JZAR JOURNAL OF ZOO AND AQUARIUM RESEARCH
www.jzar.org

EAZA

JZAR Review article

OPEN ACCESS

Review article

A review of Asian and African elephant gastrointestinal anatomy, physiology and pharmacology

Whitney Greene[1], Ellen S. Dierenfeld[2], Susan Mikota[3]

[1]Mote Marine Laboratory and Aquarium, 1600 Ken Thompson Parkway, Sarasota Florida 34236 USA
[2]LLC, 4736 Gatesbury Drive, St. Louis, MO 63128, USA
[3]Elephant Care International, 166 Limo View Lane, Hohenwald, TN 38462, USA

Corresponding author: Whitney Greene; WGreeneDVM@gmail.com

Keywords: African elephant, Asian elephant, *Elephas maximus*, gastrointestinal, *Loxodonta africana*, nutrition, pathology, pharmacology, physiology

Article history:
Received: 06 Sep 2017
Accepted: 21 Nov 2018
Published online: 01 Jan 2019

Abstract:
Elephants are susceptible to a variety of gastrointestinal problems. Knowledge of elephant nutrition and gastrointestinal anatomy, physiology and pharmacology is essential for successful treatment, especially because diagnostic options are limited. The horse is considered the most appropriate model for extrapolation to the elephant. While similarities do exist, elephant-specific information is needed, especially in the areas of nutritional requirements. This review presents the current state of knowledge regarding the elephant gastrointestinal system and encourages research in those areas where information is questionable or lacking.

Anatomy

The horse is the closest domestic anatomical and physiological model for the elephant, but the closest evolutionary relatives are sirenians (manatees and dugongs) and hyraxes, members of the taxon, Paenungulata. Female hyraxes have a pair of teats in the axillae and four additional teats in the inguinal area; elephants, dugongs and manatees have a pair of teats near their axillae. Males of all these species lack a scrotum and have intra-abdominal testicles. The tusks of hyraxes and elephants develop from incisor teeth whereas other mammalian tusks develop from canine teeth (Shoshani 2006). The elephant digestive tract consists of the mouth (including proboscis), pharynx, oesophagus, simple stomach, small and large intestines, caecum, rectum and anus. Additional organs, such as molar teeth, tongue, salivary glands, liver and pancreas, complete the gastrointestinal system. Like horses, elephants lack a gall bladder.

The dental formula of adult elephants is I 1/0 C 0/0 PM 3/3 M 3/3. Tusks (upper incisors) are a prominent structure in both male and female African (*Loxodonta africana*) and in male Asian (*Elephas maximus*) elephants; female Asian elephants may have more rudimentary tusks (called tushes).

Elephants have unique dentition; "*Loxodonta*" refers to the lozenge-shape of the enamel loops on African elephants' teeth (Tassy and Shoshani 2013). Both species possess six sets of molars throughout their lifetime. The molars emerge horizontally rather than vertically as in most mammals; the emerging posterior tooth pushes the older anterior tooth forward causing it to break off in sections (Sukumar 2003). The last set of teeth appears around 40 years of age and is usually worn by the age of 60 years. Elephants have the largest-size teeth of any mammal; tusks in African elephants can measure 345 cm (Shoshani and Tassy 1996), and the last molars may be 40 cm long and weigh over 5 kg (Tassy and Shoshani 2013).

The elephant oral cavity is small in comparison to the overall body size. The tongue cannot protrude because the underside is anchored to the floor of the mouth. The tongue can fold in the centre which aids in moving food to the back of the throat. There is essentially no difference between Asian and African

elephant tongues which can weigh up to 12 kg (Dumonceaux 2006). The trunk (proboscis) is a fusion of the nares and upper lip and is used for prehension and drinking, among other tasks. Where the nares enter the skull, muscles and cartilage are present and function as a valve, allowing air to pass when open and the trunk to draw water when closed (Isaza 2006). The trunk can be two meters long (Cavendish 2010) with a capacity of about eight litres (Shoshani and Tassy 1996). Elephants drink 140–200 litres of water per day (Fowler 1986).

Asian and African elephants have active salivary amylase and lysozyme, yet little to no salivary peroxidase activity has been found in either species. Asian elephants have significantly more salivary amylase activity than African elephants (Boehlke et al. 2016). Elephant saliva has an elevated urea content which may signify a recycling mechanism being used by bacteria and protozoa within the digestive tract for metabolic processes (Raubenheimer 1988). Elephants have well-developed salivary glands that can be observed as prominent bulges, particularly in elephants that consume large amounts of browse (*SKM personal observation*).

A pharyngeal diverticulum that holds almost four litres of fluid and functions in sound production is located just caudal to the pharyngeal opening. When the soft palate is elevated, the pouch is able to communicate directly with the oesophagus (Shoshani 2000); this structure has also been proposed as aiding in heat absorption (Tassy and Shoshani 2013). The oesophagus is short and has a narrow lumen lined with mucus glands throughout (Cavendish 2010). A histological study of the oesophagus and stomach of an African elephant revealed similar findings to other monogastric species; the middle portion of the oesophagus is partly glandular with mucus glands present (Stevens and Hume 1995).

The stomach is a simple cylindrically shaped sac that is oriented almost vertically and is able to accommodate a large volume of ingesta, with maximum capacity in an adult Asian female elephant found to be 76.6 litres (Shoshani et al. 1982). The average stomach volume of 10 adult African elephants was 60±5 litres (Van Hoven et al. 1981). Clauss et al. (2007a) found the length of the stomach to be similar between the two species with 1.8 meters in African and 1.4 meters in Asian. There are no glucagon cells in the stomach but there are endocrine cells that are immunoreactive to peptide YY (PYY) which is different compared to other mammals. The function of this is not currently known (Van Aswegen et al. 1994).

Compared to other herbivorous species, elephants have a short intestinal tract. Table 1 presents a comparison of gastrointestinal (GI) anatomical size differences among African and Asian elephants and horses. The intestinal tract of the elephant is three times the length of its body compared to the horse, which has an intestinal tract 12 times its body length (Sukumar 2006). Total gut contents measured 542 kg or 17% of body mass in a 3,140 kg clinically healthy animal that was euthanised (Clauss et al. 2005). Measurements of individual intestinal segments indicate that elephants have a comparatively less capacious caecum and a disproportionally more capacious colon compared to horses (Clauss and Hummel 2005). Figure 1 (A and B) includes relative anatomical depictions of the Asian and African elephant gastrointestinal tracts. The large and small intestines are longer in Asian than African elephants (Clauss et al. 2007a). The caecum, which is of comparable size in African and Asian elephants, comprises approximately 12% of the elephant's body weight, is 1–2 metres in length and extends from the junction of the ileum and the colon. It is a major site of fermentation and contains a large amount of fermenting vegetable matter (Lewis 2017) with an average volume of 90±10 litres (Van Hoven et al. 1981). The large intestine of an adult elephant is approximately 11–13 metres, divided into a 6–7 metre colon, followed by a 3–4 metre rectum, terminating at a muscular anus under the tail (Clauss et al. 2007a). The volume of the large intestine is about 483.2 litres (Shoshani et al. 1982).

The pancreas is adjacent to the duodenum and has both endocrine and exocrine functions (Chandrasekharan et al. 1995). It is transversely elongated in the mesoduodenum (Dumonceaux 2006). Histological findings of the elephant pancreas are similar to those in monogastric animals (Van Aswegan et al. 1996). The liver may have two or three lobes and can weigh 36–45 kg in adult

Table 1: Comparison of size and volume of major gastrointestinal anatomical components of three speciesof three species.

	African Elephant	Asian Elephant	Horse
Stomach (l)	60	76.6	8-15
Stomach (m)	1.8	1.4	<1
Small Intestine (m)	9-15	15-23+	15-22
Cecum (m)	1.5-3	1.5-3	1.25
Cecum (l)	90	90	20+
Large Intestine	10.5-12	10.5-13	7.5-8

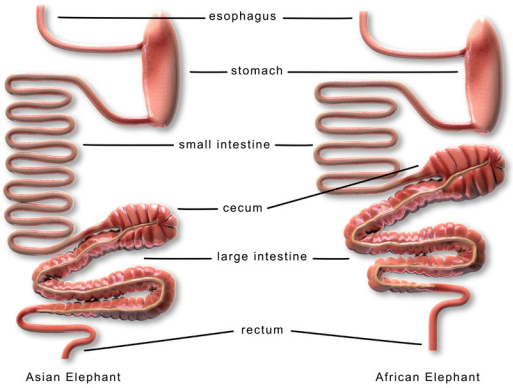

Figure 1: African and Asian elephant gastrointestinal anatomical comparison.

African cows and 59–68 kg in adult bulls (Sikes 1971). Although elephants lack a gall bladder, bile is continuously secreted and passes to the small intestine through multiple ducts (Hashek et al. 2010). Elephants have a large intramural pouch which connects with the bile and pancreatic ducts and opens into the duodenal canal via papilla (Kamiya and Fujita 1966). The bile functions to enhance lipid digestion and absorption throughout the intestine. Elephants, hyraxes and manatees are unique in that they only produce bile alcohols and not bile acids which may predispose them to cholelithiasis, especially in association with bacterial infections (Agnew et al. 2005).

