An update on equine postoperative ileus: Definitions, pathophysiology and management.

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An update on equine postoperative ileus: Definitions, pathophysiology and management

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Summary

Postoperative ileus (POI) is a serious condition which any horse undergoing abdominal surgery is at risk of developing, leading to increased hospitalisation time and resulting costs. Advances in the understanding of the development of equine POI are mainly based on human and rodent literature, where manipulation-induced inflammation has been identified as a key trigger, with activation of resident *muscularis externa* macrophages playing a crucial role in the pathophysiology. Despite many pharmacological trials in all species, there is no single completely successful treatment for POI, highlighting that the condition is multifactorial in cause and requires a multimodal approach to minimise its incidence.

Introduction

The term postoperative ileus (POI) describes the cessation of, or reduction in, gastrointestinal transit (GIT) following surgical stress [1]. Efforts have been made in human medicine to establish a standardised definition of POI [2; 3], an exercise which, based on the variation in POI definitions used amongst equine clinicians [4-10], also appears warranted in the field of equine veterinary medicine. In the horse, POI is almost exclusively associated with gastrointestinal (GI) surgery. In human medicine, it has also been reported following non-GI surgeries, including orthopaedic and

gynaecological procedures. POI has the potential to significantly increase hospitalisation time, treatment costs and postoperative morbidity and mortality and is, therefore, of significant concern to both the medical and veterinary professions. The estimated financial impact of human POI in North America alone approximates US $1.46 billion/year as a result of increased hospitalisation and treatment costs [11]. Horses that develop POI are much less likely to survive after surgery [12; 13]. In recent years, equine POI research has largely focused either on (a) the provision of descriptive statistics relating to the syndrome (e.g. incidence and survival rates), (b) the identification of associated risk factors, and (c) determining the efficacy of certain therapeutic and prophylactic interventions. There are little research-derived data focused on the pathogenesis of the syndrome in the horse, with reliance placed on the translational application of data derived from other species. Therefore, this review highlights some of the proposed key mechanisms in the pathophysiology of POI, derived from other species, and considers whether the translational application of these mechanisms to the horse can inform our interpretation of equine-derived data pertaining to risk factors and therapeutics.

Definitions and clinical features

General and human

The word ileus derives from the Greek word εἰλεός or *eileós* (meaning "twisting" or "rolling") and was initially defined in human medicine as "severe and prolonged twisting of the intestine", whereby the term could be applied to several conditions (e.g. intussusception, volvulus) which shared several presenting symptoms. This particular use of the term ceased in the 19th century following the adoption of a classification system of intestinal obstruction based on specific cause [14] and more recently its use was further restricted to a state of reduced or absent peristalsis as a result of a non-mechanical pathological response of the GI tract [1; 15]. Consequently, the majority of references to the term POI in current literature define the syndrome as a delay in the return of normal GI motility following surgery, or 'a syndrome of functional inhibition of propulsive bowel motility' [15].

In humans, overall intestinal motility should be normal by 5 days postoperatively. The small intestine (SI) recovers within 5 -10 hours, followed by return of gastric function at 24 – 48 hours, with a more prolonged time for restoration of colonic function (3-5 days) [16; 17]. Defaecation and tolerance of solid food ingestion are considered to reflect recovery of GIT following surgery in humans and are regarded as appropriate primary outcome measures in clinical trials of POI and decision-informing criteria relating to readiness for discharge [18].

In humans, various additional qualifying terms have been applied to POI, such as 'physiological (or normal) POI', 'pathological (or prolonged) POI' (PPOI) and 'recurrent PPOI' (RPPOI). The criteria used for classification vary greatly, which probably contributes to the disparity in certain study-derived data. For example, the reported incidence of human POI ranges from 2% to 60% depending on the POI or PPOI descriptors applied in the study [2; 19]. Efforts to establish more specific criteria for each of these POI subcategories [2] might facilitate comparisons between individual studies.

Equine

Similar differences in diagnostic criteria probably underlie marked variation (0 – 62%) in the reported equine POI prevalence rates following abdominal surgery (Supplementary Item 1). The presence of nasogastric reflux on intubation represents a universally applied diagnostic criteria which, along with ultrasonographic and palpable (via *per rectum* examination) evidence of distended SI are the most

commonly applied diagnostic indications [8; 9]. The ambiguity in POI definition is largely attributable to variations in the volume or rate of reflux as well as the inclusion or omission of associated clinical signs such as tachycardia and abdominal discomfort. There is a wide disparity in the volume of reflux considered to reflect the presence of POI, either on a single intubation and/or over multiple intubations within a 24-hour period (Supplementary Item 1). In an effort to standardise the definition of POI across all studies, Merritt and Blikslager (2008) proposed the following clinical criteria: gastric reflux of ≥4 l upon any given intubation, or >2 l/h on repeated intubation, of gastric contents of pH >4.0; persistent tachycardia (>40 beats/min); mild to severe signs of abdominal discomfort; rectal and/or ultrasonographic evidence of multiple loops of fluid distended small bowel [6]. Recent surveys of European and American equine clinical specialists confirmed the presence of nasogastric reflux as the most important criterion for defining POI but there was no consensus with respect to the rate and volume of reflux adopted as diagnostic markers [8; 9]. Agreement on, and adherence, to a universal syndrome definition would be a significant advance in POI research.

The term postoperative reflux (POR), proposed to describe solely the presence of reflux following surgery without any causal assumptions [20] includes both mechanical obstructions and functional motility inhibition as potential underlying mechanisms. In the interest of clarity, this review will focus on POI; namely, the functional inhibition of motility following abdominal surgery.

