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Review Paper

Fecal microbiota transplantation as a tool to treat and reduce susceptibility to disease in animals

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ABSTRACT

Fecal microbiota transplantation (FMT) is the process by which fecal microbiota are donated from a healthy individual and subsequently transplanted into a diseased or young individual. The mechanism by which FMT is effective is believed to be due to enhanced beneficial microbes, increased microbiome diversity, and restored normal flora. Beneficial gut microorganisms not only play a role in maintaining an intestinal barrier and metabolizing nutrients, but importantly, these microbes help regulate local and systemic immune function. Although FMT has been described for several centuries, only recently has it been utilized as a mainstream therapy in humans and significantly considered for applications in other species. In humans and animals, gastrointestinal diseases are by far the most widely accepted FMT-treatable conditions; however, recent research has shown exceptional promise for FMT being used to treat or prevent other conditions, including those outside of the gastrointestinal tract. Overall, FMT is likely an underutilized, widely-available, and inexpensive tool for improving the health and response to disease in animals. In this review, the effects of FMT on veterinary diseases and potential applications for FMT in animals are discussed.

1. Introduction

Fecal microbiota transplantation or FMT is the term used to describe the transplantation of fecal microbiota from a health individual into a diseased individual as a therapeutic tool. The FMT process transplants all organisms that compose an intact complex community of gastrointestinal microbiota, including viruses, bacteria, fungi, archeae, and protozoa, along with small particulate feedstuffs, colonocytes, and metabolites (Bojanova and Bordenstein, 2016). The history of FMT usage throughout the world dates as far back as the 4th century in China, where FMT was used to treat gastroenteritis and diarrheic conditions in humans (Zhang et al., 2012). In the U.S., Eiseman et al. (1958) published an early case series documenting the use of FMT through colonic enemas as a successful management tool in four human cases of pseudomembranous enterocolitis associated with *Staphylococcus aureus* (Eiseman et al., 1958). Over recent years, FMT has moved into more mainstream use in hospitals and clinics as a highly successful treatment option for recurrent *Clostridium difficile* infections non-responsive to antimicrobials (Hota et al., 2018; Orenstein et al., 2013). Although *C. difficile* infections are the most common condition currently being treated by FMT in the developed world, many other conditions have demonstrated a positive response to experimental FMT therapy, such as chronic fatigue syndrome, idiopathic thrombocytopenic purpura, and insulin sensitivity in patients with metabolic syndrome (Borody et al., 2011, 2012; Vrieze et al., 2012). For the vast majority of diseases, the exact mechanism for FMT efficacy is unknown, but is likely the result of increased microbial diversity, enhanced numbers of beneficial microbial populations, and modulation of the immune system.

In animals, the most common historical use of FMT is referred to as transfaunation and is utilized in ruminants to restore microbes to the ruminal contents of cattle, most commonly implemented for digestive or metabolic disorders, often characterized by inappetence or ruminal hypomotility (DePeters and George, 2014; Mandal et al., 2017). The history of transfaunation in ruminants dates back to the 17th century in Italy, where transfaunation was described for restoring normal rumination (Borody et al., 2004). Brag and Hansen (1994) describe the use of regurgitated digesta or cud for microbial transplantation as a tool utilized for centuries in Sweden to treat ruminal indigestion, even noting the beneficial effects of cud as a “living creature” (Brag and Hansen, 1994). More recently, FMT has also become a topic of interest in other livestock as well as domestic pets for therapeutic and prophylactic uses. For example, work in my laboratory has used FMT to successfully reduce the development of porcine circovirus associated

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disease in nursery pigs (Niederwerder et al., 2018). In work by others, FMT has been used to effectively treat canine parvovirus infections in dogs and colitis in horses (Mullen et al., 2018; Pereira et al., 2018).

Although the exact mechanism of FMT efficacy in both humans and animals is not well defined for most diseases, several possibilities have been considered. One of the most commonly described modes of action includes the restoration of normal flora through repopulating the gut with an intact complex community of microorganisms (Allegretti and Hamilton, 2014; Liu et al., 2017). Transfaunation in ruminants, for example, is largely thought to be beneficial due to the recolonization of beneficial anaerobes in the rumen, restoring normal fermentation function (DePeters and George, 2014). Additionally, increasing microbiome diversity increases the host's ability to metabolize complex carbohydrates, improving digestive capacity (Backhed et al., 2005; Sonnenburg and Backhed, 2016). Through the recolonization of normal microbes, FMT is also believed to play a role in competitive exclusion of gastrointestinal pathogens, where beneficial microbes outcompete pathogens for adhesion, attachment, and infection (Collado et al., 2007; Khoruts and Sadowsky, 2016). Recently, FMT has also been anecdotally recognized as a potential therapy for those human patients infected with multidrug resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis* (Cohen and Maharshak, 2017; Laffin et al., 2017).