Physiology

Elephants are monogastric herbivorous, non-ruminant, hindgut fermenters. Hindgut fermenters are subdivided into two groups based on the relative size of various digestive organs in relationship to the rest of the system: colonic fermenters are larger species, such as horses and elephants and caecal fermenters are smaller animals such as rabbits and rodents (Clauss et al. 2003a). Hindgut fermenters ingest and process food more rapidly than foregut fermenters; this may have facilitated the evolution of large body size (Clauss et al. 2003b).

Elephants are generalised feeders and use the digestive strategy of passing large amounts of low quality forage through their gut within a relatively short period of time (Loehlein et al. 2003). Larger animals must compensate for physiological disadvantages such as a lower gut surface: gut volume ratio, larger ingesta particle size and greater losses of faecal bacterial material due to increased fermentation. Some adaptations to compensate for these disadvantages include: increased surface enlargement in larger animals, increased absorption rates per unit of gut surface and increased gut motility to enhance ingesta mixing (Clauss et al. 2007b).

Asian elephants digest approximately 40–50% of the forage they consume (Sukumar 2006). Digestion in African elephants can be as low as 22% depending on forage quality (Clauss et al. 2003a; Pendelbury et al. 2005). Studies in elephants have compared apparent digestibility at various sections of the GI tract and found the highest value to occur in the upper portion of the colon (Clemens and Maloiy 1983). In herbivores, an increase in fibre digestibility is not necessarily accompanied by an increase in overall apparent dry matter digestibility, indicating a comparative decrease of the apparent digestibility of non-fibrous materials as well as fibre. This could be due to a reduced use of non-fibre substrates, or an increased loss of endogenous/bacterial substance (Clauss and Hummel 2005).

Gastrointestinal motility depends on a complex interaction of neural, hormonal, vascular and neuromuscular pathways and is defined as the net movement of intraluminal contents (Koenig and Cote 2006). Both motility and GIT transit time are dependent on GIT anatomy as well as the type of food eaten, with a diet higher in non-fibrous components typically displaying a faster transit time than a diet comprising primarily roughage. The mean retention time (MRT) of ingesta appears to be shorter in African than Asian elephants, which could be a result of their shorter digestive tract. African elephants fed timothy hay had a MRT of 22.8±2.1 hours while Asian elephants fed timothy hay had a MRT of 26.6±0.4 hours (Hackenberger 1987; Rees 1982).

Chromium-mordanted fibres, used to measure MRT, were found to yield longer MRT measurements than other methods (Clauss et al. 2007a). Rubber ring and orange peel markers have also been used with no statistical difference seen in the excretion pattern of the rubber rings compared to chromium-mordanted fibre (Hackenberger 1987). In elephants, increased food intake leads to only a very moderate increase of ingesta passage, thus optimising energy gain. This is consistent with the high food intake and long feeding times observed in these animals (Clauss et al. 2007a).

Foose (1982) found that equids tend to have similar feeding and digestive behaviour as elephants. Elephants resemble horses in the way dietary supplements and dietary crude fibre content influence digestibility, calcium absorption parameters, and in faecal volatile fatty acid composition. However, the absolute digestibility coefficients achieved for all nutrients are distinctively lower in elephants compared to other species, due to much faster ingesta passage rates in elephants (Clauss 2003a; Hackenberger 1987).

Asian elephants achieve higher digestion coefficients for dry matter (36–53 vs. 22–42%), hemicellulose (53 vs. 40%), and cellulose (47 vs. 37%) than African elephants when fed comparable diets (Foose 1982; Hackenberger 1987; Clauss et al. 2003a; Romain et al. 2014). This difference between the species may reflect adaptations to different ecological niches, with Asian elephants adapted to a natural diet comprising a higher proportion of grass (Clauss et al. 2007a).

Several anaerobic microbes associated with complex carbohydrate fermentation that have been identified in the caecum and colon of elephants are similar to those found in the rumen and reticulum of ruminants, as well as the hindgut of horses, including Bifidobacteria, considered one of the key genera in animal intestinal tracts. Two unique bacterial species that have been found in elephant faeces are Bifidobacteria boum (12 isolates) and Bifidobacteria adolescentis (14 isolates); (Bunesova et al. 2013). Triplumaria ovina, Raabena bella and Latteuria polyfaria were found in three wild Asian elephants (Gurelli and Ito 2014). Most of the protozoa in the digestive tract of herbivorous mammals belong to the class Kinetofragminophorea in the orders: *Prostomatida*, *Trichostomatida* and *Entodiniomorphida* (Dehority 1986).

In addition to the advantage of hind-gut fermentation, other digestive factors play an important role in explaining terrestrial herbivore body size evolution. Increasing body mass (BM) is associated with diets of lower quality and with mechanisms by which a higher BM correlates with higher digestive efficiency (Clauss et al. 2013). Large herbivores can use low quality forage, giving them greater flexibility in their food selection. This is believed to be due to unique relationships between forage quality and availability, as well as BM and feeding selectivity (Clauss et al. 2013). The proportion of stems, bark and roots eaten by African elephants increased from 30% in the wet season up to 94% in the hot dry season (Owen-Smith and Chafota 2012). This wide range indicates that large body size and hindgut digestion mechanisms may be critically linked with the variety and nutritive quality of plant parts that can be used by elephants.

Recommended dietary nutrient concentrations for captive elephants, compared with horse nutrient requirements (NRC 1989) can be found in Ullrey et al. (1997). These recommendations should be used with caution, especially regarding protein and fibre.

Feeding

Elephants are generalised feeders that consume 1.5–2% of their body weight in DM daily, and spend up to 80% of their day feeding (Sukumar 2003). A mature horse consumes typically 2–2.5% of its BW in DM on a daily basis. The feeding patterns and behaviour of both Asian and African elephants has been attributed to multiple factors and the variation is mainly attributable to habitat and season (Dierenfeld 2006).

Feeding patterns of wild Asian elephants are strongly bimodal, with peaks in the morning and evening. In contrast to the findings of Clauss et al. (2005), a study comparing feeding strategies found that wild Asian elephants spent more time browsing than grazing. Elephants spent less time feeding during the dry season than in

Table 2: Gastrointestinal disorders in Asian and African elephants. Note: All treatment references are elephant specific unless otherwise noted.

Disease	Description	Etiology	Clinical Signs	Treatment	Complications/notes
Bloat	Any abnormal general swelling, or increase in diameter of the abdominal area	Excessive fibrous foodstuff, eating sand and gravel, dry fodder, liver disease and intestinal parasites	Dullness, constipation, straining, anorexia, dehydration, hyperthermia, restlessness, may see mild jaundice	Supportive therapy; per rectum neurostimulation; antibloat agents; rectal enemas; exercise; flunixin meglumine (Miller et al. 2015)	Intestinal rupture, areas of gangrenous intestines (sometimes associated with rupture), intestinal mucosal ulceration
Cholelithiasis	The presence of gallstones	Unknown, however cholangiohepatitis or intestinal bacterial infection that result in bile stasis and change in bile composition have been suggested as probable predisposing factors	Often no clinical signs present in horses; in a single case report in a horse, chronic anorexia may have been associated with cholelolithiasis (da Silva et al. 2014)	In horses: supportive care, antiinflammatories, antibiotics (Davis and Jones 2003); findings in elephants have been at necropsy	May lead to biliary obstruction and concurrent liver disease
Clostridium difficile	Gram-positive, anaerobic, motile, spore-forming bacteria. Overgrowth causes pseudomembranous colitis in humans, hamsters and guinea pigs, and haemorrhagic necrotizing enterocolitis in foals	Normal microbe of GI tract in healthy elephants but disturbances to the normal flora in GI tract affect microbial growth	Altered behavior, depression, anorexia, listlesness, fever, emphysema	Metronidazole: 0.125-4.0 µg/ml and Vancomycin: 0.125-2.0 µg/ml (Sthitmatee et al. 2013)	A large amount of broccoli, which contains substantial amounts of sulforaphane, a substance known to have an antimicrobial effect on various micro-organisms of the human gut, had been fed to the elephants shortly before the outbreak of disease (Sthitmatee et al. 2013; Bojesen et al. 2006)
Clostridium perfringens	Clostridum perfringens biotypes (A-E) produce different enterotoxins (alpha, beta, epsilon and iota) which cause enterotoxemia in animals	Young animals are considered especially susceptible	Anorexia, fatigue, severe foul-smelling diarrheoa,behavioral changes, signs of circulatory deficiency, recumbency, shock	Fluid therapy, antibiotics (Ampicillin and Kanamycin), probiotics, gastroprotectants, antiinflammatories, glucose, corticosteroids, antitoxin (Dumonceaux 2006)	Can lead to enterotoxemia. A study of intestinal sections of three other elephants without intestinal disease revealed that strains of beta 2- toxigenic Clostridum perfringens do not occur in healthy elephants, therefore their isolation in sick animals may signify their role in enteric disease (Salzert 1982)
Colibacillosis	A group of diseases caused by pathogenic strains of Escherichia coil. E coli is a Gram-negative, lactose-fermenting, indole-positive rod	Often seen in young, immune-compormised animals that have not received adequate colostrum	Severe diarrheoa, anorexia, decreased water consumption, depression, behavioral changes	Supporthive therapy. Kaolin mixture with Belladonna (500g for 2000 kg) and suspension Lepromide 5mL/10kg body weight BID or TID (Subramanian 2006)	Common in young elephants who have not received adequate colostrum
Constipation	Difficulty in emptying the bowels, usually associated with hardened feces	Eating of excessive fibrous food stuff, dehydration, poor teeth quality, intestinal parasites	Dullness and depression, no feces or small and dry feces being passed, tenesmus, straining, anorexia, restlessness, dehydration, bloat	Fluids; rectal palpation; manual evacuation of stool, supportive therapy; enemas; purgatives; rest; broad-spectrum antibiotics; parasympathomimetics; spasmolytics (Miller et al. 2015); calcium borogluconate intravenously and calcium pantothenate intramuscularly (Radhakrishnan K 1989)	In some severe cases, constipation has been reported to lead to periotinitis and intestinal rupture (Klos and Lang 1982)
Diarrheoa	Frequent discharge of faeces from the bowel often in liquid form	Often unknown, bacterial, foreign body ingestion, parasites, nutritional disorders (Mikota et al. 1994)	Loose or watery stool (sometimes with undigested feed particles), behavioral changes, loss of appetite	Antibiotics; fluids; diet correction; astringents; antiparasitics; faecal culture (Miller et al. 2015)	Dehydration
Oesophogeal obstruction	Narrowing or complete obstruction of the esophagus caused by food material	Prior esophageal trauma, dental disease, and inappropriate food items (Bilkslager and Jones 2009)	Dysphagia, regurgitation, hyporexia, increased salivation (Phair et al. 2014)	Removal of material, intravenous and rectal fluids, anti-inflammatory and antibiotic administration, and fasting (Phair et al. 2014)	Oesophageal dissection, mural hematoma, and secondary bacterial infection (Phair et al. 2014)