As in humans, a transient decrease in intestinal motility probably occurs normally following equine abdominal surgery. Data are available on the influence of anaesthesia (with or without orthopaedic surgery) on GIT. Orally administered chromium oxide was detected in faeces for 18-90 hours following general anaesthesia alone [21] and 15-105 hours following general anaesthesia (isoflurane) and orthopaedic surgery [22]. Following experimental jejunocaecostomy, Sasaki *et al.* (2008) demonstrated an immediate reduction in caecal motility which lasted 2 days; this was followed by an unstable period lasting 7 days and then a period of gradual recovery lasting up to 31 days [23]. However, unlike humans, where large intestinal (LI) dysmotility is commonly recognised and reflected in a delay in defaecation [17; 18], the clinical significance of POI in the horse is predominantly related to the SI. Therefore, data on the time taken for normal restoration of SI motility in a cohort of horses following abdominal surgery would have greater clinical relevance.

The greater clinical significance of SI dysmotility in equine POI may mask LI involvement. Nelson *et al*. (2013) demonstrated a greater delay in postoperative passage of first faeces in horses which had postoperative GI complications, compared with those that did not, following elective non-GI surgery [24]. Little *et al.* (2001) independently demonstrated only a 12% prevalence of postoperative colic in horses with reduced faecal output following non-GI surgery [25]. Faecal output measurement might enable the early identification of cases with 'LI POI', thus enabling the implementation of treatment before the development of caecal or large colon impactions.

Diagnosis of Equine POI - Mechanical versus functional

As discussed above, equine POI is most frequently diagnosed by the presence of reflux following nasogastric intubation. The ultrasonographic and/or palpable (via *per rectum* examination) detection of distended SI, tachycardia, abdominal discomfort, reduced faecal output and reduced/absent borborygmi are also valuable means of POI diagnosis [8; 9]. Importantly, the above clinical signs may also be present in other conditions, particularly those associated with a mechanical obstruction to the aboral passage of SI ingesta and fluid. In the immediate postoperative period, most consideration is given to an obstruction at the anastomosis site [10]. Clinical distinction between a functional and physical obstruction is challenging. Although mechanical obstructions associated with

leakage at the anastomosis site would likely result in worsening pain, increasing rectal temperature and cardiovascular deterioration, those attributable to adhesions or simple intestinal kinking may, like POI, simply result in distended SI and persistent gastric reflux. The absolute distinction between these differing disorders may require a second laparotomy, re-examination of the anastomosis site and confirmation that no physical obstruction is present. In one study of 27 horses that underwent relaparotomy (out of 254 that survived the 1st surgery) the most common diagnoses were functional ileus (25.9%) and obstruction at the site of anastomosis (22.2%). However, of those that underwent a second laparotomy 62% developed POI [26]. In a more recent study of 22 horses that underwent relaparotomy, 16 out of 19 horses with precipitating clinical signs (POR and postoperative colic) had these clinical signs eliminated by relaparotomy; furthermore, the authors reported that relaparotomy did not appear to exacerbate the POR [27].

Epidemiology and risk factors for equine POI

Equine surgical cases with SI lesions are consistently associated with an increased risk of POI. Extensive manipulation of the intestines associated with decompression and performing resections and anastomoses of the intestine is likely to induce a greater degree of tissue damage and a more profound inflammatory response in the *muscularis* [28]. Additionally, studies in mice have demonstrated that even exteriorisation of SI from the abdominal cavity is also likely to contribute to the inflammatory response [29]. While some equine studies have reported a greater risk of POI in cases with strangulating, compared with non-strangulating, SI lesions [30; 31], others have failed to identify such an association [5; 7; 13]. The onset of pathology is probably attributable to endotoxin release from ischaemic bowel resulting in systemic endotoxaemia [32], which, in itself, will result in reduced intestinal motility [33]. One study identified the presence of a strangulating pedunculated lipoma as a specific risk factor for POI, a finding which may reflect a dual association with both intestinal ischaemia and age, the latter also being reported as a significant risk factor for POI [34]. Other common risk factors relate to cardiovascular and haematological status. High packed cell volume (PCV) at the time of admission [5; 7; 31; 34; 35], increased serum total protein concentration [7; 35] and tachycardia [5] have all been associated with an increased risk of horses developing POI. These parameters all reflect a degree of dehydration and/or hypovolaemia resulting from both haemodynamic consequences of endotoxaemia and fluid sequestration within obstructed bowel and, therefore, may simply reflect the strangulating nature of the underlying intestinal lesion. Performing a pelvic flexure enterotomy may reduce POI risk [7; 13]; although this may be restricted to cases with LI, but not SI lesions [35]. Although the protective influence of this procedure may be attributable to a reduction in the intraluminal source of endotoxin, the potential value of evacuating the colon should be weighed against the increased anaesthesia and surgical time required to perform the surgery, as both factors have been associated with an increased risk of POI [7; 25].

Pathophysiology of POI

The development of POI has been attributed to several causes and mechanisms. These include the following: anaesthetic agents, opioids, intravenous fluids, electrolyte imbalances, disruption to GI hormones and neuropeptides, disruption of neural continuity, autonomic dysfunction and inflammatory cell activation [36]. Such contributory factors may act in isolation or in combination, ultimately resulting in a common endpoint; namely, impaired contractility of the intestinal smooth muscle (SM).

