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The use of probiotics in the surgical patient

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Summary. *Background:* The intestinal microflora is thought to be the origin for many infectious complications seen in surgical conditions, due to dysfunction of the intestinal barrier and bacterial translocation. Probiotics may produce beneficial effects on the intestinal barrier function and help reduce the incidence of infectious complications in this group of patients.

Methods: Medical databases were searched for randomised controlled studies regarding the use of probiotics or synbiotics in surgical patients.

Results: There was no significant benefit in the use of synbiotics in elective abdominal surgery. Patients undergoing hepatopancreatobiliary surgery or liver transplantation showed significant reductions in post-operative infectious complications, as did trauma patients. Despite promising early studies, the most comprehensive study involving acute pancreatitis showed an increased mortality.

Conclusions: Probiotics or synbiotics may protect against post-operative infectious complications in certain surgical conditions, but caution must be exercised. Use in acute pancreatitis should be avoided at the present time.

Keywords: Probiotics, surgery, pancreatitis, complications, infection.

Introduction

The use of probiotics as potential therapy has been proposed for a variety of medical and surgical conditions. Defined in 2001 by an expert panel commissioned by the Food and Agriculture Organization of the United Nations and the World Health Organization as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host", probiotics have many potential ways in which to exert influence on the body.

Whilst much of the work involving probiotics has focussed on reducing the incidence of antibiotic-associated diarrhoea and *Clostridium difficile* (*C. difficile*) infection, the prevention of post-operative infectious complications in surgical patients is another novel application. With the use of prophylactic antibiotics to reduce rates of infections following surgery and the increasing problem of multi-resistant organisms, new strategies are being sought to improve outcomes.

Enhanced surgical recovery programmes have been developed to optimise peri-operative care via multiple different modalities, including pre-operative carbohydrate loading, nutrition, peri-operative fluid management and appropriate use of antibiotic prophylaxis [1]. The "gut origin of sepsis hypothesis" and possible role of bacterial translocation in post-operative sepsis have raised the question as to whether or not probiotics could also be of benefit in such patients.

Surgical conditions and operations are diverse in their nature, so this review will look at the evidence for the use of probiotics in specific surgical groups. Particular focus will be given to the use of probiotics in acute pancreatitis and the recent surrounding controversies.

Heterogeneity of probiotics

It is beyond the remit of this review to provide a detailed description of the numerous probiotic preparations available, but is it important to recognise that the products do vary significantly. Some preparations consist of a single strain of organism, whilst others comprise a combination. The concentration and numbers of organisms also vary significantly depending on the product. A summary of the probiotic preparations used in the trials covered by this review can be seen in Table 1.

Some studies have also looked at the use of synbiotics, which are combinations of prebiotics and probiotics aiming for a synergistic effect. Prebiotics are "selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora that confer benefits upon host well-being and health" [2]. Unlike probiotics, which contain live bacteria as their active ingredients, prebiotics are carbohydrates that are resistant to digestive enzymes and therefore reach the colon and act as a

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Tab. 1: A summary of trials relating to the use of probiotics in surgical conditions

