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

Christian Schiffmann *, Gabriele Unterhitzenberger and Sylvia Ortmann

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; Houssset 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
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                                            | Asian elephant (Elephas maximus)   | Decker and Krohn (1973)    |
|                  | Metabolic (cholelithiasis)                           | Undetermined, diet?, bacterial infection of biliary tract?                                           | African elephant (Loxodonta africana) | Agnew et al. (2005)       |
|                  | Metabolic (cholelithiasis)                           | Undetermined, diet?, bacterial infection of biliary tract?                                           | Asian elephant (Elephas maximus)   | Jarofke (2007)             |
|                  | Metabolic (cholelithiasis)                           | Undetermined, diet?, bacterial infection of biliary tract?                                           | African elephant (Loxodonta africana) | Pagan et al. (1999)   |
| Parasitological  | Fasciola jacksoni                                     | Parasites in bile duct                                                                                | Asian elephant (Elephas maximus)   | Caple et al. (1978); Evans (1910); Perera and Rajapakse (2009) |
| Order Chiroptera | Metabolic (cholelithiasis)                           | Conformation of choleliths in gall bladder or bile duct                                                | Flying fox (Pteropus sp.)          | Farina and Lankton (2018)  |
|                  | Neoplastic                                            | Secondary to hepatic heochromatosis?                                                                  | Egyptian fruit bat (Rousettus aegyptiacus) | Leone et al. (2016) |
| Parasitological  | Toxocara pteropodis                                  | Parasite in gall bladder                                                                               | Spectacled flying-fox (Pteropus conspicillatus) | Prociv (1990)           |
| Order Carnivora  | Infectious Pseudomonas aeruginosa                    | Cholecystitis with subsequent rupture of the gall bladder                                            | Domestic ferret (Mustela putorius furo) | Huynh et al. (2014)    |
|                  | Infectious Undetermined                              | Cholangiohepatitis, bile duct hyperplasia                                                              | Domestic ferret (Mustela putorius furo) | García et al. (2002) |
|                  | Infectious Isospora sp.                             | Neoplastic-like thickening of the common bile duct                                                    | American mink (Neovison vison)     | Davis et al. (1953)       |
|                  | Infectious Streptococcus sp., Escherichia coli       | Cholecystitis                                                                                         | Kinkajou (Potos flavus)           | Potier and Reineau (2015) |
|                  | Metabolic (cholelithiasis)                           | Calcium carbonate, phosphate, bile pigments                                                            | Polar bear (Ursus maritimus)       | Illingworth (1936)       |
|                  | Metabolic (cholelithiasis)                           | A solitary green and orange cholelith with a diameter of 2 cm in the gall bladder                     | Grizzly bear (Ursus arctos horribilis) | Moulton (1961)          |
|                  | Metabolic (cholelithiasis)                           | Conformation of choleliths (70% palmitic calcium, 30% proteins)                                       | Kinkajou (Potos flavus)           | Potier and Reineau (2015) |
|                  | Metabolic (cholelithiasis)                           | Undetermined, parasitic infection (ascariasis)?                                                       | Asiatic cheetah (Acinonyx jubatus venaticus) | Vali et al. (2016) |
|                  | Neoplastic Undetermined                              | Gall bladder adenocarcinoma, biliary cystadenoma                                                       | African lion (Panthera leo)        | Chu et al. (2012); Sakai et al. (2003) |
|                  | Neoplastic Undetermined                              | Bile duct carcinoma                                                                                    | Black panther (Panthera pardus)   | Hubbard et al. (1983)    |
|                  | Neoplastic Undetermined                              | Biliary cystadenoma                                                                                    | Striped skunk (Mephitis mephitis) | Chu et al. (2012)        |
|                  | Neoplastic Undetermined, secondary to intrahepatic biliary cysts? | Biliary cystadenoma and cystadenocarcinoma                                                           | Black-footed ferret (Mustela nigripes) | Lair et al. (2002) |
|                  | Neoplastic Undetermined                              | Adenocarcinoma of the gall bladder                                                                       | Sloth bear (Melursus ursinus)      | 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 |
|----------|------------------|------------------------------------|-------------------|-----------|
| Neoplastic | Undetermined | Biliary cystadenoma | (Helarctos malayanus) 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