Table 2: Gastrointestinal disorders in Asian and African elephants. Note: All treatment references are elephant specific unless otherwise noted (continued).

Disease	Description	Etiology	Clinical Signs	Treatment	Complications/notes
Gastritis	Inflammation of the lining of the stomach	Dietary indiscretion or intolerance, drug or toxin ingestion (antibiotics, NSAIDs, corticosteroids, plants, chemicals), systemic illness, endoparasitism, bacterial, or viral infection	Poor appetite, colic, behavioural changes, poor behaviour	H2 antagonists, omeprazole (must be given intact), sucralfate (Dumonceaux 2006)	Dehydration, ulceration can lead to acute or chronic blood loss
Impaction/ obstruction	Obstruction of feed/faecal material in the GI tract	Dehydration, poor teeth quality, abundance of fibrous feed, dietary indiscretion or intolerance	Dullness and depression, no feces or small and dry faeces being passed, tenesmus, straining, anorexia, restlessness, dehydration, bloat; tachycardia, restlessness, abdominal distension, lack of borborygmi, left shifted leukogram, streching, tenesmus (Wiedner et al. 2012)	Oral fluids and mineral oil, flunixin meglumine (1.75 mg/kg IM BID); Butorphanol 0.1mg/kg IM; Bismuth salicylate (Wiedner et al. 2012); supportive therapy; enemas; purgatives; rest; parasympathomimetics; spasmolytics (Miller et al. 2015)	Intestinal perforation or rupture; peritonitis, septicemia
Intussusception	The invagination of one portion of the gastrointestinal tract into the lumen of the adjacent portion	Intussusception results from abnormal peristalsis. Vigorous contractions force the more proximal intestine to invaginate into the adjacent distal portion, taking its mesenteric attachment with it. It can be caused due to:enteritis, foreign body, changes in diet, motility disorders, bacterial, parasitism	Diarrheoa, colic, inappetance, behavioral changes	Fluid therapy, correction of acid-base imbalances	One case of intussusception in an elephant found on necropsy and believed to be a result of parasite load leading to decreased peristalsis which resulted in intussusception (Chakraborty A., et al. 1992). Major complications include peritonitis and perforation
Malassimilation	A decreased ability of the GI tract to incorporate nutrients into the body, either due to maldigestion, transport, or malabsorption	Alterations in gastric function or activity of microflora, abnormal bacterial proliferation in the small intestine, a decrease or lack of small-intestinal brush border enzyme activity, lack or inactivity of pancreatic enzymes	Cachexia, diarrheoa, ventral edema, low serum alkaline phosphatase concentrations, sporadic hyperbilrubinemia, hypoproteinemia/ hypoalbuiminemia, intermittent hypoglycemia, hypertriglyceridemia, sporadic leukocytosis, neutrophilia/ neutropenia, and lymphocytosis (Heard et al. 1988)	Monitor vitamin and mineral levels in blood; nutritional supplements (Miller et al. 2015)	Recurrent dental disease might have accounted for some of the clinical findings including cachexia in a juvenileAfrican elephant. The cause or causes of the diarrhea were not determined but the condition spontaneously resolved (Heard et al. 1988)
Parasites	Intestinal parasites can be worm-like or single-celled and lead to a wide range of symptoms from mild to severe	Can be caused by many etiologies pending on the parasite	Anorexia, diarrheoa, eating of soil, anemia, emaciation,	Fenbendazole 5mg/kg PO (Rao et al. 1992; Roy and Mazumdar 1988); Thiophanate 14 mg/kg PO (Chandrasekharan et al. 1979)	Dehydration, weight loss, impaction, hemorrhagic diarrheoa
Salmonella	A rod-shaped gram-negative bacterium belonging to the family Enterobacteriaceae; 2000 serovars/serotypes	Recognized in all parts of the world but is most prevalent in regions with intensive animal husbandry; commonly found in an environment subject to faecal contamination	Exotoxins result in severe GI disease, septicemia	Ampicillin 6g PO BID then switched to Chloramphenicol 5g IM BID (Chooi, K.F., and Zahari., 1988); aggressive fluid therapy, antibiotics, probiotics, antiinflmmatories	Most widespread zoonosis in the world; diagnosed by fecal culture; should be on the differential list for animal animal presenting with diarrheoa
Torsion	Torsion (volvulus) occurs when the stomach or a part of the intestine rotates around itself and the mesentery that supports it	Often caused secondary to gastrointesintal stasis and/or abnormal peristalsis	Tachycardia, restlessness, abdominal distension, lack of borborygmi, left shifted leukogram, streching, tenesmus (Wiedner et al. 2012)	Oral fluids and mineral oil, flunixin meglumine (1.75 mg/kg IM BID); Butorphanol 0.1mg/kg IM; Bismuth salicylate (Wiedner et al. 2012)	Intestinal rupture, septicemia

Table 3: GI Pharmacology with specific reference to equine and elephant treatment.

Classification	Sub-classification	Uses	Mechanism of Action (MOA)	Examples	Elephant specific	Equine Doses	Adverse Effects	Notes
Antacids	Systemic	Decreases stomach acidity and excess gas	Reduces the total acid load in the GI tract; elevates gastric pH to reduce pepsin activity; helps strengthen gastric mucosa	Sodium bicarbonate	No information published	0.5-1mEq/kg IV slowly; 10-12 grams PO to adult large animals (Papich 2016)	Antacids can interfere with gastric absorption of concurrently administered drugs; Excess sodium may result in alkaline urine and systemic alkalosis	soluble, readily absorbed and capable of changing the pH of extracellular fluid; produce systemic alkalosis
	Non-systemic		Neutralize HCl, bind bile acids, decrease pepsin activity, stimulate local PGE1 production	Alluminum hydroxide, magnesium hydroxide, calciuym carbonate, combined antacids	No information published	Aluminum/magnesium hydroxide suspension: 15 ml 4 times a day (Clark and Becht 1987)		form insoluble compounds; poor absorption capacity; do not produce any systemic effects
Anticholinergics	Antimuscarinic	Block acetylcholine in the central and peripheral nervous systems. Used to treat gastrointestinal disorders including gastritis, diarrhea, colitis, and nausea	Antispasmodics directly relax smooth muscle; competitively antagnoize the actions of acetylcholine and other cholinergic agonists within the PNS	Atropine, Glycopyrrolate, Propantheline bromide, Scopolamine hydrobromide	150 mg atropine and 6 mg etorphine were administered simultaneously IM to a 3500 kg female African elephant on two occasions (Dunlop et.al. 1988)	Atropine: 0.014 mg/kg IV; Glycopyrrolate: 2–3 mg IM BID-TID (Dowling, 2015)	Tachycardia, cardiac arythmias, mydriasis, sedation, confusion	An Asian elephant became agitated following the IV administration of atropine (0.05 mg/kg) administered IV 90 minutes after azaperone was given (Gross et.al. 1994)
Antidiarrheal		Stops diarrheoa	Decrease stool water content; inhibits GI mobility and propulsion; bismuth preparations have a mild water-binding capacity	Activated charcoal, Bismusol, Loperamide, Paregoric	No information published	Activated charcoal: Foals: 250 grams (minimum). Adult horses: up to 750 grams (Oehme 1987) 1 g/kg PO ; Bismuth salicylate: up to 4 L (500 kg horse) PO BID; 30 ml q4h (foal); Loperamide: 0.04-0.2 mg/kg PO BID (Munrow, 2011) ; Paregoric: Foals: 15 - 30 ml PO; Adults: 15 - 60 ml PO (Cornell 1985)	May cause constipation, bloat and sedation. Use with caution in cases of acute diarrhea	
Antiemetics	Antihistamine	Stops or prevents vomiting and nausea	Antihistamines (H1-receptor antagonists) competitively inhibit histamine at H1 receptor sites and block the action of histamine on effector cells	Chlorpheniramine maleate, Hydroxyzine	Pheniramine: 1700-2300 mg/animal in Asian elephants (Cheeran et al. 1995)	Hydroxyzine: 0.5 - 1 mg/kg IM or PO BID (Robinson 1992)	CNS depression, vomiting, diarrhea	Use with caution in animals with hyperthyroidism, cardiovascular disease, or seizure history
	Substituted Benzamides	Used for the control of vomiting	Neuronal 5-HT4 agonism enhances cholinergic transmission in the myenteric plexus	Metoclopramide, Cisapride	250-400 mg/elephant IV as an antiemetic (Cheeran, 1995)	Continuous infusion at 0.04 mg/kg BW/h (Dart et al., 1996)	Sweating, excitement, and restlessness (Metoclopramide)	Metoclopramide restored gastric emptying in horses but had significant side effects. Cisapride has been reported to have similar positive effects and less adverse effects

Table 3: GI Pharmacology with specific reference to equine and elephant treatment (continued).

