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Rationale behind phosphate therapy to modulate the gut microbiome and protect against surgery-related infection

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Abstract

Despite major advances in infection control and the ever increasing use of broader spectrum antibiotics in surgery, postoperative infections continue to occur under the best of care and in the best institutions. Postoperative infections, also termed “surgical site infections (SSIs), can range from superficial wound infections to deep organ space infections. SSIs can be superficial and only require medical treatment (i.e antibiotics), whereas others such as deep organ space infections resulting from an anastomotic leak can require multiple surgeries leading to sepsis and occasionally shock and death. Many if not most stakeholders in the field including surgeons, infectious disease specialists, infection control nurses, etc., in general advocate the use of prophylactic antibiotics and the enforcement of greater levels of sterility reasoning that all postoperative infections must arise from some type of direct contamination event. In this piece, the alternative view is presented that today, in the era of mandated asepsis protocols, enhanced recovery programs, and enforcement of prophylactic antibiotics in all cases, many if not most postoperative infections and SSIs occur from pathogens endogenous to the patient not from sources exogenous to the patient. It is also suggested that applying broader antibiotic coverage in elective surgery is neither an evolutionarily stable strategy nor inexorable in the context of emerging knowledge in the field of gut ecology. Here this concept is reviewed and the rationale behind using agents that preserve the gut microbiome and attenuate pathogen virulence in lieu of applying broader spectrum antibiotics and greater levels of sterility.

The problem

Remarkably, overall, hospital infection rates have decreased over the last several decades while SSI rates have not (Baker et al., 2022). In fact, during the COVID-19 pandemic, one might have predicted that SSI rates would have decreased following elective surgery given the strict patient selection, mandated sterility measures (masks, hand washing, topical decontamination, etc.) and high vigilance to detect any infection were enforced (Smith et al., 2023). Surprisingly, SSI rates during the pandemic remained unchanged following elective surgery (Smith et al., 2023). One possibility to explain such findings could be

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that the extent to which exogenous pathogens (i.e., those within the operating field) versus those that arise from endogenous sources (i.e., those from pathogens within the patient's own microbiome) are responsible for a given SSI, remains unknown. While there is little doubt that intraoperative contamination from local environmental sources can certainly lead to an SSI, the extent to which alternative mechanisms of SSI pathogenesis occur remains unknown (Alverdy et al., 2020). Perhaps overlooking mechanisms of SSIs such as that proposed by the Trojan Horse hypothesis (vide infra) may underlie our inability to successfully "get to zero" as others have suggested (Krezalek et al., 2018).

Thanks to mandatory enforcement of asepsis, enhanced recovery programs, improvements in anesthesia and minimally invasive surgery, SSI rates have remained at a historically low incidence. The average length of stay is now 2 days for elective surgery and many procedures previously requiring hospitalization, are now performed as an outpatient. Although others have argued that SSI rates will never "get to zero (Thompson et al., 2011)," for procedures typically enjoying a low SSI rate, when they do occur, they can be disabling and devastating. For example, in joint arthroplasty, when a deep infection occurs, explantation of the prosthetic material is no simple matter and may require multiple subsequent operations (Agashe et al., 2022).