Condition/reference	Probiotic preparation	Main outcomes	Other outcomes	Probiotics regime
Elective abdominal surgery (31), ($n = 129$)	Proviva®: *Lactobacillus plantarum* 299v, with prebiotic	No sign. benefit		2.5×10^{10} per day, variable duration, pre + post-op
Major abdominal surgery (32), ($n = 90$)	*L. plantarum* 299, with prebiotic	No sign. benefit		2×10^{9} per day, 4 days post-op
Elective abdominal surgery (33), ($n = 137$)	Trevis®: *L. acidophilus* La5, *L. bulgaricus, Bifidobacterium lactis* Bb-12, *Streptococcus thermophilus*, with prebiotic	No sign. benefit		1.2×10^{10} per day, variable duration, pre + post-op
Elective colorectal surgery (34), ($n = 76$)	Synbiotic 2000®: *Pediacoccus pentosaceus* 5–33:3, *Leuconostoc mesenteroides* 77:1, *L. paracasei* subspecies *paracasei* F19, L. plantarum 2362, with prebiotic	No sign. benefit		8×10^{10} per day, 3 days pre-op
Colectomy (35), ($n = 92$)	Trevis®, with prebiotic	Infection rates unchanged	Sign. reduced bacterial translocation	1.2×10^{10} per day, unclear duration, pre-op
Biliary cancer surgery (36), ($n = 54$)	Yakult BL Seichōyaku®: *B. breve* strain Yakult, *L. casei* strain Shirota, with prebiotic	Sign. lower infection rates		6×10^{8} per day, 14 days post-op
Biliary cancer surgery (37), ($n = 101$)	Pre: Bifiel®: *B. breve* strain Yakult. Yakult400: *L. casei* strain Shirota. Post: Yakult BL Seichōyaku®, with prebiotic	Sign. lower infection rates		5×10^{10} pre-op, 6×10^{8} post-op per day, 14 days pre-op and 14 days post-op
Pancreato-duodenectomy (40), ($n = 80$)	Synbiotic 2000®, with prebiotic	Sign. lower infection rates	Sign. reduced antibiotic duration	8×10^{10} per day, 1 day pre-op and 8 days post-op
Pancreato-duodenectomy (41), ($n = 70$)	Bio-Three®: *Enterococcus faecalis* T-110, *Clostridium butyricum* TO-A, and *Bacillus mesentericus* TO-A, no prebiotic	Sign. lower infection rates		6×10^{7} per day, variable duration, pre + post-op
Liver transplant (42), ($n = 105$)	Probi AB®: *L. plantarum* 299, with prebiotic	Sign. lower infection rates		2×10^{9} per day, 12 days post-op
Liver transplant (43), ($n = 66$)	Synbiotic 2000®, with prebiotic	Sign. lower infection rates		8×10^{10} per day, 14 days post-op
Living donor liver transplantation (44), ($n = 50$)	Yakult BL antiflatulent®: *B. breve* strain Yakult, *L. casei* strain Shirota, with prebiotic	Sign. lower infection rates		6×10^{8} per day, 2 days pre-op and 14 days post-op
Trauma (47), ($n = 65$)	Synbiotic 2000 Forte®: *P. pentoseceus* 5–33:3, *L. mesenteroides* 32–77:1, *L. paracasei* ssp 19, *L. plantarum* 2362, with prebiotic	Sign. lower infection rates, non-sign. lower mortality	Sign. lower length of stay, ventilation time	4×10^{11} per day, 15 days post-op
Trauma (48), ($n = 72$)	Synbiotic 2000 Forte®, with prebiotic	Sign. reduced bacteraemia	Sign. lower VAP rates	4×10^{11} per day, 15 days post-op
Trauma (49), ($n = 113$)	Synbiotic 2000®, with prebiotic	Sign. lower infection rates	Sign. lower intestinal permeability	Variable, post-op
Acute pancreatitis (58), ($n = 50$)	*L. plantarum* 299, with prebiotic	Sign. lower rates of necrosis → surgery		2×10^{9} per day, 7 days post op
Acute pancreatitis (59), ($n = 83$)	Synbiotic 2000®, with prebiotic	Sign. lower rates of complications	Sign. lower SIRS, MOF	4×10^{10} per day, min. 7 days post-op
Acute pancreatitis (60), ($n = 76$)	*L. plantarum*, no prebiotic	Benefits, but with enteral feeding		1×10^{8} per day, 7 days post-op
Acute pancreatitis (61), ($n = 298$)	Ecologic 641®: *L. acidophilus, L. casei, L. salivarius, Lactococcus lactis, B. bifidum*, and *B. lactis*, with prebiotic	Increased mortality	No reduction in complications	1×10^{10} per day, max. 28 days post-op

fermentable "food source" for the resident bacteria. As summarised by Kolida et al., prebiotics have been shown to increase numbers of beneficial Bifidobacteria and Lactobacilli, decrease numbers of potentially harmful bacteria including *E. Coli* and *Clostridium*, as well as decrease luminal pH [3].

Bacteria commonly used in probiotic formulations include lactobacilli, bifidobacteria, enterococci, streptococci and *Bacillus clausii*. *Saccharomyces boulardii*, a live yeast, is also a probiotic and can be used in the treatment of recurrent *C. difficile* infection. The various probiotic organisms may exert their influence via differing mechanisms, so it can be difficult to apply the results of one probiotic preparation to another and this must be borne in mind when reviewing the evidence.