Fecal microbiota transplatation and normal gut microbes are also known to modulate the immune response, as it is well documented that germ-free or pathogen-free mice have less developed, less cellular and less responsive immune systems when compared to mice with normal gut microbiomes (Ekmekciu et al., 2017; Round and Mazmanian, 2009; Willyard, 2018). Based on size, the gut-associated lymphoid tissue (GALT) is considered a principal organ for immune function (Chattha et al., 2015) and the effects of the gut microbiota on systemic immunity should not be underestimated. FMT has also been described as a mechanism to shift populations of microbes, at the phyla or family level, to achieve a phenotypic outcome. For example, FMT from an obese donor transplanted into a thin donor is associated with an increase in the Firmicutes phylum and subsequent weight gain, thought to be primarily due to an increased ability to harvest energy (Ridaura et al., 2013; Turnbaugh et al., 2006). Phenotypes associated with systems outside the gastrointestinal tract can also be transferred through FMT. For example, Kelly et al. (2016) describes the transfer of behavior consistent with depression and anxiety through FMT (Kelly et al., 2016). Routinely utilized in swine production, another potential use for FMT includes the intentional and controlled administration of feces containing enteric viruses, such as coronaviruses or rotaviruses, to adult females in an effort to stimulate mucosal immunity; ultimately, the goal of FMT in this case is subsequent passive immunoglobulin transfer to suckling neonates through colostrum or milk (Armbrecht, 2010; Chattha et al., 2015; Schwartz et al., 2014). Overall, the mechanism of FMT efficacy is likely complex, multifactorial, and dependent on disease, species and age of both the recipient and donor.

2. FMT use in veterinary species

The use of FMT in animals can be divided into three potential applications, including 1) therapeutic use, 2) prophylactic use, and 3) use of FMT for stimulating pathogen-specific immunity (Fig. 1). Therapeutic use describes FMT when the goal of administration is to treat clinical signs or resolve disease conditions that are ongoing and current. In contrast, FMT prophylaxis would be used to provide beneficial microbiome characteristics prior to high-risk of pathogen exposure or disease onset, as a part of preventative healthcare. Finally, FMT or feedback has been used as an immunostimulatory tool similar to vaccination, where the transplant material stimulates pathogen-specific immunity with the goal of increasing immunoglobulin transfer. However, inherent risks are present in the use of FMT for live pathogen exposure and additional research is needed to define best practices for this application. Unique to veterinary medicine, the latter two uses have not been significantly explored in humans. This review serves to discuss these potential applications of FMT in the veterinary field, highlight specific examples of FMT use in animals, and provide important considerations for the future standardization of FMT to improve the health of veterinary species.

Fecal microbiota transplantation in animals is a fairly new concept, with most of the peer-reviewed literature examples having publication dates within the last 5 years (25/29, 86.2%; Table 1). Most examples are clinical cases or diseases where FMT is used therapeutically after clinical signs have occurred and the disease has been diagnosed (16/28; 57%). However, prophylactic and immunogenic applications, primarily in swine and poultry, have also been explored. Often, outcome is predominately described by clinical response with fewer publications attempting to describe a pathogenic or immunogenic mechanism to FMT efficacy. Clearly, much is to be learned with regards to defining how FMT effectively reduces disease in veterinary species; nevertheless, evidence described below sheds light on FMT as a promising alternative tool in the prevention and treatment of disease in animals.

3. FMT use in companion, zoo, and laboratory animals

Although publications documenting the clinical use of FMT in domestic dogs and cats are sparse (Chaitman et al., 2016), a few recent studies have demonstrated positive clinical outcomes in canine and feline patients treated with FMT for various gastrointestinal diseases. For example, Pereira et al. (2018) compared the use of a standard therapy for canine parvovirus (CPV) infection, consisting of antimicrobials, fluids, anti-emetics, and antacids, with a combination of FMT and the standard therapy. Puppies were administered FMT through a rectal enema within 6–12 hours after initiating the standard CPV therapy. FMT was well-tolerated and significantly improved the time course of clinical disease, with 61.5% of FMT patients resolving their diarrhea in the first 48 h compared to only 4.8% of dogs receiving the standard therapy alone. Additionally, FMT reduced the average duration of hospitalization by approximately 2.3 days (Pereira et al., 2018). In Weese et al. (2013), case reports document successful FMT therapy in 2 patients through the clinical improvement of a dog with eosinophilic inflammatory bowel disease and a cat with chronic vomiting and diarrhea. Both patients had chronic clinical signs (16–24 months duration) that had not resolved with traditional therapy. Within 24 h of FMT delivery, both cases had clinical resolution and maintained a healthy status for at least 3 months post-FMT administration (Weese et al., 2013). In another case series involving 8 dogs with *Clostridium perfringens* associated diarrhea that was non-responsive to antimicrobials, Murphy et al. (2014) reported that FMT immediately resolved diarrhea in all transplanted dogs and eliminated pathogen detection through PCR in 75% of patients (Murphy et al., 2014).