The Trojan Horse Hypothesis of SSIs

A common theme to emerge from important discoveries in a field seems to be that a hypothesis cannot simply be believed or rejected, it must be rigorously and formally tested to determine its scientific plausibility (Blackburn, 2010). The Trojan horse hypothesis of SSI posits that operative wound infections may originate from pathogens colonizing remote sites as they silently travel inside an immune cell and "home" to the operative wound area (Anderson and Yunis, 1983, Alverdy et al., 2020, Krezalek et al., 2018, Zhu et al., 2020, Outram et al., 1975). The manner by which bacteria silently migrate to an operative wound site is hypothesized to occur when colonizing bacteria normally present in a remote mucosal surface (gums, gut, lung, nose, etc), enter an immune cell, remain in a state of mutual tolerance to each other, circulate in the bloodstream and then silently "home" to the operative wound where they then release their infectious payload (Alverdy et al., 2020). It should be noted that an operative wound site is a chemoattractant for immune cells as the trauma and inflammation within a wound attracts immune cells for tissue repair. Yet, although experimentally and clinically there is little doubt that in certain cases, this mechanism of infection occurs, several molecular steps are needed to be demonstrated in order to confirm its role in SSI pathogenesis. For example, what are the molecular conditions that allow the apparent state of "molecular tolerance" or "molecular détente" in which the engulfed bacteria do not lyse the immune cell or alternatively the immune cell does not eliminate the pathogen (Thakur et al., 2019, Bourdonnay and Henry, 2016)? Such a state of mutual tolerance can now be molecularly interrogated by collecting and analyzing circulating bacterial-carrying immune cells both during and after surgery. This approach departs from simply assessing extracellular bacteria via blood cultures. It is important to recognize that in order for pathogens to "silently" circulate, they must be able to co-exist within a carrier cell (i.e immune cell). The Trojan Horse hypothesis for SSIs is supported by the observation that attempts to match the pathogens present in an SSI to those in a

cultivatable postoperative operative wound or environment site, have failed to demonstrate concurrence (Alverdy et al., 2020). In fact, there is more evidence to refute this latter assertion than support it (Alverdy et al., 2020). The question thus lingers: if some (or many?) SSIs do not originate from exogenous contamination, to what extent are endogenous microbiota (i.e pathogenic strains) responsible for subsequent SSIs?

Addressing the dictum: “if some is good, more must be better”

Virtually all stakeholders in the field, from the association of operating room nurses, surgeons, infectious disease specialists, infection control personnel etc., have enforced sterility and prophylactic antibiotic use as the two most important measures to control the incidence of SSIs. There is little doubt that the achievements of today’s low incidence of SSIs are attributable to standardized, effective and enforced mandates to minimize intraoperative contamination from the environment, instruments, operating room personnel and elements of the procedure itself (opening of contaminated mucosal surfaces such as the bowel, lung, vagina, etc.). Yet at the same time, as operating room procedures have advanced including improvements in anesthesia, faster, bloodless and more minimally invasive surgeries, lower lengths of stay, many procedures being performed as outpatients, etc., the individual elements of these enhanced recovery components cannot be unbundled from the group to assess their independent effects on SSI rates (Grant et al., 2017). Despite enjoying historically low SSI rates, it seems that the idea of “getting to zero” is not achievable. In addition, despite all that is done today from skin decontaminants to operating room wardrobe design, there is little to no enthusiasm for eliminating prophylactic antibiotics in surgery. In fact, there is growing concern that at the current rate of escalating usage, emergence of antibiotic resistance is a health threat. When framing all SSIs as somehow attributable to an intraoperative contamination event, it seems unavoidable that applying the idea of “if some is good, more must be better” will get us to zero. This practice can already be observed in newly marked devices to enhance operating room sterility including air filters, hazmat suits and even application of UV light- none of which have been shown to decrease SSI rates (Vijaysegaran et al., 2018, Jones et al., 2022, Lipsett, 2008). When these devices are marketed as “evidence-based,” the evidence is usually some type of particulate matter reduction or surface microbial reduction but not clinical SSI reduction. In fact, when formally tested for their SSI reduction effect, these devices often fail to change the incidence of clinical operative site infections or SSI rates (De Pastena et al., 2020, Vijaysegaran et al., 2018, Jones et al., 2022). Therefore since environmental sterility of the operative field during surgery has been unable to reduce SSI rates, broader spectrum antibiotic coverage is being applied (Lipsett, 2008). This latter practice is especially prevalent in high risk gastrointestinal surgery (i.e., colorectal surgery (Deierhoi et al., 2013), pancreaticoduodenectomy (D’Angelica et al., 2023)) and high risk orthopedic surgery (i.e., prosthetic joint arthroplasty (Nam et al., 2023), spine surgery (Long et al., 2022)). Although intraoperative contamination of the operative field during surgery is still considered the main mechanism of SSI development, it is remarkable that given all of the methods to sterilize the operative field today, that the need for prophylactic antibiotics at the individual case level is rarely, if ever, challenged and formally tested as absolutely necessary. Yet the application of broader spectrum antibiotic coverage to prevent SSI development is not inexorable nor