The role of the gut in sepsis and the surgical patient

The epithelial barrier of the gastrointestinal tract is designed to prevent invasion of pathogens, but it is strongly influenced by the resident microflora. Using the data from cultivation-based studies and rRNA work thus far, there would appear to be a microbial diversity in the human gastrointestinal tract of more than 1200 distinct microorganisms (including bacteria, filamentous fungi, yeasts and archaea) [4]. In a healthy gastrointestinal tract, the epithelial barrier still allows a degree of bacterial penetration, allowing the microflora to stimulate mucosal immune responses, which are usually mutually beneficial. Disruption or inflammation of the epithelial barrier can interrupt this relationship, lead to harmful mucosal immune responses that can result in further epithelial dysfunction, as well as allow bacterial translocation.

Key to the "gut origin of sepsis hypothesis" in surgical patients is the process of bacterial translocation, whereby the intestinal barrier is overcome and intestinal microflora can cross to the mesenteric lymph nodes and beyond, thus precipitating sepsis [5, 6]. In surgical patients, this may occur via a combination of increased epithelial barrier permeability, reduced gastrointestinal motility, bacterial overgrowth, changes in immune system regulation, as well as potential intestinal ischaemia and reduced nutrition around the time of surgery. Certainly, there is evidence that the proximal gastrointestinal tract may be an important occult reservoir of the predominant pathogens in multi-organ failure and that nosocomial infection may be caused by organisms originating in the gut [7, 8].

Bacterial translocation has been induced in animal models in different ways, including obstruction induced by caecal ligation [9], haemorrhagic shock [10], thermal injury [11], malnutrition in the presence of endotoxins [12], jaundice [13], as well as trauma [14]. As described below, work in humans has been more problematic. However, as reviewed by Gatt et al., there is evidence that intestinal obstruction, inflammatory bowel disease, jaundice, malignancy, pre-operative total parenteral nutrition, emergency surgery and gastric colonisation with microorganisms can be associated with increased bacterial translocation [15].

Based on experimental studies, Deitch suggested that one of three pathophysiological conditions was necessary for bacterial translocation to occur [6]. These conditions comprised disruption of the intestinal microflora, impaired host immunity and loss of the mucosal barrier. More recently, Deitch proposed the "three hit model", comprising an event causing splanchnic hypoperfusion and local inflammation, then a reperfusion injury resulting in reduced gut barrier function and further local inflammation, followed by bacterial translocation and a further inflammatory reaction [16]. Interestingly, a variation of the "gut origin of sepsis hypothesis" has recently been suggested. This is called the "gut-lymph hypothesis", whereby gut-derived factors in intestinal lymph are carried to the right side of the heart, and hence the pulmonary vasculature, where they may trigger a systemic inflammatory response and lung injury [17].

Despite the evidence available, it has been difficult to accurately assess bacterial translocation in the clinical setting. The most commonly used means of assessing bacterial translocation in humans has been culture of mesenteric lymph nodes, which is useful but not a dynamic measure of translocation. There are also the understandable practical and ethical issues with human lymph node sampling. Other methods have included intestinal permeability tests and blood/stool cultures, but all are limited in their interpretability and reliance. Newer methods are being developed, such as detecting bacterial DNA in blood, and these may provide strong supporting evidence in the future [18].

Potential mechanisms of probiotic action in surgical patients

Probiotics have been shown to influence the function of the epithelial barrier in a variety of beneficial ways depending on the particular probiotic organisms.

There is evidence that probiotics can potentially reduce bacterial translocation in a variety of ways. Firstly, they can physically reduce bacterial adhesion and translocation at the brush border via a competitive exclusion effect [19]. They may act on toll-like receptors and induce the production of protective cytokines [20], reduce epithelial permeability changes and apoptosis mediated by inflammatory cytokines [21–23], maintain epithelial tight junction function [24] and stimulate mucus gene expression [25, 26]. Secondly, probiotics can exert a direct antimicrobial effect on other organisms by reducing luminal pH, inducing the production of defensins [27], secreting bacteriocins as well as inhibiting bacterial adhesion [28]. Thirdly, there is evidence that probiotics can influence the production of certain cytokines including the anti-inflammatory cytokine IL-10 [29], as well as affect immune function by stimulating dendritic cells [30], which can in turn induce regulatory T-cell production. Not every mechanism is universal and different probiotics seem to exert their effects in different ways.