The majority of POI research has been performed on rodent models with only a relatively small number of studies in the horse. The most commonly used rodent POI model relies on small intestinal manipulation (IM) to induce ileus [29; 37], thus replicating, in part, the processes normally involved in abdominal and GI surgery. This model does not account for the additional processes of intestinal resection, enterotomies and large intestinal manipulation which are regularly undertaken and associated with an increased risk of equine POI. It is currently accepted that the pathogenesis of POI involves two phases: an initial neurogenic phase resulting in immediate postoperative impairment of bowel motility and a subsequent inflammatory phase lasting for several days. Despite representing distinct phases in POI progression, recent findings support a bi-directional interaction between the nervous and immune system.

Neurogenic phase

During abdominal surgery, the surgical incision, peritoneal breach and IM act as nociceptive stimuli that activate neural pathways (Fig 1). Surgical incision of the abdominal wall of rats creates a somatic wound activating adrenergic pathways [38; 39]. This pathway involves a spinal reflex; afferent splanchnic nerves synapse in the dorsal column of the spinal cord, stimulating glutamate release. Both activate spinothalamic projections causing the perception of pain at the surgical incision and mediate a sympathetic efferent response, resulting in reduced motility [15; 39-42]. The degree of ileus relates to the length of incision [41] and depletion of adrenergic innervation prevents this [42-44].

IM and breach of the peritoneum is a more intense stimulus than the skin incision alone, and in turn results in a longer period of inhibition of motility [38; 39], which, in rats, is only partially blocked by adrenergic antagonists [45]. As early as 1899, Starling and Bayliss observed a reduction in intestinal motility following intestinal handling in the dog, a phenomenon which was abolished by sectioning the vagus and splanchnic nerves [46]. As largely deduced from rodent studies, sensory information from the peritoneum and intestine is conveyed via the vagus nerve which, through the expression of interleukin-1 receptors (IL-1R) [47], is also sensitised by inflammatory stimuli. Afferents travel to the *nucleus tractus solitarius* of the brainstem, resulting in corticotrophin-releasing factor-mediated stimulation of neurons in the supraoptic nucleus of the hypothalamus. Hypothalamic neurons then project to sympathetic preganglionic neurons in the spinal cord, activation of which inhibits GI motility [40; 48-50]. Intense stimulation of splanchnic afferents, also triggers an inhibitory non-adrenergic, non-cholinergic vagally-mediated pathway that impairs motility via local release of nitric oxide (NO) and vasoactive intestinal peptide [38; 51]. Neuronal inhibition of GI motility is self-limiting, with normalisation of function returning upon cessation of nociceptor and mechanoreceptor stimulation. In comparison, the subsequent inflammatory response, and its effect on motility, results in a significantly more prolonged period of ileus. These two periods, an early neurogenic phase, and a later inflammatory phase have been recognised in humans [52] and hypothesised in horses [53].

Inflammatory phase

Results derived predominantly from rodent studies have attributed the prolonged phase of POI to inflammation within the intestinal *muscularis* [37; 54; 55]. Accordingly, the experimental induction of POI by IM has been prevented by the inhibition of mast cells [56], macrophages [57] or more general leukocytic infiltration [58; 59].

The activation of peritoneal mast cells, located within the serosa and mesentery and in close association with afferent nerve fibres [60], is an early event during abdominal surgery reported in the mouse [56] and human [61]. Neuropeptides (substance P or calcitonin gene-related peptide) released from afferent nerves have been hypothesised as playing a role [62; 63]. In addition to the release of histamine, mast cell proteinase-1, tryptase and IL-6 [61], activated mast cells also release IL-8 which, along with intercellular adhesion molecule-1 (ICAM-1), may directly result in neutrophil chemotaxis [64]. Alternatively, their close association with mesenteric blood vessels may facilitate the diffusion of mediators directly into the mesenteric circulation, resulting in the recognised increase in epithelial permeability following intestinal manipulation. This may in turn permit either the translocation of luminal-derived pathogen-associated molecular patterns (PAMPs) across the intestinal mucosa and/or stimulate the production of damage-associated molecular patterns (DAMPs), both of which may trigger a subsequent key step in the inflammatory cascade; namely, the activation of resident *muscularis* macrophages (MM) [37]. Notwithstanding these findings, intestinal inflammation and delayed GIT following IM were still present in a mast cell-deficient mouse strain [65].

Activation of MM occurs through DAMPs, such as adenosine triphosphate (ATP) [66], and PAMPs, such as lipopolysaccharide (LPS) [67]. In mice, the activation of toll-like receptors (TLR) and receptors for advanced glycation end products (RAGE) by PAMPs and DAMPs, results in recruitment of intracellular signalling pathways (p38, JNK/SAP), the activation of which are increased within an hour of IM [68]. This subsequently leads to the release of pro-inflammatory cytokines, including tumour necrosis factor-α (TNF-α), IL-1β and IL-6, and chemokines, including macrophage inflammatory protein -1α (MIP-1α) and monocyte chemoattractant protein-1 (MCP-1), with a resultant upregulation of ICAM-1 in the endothelium and the influx of leukocytes [28; 37; 69]. The leukocytic infiltrate, which predominantly comprises monocytes, mast cells and neutrophils, is detectable within 3 hours following surgery and continues to increase until it peaks at approximately 24 hours [54; 55]. Inducible NO synthase (iNOS) and cycloogygenase-2 (COX-2) [70] upregulation has been reported in MM in rodents, thus facilitating the production of NO and prostaglandins, both of which impair the contractile activity of SM cells [70]. Prostaglandins also increase the sensitivity of spinal afferent nerves [47]. Macrophage depletion (with chlodronate liposomes and using a mutant mouse with an inactivated colony stimulating factor-1 gene resulting in absence of *muscularis* macrophages) prevents intestinal inflammation and the development of POI [57], strongly supporting their role in the inflammatory phase of POI.