sustainable as it is not an evolutionarily stable strategy. Resistant organisms will emerge and on a global scale and will weaken our use of antibiotics overall (Makary et al., 2018). If it is the case that many SSIs actually originate from the patient's own pathogenic microbiota and if many such SSI can occur postoperative as the Trojan Horse hypothesis suggests, then alternative approaches may be beneficial beyond imposing greater levels of environmental sterility and more expanded use of antibiotics.

Environmental Phosphate levels: a universal bacterial "cue"

Universally, bacteria use the extracellular concentration of phosphate to sense the wellbeing of their environment via phosphoregulatory pathways that connect to virulence circuits such as the well-described quorum sensing system (Zaborin et al., 2009). Under conditions of phosphate abundance, such as is normally present within the thick mucus coat of the intestine, bacteria remain indolent where they feed, grow and reproduce (Zaborin et al., 2009). However when phosphate levels are scarce, as occurs during pathologic conditions of abnormal dietary intake and/or when the phosphate-rich mucus layer is eroded by the physiologic stress of surgery and/or the exposure to antibiotics, pathogenic bacteria will then seek phosphate by invading intestinal epithelial cells and migrate deeper into tissues to feed off the phosphate rich sources in cells (i.e., ATP, DNA). Bacteria can accomplish this by expressing fimbriae that allow for mucus and epithelial attachment, by expressing enzymes such as mucinases and collagenases that allow for mucus and cellular degradation and by activating motility factors such as twitching and swimming that allow for migration into and movement toward deeper tissues. Most investigators are not aware that gut Pi levels become depleted during surgery (Long et al., 2008) and may be related to the release of the hormone phosphatonin (Long et al., 2008), which further accelerates the urinary excretion of phosphate. Interestingly, under conditions of physiologic stress, urinary phosphate excretion is increased and, although rare, can lead to hypophosphatemia (Salem and Tray, 2005). While it is possible to administer phosphate either orally or intravenously to such patients, once cannot simple shut off the phosphatonin-driven phosphate excretion. As such, administration of singlet Pi orally will not distribute within the distal gastrointestinal track when most bacteria reside (Long et al., 2008). Similarly, parenteral phosphate will not replenish the depleted gut phosphate concentration. As a solution, durably embedding Pi along the entire gut length was created by bonding a long chain (MW=20,000 Daltons) polyethylene glycol (PEG) onto which Pi was covalently bonded (Wiegerinck et al., 2018, Mao et al., 2017, Yu et al., 2020). This compound, Pi-PEG was designed to re-establish the Pi rich mucus layer of the intestinal track so that, under condition of surgical stress and antibiotic exposure, proliferating pathogenic strains would be ***disincentivized*** to seek resources in deep tissues (Figure 1). The Pi portion of Pi-PEG is NOT systemically absorbed and remains biologically inert in the gut. Its PEG moiety durably binds to the epithelium via lipid rafts (Valuckaite et al., 2009). Pi-PEG has a unique identify that is *de novo* synthesized in the Alverdy lab and is being commercialized by a startup company from the University of Chicago, Covira Surgical (https://www.covirasurgical.com). This agent suppresses bacterial virulence by not allowing phosphoregulatory circuits in bacteria to communicate with deeper quorum sensing virulence expressing circuits- all without affecting bacterial growth. Thus by preserving the growth of the gut microbiome by providing a Pi rich thick mucus

coat while at the same time suppressing the virulence of pathogenic strains, it is proposed that Pi-PEG will: 1. competitively exclude antimicrobial resistant strains from taking up residence within the gut microbiome as it will retain its colonization resistance, 2. Suppress bacterial virulence expression among those pathobiota that survive and 3. Will allow the normal gut microbiota to reproduce and generate metabolites that are known to stimulatory the immune system such as indoles (Figure 1).