Probiotics in surgical patients

When looking at the use of probiotics in surgical patients, it is helpful to try and group the studies by surgical condition or operation type to allow for a meaningful comparison.

Elective abdominal surgery

McNaught et al. looked at the use of *Lactobacillus plantarum* 299v, given peri-operatively, in reducing the incidence of post-operative infectious complications and bacterial translocation in 129 patients undergoing elective abdominal surgery [31]. The authors found no significant difference in the frequency of post-operative infectious complications between treatment and control (12% *vs.* 14%), and no reduction in bacterial translocation in the probiotic group (12% *vs.* 12%), although there was no placebo or blinding in this study. A similar study using Lactobacilli post-operatively in 90 patients showed similar results [32]. The incidence of infections was the same in the treatment and placebo groups (10%), although the treatment group required antibiotics for a significantly shorter time ($p = 0.04$).

More recently, Anderson et al. looked at the use of peri-operative synbiotics *vs.* placebo in 137 patients undergoing elective abdominal surgery in a randomised double-blind study [33]. The authors found no significant difference in infectious complication (32% *vs.* 31%) or bacterial translocation rates (12.1% *vs.* 10.7%). Despite a more robust design, patient numbers were still small and the overall prevalence of bacterial translocation was also much lower than estimated. Therefore, the calculated sample size required was probably far too small, thus making the results difficult to interpret. However, the findings were in keeping with those of Horvat et al. in a study investigating the use of synbiotics in 76 patients undergoing elective colorectal surgery [34]. No benefit was found in the use of synbiotics or prebiotics when compared to mechanical bowel cleaning. However, other work involving 92 patients in a non-blinded study has suggested that pre-operative synbiotics can reduce the rate of bacterial translocation in patients undergoing elective colectomy ($p < 0.001$), although this did not translate into a reduction in septic episodes [35].

Hepatopancreatobiliary surgery

There is some evidence that synbiotics may reduce infectious complications following elective surgery for biliary cancer. A non-blinded study involving 54 patients found that rates of infection were significantly lower with the post-operative use of synbiotics (19% *vs.* 52%, $p < 0.05$) [36]. Subsequent work, with a similar group of 101 participants, showed a significant reduction in post-operative infectious complications when synbiotics were given pre and post-operatively rather than just post-operatively (12.1% *vs.* 30.0%, $p < 0.05$) [37]. This particular study was not blinded or placebo-controlled, but is interesting in terms of the timing of treatment, as it suggests that "priming" the bowel with synbiotics pre-operatively may confer additional benefits to those shown with post-operative synbiotics in these patients.

Pancreatoduodenectomy is still associated with a significant risk of post-operative infection, with around 10% of patients liable to develop an abscess and 10% to suffer from a wound infection [38, 39]. The evidence for the potential use of probiotics or synbiotics has again been encouraging. In a study with 80 participants undergoing pylorus-preserving pancreatoduodenectomy (49 carcinoma = 49, chronic pancreatitis = 31), peri-operative synbiotics significantly reduced the rate of infectious complications when compared to placebo (12.5% *vs.* 40%) and also significantly reduced the duration of antibiotic therapy [40]. Elsewhere, peri-operative probiotics have also been shown to significantly reduce infection rates in this type of surgery when compared to placebo (23% *vs.* 53%, $p = 0.02$) [41].

Patients undergoing liver transplantation have a particularly high risk of post-operative infectious complications. Not only is it a very substantial operation, but the patients are often in a poor pre-operative condition, they are commenced on post-operative immunosuppressive agents and cirrhosis is also associated with relatively high levels of bacterial translocation. In a randomised placebo-controlled trial with 105 patients, synbiotics containing *Lactobacillus plantarum* 299 were shown to significantly reduce the rate of post-operative bacterial infections in liver transplantation compared to selective bowel decontamination (13% *vs.* 48%), whilst an inactivated preparation resulted in a much smaller reduction (34%) [42]. A further study by the same group ($n = 66$) showed a significant reduction in infection rates with synbiotics compared to prebiotics alone (3% *vs.* 48%) [43], although it did not involve a placebo group.