In a domestic cat case report from Israel, Furmanski and Mor (2017) documented the successful use of FMT in a feline patient with chronic ulcerative colitis, characterized by bloody, mucoid and malodorous large-bowel diarrhea. The cat was unresponsive to treatment with numerous medications, diet changes and probiotics for approximately 1 year prior to FMT administration. Although rapid stool improvement was noted after the first transplant, clinical signs relapsed and a second transplant was required, which ultimately resulted in long-term resolution of clinical signs (Furmanski and Mor, 2017). In equine patients, there is a paucity of documented clinical FMT use in the peer-reviewed literature. However, small case series, case reports, or anecdotes of horses with antibiotic-induced or undifferentiated colitis, *Clostridium difficile* infections, or chronic diarrhea have reported FMT as a potential therapeutic option resulting in a positive clinical response after nasogastric administration (Feary and Hassel, 2006; McGovern, 2013; Mullen et al., 2014, 2018).

Hensley-McBain et al. (2016) describe the effects of FMT after antimicrobial administration to rhesus macaques chronically infected

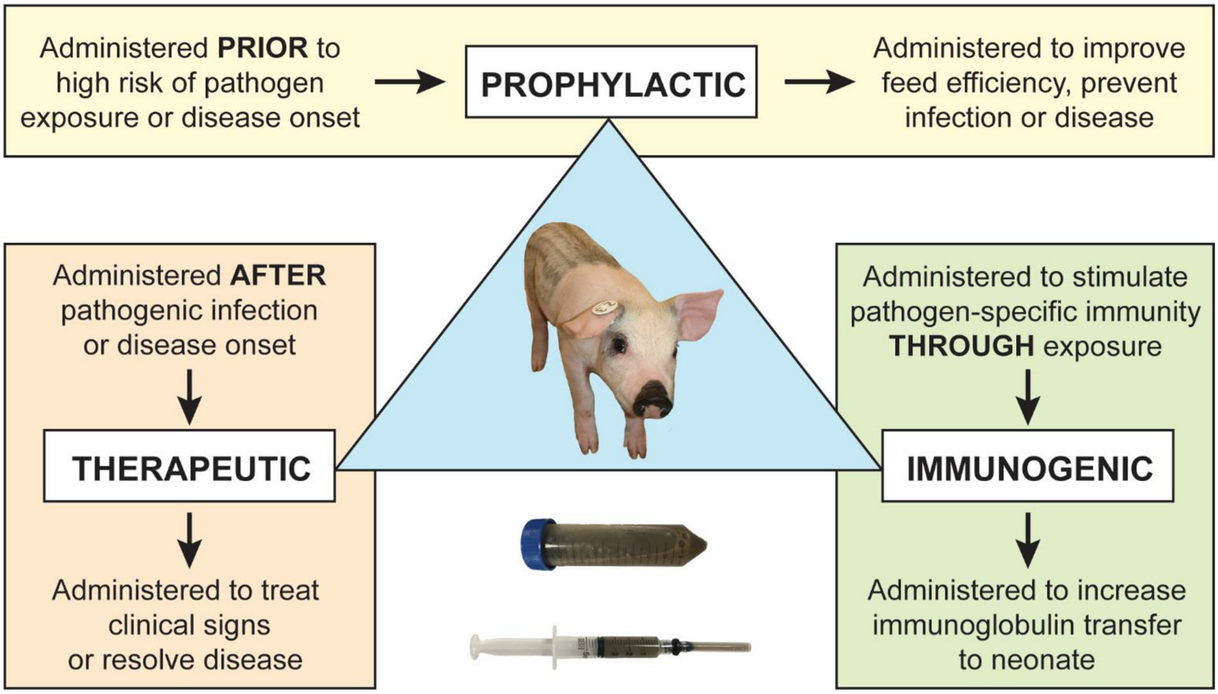

Fig. 1. Applications and intended outcomes for use of fecal microbiota transplantation (FMT) in pigs including therapeutic, prophylactic and immunogenic uses.

with simian immunodeficiency virus (SIV) and undergoing antiretroviral therapy. As microbiome dysbiosis is a common outcome in patients with human immunodeficiency virus, the authors were exploring the possible use of FMT to improve immune parameters and restore normal flora in immunocompromised individuals. Overall, FMT was well-tolerated and appeared to positively impact several immune parameters, including an increase in Th17 and Th22 cells as well as a reduction in CD4 + T cell activation, albeit a slight reduction in the weight of transplanted macaques two weeks post-transplantation (Hensley-McBain et al., 2016). In a second study on rhesus macaques, FMT was investigated as a potential therapeutic tool in the treatment of chronic diarrhea, as the authors note that diarrheic conditions in non-human primates are a significant cost and welfare concern in research settings. FMT was delivered as a single orogastric infusion and significantly improved fecal consistency scores post-treatment in transplanted macaques. However, overall post-treatment fecal scores were not significantly different when compared with controls, who received a saline infusion (Ferrecchia and Hobbs, 2013).