As mentioned previously, most of the studies of POI are performed on the SI. A recent study by Pohl *et al*. has shown differences in the inflammatory response of resident cells in the SI and colon in a mouse model of POI [71]. Whilst activation of resident MM in the SI is a result of translocation of luminal derived DAMPs or PAMPs, this does not occur with the colonic MM, a result of the colonic MM macrophages being less reactive, most likely reflecting the larger microbial load in the colon. In addition, differences in the response of infiltrating monocytes, and evidence that monocytes in the colon are affected by the microbiota, highlights significant regional differences in the response of the SI and colon to IM [71].

As in every tissue injury, immune cells and their products also contribute to the resolution of inflammation and POI; one key effector is IL-10. IL-10 knockout mice fail to resolve their *muscularis* inflammatory response compared to wild type mice, resulting in high mortality rates [72]. Administration of exogenous IL-10 improved GIT postoperatively and reduced inflammatory cytokines, chemokines and NO. Additionally, whilst the initial leukocytic infiltrate of neutrophils and

monocytes to the *muscularis* has been associated with SM dysfunction leading to POI, the role of monocytes/macrophages in resolution of POI has not been studied, until recently. Farro *et al*. (2017) demonstrated that blocking the influx of monocytes to the *muscularis* did not prevent POI but resulted in a prolonged period of smooth muscle dysfunction and an increased neutrophilic inflammatory response [55]. The administration of macrophage colony stimulating factor-1 fusion protein (CSF1-Fc) [73] not only restored monocyte and MM numbers but reduced neutrophil infiltration in the *muscularis*, increased anti-inflammatory gene expression and improved GIT transit time following IM [55]. Continued work focusing on the recovery process is warranted, with the potential to inform the development of therapeutic interventions which accelerate this process rather than solely targeting the onset of inflammation.

In the horse, postoperative neutrophilic and eosinophilic inflammation of the jejunum has been identified up to 18 hours postoperatively [28; 74; 75]. Direct manipulation of the LI in the horse resulted in an inflammatory response; this also occurred following manipulation of the SI alone [75]. A similar response has been reported in rodents [76]. In addition to this pan enteric response, an increase in apoptotic cells (neurons, SM and glial cells) has been demonstrated in strangulating lesions of the LI and SI at sites distant to the lesion, most likely reflective of a generalised stress response of the GI tract to ischaemia, reperfusion and inflammation [77]. A localised stress response in the SM and neurons has been reported in the borders of healthy resection margins [78].

Activation of MM by manipulation-induced translocation of luminal-derived LPS is a recognised phenomenon in humans and rodents leading to loss of SM contractility [67; 79]. In light of IM-induced loss of mucosal epithelial cells in the horse it is likely that a similar LPS translocation process also occurs in this species [75]. IM-induced inflammation in a TLR-2 and TLR-4 double knockout mouse model, was only partially protected against a delay in GIT [80], demonstrating that alternative TLR-2 and TLR-4 independent pathways must also exist.

Although the translational application of data derived from rodent models can provide a valuable insight into the basic cellular and molecular responses of the equine GI tract to celiotomy and IM there are significant differences in innate immune biology. For example, handling-induced NO liberation by murine MM contributes towards intestinal SM dysfunction in the mouse GI tract [81], but like other large animals (pigs and humans [82]) equine alveolar and peritoneal macrophages do not produce NO, so this mediator is not likely to be involved in equine inflammation [83].

Another important factor to consider when extrapolating findings from rodent studies to equine colic cases is the absence of pre-existing conditions, such as ischaemic bowel, peritonitis and endotoxaemia in rodent models of IM used to study POI. A model of caecal ligation and perforation in rats resulted in reduced GI motility and a leukocytic inflammatory response within the *muscularis* [84]. Whilst not a model of POI that is used in the majority of rodent studies, it does demonstrate the effect of polymicrobial sepsis on GI motility. Horses undergoing abdominal surgery will usually have significant primary disease, such as ischaemic bowel, peritonitis associated with non-viable intestine and intestinal distention secondary to a strangulation/amotility. As mentioned earlier, endotoxin release from ischaemic bowel can cause reduced intestinal motility [32; 33]. Horses with amotile intestine may also have increased bowel oedema because of reduced lymphatic drainage [85; 86]. How these pre-surgical factors affect the pathogenesis of equine POI is not known, but given horses presenting with compromised cardiovascular status/endotoxaemia [5; 7] and with pre-operative reflux [13] are at increased risk of developing POI (see section above) one could assume that they play a significant role in the pathogenesis of equine POI.

Pharmacological/therapeutic influences

In addition to the key neurogenic and inflammatory phases of POI, a variety of pharmacologic agents and therapeutic interventions have also been identified as either increasing the risk or duration of POI.