More recently, these findings were supported by a study into the use of peri-operative synbiotics in elective living donor liver transplantation ($n = 50$) [44]. When compared to a control group, patients receiving synbiotics suffered from significantly fewer infectious complications. Although the results from these studies are very encouraging, caution must clearly be expressed regarding the use of probiotics and synbiotics in immunosuppressed patients such as in liver transplantation, as there may be a risk of resulting bacteraemia or fungaemia [45, 46].

Trauma

Many studies have investigated the use of prebiotics in the critical care environment, some of which have focussed on patients with multiple injuries. This has often proved a difficult area to study, with criticisms highlighting difficulties in comparable product delivery, intolerance of the regimes, the common use of proton pump inhibitors, differences in feeding, poor nasogastric tube tolerance, gut stasis, aggressive antibiotic therapy, relative immunosuppression, as well as the complicating use of drugs such as opiates, sedatives and broad-spectrum antibiotics.

Trauma patients requiring treatment in an intensive care unit are at considerable risk of developing infections. A variety of factors can play a role in this, including the systemic inflammation involved, increased catabolism, reduced immune function, increased bacterial translocation in the gastrointestinal tract, the primary injuries themselves (for example, a chest wall injury can predispose a patient to pneumonia), the potential need for prolonged ventilation, as well as the possible need for invasive procedures and central venous access.

With regard to ventilated trauma patients, a double-blind placebo-controlled trial looked at the use of synbiotics in 65 patients with some encouraging results [47]. The rate of infections, severe sepsis, length of stay on the intensive care unit, and the number of days with mechanical ventilation were all significantly reduced. Whilst not reaching statistical significance, patient mortality was also lower in the symbiotic group (14.3% compared to 30% in the placebo group, $p = 0.12$). A further study by the same group showed a significant reduction in bacteraemia and ventilator-associated pneumonia (VAP) rates with synbiotic use [48].

A separate group also showed significantly reduced rates of infection with synbiotics in 113 trauma patients ($p = 0.03$) [49]. Intestinal permeability rates, measured using lactulose/mannitol excretion ratios, were also significantly reduced, but there was no significant difference in length of stay on the intensive care unit, days with mechanical ventilation or multiple-organ failure scores. However, there were some differences in administration methods between the different study arms, making the results more difficult to interpret.

Acute pancreatitis

Acute pancreatitis is a serious condition with an incidence that continues to increase worldwide [50]. It ranges from a mild, self-limiting illness to pancreatic necrosis and infected pancreatic necrosis with a mortality rate of up to 30% [51]. Systemic antibiotic prophylaxis is used to prevent secondary infection in acute pancreatitis, despite two double-blind, placebo-controlled trials [52, 53] and two meta-analyses that do not support this practice [54, 55]. It is thought that increased gut permeability and bacterial translocation are important factors in the development of infectious complications in these patients [56], so selective gut decontamination, whereby non-absorbable antibiotics are given enterally in addition to intravenous antibiotics, has also been tried [57]. There was no significant reduction in mortality and supporting work is lacking, so the UK Working Party on Acute Pancreatitis does not recommend the use of this treatment [51].

The idea of increased gut permeability and bacterial translocation has also led to research into the potential use of probiotics in acute pancreatitis. The first of these studies was by a Hungarian group, looking at the use of probiotics in 50 patients with acute pancreatitis compared to an inactivated product [58]. All patients also had feeding via nasojejunal tubes. They found significantly lower rates of infected pancreatic necrosis requiring surgery in the probiotic group, although patients with biliary tract disease were excluded making it difficult to draw broad conclusions. A further randomised and double-blind study by the same group involved 83 patients, including those with biliary tract disease, with synbiotics rather than probiotics [59]. There was a significant reduction in overall complications in the synbiotic group ($p < 0.05$), as well as the combined rate of Systemic Inflammatory Response Syndrome (SIRS) and multiple organ failure (8 *vs.* 14, $p < 0.05$), but there was no significant difference in mortality.

A subsequent study by Qin et al. in China showed a significant reduction in bacterial translocation with *Lactobacillus plantarum*, along with the incidence of SIRS, Multiple Organ Dysfunction Syndrome, pulmonary complications, catheter-related septic complications, positive blood cultures, antibiotic therapy, paralytic ileus and gastrointestinal bleeding [60]. APACHE II scores were also significantly lower. Unfortunately, the probiotic group also received enteral feeding in addition to the parenteral nutrition received in both groups, making it difficult to determine whether it was the enteral feeding or the probiotics that were of most benefit.