Classification	Sub-classification	Uses	Mechanism of Action (MOA)	Examples	Elephant specific	Equine Doses	Adverse Effects	Notes
	Dopamine antagonists	Used for the control of vomiting	Selective peripheral dopamine (DA2 receptor) antagonist	Domperidone	No information published	0.2 mg/kg BW, IV (King and Gerring, 1989)	May cause gastropareses, cardiac arythmias, or kypokalemia	Doperidone has similar actions as metoclopramide but does not appear to cross as readily into the CNS therefore believed to not have the same CNS signs as metoclopramide
Anti-inflammatory	NSAID	Anti-inflammatory, anti-pyretic, analgesia	Inhibits cyclooxygenase catalysis of arachidonic acid to prostaglandin precursors, thereby inhibiting the synthesis of inhibition of cyclooxygenase catalysis of arachidonic acid to prostaglandin precursors (endoperoxides), thereby inhibiting the synthesis of prostaglandins in tissues	Flunixin meglumine, Phenylbutazone, Ketoprofen, Ibuprofen	• Flunixin meglumine: 1 mg/kg every 24 hours (route of administration not specified) (Mortensen, 1998); 0.28-1.1mg/kg PO SID-BID (African and Asian) (Kottwitz et al 2016) • Ibuprofen: 6mg/kg PO BID (Asian), 7mg/kg PO BID (African) (Bechert and Christensen, 2007); 1-6mg/kg (Asian) 1-7mg/kg (African) PO SID-BID (Kottwitz et al 2016) • Ketoprofen: 1-2mg/kg every 24-48 hours IV (Hunter et al 2003); 2700mg IM (Phair et al., 2014) • Phenylbutazone: 0.25-6mg/kg PO SID-BID (Kottwitz et al 2016); 3mg/kg PO q48 hours (African), 2mg/kg PO q48 hours (Asian) (Bechert et al. 2008); 1-2mg/kg SID (Mortensen 1998, 2001)	• Carprofen (0.7 mg/kg, IV) (Matthews and Carroll 2007; Papich 2016) • Dipyrone: 1.1 mg/kg IV, or 500 mg/450kg (Abrahamsen, 2009) • Flunixin Meglumine: 1.1mg/kg IV or IM q24 hours up to five days; 1.1mg/kg PO SID (paste and granules) (Papich 2016) • Ketoprofen: 2.2-3.3 mg/kg/day IV or IM (Papich 2016) • Meloxicam (0.6 mg/kg, IV) (Matthews and Carroll 2007) • Phenylbutazone 4.4-8.8 mg/kg/day PO; 2.2-4.4mg/kg/day for 48-96 hours IV (Papich 2016)	Gastrointestinal ulcers/ perforations, liver, and kidney toxicity	Fluinixin Meglumine: in horses with colic are often treated with low doses of 0.25mg/kg IV q8 hours (Papich 2016)
Antispasmodic	Benzodiazepines# and nonbenzodiazepines	Relieves spasms in the gastrointestinal tract	Blocks the action of acetylcholine on the receptors found within the smooth muscle of the gastrointestinal and urinary tract and thus reduces spasms and contractions	Buscopan	20 mg/mL ampoules, 10-12 ampoules, 200-240mg injections (Gairhe, 2012)	0.15-0.3 mg/kg IV, or 67.5-135 mg/450kg (Abrahamsen, 2009)	Transient tachycardia, decreased borborygmy, transient pupillary dilation may also be observed.	

Table 3: GI Pharmacology with specific reference to equine and elephant treatment (continued).

Classification	Sub-classification	Uses	Mechanism of Action (MOA)	Examples	Elephant specific	Equine Doses	Adverse Effects	Notes
Histamine (H2) receptor antagonists		Treats and prevents gastric ulcers by causing a decrease in acid	Inhibits histamine action at H2 receptors in gastric parietal cells, reduces gastric acid output and concentration	Cimetidine, Famotidine, Omeprazole, Ranitidine	Omeprazole: 10,800MG PO (Phair et al. 2014)	Famotidine: 2.8mg/kg PO q12 hours; 0.3mg/kg IV q12 hours; Omeprazole: 4mg/kg q24 hours; Ranitidine: 6.6mg/kg {P q8 hours; 1.5mg/kg IV q6hours (Andrews, 2012)	Diarrhea has been reported in dogs on omeprazole, minimal side effects for other drugs but some CNS signs have been reported in animals with decreased renal clearance	Omeprazole is encapsulated and must be given intact for maximum effectiveness (Dumonceaux, 2006)
Laxitives	Bulk forming	Stool softener	Uses fiber to draw water into the bowel --> increase mass of stool --> distension --> enteric reflexes --> increases GI motility	Psyllium	No information published	500g in 2-4 liters of mineral oil via nasogastric tube q24 hours for 3-5 days (Sanchez, 2015).	Minimal adverse effects. Intestinal impaction can occur with overuse or in dehydrated animals	Site of Action: small and large intestines
	Emollient	Stool softener	Contains anionic surfactants that enable additional water and fats to be incorporated in the stool, making it easier for them to move through the gastrointestinal tract	Docusate	10 to 30 mg/kg as a 10% solution	5-10mcg/kg/min (0.005-0.01 mg/kg/min) IV infusion (Papich, 2011)	DSS should not be administered to horses with sand impaction because it may cause sand to become more solidified (Moore and Leise, 2009). Serious side effects reported in horses. Single doses of 0.65 - 1.0 g/kg can lead to dehydration and damage to the intestinal mucosa which can be fatal (Plumb, 2008)	Site of action: small and large intestines Some evidence that DSS increases colonic mucosal cell cAMP concentration and thus increases both ion secretion and fluid permeability
	Hyperosmolar/ osmotic	Laxative	Hyperosmotic laxatives are substances that cause the intestines to hold more water within and create an osmotic effect that stimulates a bowel movement	Magnesium sulfate, Lactulose, Phosphate enemas, Miralax	No information published	0.1-0.2mL/kg PO q8-24 hours (Hallowell, 2008); 333 mg/kg PO (Scarratt and Warnick, 1998)	Dehydration, electrolyte loss, colic, diarrhea, gas	Site of Action: colon Poorly absorbed in the GI tract but osmotically active
	Stimulant	Most powerful laxative type	Stimulant laxatives are substances that act on the intestinal mucosa or nerve plexus, altering water and electrolyte secretion. They also stimulate peristaltic action	Bisacodyl, Docusate sodium, Glycerol	Bisacodyl: 300mg PO BID for 3-5 days; suppositories: 400mg applied to rectal mucosa q12 hour intervals (Greene et al., 2018; Silva and Dangolla, 2006)	DSS: 10–20 mg/kg in 2 L water (Robinson, 1997)	Dehydration, electrolyte loss, colic, diarrhea, gas	Site of Action: colon reported to be minimally absorbed after oral administration. Bisacodyl should not be given concurrentl;y with antacids as both can cause premature disintegration of enteric coating

Table 3: GI Pharmacology with specific reference to equine and elephant treatment (continued).

Classification	Sub-classification	Uses	Mechanism of Action (MOA)	Examples	Elephant specific	Equine Doses	Adverse Effects	Notes
	Lubricant	Stool softener/ laxative	Coats the stool with lipids and retards colonic absorption of water--> stool slides through the colon more easily	Mineral oil, paraffin	No information published	Mineral oil: up to 4 L SID to BID via nasogastric tube (Moore and Leise, 2009)	Dehydration, electrolyte loss, colic, diarrhea, gas	Chronic administration of mineral oil may affect Vitamin K and other fat soluble vitamin absorption; Lubricant laxatives increase the weight of stool and decrease intestinal transit time
	Stimulant	Most powerful laxative type	Stimulant laxatives are substances that act on the intestinal mucosa or nerve plexus, altering water and electrolyte secretion. They also stimulate peristaltic action	Bisacodyl, Docusate sodium, Glycerol	Bisacodyl: 300mg PO BID for 3-5 days; suppositories: 400mg applied to rectal mucosa q12 hour intervals (Greene et al., 2018; Silva and Dangolla, 2006)	DSS: 10–20 mg/kg in 2 L water (Robinson, 1997)	Dehydration, electrolyte loss, colic, diarrhea, gas	Site of Action: colon reported to be minimally absorbed after oral administration. Bisacodyl should not be given concurrentl;y with antacids as both can cause premature disintegration of enteric coating
Gastroprotectant		Protect and coat the lining of the stomach and upper GI	A locally acting substance that reacts with Hcl acid in the stomach to form a material capable of acting as an acid buffer. It attaches to proteins on the surface of ulcers to form stable insoluble complexes which serve as protective barriers at the ulcer surface, preventing further damage from acid, pepsin, and bile. It also prevents back diffusion of hydrogen ions, and adsorbs both pepsin and bile acids	Sucralfate	No information published	20-40mg/kg PO q8 hours (Andrews, 2012); 2 mg/kg PO tid; Foals: 1–2 g, QID (Robinson, 1992)	Side effects rare. Most commong: diarrhea, vomiyting, lethargy	In horses it is usually is used with an H2 receptor antagonist or a proton pump inhibitor such as omeprazole

Table 3: GI Pharmacology with specific reference to equine and elephant treatment (continued).

