under the conditions of captivity.

In *Primates*, the vast majority of reports describe cholelith formation or neoplasia. Whether the former is primarily due to the species-specific septation of the gall bladder as presumed in tamarins and marmosets [Pissinatti et al., 1992] or dietary composition [Kleinlützum & Plesker, 2017; Martin et al., 1973; Plesker et al., 2012] needs further investigation. The frequency of neoplasia might correlate with the age reached by individuals under human care with the exception of experimentally induced adenocarcinoma through the ingestion of aflatoxin B_1 [Sieber et al., 1979].

In *Rodentia*, cholelith formation was the most frequently reported pathology of the extrahepatic biliary tract, and dietary composition is considered the main risk factor. Some evidence for the latter presumption exists in the form of two investigations on free-ranging deer mouse (*Peromyscus maniculatus gambelii*) populations [Ginnett et al., 2003; Schwab & Theis, 1989]. In these studies, seasonally increased dietary fiber content has been postulated to cause cholesterol supersaturation in bile fluids with subsequent cholelith formation.

Trematode infestation represents the single pathology reported for free-ranging *Lagomorpha* species. With respect to reports on domestic rabbits [DeCubellis et al., 2010; Hofmann et al., 1968; Starost, 2007], cholelithiasis as well as neoplasia can be expected to occur in *Lagomorpha*. The lack of corresponding reports might be mainly due to limited investigation conducted yet and the presumably low average life expectancy of free-ranging individuals.

Conclusions

In conclusion, extended gaps of knowledge are existing regarding the prevalence and etiology of pathologies of the extrahepatic biliary tract in mammalian exotic pets and wildlife species. Further insights regarding the correlation of dietary aspects and the occurrence of cholelithiasis will be of importance for animal management concepts. Availability of specific information will enable zoo nutritionists to compose species-specific diets by taking into account the biliary tract. In the perspective of scientists, a more complete dataset of extrahepatic biliary tract pathologies would facilitate the investigation of potential drivers of the evolutionary development of the biliary tract in mammals. Therefore, we strongly encourage further research in this field by pathologists, veterinary practitioners, and scientists. The compilation provided here might serve as a basis for the identification of specific gaps by presenting the current status of knowledge.

Acknowledgements
Not applicable.

Authors' contributions
CS: data collection and analysis and wrote the manuscript. GU: data collection
SO: wrote the manuscript. The author(s) read and approved the final manuscript.

Funding
This work was funded by the Leibniz Association (SWA-2016-SGN-2).

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Not applicable in this review.

Consent for publication
Not applicable in this review.

Competing interests
The authors declare that they have no competing interests.

Received: 12 November 2019 Accepted: 4 May 2020
Published online: 12 May 2020

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