The Dutch Acute Pancreatitis Study Group reported results of a randomised, placebo-controlled, multi-centre trial [61]. This much anticipated trial was termed PROPATRIA and was designed to clarify the potential role for probiotics in this difficult patient group. The group enrolled 298 patients from eight university medical centres and seven major teaching hospitals in Holland over a three-year period. They all had predicted severe acute pancreatitis, and randomly assigned to a multi-species probiotic product or placebo, twice daily and initially via a nasojejunal tube, for a maximum of 28 days. The probiotic product was Ecologic 641, a combination of six strains of bacteria with corn-starch and maltodextrins. It was given enterally with a total daily bacterial dose of 10^{10} bacteria.

The results were very unexpected, well publicised and have been widely debated. There was no significant difference in the primary outcome measure (infectious complications). However, there were significantly more deaths in the probiotic group than the placebo group ($p = 0.01$, with a relative risk for mortality of 2.53 and CI 1.22–5.25). In both groups, the majority of patients died from multiple-organ failure, but bowel ischaemia was a notable feature of the probiotic group. Nine cases were noted in this group, eight of which died, meaning that eight of the twenty four deaths in the probiotic group had evidence of bowel ischaemia, as will be discussed later. There were no cases of bowel ischaemia found in the placebo group.

These findings clearly contrast with those of the preceding studies and were unforeseen. Looking at the primary outcome measure, whilst no difference was found in infectious complications, the observed incidence of sepsis was deemed to be as expected for this cohort of patients. Antibiotic use was also examined and seemed reasonable.

With regard to patient randomisation, the authors noted that rates of organ failure were higher in the probiotic group, but found no significant differences in SOFA scores or rates of organ failure post-randomisation between the groups. They also found, using logistic regression, that having adjusted for potential imbalance in the proportion of patients with organ failure on the day of randomisation, mortality was still twice as high and bowel ischaemia significantly more frequent in the treatment group.

The dose of probiotic, although high, was similar to that used in previous studies and the individual strains in the preparation have had no previous safety issues. The authors also argue that the preparation itself has been used in an animal model of pancreatitis, with good effect, as well as in healthy volunteers with no ill-effect [62].

Much of the subsequent discussion has understandably focussed on the increased mortality rate in the probiotic group. With regard to methodology, the authors questioned whether the significantly larger numbers in this study enabled the detection of mortality differences and rare complications that may have been missed by the preceding studies. However, this does not explain the occurrence of these events. The most likely factor would seem to be the bowel ischaemia noted in the probiotic group.

Non-occlusive mesenteric ischaemia is recognised in both acute pancreatitis and critically ill patients [63, 64]. Furthermore, enteral feeding can also be associated with bowel ischaemia in the critically ill [65]. The probiotic group may therefore have been at high risk of this complication. The authors suggested that the probiotics may put an additional oxygen demand onto the bowel wall and possibly also induce inflammation of the enterocytes. These must indeed be possibilities, although any such effect was not cumulative as one might have expected.

A more likely possibility is that the damaged, ischaemic bowel becomes more permeable to bacteria and suffers further degree of enteropathy from the presence of the high-dose probiotics. In a different model, there is certainly evidence that metronidazole can reduce the severity of NSAID induced enteropathy, suggesting a secondary microbial influence on the inflammation and damage [66]. This theory is supported by subsequent work by the PROPATRIA group, which showed that the same high-dose probiotic preparation reduced bacterial translocation in acute pancreatitis, but conversely increased bacterial translocation and enterocyte damage in those patients with organ failure [67].

The results of this study have understandably had a huge impact on this field of research. It is unlikely that there will be further work involving the use of probiotics in acute pancreatitis until we have a better understanding of the processes that led to the results of the PROPATRIA study.

Meta-analysis

A recent meta-analysis looked at the use of probiotics and synbiotics in abdominal surgery (excluding trauma and acute pancreatitis) [68]. Nine randomised controlled trials were included, with a total of 733 patients. The authors found that the incidence of infectious complications was significantly lower with prebiotics/synbiotics (OR 0.26, 95% CI 0.12–0.55), along with duration of antibiotic therapy and length of hospital stay. However, the incidence of post-operative wound infection, intra-abdominal abscess formation and mortality was not significantly lowered. Again, the heterogeneity patients and trial design were noted as possible confounding factors in the meta-analysis.