Classification	Sub-classification	Uses	Mechanism of Action (MOA)	Examples	Elephant specific	Equine Doses	Adverse Effects	Notes
Prokinetic	Adrenergic antagonists	A sympatholytic that inhibits the action of catecholamines at the adrenergic receptors	Sympatholytic agents that block alpha-2 receptors within the enteric nervous system and allow release of ACh from cholinergic neurons	Yohimbine, Acepromazine, Phenoxy-benzamine	Asian elephants: For sedation: 0.04-0.08 mg/kg (180-360 mg total dose); For immobilization 0.15-0.20 mg/kg alone or 0.12 mg/kg xylazine in combination with 0.33 mg/kg ketamine. Captive African elephants: For sedation: 0.08-0.10 mg/kg (100-640 mg total dose); For immobilization (opiates are preferred): 0.15-0.20 mg/kg xylazine; For babies and juveniles: 0.14 mg/kg xylazine in combination with 1.14 mg/kg ketamine (Fowler, 1995). 0.10-0.11 mg/kg xylazine IM for Asian elephants; can be combined with acepromazine or ketamine (Nayer et.al. 2002).	Xylazine: for colic 0.22-0.66 mg/kg IV, or 100-300 mg/450kg (Abrahamsen, 2009); Phenoxybenzamine (200 mg diluted in 500 mL sodium chloride) (Beadle et al., 1986)	Sedation, ataxia, altered blood pressure, vomiting, diarrhea	Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Yohimbine has been reported to produce a variety of responses in horses (excitation, rearing, striking, muscle tremors) and has resulted in increased heart rate observed in horses
	Cholinomimetic	A parasympathomimetic drug that stimulates the parasympathetic nervous system (PSNS).	Increases acetylcholine (Ach) either by stimulating ACh receptors (directly acting parasympathomimetic agents) or by inhibiting cholinesterase (indirectly acting parasympathomimetic agents)	Bethanechol chloride, Neostigmine methylsulfate	Neostigmine: 4-5 mg/animal IM as a purgative in impactions; author's clinical experience (Cheeran, 1995).	Bethanechol chloride: 0.025 mg/kg BW, IV (Lester et al., 1998) Neostigmine methylsulfate: 5-10 mg IM or SQ (Van Hoogmoed and Nieto, 2003)	Increased salivation and mild abdominal pain (Bethanechol chloride); increased gastric secretion, delayed gastric emptying, and abdominal pain (Neostigmine methylsulfate) (Koenig and Cote 2006)	

the wet season (22–60% time feeding in the dry season vs. 52–72% time feeding in the wet season) and feeding time decreased (r=−0.767) with increasing ambient temperature (Baskaran et al. 2010). Peak feeding times for wild African elephants were between early morning and late afternoon (Guy 1976).

Animal behavioural choices can shape the way a species evolves. Grazing animals evolved from browsers (Janis 2008) and for proboscideans, teeth only started to evolve after their diet changed, thus supporting the idea that behaviour shaped the evolutionary change (Lister 2013). Asian elephants have more tightly compressed teeth, possibly a result of their tendency to eat more grasses than leaves compared to African elephants.

African elephants are mixed feeders. They prefer grasses, but also consume leaves, branches, tree bark (Anderson and Walker 1974) and at times shrubs (Owen-Smith and Chafota, 2012). The natural diet of the Asian elephant typically includes a higher proportion of grasses but is habitat dependent (Dierenfeld 2006). Asian elephants are more likely to consume browse during the dry season, while both species browse and consume grasses during the rainy season (Koirala et al. 2016). Elephants favour leaves and twigs more than other plant parts and there is a negative correlation between plant availability and preference. This suggests that food selection is not passively driven by relative availability, but related to specific individual preferences (Koirala et al. 2016).

Geriatric animals may encounter difficulties feeding when their last set of molars are in wear and especially after this final set is lost. The inability to mechanically break down food can lead to GI problems such as: colic, impactions, malabsorption and weight loss. In nature, older African elephants with little molar surface remaining often stay in swamp or river bank areas and eat soft moist stems of low sedges, rushes and papyrus (Sikes 1971). Some diet modifications that can be applied to geriatric Asian elephants in captivity include: changing from a pelleted dry product to a softer pellet designed for older horses; adding soaked beet pulp, wheat bran and/or psyllium husk twice a week (for combined soluble and insoluble fibre sources as prophylaxis against impaction); and using chopped hay (Greene et al. 2018). One author (SKM) has observed soft rice-based gruels used for geriatric elephants in Asia. Vitamin E is another useful addition to help promote peristalsis and smooth muscle tone and has also been used in horses (Siciliano et al. 1997).

Gastrointestinal Pathology

Gastrointestinal disease has been reported as one of the most common syndromes responsible for elephant morbidity (Miller et al. 2015). GI tract pathologies are due to impairment of one or more of the basic functions of the tract including: secretion, absorption and/or motility. Table 2 provides a summary of GI diseases in elephants.

Colic is common in both horses (Bernard 2004) and elephants, but unlike horses, elephants often show more subtle signs of discomfort. In adult elephants, inappetence or minor changes in behaviour are often the only signs. Diagnosis and treatment for GI disorders can prove difficult, thus a strong relationship and knowledge of the animal is vital to identify disease early. Two types of colic have been described in elephants, spasmodic and obstructive (Du Toit 2001). Spasmodic colic has been treated successfully with Buscopan injections in both elephants and horses (Gairhe 2012; Abrahamsen 2009). Obstructive colic results when faecal material is unable to move through the intestinal tract. In Asian elephants, obstructive colic is often linked with feeding coarse stems from banana plants and/or other high fibre food stuffs, defective teeth and/or poor chewing (Cheeran and Chandrasekharan 2006). Colic and impactions have been successfully treated with psyllium powder (200 g), pain management, and supportive care (Warren et al. 1996). The longest successfully resolved impaction case in an elephant lasted 75 days (Cheeran and Chandrasekharan 2006). Psyllium powder at a dosage of 200g PO daily was used successfully to treat clay impactions in a two-year old Asian elephant (Warren et al. 1996). Horses that live in a sandy environment or that persistently develop impactions are given psyllium at 400 g/500 kg/day in their feed daily for seven days. This treatment is repeated prophylactically two or three times per year (Moore and Leise 2009). In addition to anti-inflammatory medications, muscle relaxants such as diazepam have been used for the treatment of obstructive colic (Firyal and Naureen 2007). Vitamin E supplements have also been helpful in alleviating colic in horses, and may also be applied to elephants.

Gastrointestinal parasites can lead to varying levels of pathology. Smith et al. (1982) found the gut microfauna of captive elephants to be less varied than wild elephants. In a study of African elephants at the Chad Basin National Park, 37% of 274 elephants were infected with GI parasites; strongyloides, coccidia and strongyles were found most often. The parasite burden and prevalence according to sex and age were highest in August (rainy season), with males and young displaying higher parasite loads than their counterparts (Mbaya et al. 2013). Five elephant-specific nematode parasites in the Strongylidae family have been found in African elephants: *Murshidia linstowi, Murshidia longicaudata, Murshidia africana, Quilonia africana,* and *Khalilia sameera.* Levels of genetic diversity in strongyles from elephants are consistent with the genetic diversity seen within other strongyle species (McLean et al. 2012).

Gastrointestinal Pharmacology and Treatment

Most of the current knowledge on drug dosage and administration in elephants has been extrapolated from equine medicine. Table 3 lists the classes of GI drugs and dosage and administration information for horses and elephants.

Administering medication to elephants can be challenging. Oral administration can be difficult, especially in a sick elephant that refuses to eat. Oral administration of antimicrobials may adversely affect the colonic microflora. Intramuscular injections (IM) can inadvertently be deposited subcutaneously (SQ) which can affect drug absorption (Isaza and Hunter 2004). Proper skin cleansing is essential to prevent abscess formation at IM injection sites. Perivascular injection or prolonged use of IV catheters can result in ischemic necrosis of the external pinnae.

In most cases of GI disease, fluid therapy is vital. Adult elephants require 30–50 mL/kg/day for maintenance, and requirements for younger animals may be higher (Fowler 1986). Extrapolating from the horse, adult elephants may require 40–60 mL/kg/day and calves 100–120 mL/kg/day (Mikota 2006). Sick animals may need two to four times this amount daily (Isaza and Hunter 2004; Fowler 1986). Providing even maintenance fluid needs requires the use of several large bore catheters and large amounts of fluids. The rectal mucosa provides an absorptive surface comparable to the upper GI tract, and rectal fluid administration can be used in place of IV administration or in conjunction. Rectal fluid therapy was successful in maintaining adequate hydration of a completely obstructed elephant (Greene et al. 2018).