The microbiome at the center of outcome from injury and infection.

By supporting the growth and fitness of the gut microbiome, Pi-PEG creates a three pronged approach that collaborates with the microbiome when surgery imposes its multiple disturbances in: 1. oral intake, 2. physiologic stress 3. exposure to antibiotics and 4. dietary modulation. Mice consuming a western diet, exposed to antibiotics and then subjected to a surgical injury is rarely, if ever used to model how the gut microbiome plays a critical role in driving a recovery directed immune response, survival and prevention of postoperative infection. Yet such modeling is essential as it recapitulates the clinical scenario

Our preliminary data, and now accumulating data from others, demonstrate that gut-microbiota-derived indoles play a key causative role in activating macrophages so their polarity smoothly transitions from the M1 (bacterial clearance) to M2 (immune damping, cellular recovery) phenotype (Hao and Whitelaw, 2013, Yang et al., 2023). This provides compelling evidence that maintaining the composition and function of the gut microbiota during injury/infection is critical for immune recovery. The mechanism of this response lies in the ability of gut microbiota-derived indole metabolites to ligate/activate the aryl hydrocarbon receptor on macrophages over the course of injury (Keskey RC).

Pi-PEG, economic game-theory, public goods and virulence expression

Phosphate (Pi) is a critical element needed to support the growth and fitness of all life on earth, similar to nitrogen (N) and carbon) (C). Yet, some have argued that Pi gave rise to life on earth when the seas washed onto the rocks and enriched the waterways with Pi allowing bacteria to arise and grow (Brady et al., 2022). It is therefore not surprising that bacteria, the earth's first life forms, have evolved phosphosensory and phosphoregulatory circuits that sense phosphate as a universal "cue" to define the overall health and wellness of their surrounding environment (Mc and Snell, 1948). Pi-PEG exploits this knowledge by flooding the gut with phosphate at a time when the Pi-rich mucus lining of the gut, the site at which bacteria normally feed, becomes depleted from surgical injury, infection and the invariable use of antibiotics. This Pi depleted environment of the gut forces bacteria to seek Pi sources deep within tissues (i.e., ATP/DNA), by expressing virulence and invading tissues. Recent studies examining the world's most abundant mutualism, the rhizosphere (plants and soil microbes), demonstrates that mutual cooperation and prevention of predation is tightly regulated by Pi sharing (Kiers et al., 2011). Pi-PEG enriches the gut with Pi as a mucoadherent cytoprotective high molecular weight polymer (PEG) that provides Pi to bacteria, prevents its systemic absorption, is non-diarrheagenic, shields the epithelium and promotes the production of immune stimulating metabolites (indoles) by the gut microbiota (Figures 1, 2).

Maintaining the abundance, diversity of function of the gut microbiome

The process of preparing a patient suffering from a major disease for surgery can not only involve highly invasive procedures to diagnose the problem (biopsies, antibiotic exposure, endoscopy), but also the need for neoadjuvant (preoperative) chemo-radiation therapy. These "stressors" add to the anxiety a patient might suffer prior to the surgery and may even include the need for a "bowel prep" the night before surgery, the disease burden itself, and the need for oral antibiotics prior to surgery. In the aggregate, the untoward cumulative effect of these preparatory agents on the gut microbiome have been shown to be significant (Gouin and Kiecolt-Glaser, 2011). This, of course does not include the changes in dietary intake and antibiotic exposure that occur both prior to, during and after the surgical procedure. The extent to which the gut microbiome is disrupted in patients undergoing surgery is now just coming to light. Furthermore, the disruption in diversity, membership, abundance and function of the gut microbiome as a determinant of outcome following a major operative intervention is also just coming to light (Keskey et al., 2022).

Gut microbiota-derived metabolites drive a recovery directed immune response.