Regarding acute pancreatitis alone, a recent meta-analysis looked at a total of 559 patients across seven randomised studies (including small and non-English language) [69]. The authors found that there was no significant reduction in infectious complications or mortality with the use of pre-, pro- or synbiotics in acute pancreatitis, although length of hospital stay was significantly reduced.

Conclusions

The appeal of the potential use of probiotics in clinical medicine is clear. Although they are a varied group of products, they have been deemed safe for human consumption and exhibit beneficial properties when consumed. As well as the direct effects of their presence within the bowel lumen, they also display immunomodulatory attributes which have been of great interest to researchers.

This review has looked at the use of probiotics in surgery, a field in which most studies have focussed on reducing the incidence of infective complications. From the evidence that we have, meta-analysis suggests that probiotics/synbiotics may reduce infectious complications in abdominal surgery, as well as shorten the duration of antibiotic therapy and length of post-operative stay. However, surgical patients vary according to the particular condition or surgery involved, making it necessary to group the studies accordingly. Even the related trials often differ in methodological approach and in the probiotic preparations used. Many of the studies have been small in size and some have lacked placebo control or blinding. Also, some studies only gave the intervention post-operatively, whilst there is some suggestion that pre-operative "priming" may confer additional benefits [37]. These factors can make interpretation of the current evidence difficult and further work is certainly required.

Looking at the different patients groups, patients undergoing hepatopancreatobiliary surgery seem to have lower rates of infectious complications with synbiotics and perhaps probiotics. This is often complex surgery, with significant risks of complications including infections, but is frequently elective and patients will not usually be in organ failure at the time of surgery (liver transplantation patients will vary in this aspect as they are a very heterogenous group, needing transplantation for a variety of reasons which may not be acute). The results are interesting in this context and it appears the most promising application of probiotics in surgery, although clearly further work is required. From the evidence that we have, ventilated trauma patients may also benefit from synbiotics, not only from a reduction in the incidence of infections and severe sepsis, but also duration of mechanical ventilation and duration of stay in critical care.

With regard to elective abdominal surgery and elective colectomy there is very little evidence of benefit with either probiotics or synbiotics. It may be that these studies were too small to detect a significant benefit, but the majority of the studies covered a wide range of pathology and surgery, making them difficult to interpret. Alternatively, it may be that an elective colectomy is less complex than hepatopancreatobiliary surgery and that the patients will potentially be less unwell in the post-operative period.

The most controversial and striking work has involved probiotics in acute pancreatitis. Following encouraging results from smaller studies, the PROPATRIA multi-centre trial produced markedly different findings. Not only was there no reduction in infectious complications, but also the mortality rate was significantly higher in the treatment group, where bowel ischaemia was a notable feature. The reasons for this are not entirely clear, but it is notable that non-occlusive mesenteric ischaemia is recognised in both acute pancreatitis and critically ill patients. It is quite possible that in a patient with acute pancreatitis, with a degree of bowel ischaemia and increased bowel wall permeability, high dose probiotics could cause a further enteropathy and further morbidity.

It should be noted that, as discussed above, results with ventilated trauma patients were encouraging. Despite these patients being critically ill and with a degree of organ failure, there were no such problems as with the acute pancreatitis cohort. It may be that the acute pancreatitis patients have an additional drive towards bowel ischaemia above that of a less specific critical illness, leaving them at greater risk to further damage.

There would appear to be potential for the use of probiotics in surgical patients, but it is clear that each particular type of surgery or condition needs to be considered separately and that probiotics may actually be harmful in certain circumstances. Certainly, as things stand, it would seem advisable that high-dose probiotics should not be used in situations where the bowel wall may already be significantly ischaemic and hence permeable, such as in acute cases of pancreatitis. Large scale, well-designed trials, with pre-operative rather than just post-operative probiotics, are needed to advance our knowledge in this field. It would also be helpful to try and standardise such work with regard to the probiotics used and their dosage, so that they may be more comparable. With regard to acute pancreatitis, further research is necessary to determine the exact underlying mechanism behind the results from the PROPATRIA study.

Conflict of interest

The authors declare that there is no conflict of interest. No funding or additional support was received for this work.

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