Opioids

The negative effects of opioids on GI motility have been well documented in the literature for both horses [87-89] and man [90], with opiate administration in man being recognised as a contributing factor to POI development [91; 92]. Two large scale questionnaire surveys of American and European equine clinical specialists revealed a widely-held view that opioid use was 'not a very important' risk factor for the development of POI [8; 9]. However, despite this dominant opinion, 87% of those reporting a POI incidence greater than the median incidence, declared the use of opioids in their treatment regimens. Opioids mediate their effect on opioid receptors, of which there are three types: delta (δ) kappa (κ) and mu (μ). These receptors are found throughout the central (CNS) and peripheral nervous systems, with μ and κ receptors present in the excitatory neurons innervating the intestine. Stimulation of CNS opioid receptors induces analgesia, but stimulation of μ- and κ-receptors in the GI tract influences several physiological functions including motility. Opioid receptor agonists inhibit acetylcholine (Ach) release, resulting in an increase in SM tone and reduced intestinal motility [93]; in contrast, opioid antagonists may reduce this effect. This is evidenced by the accelerated postoperative recovery of GI motility following the oral administration in humans of the peripherally-acting μ-opioid antagonist, alvimopan [94]. In the horse, administration of the μ-opioid receptor antagonist naloxone resulted in an increase in LI motility, potentially reflecting a role for endogenous opioids in modifying intestinal activity [95-97]. Predictably, μ-agonists without anticholinergic activity have the least detrimental effect on jejunal motility [98], potentially rendering them more suitable analgesics for postoperative use although a study assessing the benefit of butorphanol, a partial agonist and antagonist of the μ-opioid receptor and partial agonist of the κ-receptor, following celiotomy produced a transient decrease in faecal production 24 hours postoperatively [99]. Despite this decrease being short-lived, the prolongation of time to first passage of faeces may impair the ability of the clinician to accurately assess the postoperative case. The overall evidence for their inhibitory effects on intestinal motility generally precludes their routine perioperative use in horses undergoing abdominal surgery.

Anaesthetic agents

All anaesthetic agents affect GI motility by affecting the myoelectric activity of the intestine [100]. Drugs used for anaesthetic maintenance such as halothane and isoflurane reduce GI motility in horses undergoing non-GI abdominal procedures with halothane having a more profound affect than isoflurane [22]. Although duration of anaesthesia has been identified as an increased risk factor for POI in the horse (Supplementary Item **1**), it is unclear whether this association is attributable to increased exposure to anaesthetic agents, increased bowel handling in more protracted surgeries or a combination of both.

Intravenous fluid therapy and electrolyte imbalances

Electrolyte disturbances, particularly hypocalcaemia and hypomagnesaemia, are commonly associated with equine GI disease and horses with low postoperative serum magnesium and calcium levels are at increased risk of developing POI [101; 102]. Similarly, in man, POI is associated with electrolyte disturbances such as hypokalaemia and hyponatraemia [91; 103]. From both a

prophylactic and therapeutic viewpoint, it is important to monitor at-risk patients for underlying electrolyte derangements and apply the appropriate corrective approach. This often necessitates the intravenous administration of polyionic crystalloid fluid. However, despite the associated benefits of restoring and maintaining an appropriate electrolyte status, certain detrimental effects of overzealous crystalloid fluid administration have also been reported. In humans, crystalloid overload is associated with an increased duration of ileus and bowel recovery times [104; 105] and a higher risk of leakage at the anastomoses site has been demonstrated in rodent models [106]. Oedema of the intestine as a result of fluid overload results in delayed intestinal transit and altered gut barrier functions due to decreased mesenteric blood flow, increased stretch of the intestine and altered sodium channel exchange expression [107]. These three factors consequently cause signal transducer and activator of transcription 3 (STAT-3) and nuclear factor-κβ (NFκβ) activation and reduction of myosin light chain phosphorylation of the intestinal SM, such that the contractile activity of the muscle is reduced [86; 108]. Oedema subsequent to reduced or absent peristalsis could arise from a reduction in lymphatic drainage and a subsequent accumulation of interstitial fluid [85; 86]. Colloid administration has not been shown to increase the risk of POI in humans in a retrospective study, potentially due to avoidance of third space fluid loss or a reduction in any third space fluid loss associated with crystalloid administration [109]. IVFT fluid regimes in humans undergoing abdominal surgery are varied but broadly come under 3 categories; liberal, zero balance and restrictive fluid regimes. Liberal is defined as greater than 2.75 L/day (1.9 ml/kg/h for a 60 kg human); zero balance between 1.75-2.75 L/day and restrictive as less than 1.75 L/day in the postoperative period [110]. Several studies have shown the potential benefit of restrictive regimes in postoperative recovery [104; 105; 110], with oral fluids being introduced as soon as possible following surgery [111]. As a result, there is currently a large clinical study being performed in humans to fully evaluate fluid regimes and postoperative recovery, with results due in 2018 [112]. Fluid rates usually used in the horse are maintenance at 2.5 ml/kg/h with an anaesthesia maintenance rate of 10 ml/kg/h [113] meaning equine fluid rates used are similar to liberal regimes in humans. Whilst no study has specifically addressed different fluid regimes in the horse and their effect on postoperative recovery, one study in the horse has identified duration of fluid therapy with an increased risk of POI [114].

Surgical factors

Good surgical technique is important to ensure a successful surgical outcome postoperatively. Any surgical procedure involving resection of the intestine will affect the migrating myoelectrical complex resulting in a disruption to the contractile activity of the SM [115].