African turquoise killifish, which have been proposed as a model for aging in biomedical research due to their naturally short lifespan, were utilized by Smith et al. (2017) to investigate the use of FMT from young fish (6 weeks old) into middle-aged fish (9.5 weeks old) to determine if microbiome transplantation may effect aging. Interestingly, the authors reported that FMT increased the median lifespan of transplanted fish between 37–41% when compared to nontransplanted fish and fish transplanted with microbiota from the same age group. Additionally, FMT maintained exploratory behavior and locomotor distance in transplanted fish as they aged, when this activity typically decreases. Transplantation also increased gene expression associated with bacterial defenses, suggesting an increased ability to respond to pathogens (Smith et al., 2017).

4. FMT use in livestock

Use of FMT in livestock has been considered not only as a tool for improvement of various disease conditions but also as a potential means to improve feed efficiency and weight gain in food producing animals. Transfaunation as a treatment of indigestion or rumen atony has been utilized for decades in domestic ruminants. An important distinction between FMT and transfaunation is the location of gastrointestinal microbe collection (i.e., feces versus the rumen); however, conceptually and likely functionally, these two methods are considered similar. In domestic sheep used for biomedical research, Jasmin et al. (2011) reported resolution of ruminal acidosis, atony and inappetence in post-operative sheep undergoing orthopedic surgeries that were administered rumen contents (Jasmin et al., 2011). In Rager et al. (2004), transfaunation was investigated as a supplemental therapy administered to cows after surgical correction of left-sided displacement of the abomasum. Transfaunation helped prevent co-morbidities commonly observed post-operatively, as demonstrated by a significant increase in feed intake and milk yield as well as less ketonuria when compared to post-operative cows which did not receive the transfaunate (Rager et al., 2004). Rumen transfaunation has also been investigated as a potential therapy for transportation stress associated outcomes, such as depleted muscle glycogen and reduced feed intake. When administered immediately after a 24-hour transportation period, rumen transfaunation increased hay intake and body weight of transfaunated cattle during a 10-day post-transport feeding period compared to cattle administered deionized water. However, no beneficial effects of transfaunation were demonstrated on restoration of muscle glycogen (Leo-Penu et al., 2016).

In swine and poultry, prophylactic and immunogenic investigations into the use of FMT have been most commonly explored. In recent work performed by my laboratory, FMT was used as a prophylactic tool to improve the response of pigs to co-infection with two common viral pathogens of swine, porcine reproductive and respiratory syndrome virus (PRRSV) and porcine circovirus type 2 (PCV2). FMT was administered to 3-week-old pigs at weaning, when the microbiome is inherently plastic due to a shift in diet from milk to solid feed and a change in environment post-shipping. Transplant material was delivered orally to pigs once daily for 7 days prior to being co-infected with PRRSV and PCV2. Compared to mock-transplanted controls, FMT significantly reduced the number of pigs affected by porcine circovirus associated disease, as demonstrated by a reduction in morbidity, mortality, pathology, and virus replication (Niederwerder et al., 2018). In another experimental study, FMT was evaluated in young piglets as a

Table 1
Published cases and effects of fecal microbiota transplantation (FMT) in various veterinary species*.