| Category | Underlying cause | Described pathological alterations | Species concerned | Reference |
|----------|------------------|------------------------------------|-------------------|-----------|
| 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); Ducháček and Lamka (2003) |
| Parasitological | Dicrocoelium dendriticum | Bile duct thickening | Fallow deer (Dama dama) f | reviewed in Bindernagel (1972); Ducháček and Lamka (2003) |
| Parasitological | Dicrocoelium dendriticum | Bile duct thickening | Chamois (Rupicapra rupicapra) f | reviewed in Bindernagel (1972); Ducháček and Lamka (2003) |
| Parasitological | Dicrocoelium dendriticum | Bile duct thickening | Roe deer (Capreolus capreolus) f | reviewed in Bindernagel (1972); Ducháček and Lamka (2003) |
| Parasitological | Dicrocoelium dendriticum | Bile duct thickening | Red deer (Cervus elaphus) f | reviewed in Bindernagel (1972); Ducháček and Lamka (2003) |
| Parasitological | Dicrocoelium dendriticum | Bile duct thickening | White-tailed deer (Odocoileus virginianus) f | reviewed in Bindernagel (1972); Ducháček 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

| Category | Underlying cause | Described pathological alterations | Species concerned | Reference |
|----------|------------------|------------------------------------|-------------------|-----------|
| 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                                      |
|------------------------------|------------------|------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------|
| Metabolic (cholelithiasis)   | Septation gall bladder? | Conformation of choleliths (mainly composed of cystine and calcium oxalate)                        | Golden lion tamarin                                      | Pissinatti et al. (1992)                       |
| Metabolic (cholelithiasis)   | Septation gall bladder? | Conformation of choleliths (mainly composed of cystine and calcium oxalate)                        | Golden-headed lion tamarin                               | Pissinatti et al. (1992)                       |
| Metabolic (cholelithiasis)   | Septation gall bladder? | Conformation of choleliths (mainly composed of cystine and calcium oxalate)                        | Black lion tamarin                                       | Pissinatti et al. (1992)                       |
| Metabolic (cholelithiasis)   | Septation gall bladder? | Conformation of choleliths (mainly composed of cystine and calcium oxalate)                        | Wied’s marmoset                                          | Pissinatti et al. (1992)                       |
| Metabolic (cholelithiasis)   | Undetermined      | Conformation of choleliths (100% composed of calcium bilirubinate), cholecystitis                     | Rhesus monkey                                            | 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                                            | Martin et al. (1973)                           |
| Metabolic (cholelithiasis)   | Undetermined      | Conformation of choleliths                                                                         | Baboon                                                 | McSherry et al. (1971)                         |
| Metabolic (cholelithiasis)   | Cholesterol       | Conformation of choleliths (100% cholesterol), gall bladder fibrosis                               | Slender loris (Loris tardigradus)                       | Plesker et al. (2012)                          |
| Metabolic (cholelithiasis)   | Undetermined      | Conformation of choleliths                                                                         | Galago (Galago crassicaudatus)                          | Burkholder et al. (1971)                       |
| Metabolic (cholelithiasis)   | Undetermined      | One single cholelith                                                                                | Common marmoset (Callithrix jacchus)                    | Tucker (1984)                                 |
| Metabolic (cholelithiasis)   | Undetermined, diet? | Single gallstone (70x30 mm) obstructed the common bile duct                                       | Chimpanzee (Pan troglodytes)                            | Chatterton et al. (2011)                       |
| Metabolic (cholelithiasis)   | Age?, bacterial infection of biliary tract?                                                                 | Choleliths composed exclusively out of pigments          | Callithrix sp.                                           | Chenet and Petit (2018)                        |
| Metabolic (cholelithiasis)   | Age?, bacterial infection of biliary tract?                                                                 | Choleliths composed exclusively out of pigments          | Leontopithecus sp.                                      | Chenet and Petit (2018)                        |
| Metabolic (cholelithiasis)   | Undetermined      | Dilated ductus choledochus containing biliary sludge with stenosis of the duodenal papilla          | Sumatran orangutan (Pongo pygmaeus abelii)              | Schuele et al. (2018)                          |
| Metabolic (cholelithiasis)   | Inflammatory ileal disease?, abnormal protein metabolism? | Cholelith in bile duct (95% cystine, 5% miscellaneous)                                              | Black lion tamarin                                       | 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                                      | 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                                      | Smith et al. (2006)                           |
| Metabolic (cholelithiasis)   | Inflammatory ileal disease?, abnormal protein metabolism? | Cholelith in gall bladder                                                                           | Wied’s marmoset                                         | Smith et al. (2006)                           |
| Metabolic (cholelithiasis)   | cholesterol and proteins | Conformation of choleliths                                                                         | African green monkey (Chlorocebus aethiops)             | Kleinlützum and Plesker (2017)                |
| Metabolic (cholelithiasis)   | Undetermined      | Conformation of choleliths                                                                         | Squirel monkey (Saimiri sciureus)                       | 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.)                                    | Fox (1930)                                    |
| Metabolic (cholelithiasis)   | Undetermined      | Multiple (10-15) choleliths in gall bladder with a                                                  | Owl monkey (Aotus)                                      | Anver et al. (1972)                           |
| Metabolic (cholelithiasis)   | Undetermined      | Conformation of choleliths                                                                         |                                                        |                                               |
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 (Loxodonta africana) even though the animal had ceased 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