Analgesia in another important component for the treatment of GI disease. Kottwitz et al. (2016) conducted an analgesia survey for elephants and rhinoceros and divided analgesia into three categories: NSAIDs, opioids and other non-NSAID-

non-opioid drugs. The most commonly used NSAIDs in elephants included: phenylbutazone, flunixin meglumine and ibuprofen. Other NSAIDs were reported to be used but less frequently and included ketoprofen, firocoxib, carprofen, meloxicam, acetaminophen, vedaprofen, etodolac and asprin. The most commonly used opioids were tramadol and butorphanol (Kottwitz et al. 2016).

The use of alternative therapies for the treatment of GI disease in elephants is limited. Faecal transfaunation has been used extensively for its success in treating recurrent *Clostridium difficile* infection in humans. There are reports of successful use in equine medicine (Mullen et al. 2018; Schoster et al. 2014), one case with elephants (Greene et al. 2018) and many anecdotal cases in other species. It has been effective in horses with acute colitis or chronic diarrhoea (Feary and Hassel 2006) and may have lasting effects on microbial colonisation (Grehan et al. 2010).

Mikota (2016) developed an elephant acupuncture chart that was used as adjunct treatment of a completely obstructed elephant (Greene et al. 2018). There are a few reports of acupuncture being used in equine GI disorders (Dill and Bierman 2001; Fleming 2001) and many in domestic species. Information is lacking about herbal remedies for GI disease in elephants.

Conclusion

The elephant has unique anatomy and physiology that necessitates specific nutritional requirements. Gastrointestinal disease is often multi-factorial and treatment may require innovation. Drug dosages for elephants are often extrapolated from the equine literature; however, there is a need for pharmacokinetic studies in elephants as well as further investigation of alternative treatments such as acupuncture and faecal transfaunation. We hope that this review not only summarises current knowledge, but also encourages additional research.

Conflict of Interest: The authors declare no conflict of interest.

Acknowledgements

The authors gratefully acknowledge Mr. John Liebler from Art of the Cell for developing the comparative elephant GI image used in this paper. We would also like to thank Dr. Jennifer Buur of Western University of Health Sciences College of Veterinary Medicine for her help and expertise in reviewing the GI drug table.

References

Abrahamsen A. (2009) Options for managing colic pain. *Hagyard Equine Medical Institute's Pain Management Seminar*, Ocala, Florida.

Agnew D.W., Hagey L., Shoshani J. (2005) The elephant of Zoba Gash Barka, Eritrea: Part 4. Cholelithiasis in a wild African elephant (*Loxodonta Africana*). *Journal of Zoo and Wildlife Medicine* 3614(677): 677–683.

Anderson G.D., Walker B.H. (1974) Vegetation composition and elephant damage in the Sengwa Wildlife Research Area, Rhodesia. *Journal of the South African Veterinary Association* 1–14.

Andrews F.M. (2012) Gastric Ulcers: a pain in the gut! *The Practitioner* 3: 1–13.

Baskaran N., Balasubramanian M., Swaminathan S., Desai A.A. (2010) Feeding ecology of the Asian elephant *Elephas maximus* linnaeus in the Nilgiri Biosphere reserve, Southern India. *Journal of the Bombay Natural History Society* 107(2): 3–13.

Beadle R., Brooks D., Martin G. (1986) Phenoxybenzamine as an adjunct in the therapy for ileus in the horse. *Proceedings of the Second Equine Colic Research Symposium* Athens, Georgia, 112–115.

Bechert U., Christensen, J.M., Nguyen C., Neelkent R., Bendas E. (2008) Pharmacokinetics of orally administered phenylbutazone in African and Asian elephants (*Loxodonta africana* and *Elephas maximus*). *Journal of Zoo and Wildlife Medicine* 39: 188–200.

Bechert U., Christensen, J.M. (2007) Pharmacokinetics of orally administered ibuprofen in African and Asian elephants (*Loxodonta africana and Elephas maximus*). *Zoo Wildlife Medicine* 38: 258–268.

Bernard W. (2004) Colic in the foal. *Equine Veterinary Education* 16:319–323.

Blikslager A.T., Jones S.L. (2009) Disorders of the esophagus. In: Smith B.P, (ed.). *Large animal internal medicine*. St. Louis, Missouri: Mosby Elsevier, 688–695.

Boehlke C., Potschke S., Behringer V., Hannig C., Zierau O. (2016) Does diet influence salivary enzyme activities in elephant species? *Journal of Comparative Physiology B* 187(1): 213–226.

Bojesen A.M., Olsen K.E., Bertelsen M.F. (2006) Fatal enterocolitis in Asian elephants (*Elephas maximus*) caused by *Clostridium difficile*. *Veterinary Microbiology* 116(4): 329–335.

Bunesova V., Vlkova E., Rada V., Killer J., Kmet V. (2013) Identification of bifidobacteria isolated from Asian elephant (*Elephas maximus*). *Journal of Bioscience* 38: 239–243.

Cavendish M. (2010) *Mammal Anatomy: An Illustrated Guide*. Third Edition. New York, New York: Marshall Cavendish Square Publishing, 44–63.

Chakraborty A., Chaudhury B., Rahman H., Hussain A., Baruah M.C. (1992) Intussusception and gangrene in elephants. In: *The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management* (*Proceedings of the National Symposium on the Asian Elephant* held at the Kerala Agricultural University, Trichur, India, January 1989). E. G. Silas, M. K. Nair and G. Nirmalan, eds. Trichur, India, Kerala Agricultural University, 164–165.

Chandrasekharan K., Radhakrishnan K., Cheeran J.V., Nair K.N.M., Prabhakaran T. (1995) Review of the incidence, etiology and control of common diseases of Asian elephants with special reference to Kerala. In Daniel, J.C., (ed.) *A Week with Elephants, Proceedings of the International Seminar on Asian elephants*. Bombay, India, Bombay National History Society, Oxford University Press, 439–449.

Chandrasekharan K., Sathianesan V., Pythal C. Sundaram R.Kl. (1979) Anthelmintic activity of thiophanate (Nemafax) in elephants and zoo animals. *Kerala Journal of Veterinary Science* 1: 167–170.

Cheeran J.V,. Chandrasekharan K. (2006) Veterinary Problems of Geographical Concern. In: *Biology, Medicine, and Surgery of Elephants* (eds.) M. E. Fowler and S. K. Mikota, Oxford, UK: Blackwell Publishing Ltd, 439–474.

Cheeran J.V. Chandrasekharan K., Radhakrishnan K. (1995) Principles and Practice of Fixing Dose of Drugs for Elephants. In: Daniel, J.C. (Editor), *A Week with Elephants; Proceedings of the International Seminar on Asian Elephants*. Bombay Natural History Society; Bombay, India: Oxford University Press, 430-438.

Chooi K.F., Zahari Z. (1988) Salmonellosis in a captive Asian elephant. *Journal of Zoo and Wildlife Medicine* 19(1–2): 48–50.

Clark E.S., Becht J.L. (1987) Clinical pharmacology of the gastrointestinal tract. Veterinary Clinics of North America: *Equine Practice* 3(1): 101–122.

Clauss M., Steuer P., Müller D.W.H., Codron D., Hummel J. (2013) Herbivory and body size: allometries of diet quality and gastrointestinal physiology, and implications for herbivore ecology and dinosaur gigantism. *PLoS ONE* 8(10): e68714. doi:10.1371/journal.pone.0068714.

Clauss M., Steinmetz H., Eulenberger U., Ossent P., Zingg R., Hummel J., Hatt J. (2007a) Observations on the length of the intestinal tract of African *Loxodonta africana* (Blumenbach 1797) and Asian elephants *Elephas maximus* (Linné 1735). *European Journal of Wildlife Research* 53: 68–72.

Clauss M., Streich J., Schwarm A., Ortmann S., Hummel J. (2007b) The relationship of food intake and ingesta passage predicts feeding ecology in two different megaherbivore groups. Oikos 116(2): 209–216.

Clauss M, Schwarm A., Ortmann S., Streich W.J., Hummel J. (2007c) A case of non-scaling in mammalian physiology? Body size, digestive capacity, food intake, and ingesta passage in mammalian herbivores. *Comparative Biochemistry and Physiology Part A* 148: 249–265.

Clauss M., Hummel J. (2005) The digestive performance of mammalian herbivores: why big may not be that much better. *Mammal Review* 35: 2(174–187).

Clauss M., Robery N., Walzer C., Witaud C., Hummel J. (2005) Testing predictions on body mass and gut contents: dissection of an African elephant *Loxodonta africana* Blumenbach 1797 *European Journal of Wildlife Research* 51: 291–294.

Clauss M., Loehlein W., Kienzle E., Wiesner H. (2003a) Studies on feed digestibilities in captive Asian elephants (*Elephas maximus*). *Journal of Animal Physiology and Animal Nutrition* 87: 160–173.