Species	Disease/Pathogen/Condition	Use	Clinical/Pathological Outcome	Immune/Pathogen Outcome	Reference
Dog	Canine parvovirus, acute hemorrhagic diarrhea syndrome	T	More rapid resolution of diarrhea, reduced duration of hospitalization compared to standard therapy	ND	(Pereira et al., 2018)
Dog	Eosinophilic inflammatory bowel disease	T	Rapid improvement in fecal consistency, long term (3 months) resolution of C/S	ND	(Weese et al., 2013)
Dog	Idiopathic inflammatory bowel disease	T	Clinical improvement, reduced Canine Chronic Enteropathy Clinical Activity Index	ND	(Bottero et al., 2017)
Dog	Refractory *Clostridium perfringens* diarrhea	T	Rapid resolution of diarrhea	Most transplanted dogs (6/8) tested negative for *C. perfringens* on PCR	(Murphy et al., 2014)
Dog	Postweaning diarrhea	P	No diarrhea development, no clinical difference from controls	ND	(Burton et al., 2016)
Cat	Chronic vomiting and diarrhea	T	Rapid improvement in fecal consistency and appetite, long term resolution of vomiting and diarrhea (3 months)	ND	(Weese et al., 2013)
Cat	Ulcerative colitis	T	Improvement in fecal texture, odor and color (history of bloody, mucoid, malodorous diarrhea), long term resolution of diarrhea (11 months)	ND	(Furmanski and Mor, 2017)
Equine	Acute colitis	T	Improved fecal consistency, clinical response	ND	(Mullen et al., 2014, 2018)
Rhesus macaque	Simian immunodeficiency virus (SIV)	T	Well tolerated, no change in behavior, minor reduction in weight	Increased peripheral Th17 and Th22 cells, reduced CD4 + T cell activation in GI, reduced peripheral monocytes, decreased vascular endothelial growth factor	(Hensley-McBain et al., 2016)
Rhesus macaque	Idiopathic chronic diarrhea	T	Significant improvement in fecal consistency and clinical scores post FMT	ND	(Ferrecchia and Hobbs, 2013)
Marmoset	Recurrent *Clostridium difficile*	T	Complete and immediate resolution of chronic diarrhea, no reoccurrence of C/S (10 months)	Eliminated *Clostridium difficile* from GI, negative tests for antigen and toxin	(Yamazaki et al., 2017)
African turquoise killifish	Aging	P	Significant increase in median lifespan, maintained exploratory behavior and activity with age	Transcriptome showed enhanced defense responses to bacteria	(Smith et al., 2017)
Asian elephant	Potential dysbiosis post-bowel obstruction and ileus	T	Normal motility and function restored post-treatment with several therapies	ND	(Greene et al., 2018)
Swine	Necrotizing enterocolitis	P	Decreased diarrhea, lower frequency of blood in feces, reduced necrotizing enterocolitis lesions, improved GI motility, increased GI enzyme activity, increased mortality	Increased bacterial colonization and sepsis	(Martin et al., 2015)
Swine	Porcine reproductive and respiratory syndrome virus (PRRSV) and porcine circovirus type 2 (PCV2)	P	Decreased clinical signs of porcine circovirus associated disease, reduced mortality, improved weight gain, decreased macroscopic lung lesions	Reduced PRRSV and PCV2 viremia, increased levels and sustained production of antibodies	(Niederwerder et al., 2018)
Swine	*Mycoplasma hyopneumoniae*	P	Reduced coughing frequency, delayed coughing onset, decreased macroscopic lung lesions	Stronger delayed type hypersensitivity response against allergens, reduced TNF-α variance in bronchoalveolar lavage fluid, more rapid seroconversion	(Schachtschneider et al., 2013)
Swine	Feed efficiency	P	Reduced weight gain, decreased serum protein and cholesterol, reduced intestinal absorptive capacity, altered volatile fatty acid concentrations in intestine	Upregulated Toll-like receptor 2 (TLR2) expression in duodenum	(McCormack et al., 2018)
Swine	Intestinal structure, immunity, growth	P	Higher average daily weight gain, reduced diarrhea incidence, reduced intestinal crypt depth, increased tight junction protein expression, increased goblet cell numbers and mucin expression	Increased β-defensin 2 expression in ileum, increased concentration of sIgA$^+$ colonic cells, increased TLR2 and TLR4 expression in colon	(Hu et al., 2017)
Swine	Dextran sulphate sodium (DSS) induced acute colitis	P	Tibetan FMT provided resistance to colitis, transplanted pigs had lower clinical scores, less severe colonic bleeding, lacked inflammation and intestinal injuries	No increase in CD4$^+$/CD8$^+$ ratio, IgA$^+$ plasma cells, or MAC387$^+$ macrophages in colon, no increase in inflammatory markers INF-γ, IL-1β, IL-6 and PGE2 in colon, no increased expression of TLR4, TLR8, NOD1, MYD88, and NF-κB	(Xiao et al., 2017)
Swine	Porcine epidemic diarrhea virus (PEDV)	I	Reduced diarrhea and associated mortality in piglets	Significant reduction of virus detected in intestine	(Goede et al., 2015)
Swine	Porcine epidemic diarrhea virus (PEDV)	I	Increased frequency and duration of FMT resulted in clinical sign resolution 6 weeks after infection	Increased frequency and duration of FMT resulted in significantly higher serum neutralizing antibody titers in sows and increased prevalence of neutralizing antibodies in piglet serum	(Clement et al., 2016)
Chicken	*Salmonella infantis*	P	ND	Significant reduction in prevalence of *Salmonella* carriers and level of *Salmonella* colonization	(Nurmi and Rantala, 1973)
Chicken	Feed efficiency	P	No effect on residual feed intake or nutrient retention, increased total feed intake and weight gain in females	ND	(Siegerstetter et al., 2018)