| Category | Underlying cause | Described pathological alterations | Species concerned | Reference |
|----------|------------------|-----------------------------------|-------------------|-----------|
| Neoplastic | Undetermined | Cholecystitis with greatly thickened walls | Viscacha (Lagostomus maximus) | Hamerton (1932) |
| Metabolic | Calcium carbonate, phosphate, bile pigments | Conformation of choleliths | Beaver (Castor sp.) | Illingworth (1936) |
| Metabolic | Diet (fiber content), season | Conformation of choleliths (100% cholesterol) | Deer mouse (Peromyscus maniculatus gambelii) | Ginnett et al. (2003); Schwab and Theis (1989) |
| Metabolic | Diet (rich in cholesterol?) | Conformation of choleliths | Cottonrat (Sigmodon hispidus) | Pence et al. (1978) |
| Parasitological | Dicrocoelium dendriticum | Bile duct thickening | European hare (Lepus europaeus) | reviewed in Bindernagel (1972); Ducháček and Lamka (2003) |
| Parasitological | Dicrocoelium dendriticum | Bile duct thickening | European rabbit (Oryctolagus cuniculus) | reviewed in Bindernagel (1972); Ducháček and Lamka (2003) |

* c captive, f free-ranging, ns not specified
applied under field conditions. Further research would be needed to confirm or reject these assumptions in an evidence-based manner.

In Proboseidea, 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 & Rajakapakse, 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 B1 [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 gambelli) 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