Leakage at the anastomosis site for any reason is associated with prolonged recovery times in humans. This can manifest as the development of either acute, severe symptoms in the early post-operative period or delayed, more subtle symptoms [116]. In general, anastomotic leaks in humans are diagnosed 5-8 days post-operatively, although more delayed recognition (up to 12 days) has been reported [117]. Rarely do equine POI cases present clinically following such a protracted post-operative period [118], a finding which questions the relative importance of anastomotic leaks, compared with functional inhibition of intestinal motility, in equine POI. In addition, most human studies refer to colorectal surgery; consequently, data on human anastomotic leaks may not directly correlate with leakage at the site of SI anastomoses in horses. The identification of anastomotic leaks in humans is facilitated by the use of abdominal radiography and contrast CT, both techniques which are not applicable to the horse. Although clinical signs (e.g. pyrexia, inappetence, tachycardia),

worsening endotoxaemia, clinical pathology results (e.g. haematology, peritoneal fluid analysis) and ultrasonographic findings (e.g. increased peritoneal fluid volume, fibrin deposition) may raise diagnostic suspicion of anastomotic leaks in the horse, ultimate diagnostic confirmation can only be achieved by a repeat laparotomy. Considering the relative rarity of a repeat laparotomy in horses that develop POI, it remains possible that anastomotic leaks are underdiagnosed in this species.

Management of POI

In human medicine, Enhanced Recovery After Surgery (ERAS) programmes, which include multiple pre-, intra- and postoperative interventions, aim to reduce the surgical stress response and rapidly return the GI tract to normal physiological function [119].

In veterinary medicine, no universally-accepted approach to the management of equine POI currently exists; however, Figure 2 represents an adaptation of the human ERAS system, which may be applicable to horses undergoing abdominal surgery. Veterinary clinicians, who are largely informed by knowledge of the relevant veterinary literature, use various pre-, intra- and postoperative supportive and therapeutic approaches [8; 9]. These preventive and management measures consist mainly of anti-inflammatories, prokinetic and antimicrobial (with prokinetic action) medications, along with intravenous fluid therapy (IVFT). Any horse undergoing abdominal surgery is 'at risk' of POI, especially those with SI lesions and a compromised cardiovascular status. Early identification of high risk cases permits the prompt adoption of early management strategies.

Intravenous fluid therapy and electrolytes

Rehydration and the maintenance of normovolaemia will sustain physiological intravascular volume and minimise the development of bowel oedema due to over-hydration. As the risk of bowel oedema consequent to over-hydration is greater with intravenous crystalloid fluids, the additional or alternative use of colloids may be preferable in some cases [109]. The current recommendation in human medicine is to avoid fluid excess by using a near-zero fluid balance approach or using restricted IVFT regimens [105; 120; 121]. The intravenous administration of hydroxyethyl starch (HES) in conjunction with isotonic saline to horses with colitis or ileus of the SI and LI led to a decrease in PCV and heart rate and normalisation of serum urea and creatinine within 24 hours [122]; a repeat of this study with larger cohorts is warranted. Hypertonic saline administration to rats with interstitial intestinal oedema was found to be beneficial [123]. Postoperatively, ERAS schemes recommend oral intake of fluids and discontinuation of IVFT [120; 121].

Intestinal manipulation

Minimisation of tissue handling is likely to have beneficial effects via reduced induction of inflammation within the *muscularis* [28; 29; 37]. However, the potential benefit of limiting the degree of intestinal manipulation in equine surgery must be weighed against the increased risk of POR associated with inadequate decompression of the SI which may result in kinking, and therefore obstruction, of distended SI loops [20]. Studies conducted in rodent models have clearly demonstrated an association between the force of manipulation and both the resulting inflammatory response and the delay in recovery of GIT motility [29]. Extrapolation of these data may suggest that short duration severe handling could have a more detrimental effect on motility than longer duration, yet less severe handling. Therefore, despite the inevitable inflammatory response induced by the oftentimes multiple manipulations required to fully decompress the SI, it would appear prudent to be aware of the potential value of maintaining a gentle technique

throughout this procedure. Although multiple enterotomies may theoretically reduce the requirement for repeated manipulation of certain intestinal segments, this approach will inevitably increase the duration of surgery and would likely increase the risk of postoperative adhesion formation and a single enterotomy to decompress the SI is therefore recommended. For strangulating obstructions, the bowel to be resected and discarded can be placed over the edge of the surgical field to evacuate contents. In strangulating lesions where resection is not deemed necessary, performing a single enterotomy to evacuate small intestinal content is less traumatic and therefore preferable to manual decompression of the SI, by pushing the contents into the caecum. This also has the added benefit of not over-filling the caecum with foul SI luminal contents,
The use of carboxymethylcellulose (CBMC) should also be considered in at risk cases. Several studies in the horse show evidence of the use CBMC reducing adhesion formation, with no adverse effects on anastomotic healing [124-128]. If injury, and therefore inflammation can be reduced in the serosa of manipulated intestine, then this may also reduce inflammation within the remaining layers of the intestine, In the horse, neutrophilic inflammation occurs on the serosal surface of manipulated intestine, and within the *muscularis,* myenteric plexus and submucosal plexus [74]. What is not known is if neutrophils migrate from the serosal surface towards the mucosa, or vice versa, following manipulation.