Clauss M., Frey R., Kiefer B., Lechner-Doll M., Loehlein W., Polster C., Roessner G. E., Streich W. J. (2003b) The maximum attainable body size of herbivorous mammals:

morphophysiological constraints on foregut, and adaptations of hindgut fermenters. *Oecologia* 136(1): 14–27.
Clemens E., Maloiy G.M.O. (1983) Nutrient digestibility and gastrointestinal electrolyte flux in the elephant and rhinoceros. *Comparative Biochemistry and Physiology Part A* 75A: 4(653–658).
Cornell Staff (1985) *Veterinary Drug Formulary:* Cornell Research Foundation, Inc. Baltimore: Williams & Wilkins.
da Silva V.C., Magalhaes J.F., Ecco R., Faleiros R.R., Guedes R.M.C. (2014) Pathological Findings of Cholelithiasis in Two Horses. *Brazilian Journal of Veterinary Pathology* 7(1): 35–37.
Dart A.J., Peauroi J.R., Hodgson D.R., Pascoe J.R. (1996) Efficacy of metoclopramide for treatment of ileus in horses following small intestinal surgery: 70 cases (1989–1992) *Australian Veterinary Journal* 74: 280–284.
Davis J.L., Jones S.L. (2003) Suppurative cholangiohepatitis and enteritis in adult horses. *Journal of Veterinary Internal Medicine* 17: 583–587.
Dehority B.A. (1986) Protozoa of the digestive tract of herbivorous mammals. *International Journal of Tropical Insect Science*, 279–29.
Dierenfeld E.S. (2006) *Nutrition, in Biology, Medicine, and Surgery of Elephants* (eds.) M. E. Fowler and S. K. Mikota, Oxford, UK: Blackwell Publishing Ltd, 57–67.
Dill S.G., Bierman N. (2001) Acupuncture for gastrointestinal disorders. In: Schoen, A.M. (ed.) *Veterinary Acupuncture.* St. Louis, Missouri: Mosby, 239–260.
Dumonceaux G.A. (2006) Digestive System. In: *Biology, Medicine, and Surgery of Elephants* (eds.) M.E. Fowler, S.K. Mikota, Oxford, UK: Blackwell Publishing Ltd, 299–307.
Dunlop C.I., Hodgson D.S., Cambre R.C., Kenney D. (1988) Prolonged isoflurane anesthesia of an adult elephant on two occasions. *Veterinary Surgery* 17:(3): 167–168.
Du Toit J.G. (2001) *The Veterinary Care of African Elephants. Norvartis and South Africa Veterinary Foundation Publication. Novartis SA* (Pty) Ltd, PO Box 92, Isando 1600.
Feary D.J. Hassel D.M. (2006) Enteritis and colitis in horses. Veterinary Clinics of North America: Equine Practice 22: 437–479.
Firyal S., Naureen A. (2007) Elephant as a veterinary patient. *Pakistan Veterinary Journal* 27(1): 48–54.
Fleming P. (2001) Treatment of equine gastrointestinal disease with Acupuncture. In:Schoen, A.M. (ed.) Veterinary Acupuncture St. Louis, Missouri: Mosby, 475–480.
Foose T.J. (1982) *Trophic strategies of ruminant vs non-ruminant ungulates.* Ph.D. thesis. Chicago, IL, University. Chicago.
Fowler M.E. (1995) Elephants. In: Restraint and handling of wild and domestic animals. Ames, Iowa: Iowa State University Press, 265–269.
Fowler M.E. (1986) *Zoo and Wild Animal Medicine: Current therapy,* 4th ed. Philadelphia, W.B. Saunders, 58–62.
Gairhe K.P. (2012) Veterinary care and breeding of elephants in Nepal. Short Communication *Gajah* 37: 27–30.
Gerring E.L., King J.N. (1989) Cisapride in the prophylaxis of equine post operative ileus. *Equine Veterinary Journal Supplement* 52-55
Greene W., Mikota S., Pitcairn J., Ryer M. (2018). Clinical management of a complete gastrointestinal obstruction and ileus in a geriatric female Asian elephant (*Elephas maximus*). *Journal of Zoo Biology* 2: 1.
Grehan M.J., Borody T.J., Leis S.M., Campbell J., Mitchell H., Wettstein A. (2010) Durable alteration of the colonic microbiota by the administration of donor fecal flora. *Journal of Clinical Gastroenterology* 44: 551–561.
Gross M.E., Clifford C.A., Hardy D.A. (1994) Excitement in an elephant after intravenous administration of atropine. *Journal of the American Veterinary Medical Association* 205(10): 1437–1438.
Gurelli G., Ito A. (2014) Intestinal ciliated protozoa of the Asian elephant *Elephas maximus* Linnaeus, 1758 with the description of *Triplumaria izmirae*. *European Journal of Physiology* 50(1): 25–32.
Guy P. (1976) The feeding behaviour of elephant (*Loxodonta africana*) in the Sengwa Area, Rhodesia. *South African Journal of Wildlife Research* 6: 55–63.
Hackenberger M. K. (1987) Diet Digestibilities and Ingesta Transit Times of Captive Asian and African Elephants. MS Thesis, University of Guelph, Canada.
Hallowell G.D. (2008) Retrospective study assessing efficacy of treatment of large colonic impactions. *Equine Veterinary Journal* 40(4):411-413.
Hashek W.M., Wallig M.A., Rousseaux C. (2010) *Fundamentals of toxicologic pathology.* London, UK: Elsevier Inc. ISBN 9780123704696.
Heard D., Kollias G., Merritt A., Jacobson E. (1988) Idiopathic Chronic Diarrhea and Malabsorption in a Juvenile African Elephant (*Loxodonta africana africana*). *The Journal of Zoo Animal Medicine* 19(3): 132–136.
Hunter R.P., Isaza R., Koch D.E. (2003) Oral bioavailability and pharmacokinetic characteristics of ketoprofen enantiomers after oral and intravenous administration in Asian elephants (*Elephas maximus*). *American Journal of Veterinary Research* 64(1): 109–114.
Isaza R. (2006) Respiratory System. In: *Biology Medicine and Surgery of Elephants*. London, UK: Blackwell Publishing, 291–298.
Isaza R., Hunter R.P. (2004) Drug delivery to captive Asian elephants- treating Goliath. *Current Drug Delivery* I: 291–298.
Janis C. (2008) An evolutionary history of browsing and grazing ungulates. In: Gordon, IJ., and HHT. Prins. 2008. *The ecology of browsing and grazing*. Berline, Heidelberg: Springer, 21–45.
Kamiya T., Fujita T. (1966) The intramural pouch in the duodenum of the Indian elephant: a macro- and microscopic study of six cases Okajimas *Fol. Anat. Jap.* 42: 281–294.
King J.N. Gerring E.L. (1989) Antagonism of endotoxin-induced disruption of equine bowel motility by flunixin and phenylbutazone. *Equine Veterinary Journal* 7: 28–42.
Klös, H.G., Lang, E.M. (eds). (1981) Handbook of Zoo Medicine: Diseases and Treatment of Wild Animals in Z*oos, Game Parks, Circuses and Private Collections.* New York, New York: Van Nostrand Reinhold Company, 152–186.
Koenig J., Cote N. (2006) Equine gastrointestinal motility — ileus and pharmacological modification. *The Canadian Veterinary Journal* 47(6): 551–559.
Koirala R.K., Raubenheimer D., Aryal A.M., Pathak M.L., Ji W. (2016). Feeding preferences of the Asian elephant (*Elephas maximus*) in Nepal. *BMC Ecology,* 16: 54.
Kottwitz J., Boothe M., Harmon R., Citino S.B., Ziba J.R., Boothe D.M. (2016) Results of the megavertebrate analgesia survey: elephants and rhinos. *Journal of Zoo and Wildlife Medicine* 47: 1): 301–310.
Lester G.D., Merritt A.M., Neuwirth L., Vetro-Widenhouse T., Steible C., Rice B. (1998) American *Journal of Veterinary Research* 59(3): 320–7.
Lewis C. (2017) *Enteroimmunology: a guide to the prevention and treatment of chronic inflammatory disease.* Psychology Press. ISBN 978-1938318061.
Lister A.L. (2013) The role of behaviour in adaptive morphological evolution of African proboscideans. *Nature* 500: 331–334.
Loehlein W., Kienzle E., Woesner H., Clauss M. (2003) Investigations on the use of chromium oxide as an inert external marker in captive Asian elephants (*Elephas maximus*): passage and recovery rates. In: Fidgett A., Clauss M., Ganslosser U., Hatt J.M., Nijboer, J. (eds.) *Zoo Animal Nutrition Volume 2*. Fürth: Filander Verlag: 223–232.
Mbaya A.W., Ogwil M., Kumshe H.A. (2013) Effects of host demography, season and rainfall on the prevalence and parasitic load of gastrointestinal parasites of free-living elephants (*Loxodonta africana*) of the Chad Basin National Park, Nigeria. Pakistan *Journal of Biological Sciences* 16(20): 1152–1158.
McLean E.R., Kinsella M., Chiyo P.I., Archie E.A. (2012) Genetic identification of five strongyle nematode parasites in wild african elephants (*Loxodonta africana*)." *Journal of Wildlife Disease* 48(3): 707–716.
Mikota S.K. (2006) Therapeutics. In: *Biology Medicine and Surgery of Elephants.* London, UK: Blackwell Publishing, 211–231.
Mikota S.K. (2016) Acupuncture in Elephants. In: *Practical Guide to Traditional Chinese Veterinary Medicine Volume 4. Exotic Animals*. (eds.) Xie, H., and Ramirez, H. Reddick, Florida: Chi Institute Press, 299–325.
Mikota S.K., Sargent E.L., Ranglack G.S. (1994) *Medical management of the elephant.* Bloomfield, MI: Indira Publishing House, 8–29.
Miller D., Jackson B., Riddle H.S., Stremme C., Schmitt D., Miller T. (2015) Elephant (*Elephas maximus*) Health and Management in Asia: *Variations in Veterinary Perspectives*. Veterinary Medicine International 614690.
Moore M.R., Leise B.S. (2009) Medical treatment of horses with colic. *Proceedings of the 11th International congress of the world equine veterinary association*. September 24–27, Guarujá, SP, Brazil.
Mortenson J. (1998) Determining dosages for anti-inflammatory agents in elephants. *Proceedings AAZV and AAWV Joint Conference.* Omaha, Nebraska, 477–479.
Mortenson J. (2001) Determining dosages for antibiotics and anti-inflammatory agents. In: Csuti, B., Sargent, E.L., Bechert, U.S. (Eds.), *The Elephant's Foot.* Ames, Iowa: Iowa State University Press, 141–144.
Mullen K.R., Yasuda K., Divers T.J., Weese J.S. (2018). Equine faecal microbiota transplant: current knowledge, proposed guidelines and future directions. *Equine Veterinary Education.* doi:10.1111/eve.12559.
Munrow J. (2011) *Equine Clinical Medicine, Surgery, and Reproduction.* Boca Raton, Florida: Manson Publishing Limited, 516–598, ISBN: 1840761199.