References
Agnew, D. W., Hagey, L., & Shoshani, J. (2005). The elephants of Zoba Gash Barka. Entrea: Part 4. cholelithiasis in a wild African elephant (Loxodonta africana). Journal of Zoo and Wildlife Medicine, 36, 677–683.
Anver, M. R., Hunt, R. D., & Chalifoux, L. V. (1972). Cholesterol gallstones in Atlas trivirgatus. Journal of Medical Primatology, 1, 241–246.
Bindernagel, J. A. (1972). Liver fluke Fasciola gigantica in African buffalo and antelopes in Uganda, East Africa. Journal of Wildlife Diseases, & 315–317.
Boyden, E. A. (1937). The sphincter of oddi in man and certain representative mammals. Surgery, 1, 25–37.
Burkholder, P. M., Bergeron, J. A., Sherwood, B. F., & Hackel, D. B. (1971). A histopathologic survey of Gallop in captivity. Virchows Archiv A Pathological Anatomy and Histology, 334, 80–98.
Caple, I. W., Jainudeen, M. R., Buck, T. D., & Song, C. Y. (1978). Some clinicopathologic findings in elephants (Elephas maximus) infected with Fasciola jaksoni. Journal of Wildlife Diseases, 14, 110–115.
Chalmers, D. T., Muguratrovd, L. B., & Wadsworth, P. F. (1983). A survey of the pathology of mormosets (Callithrix jaccus) derived from a mormoset breeding unit. Laboratory Animals, 17, 270–279.
Chatterton, J., Unwin, S., & Sanderson, S. (2011). Successful surgical treatment of extra-hepatic obstructive liver disease in a captive chimpanzee (Pan troglodytes). Lisbon, Portugal: Paper presented at the International Conference on Diseases of Zoo and Wild Animals.
Chenet, B., & Petit, T. (2018). Cholelithiasis in callithrichids in European zoos. Paper presented at the Joint. Prague, Czech Republic: EAZWV/AAZV/Leibniz-ZW Conference.
Cho, H. S., Han, J. I., & Oh, Y. (2017). Cholangiocarcinoma with multiple organ metastasis in a captive puma (Puma concolor). Berlin, Germany: Paper presented at the Zoo and Wildlife Health Conference.
Chu, P.-Y., Zhuo, Y.-X., Wang, F.-I., Jeng, C.-R., Pang, V. F., Chang, P.-H., … Liu, C.-H. (2012). Spontaneous neoplasms in zoo mammals, birds, and reptiles in Taiwan - a 10-year survey. Animal Biology, 62, 95–110.
Crisp, E. (1862). On the situation, form, and capacity of the gallbladder in the vertebrata; on its absence in certain animals; and on the colour of the bile. Proceedings of the Zoological Society of London, 30, 132–139.
Cuvier, G. (1835). De la vesicule du fiel et ses conduits. Lecons d’anatomie comparee. Vingtieme lecon. Tome 4, 2e partie, 548.
Davis, C. L., Chow, T. L., & Gorham, J. R. (1953). Hepatic coccidiosis in mink. Veterinary Medicine, 48, 371–375.
Decker, R. A., & Krohe, A. F. (1973). Cholelithiiasis in an Indian elephant. Journal of the American Veterinary Medicine Association, 163, 546–547.
DeCubellis, J., Kruse, A. M., McCarthy, R. J., Zacher, L. A., Penninck, D., Watson, A. T., … Mayer, J. (2010). Biliary cystadenoma in a rabbit (Oryctolagus cuniculus). Journal of Exotic Pet Medicine, 19, 177–182.
Dorn, C. R. (1964). Bilary and hepatic carcinomas in bears at the San Diego Zoological Gardens. Nature, 202, 513–514.
Duchêcék, L., & Lamka, J. (2003). Dicrocoeliosis - the present state of knowledge with respect to wildlife species. Acta Veterinaria Brno, 72, 613–626.
Evans, H. E. (1910). Elephants and their diseases. Rangoon, Burma: Government Printing, Burma.
Farina, L. L., & Lankton, J. S. (2018). Chiroptera. In K. Terio, D. McAloose, & J. S. Legier (Eds.), Pathology of Wildlife and Zoo Animals (pp. 607-632). Academic Press.
Flower, W. H. (1872). Lectures on the comparative anatomy of the organs of digestion. Medical Times and Gazette, Feb. 24 - Dec. 11.
Fox, H. (1930). Animals special interest. Report of the laboratory of comparative pathology, 12–22.
Gallivan, G. J., Barker, I. K., Culverwell, J., & Girdwood, R. (1996). Prevalence of hepatic helminths and associated pathiology in impala (Aepyceros melampus) in Swaziland. Journal of Wildlife Diseases, 32, 137–141.
Garcia, A., Erdman, S. E., Xu, S., Feng, Y., Rogers, A. B., Schrenzel, M. D., … Fox, J. G. (2002). Hepatobiliary inflammation, neoplasia, and argyrophilic bacteria in a ferret colony. Veterinary Pathology, 39, 173–179.
Ginnett, D. A., Theis, J. H., & Kaneko, J. J. (2003). Spontaneous gallstone formation in deer mice: Interaction of cholesterol, bile acids, and dietary fiber. Journal of Wildlife Diseases, 39, 105–113.
Gorham, F. W., & Ivy, A. C. (1937). Evolutionary contributions to the general function of the gall bladder. The American Journal of Digestive Diseases, 4, 792–796.
Gorham, F. W., & Ivy, A. C. (1938). General function of the gall bladder from the evolutionary standpoint. Zoological Series Field Museum of Natural History, 22, 159–213.
Hagely, L. R., Vital, N., Hofmann, A. F., & Krasowski, M. D. (2010). Evolutionary diversity of bile salts in reptiles and mammals, including analysis of ancient human and extinct giant ground sloth coprolites. BMC Evolutionary Biology, 10.
Hamerton, A. E. (1932). Report on the deaths occurring in the Society’s Gardens during the year 1931. Proceedings of the Zoological Society of London, 102, 613–638.
Hawkins, C. J., Caffrey, J. M., Stuart, P., & Lawton, C. (2010). Biliary parasite Pseudoprostomum truncatum (Opisthochaeta) in American mink (Mustela vison) and Eurasian otter (Lutra lutra) in Ireland. Parasitology Research, 107, 993–997.
Higashiyama, H., Uemura, M., Igarashi, H., Kurohmaru, M., Kanai-Azuma, M., & Kanai, Y. (2018). Anatomy and development of the extrahepatic biliary system in mouse and rat: a perspective on the evolutionary loss of the gallbladder. Journal of Anatomy, 232, 134–145.
Hofmann, A. F., Bokkenheuser, V., Hirsch, R. L., & Mosbach, E. H. (1968). Experimental cholelithiasis in the rabbit induced by cholestatol feeding: effect of neomycin treatment on bile composition and gallstone formation. Journal of Lipid Research, 9, 244–253.
Houset, C., Chettle, Y., Debray, D., & Chignard, N. (2016). Functions of the galbladder. Comprehensive Physiology, 6, 1549–1577.
Hubbard, G. B., Schmidt, R. E., & Fletcher, K. C. (1983). Neoplasia in zoo animals. The Journal of Zoo Animal Medicine, 13, 44–30.
Huynh, M., Guillamot, P., Hernandez, J., & Ragetly, G. (2014). Gall bladder rupture associated with cholecystitis in a domestic ferret (Mustela putorius). Journal of Small Animal Practice, 55, 479–482.
Illingworth, C. F. W. (1936). The gallbladder in animals. Edinburg Medical Journal, 43, 459–461.
Jarofkes, J., & Plesker, R. (2017). A case of gallstones in an African green monkey. Primate Biology, 4, 33–37.
Moulton, J. E. (1961). Bile duct carcinomas in two bears. The Cornell Veterinarian.