Nasogastric intubation

In humans, the routine use of nasogastric tubes is not associated with an improvement in return to normal bowel function [121; 129]; indeed, patients undergoing elective laparotomies had increased gastroesophageal reflux when a nasogastric tube was placed [130]. Current recommendations in humans is to restrict the use of nasogastric tubes to patients that have delayed gastric emptying following surgery [121]. Nasogastric intubation in horses is required to alleviate the clinical signs associated with excessive fluid accumulation within the stomach. In contrast to the inclination of European equine clinicians to pass a nasogastric tube when required, there is a preference amongst North American equine clinicians to retain an indwelling tube [8; 9]; however, there is no evidence to suggest that this practice reduces the incidence of POI. Although no evidence based recommendations can be offered, the decision to retain an in-dwelling tube is likely informed by a variety of case-specific factors, including the rate and amount of reflux, the duration of POI, the compliance of the equine patient and the availability of hospital staff. In those cases where an in-dwelling tube is not retained, the requirement for periodic intubations can be determined by serial ultrasonographic examinations to determine the caudal extension of the gastric margin on the left side of the horse and the degree of duodenal distension on the right.

Early feeding and mobilisation

Early feeding following surgery is a commonly applied prophylactic approach in human medicine. It is hypothesised to promote restoration of GI motility via the release of neuropeptides in response to solid feed ingestion. Some studies have demonstrated a beneficial effect of chewing gum as a form of sham feeding [131]. Early postoperative feeding has been shown to be effective in equine surgical cases [30]. The careful introduction of small amounts of good quality roughage at regular intervals as soon as possible postoperatively may be indicated in at-risk cases. For horses with gastric reflux for which the provision of enteral nutrition is not possible, the provision of a lick (e.g. mineral block) has been suggested as a form of sham feeding, equivalent to gum chewing in humans. In the horse, bit

chewing has been suggested as being potentially beneficial to gut motility [132]. Similarly, hanging a haynet outside the stable, yet within view, has also been suggested as a potential means of providing visual stimulation of GI motility.

In humans, bed rest increases insulin resistance and muscle loss and decreases muscle strength, pulmonary function and tissue oxygenation. Patients are recommended to initiate progressive mobilisation after abdominal surgery as early as the first day postoperatively, provided the level of analgesia is effective [120]. In horses, the reported benefits of early mobilisation are largely anecdotal; however, those that adapt and apply the human ERAS protocol to their equine postoperative cases instigate early mobilisation as one of the components of this approach [20].

Therapeutics

The two principle pharmacological components of POI treatment include the use of prokinetic and anti-inflammatory drugs (Supplementary Item 2). As the neurogenic phase of intestinal amotility is considered to resolve upon cessation of the surgical stimuli, targeting the subsequent inflammatory phase is a more appropriate approach in the management and treatment of POI.

Anti-inflammatories

Non-steroidal anti-inflammatory drugs (NSAIDs)

In human medicine, the main perceived benefits of NSAID administration include a reduced requirement for opioid administration, the commencement of early ambulation and a reduction in the COX-2-mediated inflammatory response [133]. The relative merits of each remain unclear. Questionnaire-based surveys of North American and European equine veterinary specialists revealed flunixin meglumine to be the preferred NSAID of choice for POI prophylaxis and treatment [8; 9], but there is no evidence that flunixin reduced the incidence of POI, when compared with meloxicam [114]. Indeed, no studies have been performed in horses showing NSAIDs reduce the incidence of POI; however, studies have been performed showing effects of flunixin meglumine and phenylbutazone on GI motility in horses with abdominal pain and inflammation. Those NSAIDs are believed to have a beneficial effect on the acute systemic side effects of endotoxins, including the deterioration in cardiovascular parameters [134]. There is some concern in the human literature that NSAIDs affect anastomotic healing [135]. Similarly, studies using various models of equine intestinal mucosal injury have highlighted detrimental effects of non-cox-selective NSAIDs on mucosal healing and restoration of mucosal integrity [136]. Anastomotic healing, although not directly represented by these models, likely shares certain endogenous prostaglandin-dependent processes and is theoretically susceptible to disruption by NSAID administration.

Other anti-inflammatory targets

Preliminary studies in mice looking at blocking ICAM-1 and the IL-1R either reduced the inflammatory response in the *muscularis* [58] or prevented the development of POI [80]. Alicaforsen (an ICAM-1 specific antisense oligonucleotide that reduces receptor expression) is being used in human clinical trials for inflammatory bowel disease, but not in POI. Semanipod and the salt CPSI-2364 inhibits p38 mitogen-activated protein kinase (an intracellular signalling pathway in macrophage activation) have been used in mouse and pig models of POI, and have reduced inflammation and severity [68; 137; 138]. Another approach is the prophylactic application of vagal nerve stimulation, which inhibited macrophage activation in a mouse model [139]. This was termed the cholinergic anti-inflammatory pathway, as Ach is the parasympathetic neurotransmitter involved. The anti-inflammatory effect is mediated by the release of ACh interacting with nicotinic

ACh α-7 receptors (nAChα7R) on macrophages, which is required for the inhibition of cytokine synthesis and release [140]. In murine POI models, vagal nerve stimulation reduced the activation of MM with a subsequent reduction in infiltrating inflammatory cells and improved GIT [141; 142]. A preclinical model using pigs, has demonstrated that laparoscopic abdominal vagal nerve stimulation is safe and a potentially viable method [143] as well as a pilot study in humans [144] shows promise for its translation into human and even potentially equine medicine.