(*continued on next page*)

Table 1 (*continued*)

Species	Disease/Pathogen/Condition	Use	Clinical/Pathological Outcome	Immune/Pathogen Outcome	Reference
Sheep	Ruminal acidosis and atony, inappetence	T	Appetite normalized, resolution of clinical signs	ND	(Jasmin et al., 2011)
Cattle	Left-displaced abomasum (post-surgical)	T	Increased feed intake, greater milk production, less ketonuria	ND	(Rager et al., 2004)
Cattle	Unthrifty, poor growth in experimental calves	T	Smoother coats, improved growth rates and condition	ND	(Pounden and Hibbs, 1949)
Cattle	Transportation stress	T	Increased feed intake, no effect on glycogen concentrations in muscle	ND	(Leo-Penu et al., 2016)
Cattle	Feed efficiency	T	Increased feed intake and nitrogen digestibility, no effect on fiber digestibility	ND	(Ribeiro et al., 2017)

*Key: ND, not determined; C/S, clinical signs; GI, gastrointestinal; T, therapeutic; P, prophylactic; I, immunogenic.

modulator of immunity and as a tool to improve the response to *Mycoplasma hyopneumoniae*. Transplantation provided benefits to the systemic immune response of pigs, including a reduction in clinical respiratory disease and more rapid antibody production (Schachtschneider et al., 2013).

In Hu et al. (2017), FMT from adult Jinhua pigs was investigated for its effects on intestinal health, immunity, and weight gain in neonatal three-way crossbred piglets. FMT resulted in several beneficial outcome characteristics, including an increase in weight gain and a reduction in diarrhea over the first four weeks of life. Histology as well as protein expression analysis demonstrated an improved gut barrier in transplanted pigs. Additionally, several immune parameters were increased, including colonic expression of TLR2 and TLR4, which are important for pathogen recognition and innate immunity. Under the conditions of this study, FMT improved intestinal health, immunity and growth in non-challenged neonatal pigs (Hu et al., 2017). In an experimental model of induced colitis, Xiao et al. (2017) evaluated the effects of FMT from two different pig breeds, Yorkshire and Tibetan, on the development of colonic inflammation after induction by dextran sulphate sodium (DSS). Interestingly, the Tibetan FMT protected pigs from colitis, reducing clinical signs and colonic bleeding as well as preventing an inflammatory response, as shown by a lack of increased immune cell infiltrate and cytokine expression in the colon. In contrast, pigs transplanted with Yorkshire FMT were susceptible to DSS-induced colitis (Xiao et al., 2017). One of the earliest published reports of FMT in poultry was in 1973, when Nurmi and Rantala investigated the effects of ingesta transplantation from adult cocks to broiler chicks on *Salmonella infantis* infection. When compared to non-transplanted control chicks, FMT reduced the number of *Salmonella* carriers and reduced *Salmonella* colonization, most notably in the caeca. The authors proposed that normal flora in the chicks provided a defense mechanism against *Salmonella* growth and shedding (Nurmi and Rantala, 1973).

Recently, there has been significant interest in evaluating the potential for transfaunation or FMT in livestock production as a mechanism to improve feed efficiency (Zhou et al., 2018). The rationale behind much of this interest is due to the knowledge that variation in feed efficiency between breeds or genetic lines of food producing animals likely has a gut microbial component, where certain livestock have gut microbes capable of harvesting energy from the diet at higher rates. Ribeiro et al. (2017) investigated the interspecies transfer of bison rumen microbes to beef cattle in an effort to improve feed efficiency. The authors hypothesized that rumen microbes from bison may be more adapted to fiber digestion in low quality feedstuffs. After removal of 70% of the endogenous rumen microbes in the recipient cattle, two transfaunates from bison resulted in increased nitrogen digestion and feed intake of the cattle, but did not affect fiber digestion of a barley straw diet (Ribeiro et al., 2017). In another study with poultry, FMT from highly feed-efficient donors was administered in the first several days of a chicken's life in an effort to enhance feed efficiency over subsequent weeks. Interestingly, there was no effect of the FMT on residual feed intake or nutrient retention; however, in female chickens, FMT appeared to increase total feed intake and overall weight gain. This study highlights that host characteristics, such as sex, may play an important role in the effect and success of FMT administration (Siegerstetter et al., 2018).