Leone, A. M., Crawshaw, G. J., Garner, M. M., Frasca, S., Stasiak, I., Rose, K. S., … Fatina, L. L. (2016). A retrospective study of the lesions associated with iron storage disease in captive Egyptian fruit bats (Rousettus aegyptiacus). Journal of Zoo and Wildlife Medicine, 47, 45–55.

Lieberman, M. T., Wachtmann, L. M., Marin, R. P., Bakhvatchalov, V., & Fox, J. G. (2016). Spontaneous cholelithiasis in a squirrel monkey (Saimiri sciureus). Comparative Medicine, 66, 63–67.

Lombard, L. S., & Witte, E. J. (1959). Frequency and types of tumors in mammals and birds of the Philadelphia Zoological Garden. Cancer Research, 19, 127–141.

Mann, F. C. (1920). The extrahepatic biliary tract in Man. Mansfield, England. Journal of Zoo and Wildlife Medicine, 30, 315–321.

Mann, R. J., Hoopes, P. J., & Bush, M. (1981). Extrahepatic biliary carcinomas in Asiatic bears. Journal of the National Cancer Institute, 66, 603–608.

Moulton, J. E. (1961). Bile duct tumors in two bears. The Cornell Veterinarian.

Munoz, L. E., Boeltz, S., Bilyy, R., Schauer, C., Mahajan, A., Widulin, N., … Neimanis, A. S., Moraeus, C., Bergman, A., Bignert, A., Höglund, J., Lundström, K., Lombard, L. S., & Witte, E. J. (1959). Frequency and types of tumors in mammals and birds of the Philadelphia Zoological Garden. Cancer Research, 19, 127–141.

Mann, F. C. (1924). The functions of the gall bladder. A study of the origins and development of the mammalian biliary tract. New York: Urban & Schwarzenberg.

Oldham-Ott, C. K., & Gilloteaux, J. (1997). Comparative morphology of the gallbladder and biliary tract in vertebrates: Variation in structure, homology and function in function and gallstones. Microscopy Research and Technique, 38, 571–597.

Pagan, O., Völlm, J., Euler, M., Heldstab, A., Bacciarini, L. N., & Gröne, A. (1999). Cholelithiasis in four callitrichid species (Leontopithecus, Callithrix, J. and Zoo and Wildlife Medicine, 37, 44–48.

Pence, D. B., Mollhagen, T., & Swindle, B. (1978). Cholelithiasis in the cottonrat, Sigmodon hispidus. Journal of Wildlife Diseases, 14, 208–211.

Peck, S. F., & Divers, T. J. (2000). Medical treatment of cholangiohepatitis and cholelithiasis in mature horses: 9 cases (1991–1998). Equine Veterinary Journal, 32, 301–306.

Pence, D. B., Molhagen, T., & Swindle, B. (1978). Cholelithiasis in the cottonrat, Sigmodon hispidus, from the high plains of Texas. Journal of Wildlife Diseases, 14, 208–211.

Perera, V., & Rajapakse, R. (2009). Mortality and morbidity of wild elephants (Elephas maximus maximus) of Sri Lanka, as a result of liver flukes (Fasciola jacksoni) infestation. Paper presented at the International Conference on Diseases of Zoo and Wild Animals. The Netherlands: Hvilarenbeek.