Nayar K.N.M., Chandrasekharan K., Radhakrishnan K. (2002) Management of surgical affections in captive elephants. *Journal of Indian Veterinary Association Kerala* 7: (3): 55–59.
Oehme F.W. (1987) General principles in treatment of poisoning. In: NE Robinson (Ed.) *Current Therapy in Equine Medicine.* Philadelphia, Pensylvania: WB Saunders Co, 668–670.
Owen-Smith N., Chafota J. (2012) Selective feeding by a megaherbivore, the African elephant (*Loxodonta africana*). *Journal of Mammalogy* 93: 698–705.
Papich M.G. (2016) *Saunders Handbook of Veterinary Drugs: Small and Large Animal Third Edition.* Saint Louis, Missouri: Elsevier, 251–252.
Pendelbury C., Odongo NE., Renjifo., Naelitz J., Valdes EV., McBride BW. (2005). Acid-insoluble ash as a measure of dry matter digestibility in captive African elephants (*Loxodonta africana*). *Zoo Biology* 24(3): 261–265.
Phair K.A., Sutherland-Smith M., Pye G.W., Pessier A.P., Clippinger T.L. (2014) Esophageal dissection and hematoma associated with obstruction in an Indian elephant (*Elephas maximus indicus*). *Journal of Zoo and Wildlife Medicine* 45(2): 423–2427.
Radhakrishnan K. (1989) Non-specific disease of Asian elephant with particular reference to their prevalence in Kerala. *The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management. Proceedings of the National Symposium on the Asian Elephant* held at the Kerala Agricultural University, Trichur, India, 168–170.
Rao D.S.T., Yathira S., Choudrhuri P.C. Konda Reddy P. (1992) *Treatment of helminthosis in elephants.* Indian Council of Agricultural Research, New Delhi, India, 1931–1968.
Raubenheimer E.J., Dauth J., Dreyer M.J.., DeVos V. (1988) Parotid salivary gland of the African elepehant (*Loxodonta africana*): structure and composition of saliva. *Journal of the South African Veterinary Association* 59(4): 184–187.
Rees P.A. (1982) Gross assimilation efficiency and food passage time in the African elephant. *Journal of African Ecology* 20: 193–198.
Robinson N.E. (1992) Table of Common Drugs: Approximate Doses. In: *Current Therapy in Equine Medicine,* 2. N.E. Robinson (ed.). Philadelphia, Pennsylvania: W.B. Saunders, Appendix 1.
Romain S., Angkawanish T., Bampenpol P., Pongsopawijit P., Sombatphuthorn P., Nomsiri R., Silva-Fletcher A. (2014) Diet composition, food intake, apparent digestibility and condition score of the captive Asian elephant (*Elephas maximus*): a pilot study in two collections in Thailand. *Journal of Zoo and Wildlife Medicine* 45(1): 1–14.
Roy S., Mazumdar B.K. (1988) Anthelmintic activity of fenbendazole (Panacur) against *Murshidia murshida* in zoo elephants. *Indian Veterinary Association,* Chennai, India. ISSN: 0019–6479.
Salzert W. (1982) Elephants. In: Klös, H.G. and Lang, E.M. (eds). *Handbook of Zoo Medicine: Diseases and Treatment of Wild Animals in Zoos, Game Parks, Circuses and Private Collections.* New York, New York: Van Nostrand Reinhold Company, 152–186.
Sanchez L.C. (2015) Clinical application of gastrointesinal therapeutics. In: *Equine Pharmacology*. Cole, C., Bentz., B., L. Maxwell. Amers, Iowa: Wiley Blackwell, 183–192.
Scarratt W.K., Warnick L.D. (1998) Effects of oral administration of lactulose in healthy horses. *Journal of Equine Veterinary Science* 18(6): 405–408.
Shoshani J. (2006) Taxonomy, Classification, History, and Evolution of the Elephants. In: *Biology, Medicine and Surgery of Elephants.* Ames, Iowa: Blackwell Publishing. p. 3–14.
Shoshani, J. (2000). The elephant pharyngeal pouch — was the mystery resolved? *Elephant,* 2(4): 75–76.
Shoshani J., Tassy P. (1996) *The Proboscidea, Evolution and Palaeoecology of Elephants and their Relatives.* New York, New York: Oxford University Press, 49–54.
Shoshani J., Williams J., Yehiel D. (1982) On the dissection of a female Asian elephant (*Elephas maximus maximus* Lennaeus, 1758) and the data from other elephants. *Elephant* 2(1): 3–93.
Schoster A., Weese J.S., Guardabassi L. (2014) Probiotic Use in Horses – What is the Evidence for Their Clinical Efficacy? *Journal of Veterinary Internal Medicine* 28(6): 1640–1652.
Siciliano P.D., Parker A.L. Larence L.M. (1997) Effect of dietary vitamin E supplementation on the integrity of skeletal muscle in exercised horses. *Alliance of Crop, Soil, and Environmental Science Societies* 75: 6: 1553–1560.
Sikes S.S. (1971) *The natural history of the African elephant.* New York, New York: American Elsevier Inc, 78–109.
Silva I., Dangolla A. (2006) Veterinary problems of geographical concern In: *Biology, Medicine, and Surgery of Elephants* (eds.) M. E. Fowler and S. K. Mikota, Oxford, UK: Blackwell Publishing Ltd, 468–475.
Smith T.P., Jollie K.G., Mohr J.L. (1982) Gut protozoans of zoo elephants. *Journal of Protozoology* 29: 482.
Stevens C.E., Hume I.D. (1995) *Comparative physiology of the vertebrate digestive system.* Cambridge, UK: Cambridge University Press, 90–92.
Sthitmatee N., Warinrak T., Wongkalasin W. (2013) Susceptibility of *Clostridium difficile* Isolated from Healthy Captive Asian Elephants to Metronidazole and Vancomycin. *Thai Journal of Veterinary Medicine* 43(2): 313–316.
Subramanian V. (2006) Malaysia, in Biology, Medicine, and Surgery of Elephants (eds.) M. E. Fowler and S. K. Mikota, Oxford, UK: Blackwell Publishing Ltd, 457–460.
Sukumar R. (2006) A brief review of the status, distribution and biology of wild Asian elephants. International Zoo Yearbook 40, 1–8.
Sukumar R. (2003) *The Living Elephants.* New York, New York: Oxford University Press, p. 478.
Tassy P., Shoshani J. (2013) *Family Elephantidae, elephants.* In: Kingdon J, Happold D, Hoffman M, Butynski TM, Happold M, Kalina J (eds.). *Mammals of Africa: introductory chapters and Afrotheria.* London: Bloomsbury Publishing, 176–180.
Ullrey D.E., Crissey S.D., Hintz H.F. (1997) *Elephants: nutrition and dietary husbandry.* Fact Sheet 004, AZA Nutrition Advisory Group. http://www.elephanttag.org/professional/Nutrition%20Advisory%20Group%20Handbook.pdf
Van Aswegen G., Schoeman J.H., Vos D.V., Van Noorden S. (1994) The oesophagus and stomach of the African elephant: a histological, immunocytochemical and immunofluorescence study. *Journal of Veterinary Research* 61: 223–229.
Van Hoogmoed LM., Nieto J.E., Snyder J.R., Harmon F.A. (2004) Survey of prokinetic use in horses with gastrointestinal injury. *Veterinary Surgery* 33: 279–285.
Van Hoven W., Prins R.A., Lankhorst A. (1981) Fermentative digestion in the African elephant. *South African Journal of Wildlife Research* 11: 78–86.
Van Soest P.J. (1986) Allometry and Ecology of feeding behaviour and digestive capacity in herbivores: a review. *Journal of Zoo Biology* 15: 455–479.
Warren K., Bolton J., Swan R., Gaynor W. Pond L. (1996) Treatment of gastrointestinal tract impaction of a 2-year-old Asian elephant (*Elephas maximus*). *Australian Veterinary Journal* 73(1): 37–38.
Warren K., Bolton J., Swan R., Gaynor W. Pond L. (1996) Treatment of gastrointestinal tract impaction of a 2-year-old Asian elephant (*Elephas maximus*). *Australian Veterinary Journal* 73(1): 37–38.
Wiedner E.B., Peddie J., Peddie L.R., Abou-Madi N., Kollias G.V., Doyle C., Lindsay W.A., Isaza R., Terrell S., Lynch T.M., Johnson K., Johnson G., Sammut C., Daft B., Uzal F. (2012) Strangulating intestinal obstructions in four captive elephants (*Elephas maximus* and *Loxodonta africana*). *Journal of Zoo and Wildlife Medicine* 43(1): 125–130.