Two studies in swine have demonstrated the potential negative effects of FMT when administered very early in neonatal life. In McCormack et al. (2018), FMT from highly feed-efficient donors was administered to sows prefarrowing and/or neonatal piglets at birth and within the first several weeks of life. Pigs from transplanted sows and pigs administered the transplant had significantly lower body weights in the grow/finish phases when compared to controls. Histopathologic examination of intestinal segments showed several changes associated with FMT, such as a reduction in ileal villus height, width and area. Overall, the authors suggested that a reduced ability to absorb nutrients, due to FMT-associated microbiome and intestinal alterations, likely contributed to the overall reduction in weight gain of transplanted pigs (McCormack et al., 2018). In another study, FMT was investigated as a mechanism for reducing formula-induced necrotizing enterocolitis in a caesarean-derived neonatal pig model. Although FMT reduced diarrhea and colitis lesions in neonatal pigs when administered at one and two days of life, overall mortality was increased, with the authors attributing this to sepsis and bacterial translocation after FMT colonization (Martin et al., 2015). These studies highlight an important consideration of recipient age, which also likely plays a major role in success of FMT and reducing the incidence of potential negative side effects.

Although the use of FMT for immunogenic purposes, or “feedback” as it is typically referred, is fairly common practice in swine production, very few controlled experimental or field studies describing its efficacy and guidelines have been published. Schwartz et al. (2014) outlined the use of feedback for stimulating immunity to porcine epidemic diarrhea virus (PEDV) based on the experience of several practitioners, including overall goals, rationale, strategies, material collection and administration (Schwartz et al., 2014). It is noteworthy that the objective of this use of FMT as well as the ultimate recipient of the FMT benefits are novel when compared to the more common therapeutic and prophylactic uses. The primary goal of FMT, in this case, is stimulation of mucosal immunity through exposure to a virulent enteric pathogen present in the FMT. Although the sow or gilt are administered the FMT, their piglets are ultimately the intended recipients of the beneficial effects through lactogenic immunoglobulins in the milk and colostrum. Some of the earliest reports describing the benefits of administering virulent enteric viruses orally for immunogenic stimulation in sows or gilts to increase passive transfer were associated with protecting piglets from transmissible gastroenteritis virus (Bohl et al., 1972; Saif et al., 1972). Recent published reports of the benefits of feedback are primarily focused on PEDV. For example, in Goede et al. (2015), long term benefits of administering FMT to reproducing sows was demonstrated in piglets born seven months after whole herd exposure. Piglets born to sows that received feedback had significantly less diarrhea, greater survival, and less virus detected in the small intestine after PEDV infection compared to piglets born from naïve sows (Goede et al., 2015). In Clement et al. (2016), two sow sites with recent PEDV exposure and feedback protocols were compared with regards to sow and piglet antibody levels as well as clinical disease. The first site administered feedback three times per week for the first two weeks followed by one to two times per week for the following three to six weeks, whereas the second site only administered feedback once weekly for the first two weeks. Interestingly, the site that had implemented a feedback protocol at a greater frequency and longer duration resulted in more rapid clinical disease resolution, increased serum neutralizing antibody titers in sows, and increased prevalence of serum neutralizing antibodies in piglets (Clement et al., 2016).

5. Considerations for FMT therapy and mainstream application

Although several case reports or small experimental studies have shown mostly beneficial effects of FMT in numerous diverse animal species, several questions and concerns remain in regards to the feasibility of wide-spread application of FMT in food production and domestic companion animals. For the majority of animals in which FMT is being utilized, widely-accepted standardized guidelines for administration and donor selection is typically lacking (Chaitman et al., 2016; Niederwerder and Hesse, 2018). Transfaunation may be an exception, as several publications have described best practices in ruminants (DePeters and George, 2014; Mandal et al., 2017; Shanks, 2012; Stockler, 2016); however, even transfaunation is likely an underutilized tool in cattle due to a lack of controlled studies for most disease conditions. Very recently, additional publications have attempted to suggest considerations for FMT guidelines in other species, including swine (Hu et al., 2018), dogs and cats (Redfern et al., 2017), and horses (Mullen et al., 2018).

One important hurdle is how to ensure the safety of the FMT material, including the lack of pathogens, diseases or phenotypes that may be transmissible to the recipient. Similar to FMT transmission of obesity (Turnbaugh et al., 2006), transmission of phenotypes related to reduced feed efficiency and fat deposition in food animals must be considered. FMT delivered to food-producing animals should lack not only host pathogens but human pathogens as well. For example in cattle, certain rumen protozoa are known to increase the pathogenicity and virulence of antibiotic-resistant *Salmonella enterica* serotype Typhimurium, a major foodborne pathogen risk to humans (Rasmussen et al., 2005). Transplantation of these protozoa through a fecal transplant may not only increase risks to the bovine recipient, but may also be contraindicated due to the subsequent impact on food safety.