Peters, M., Wohlsche, P., & Osmann, C. (2007). Leiomysarcoma of the gallbladder in a giant otter (Pteronura brasiliensis) and a river otter (Lontra canadensis). Journal of Zoo and Wildlife Medicine, 43, 473–478.

Portugaliza, H. P., Romero, S. N., & Bagot, M. A. (2015). Two potentially zoonotic parasites infecting Philippine brown deer (Cervus mamiurus Desmarest, 1822) in Leyte Island. Journal of Advanced Veterinary and Animal Research, 2, 489–493.

Potter, R., & Reineau, O. (2015). Obstructive cholelithiasis and cholecystitis in a kinkajou (Potos flavus). Journal of Zoo and Wildlife Medicine, 34, 145–178.

Prociv, P. (1990). Aberrant migration by Toxocara parasitoides in foxes and dogs - two case reports. Journal of Wildlife Diseases, 26, 532–534.

Sakai, H., Yanai, T., Yonemaru, K., Hagara, A., & Masegi, T. (2003). Gallbladder adenocarcinomas in two captive African lions (Panthera leo). Journal of Zoo and Wildlife Medicine, 34, 302–306.

Schuefl, A., Fritsch, G., Hölte, S., Muehdorfer, K., Ochs, A., Hartmann, D., & Hildebrandt, T. B. (2018). First detection of cholelithiasis and treatment with an enteral radiographic cholangiopancreatography in a Sumatran orangutan (Pongo pygmaeus abeli). Paper presented at the Joint Conference, Prague, Czech Republic: EAZWV/AAZV/Leibniz-IZW Conference.

Schwab, R. G., & Theis, J. H. (1989). Annual cyclicity of gall stone prevalence in deer mice (Peromyscus maniculatus gambelii). Journal of Wildlife Diseases, 25, 462–468.

Sieber, M. S., Correa, P., Dalgaard, D. W., & Adamson, R. H. (1979). Induction of osteogenic sarcomas and tumors of the hepatobiliary system in nonhuman primates with aflatoxin B1. Cancer Research, 39, 4545–4548.

Simmons, P. R., Gibbons, L. M., Khalil, L. F., & Williams, J. L. R. (2005). Cholecystitis in otters (Lutra lutra) and mink (Mustela vison) caused by the fluke Pseudophaneromorphus truncatus. The Veterinary Record, 157, 49–52.

Smith, K. M., Calle, P., Raphael, B. L., James, S., Moore, R., McMoore, D., & Baintchman, E. (2006). Cholelithiasis in four callitrichid species (Leontopithecus, Callithrix, J. and Zoo and Wildlife Medicine, 37, 44–48.

Starost, M. F. (2007). Solitary biliary hamartoma with cholelithiasis in a domestic rabbit (Oryctolagus cuniculus). Veterinary Pathology, 44, 92–95.

Starost, M. F., & Martino, M. (2002). Adenoma of the gallbladder in a chimpanzee (Pan troglodytes). Journal of Zoo and Wildlife Medicine, 33, 176–177.

Thomson, S. C. (1938). Studies in the comparative anatomy of the extrahepatic biliary tract in mammals. Master’s Thesis, Loyola University Chicago, Chicago.

Tucker, M. J. (1984). A survey of the pathology of marmosets (Callithrix jaccus) under experiment. Laboratory Animals, 18, 351–358.

Turumina, J. L., Shantarov, V. A., & Turumina, H. E. (2013). Cholelithiasis in otters (Lutra lutra). Journal of Wildlife Diseases, 29, 177–187.

Vall, Y., Memarian, I., Molzen, M., & Shahidi, A. (2016). Ultrasonicographic characteristics of intestinal ascariasis coincident with cholecystitis and cholelithiasis in Asiatic cheetahs (Acinonyx jubatus venaticus). Paper presented at the Joint Conference AAZV. Atlanta, Georgia: EAZWV and IZW.

Warwick, C., Steelman, C., Jessop, M., Arena, P., Pilny, A., & Nicholas, E. (2018). Exotic pet suitability: Understanding some problems and using a labeling system to aid animal welfare, environment, and consumer protection. Journal of Veterinary Behavior, 26, 17–26.

Williams, B. H., Chimes, M. J., & Gardiner, C. H. (1996). Biliary coccidiosis in a ferret (Mustela putorius furo). Veterinary Pathology, 33, 437–439.