Prokinetics

The most commonly used prokinetics in equine POI management are lidocaine (lignocaine), metoclopramide, erythromycin lactobionate and neostigmine [8; 9; 145] and their use and efficacy have been much debated in the human and equine clinical literature. The reader is directed to review of Wong *et al.* (2011) for a comprehensive overview of the clinical indications for the use of various prokinetic drug classes in the horse, including their modes of action and suggested dosing regimens [146]. Whilst there are several studies supporting the use of lidocaine in the management of equine POI [35; 118] a recent review failed to identify any beneficial effects of its use [147]. Traut *et al.* (2008) reviewed the evidence for the clinical efficacy of various prokinetics in man and concluded that there was no evidence of efficacy of erythromycin, cholecystokinin, cisapride, dopamine-antagonists, propranolol or vasopressin and inconclusive evidence for lidocaine and neostigmine [148]. In addition to the lack of evidence regarding their efficacy in POI, the use of any antimicrobial product (such as erythromycin) for purposes other than their antimicrobial effects remain controversial.

Evidence of the prokinetic properties of lidocaine is contradictory; some studies demonstrate an increase in contractile activity [149; 150], others fail to report any change [151] and one study reported an increase in faecal transit time following a continuous lidocaine infusion [152]. Whilst lidocaine has always been labelled as a prokinetic drug in the context of POI treatment, any affect may be mediated via its analgesic and/or anti-inflammatory properties [153-155], Lidocaine, and other local anaesthetics, inhibit several functions of neutrophils, such as adhesion and phagocytosis [154]. In an equine jejunal ischaemia model, co-treatment of lidocaine with flunixin resulted in reduced mucosal inflammation, characterised by reduced neutrophilic migration, mucosal COX-2 expression and serum prostaglandin levels [155]. Conversely, the same group, using an *in vitro* model, reported an increase in neutrophilic migration in response to lidocaine [156]. In horses, lidocaine did not reduce neutrophil migration into the abdominal cavity following intraperitoneal LPS injection, despite a reduction in TNF-α concentration [157]. These equine-derived data somewhat contradict reports in the human literature documenting lidocaine-induced suppression of neutrophilic function [158]. Consequently, inter-species variation may exist with respect to the effect of lidocaine on neutrophil function. Furthermore, the *in vitro* effects of lidocaine on neutrophil function may differ from the *in vivo* effects.

Conclusion

Most of the proposed mechanisms underlying equine POI are based on rodent and human derived data. There is a clear need for the development and application of a standard POI definition in the horse to facilitate inter-study comparisons. Such an exercise should lead to the generation of less conflicting data on incidence and risk factors and increase the robustness of studies designed to evaluate the efficacy of prophylactic and/or therapeutic interventions.

Although lidocaine remains one of the most popular drugs of choice for the treatment of equine POI, the evidence supporting its clinical efficacy is inconclusive and systematic evaluation of alternative pharmacological and physiological approaches in the horse, including alvimopan and vagal nerve stimulation is warranted. Whilst the discovery of new and effective therapeutics is important, it remains likely that a multimodal approach to POI in the horse, such as an Enhanced Recovery After Surgery for Equines (ERASE) scheme (Figure 2) addressing pre-, intra- and postoperative factors, is likely to be met with greater success, as it has in human medicine. Such an approach would include consideration of surgical factors such as the minimisation of tissue handling, good surgical technique and duration of surgery as well as therapeutic interventions.

Authors' declaration of interests

No competing interests have been declared.

Ethical animal research

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All authors contributed to the design and preparation of this manuscript.

Figure legends:

Fig 1: Proposed role of the intra-operative factors, surgical incision, intestinal manipulation and anastomosis, in the neurogenic and inflammatory phases of POI.

Fig 2: Suggested Enhanced Recovery after Surgery for Equines (ERASE) protocol. Adapted from Lassen *et al*. 2009.

Supplementary Information

Supplementary Item 1: Summary of definitions, incidence and identified risk factors of POI in equine studies. *HR = heart rate; NG = nasogastric; PCV = packed cell volume; POI = postoperative ileus; SI = small intestine; TP = total protein.*

Supplementary Item 2: Summary of pharmacological treatments used in the management and treatment of POI across the species. *Ach = acetylcholine; COX-2 = cycloogygenase-2; D2 = dopamine receptor 2; HT =* hydroxytryptamine receptor; IL = interleukin; *nAChα7R = nicotinic acetylcholine α-7 receptors; NSAID = non-steroidal anti-inflammatory; POI = postoperative ileus.*

List of abbreviations

Ach	acetylcholine
ATP	adenosine triphosphate
CNS	central nervous system
COX-2	cycloogygenase-2
CSF1R	colony stimulating factor-1 receptor
CT	computed tomography
DAMPs	damage-associated molecular patterns
D2	dopamine receptor 2
ERAS	Enhanced Recovery After Surgery
GI	gastrointestinal
GIT	gastrointestinal tract
HES	hydroxyethyl starch
HR	heart rate
HT	hydroxytryptamine receptor
ICAM-1	intercellular adhesion molecule 1
IL	interleukin
IL-1R	interleukin-1 receptors
IM	intestinal manipulation
iNOS	inducible NO synthase
IVFT	intravenous fluid therapy
LI	large intestine
LPS	lipopolysaccharide
MCP-1	monocyte chemoattractant protein-1
MIP-1α	macrophage inflammatory protein -1α
MM	muscularis macrophages
nAChα7R	nicotinic acetylcholine α-7 receptors
NFκβ	nuclear factor-κβ
NG	nasogastric
NO	nitric oxide

NSAIDs	non-steroidal anti-inflammatory drugs
PAMPs	pathogen-associated molecular patterns
PCV	packed cell volume
POI	postoperative ileus
POR	postoperative reflux
RAGE	receptors for advanced glycation end products
SI	small intestine
SM	smooth muscle
STAT-3	signal transducer and activator of transcription 3
TLR	toll-like receptor
TP	total protein

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