To address the safety concern of FMT when administered in human medicine, several donor characteristics and standard screening tools have been implemented. For example, donors are commonly tested for several infectious diseases, such as intestinal parasites, hepatitis C virus, human immunodeficiency virus, and *Helicobacter pylori*, as well as interrogated with regards to gastrointestinal health conditions, such as a history of chronic constipation, diarrhea or colorectal cancer (Choi and Cho, 2016; Paramsothy et al., 2015). In addition, potential donors are often excluded if they have a recent history of receiving antimicrobials. Further, the microbiome of the donor may be considered based on certain characteristics, such as bacterial richness, which may assist in ideal donor selection for specific diseases (Sokol, 2016). Similar donor requirements and standardized screening tools for infectious and non-infectious diseases need to be outlined for each animal species where FMT would be implemented as a therapeutic, prophylactic, or immunogenic tool. Furthermore, in production animals, food safety for the consumer must be maintained.

A second challenge includes maintaining consistency in FMT material as well as determining the standard volume, frequency, and duration of therapy. Consistency between FMT donations can be problematic, even when collected from the same donor over time due to changes in diet and microbial exposure. In Hamilton et al. (2012), a standardized method for preparation of frozen FMT material was described, which allowed donor FMT material to be stored in glycerol at −80 °C for as long as necessary prior to administration (Hamilton et al., 2012). Protocols which eliminate the need for fresh donated stool prior to each transplantation ensure consistency between treatments of the same patient over time. Importantly, frozen FMT material has shown similar success rates in the treatment of recurrent *Clostridium difficile* infections when compared to fresh FMT material (Hamilton et al., 2012; Lee et al., 2016; Youngster et al., 2014).

Regarding the frequency and duration of FMT therapy, published work in both animals and humans vary significantly, with therapeutic regimens in the latter often being tailored to the individual patient. In a mouse model for human FMT, Staley et al. (2017) demonstrated that a single application of FMT material was successful at stable colonization, as indicated by approximately 60% of colonized microbes associated with the donor source for up to 3 weeks (Staley et al., 2017). Grehan et al. (2010) reported that daily administration of FMT for 5–15 days resulted in stable colonization for up to 24 weeks (Grehan et al., 2010). Yet, others describe protocols or cases that may require several FMT doses over several weeks for stable colonization and/or resolution of severe disease conditions (Fischer et al., 2017; Hintze et al., 2014). Protocols necessitating frequent administration or prolonged duration for FMT success may prohibit widespread feasibility and application in many animal populations.

A third consideration includes the common standard practice of antibiotic administration to humans or mice models in studies of FMT therapeutic efficacy (Grehan et al., 2010; Lagier et al., 2017; Lundberg et al., 2016; Staley et al., 2017). Prior to FMT, antibiotic administration or antibiotic conditioning, as it is commonly referred (Staley et al., 2017), presumably increases the likelihood of exogenous microbial engraftment. However, even in human cases of recurrent *Clostridium difficile* with antibiotics administered prior to FMT, complete microbiota engraftment is not necessary for resolution of disease (Staley et al., 2016). Similarly in our work, prophylactic administration of FMT to pigs without antibiotic conditioning resulted in incomplete engraftment of donor microbes, yet significant benefits were shown with regards to health outcome. In veterinary medicine as well as human health, significant concerns about antibiotic resistance over the last decade have surged, partially due to the increase in humans infected with antibiotic resistant bacteria, but also due to the lack of novel antimicrobials being discovered. Antibiotic resistance is a major deterrent to FMT protocols in animals that require antimicrobial administration prior to transplantation. Thus, it would be important for future studies to define FMT efficacy in animals in the absence of antimicrobial conditioning. Furthermore, the antimicrobial resistome of donor animals should be considered as important selection criteria to reduce the transfer of antibiotic resistance to recipients.

6. The future of FMT as a tool in animal health

Alternatives to antimicrobials are a much needed tool for disease control in veterinary medicine, particularly in food animal production, where there is an urgent need to increase efficiency while eliminating the use of growth-promoting antimicrobials. Microbiome therapeutics, such as fecal microbiota transplantation, provide the opportunity to utilize beneficial microbes to improve immunity, gastrointestinal health, and growth. Chronic and/or infectious gastrointestinal conditions often plague laboratory research animals, companion animals and livestock. FMT provides an alternative therapeutic which may be utilized after conventional treatment failure, as a supplement to conventional therapy, or even as a stand-alone treatment in these patients.

Ultimately, FMT may emerge as a prophylactic tool, to be utilized during high risk time periods in the lives of veterinary species. Beneficial microbes would ideally be used to prevent, as opposed to treat, disease. In veterinary medicine, we are in the beginning stages of understanding and investigating the potential applications of FMT on gastrointestinal conditions. Furthermore, we know very little about the effect of FMT on most extra-gastrointestinal diseases in animals, such as neurologic behavioral abnormalities, respiratory diseases, neoplasia, or geriatric conditions. Albeit FMT being in the early stages of exploration in veterinary medicine, work thus far proves it to be a promising tool worthy of significant investigation and application.

Declarations of interest

None.

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