There is now significant and compelling evidence to suggest that survival from a major injury (radiation exposure (Guo et al., 2020), chemotherapy (Nguyen et al., 2023), adenocarcinoma of the pancreas (Tintelnot et al., 2023)) is dependent on metabolites produced by the gut microbiome that activate immune cells to drive recovery. Results from these studies indicate that key metabolites produced by the gut microbiota (indoles, short chain fatty acids, bile salts) in response to dietary substrates (tryptophan, fiber) enter the plasma and bind to key receptors (aryl hydrocarbon receptor) on immune cells (macrophages) to drive a recovery-directed immune response. Therefore the extent to which the microbiome is preserved before, during and after these physiologic insults, may play a direct role in overall recovery. Agents that can preserve the diversity, abundance and function of the microbiome through the course of disease management may determine outcome.

Practical aspects of phosphate-based therapies to prevent infection-related complications from surgery

Often, the process of diagnosing surgical pathology and preparing a patient for surgical procedure involves many invasive diagnostic maneuvers such as biopsies and endoscopies. In addition, many of such procedures involve antibiotic exposure and the psychological stress, anxiety and sleep deprivation of life-threatening and life-altering disease and treatment consequences. Were an odorless and easily palatable oral solution available to drink two to three time a day that could maintain the resilience and metabolomics output of the gut microbiome, it would be highly desirable. In addition if such a solution were verified to reduce complex complications such as stoma formation, anastomotic leak and cancer recurrence, it might allay some of the patients fears when confronting a life-altering disease and life-altering surgery. Confirmation of the safety and efficacy of such a compound is

needed and would require several randomized controlled trials in humans. Yet the theoretical advantage and already available experimental evidence for this approach is solid (Hyoju et al., 2022, Li et al., 2022, Mao et al., 2017, Olivas et al., 2012, Valuckaite et al., 2009, Wiegerinck et al., 2018, Yu et al., 2020, Zaborowski et al., 2021). An oral solution consisting of a volume of 50–100 milliliters, taken two to three times a day to coat the gastrointestinal track and prepare it for the multiple insults that are required to diagnose and treat a major disease process such as cancer or infection would be highly desirable and acceptable to patients (Figure 2). In many of such aspects, phosphate-based therapies are ideal given the abundance of information on the role of phosphate on microbial life. The novelty of this approach is the development of a phosphate rich oral compound that does not allow the phosphate to become systemically absorbed and renally excreted, yet remains functionally durable in the gut so that intestinal bacteria can feed off a phosphate rich epithelial layer. It is for this reason that phosphate has been covalently bonded onto a polyethylene glycol backbone so that the PEG moiety can bind to the epithelium and be locally retained to supply a critical nutrient to bacteria so they can grow, survive, remain indolent and reproduce. Collaborating with the gut microbiome so that it can execute its critical function of maintaining health and homeostasis following a major physiologic perturbation is much preferred over the escalating use of broader and more powerful antibiotics. Covira Surgical is intended to fill this unmet need.

Conclusions and future prospects

It is becoming increasingly clear that preserving key compositional and functional element within the gut microbiome over the course of surgery is desirable from the standpoint of improving outcome. Surgery involves many aspects of care that can erode the composition and function of gut microbiome (anxiety, altered diet, exposure to antibiotics, etc.). Understanding how to preserve those elements of the gut microbiome that are beneficial while at the same time suppressing those elements that are potentially harmful cannot simply be achieved by apply more of the same. Future prospects in this field will include continued demonstration that, in many cases, prophylactic antibiotics prior to surgery are unnecessary and in some cases, harmful. The development of agents that can enhance the beneficial function of the gut microbiome yet contain the proliferation and virulence of its pathogenic members would be highly useful given the emerging role of the gut microbiome in health and disease. In this regard, phosphate therapy hold much promise to fulfill this unmet need. If demonstrated to be clinically efficacious and safe, such therapy would be easily adopted and deliverable to all patients undergoing major surgery.

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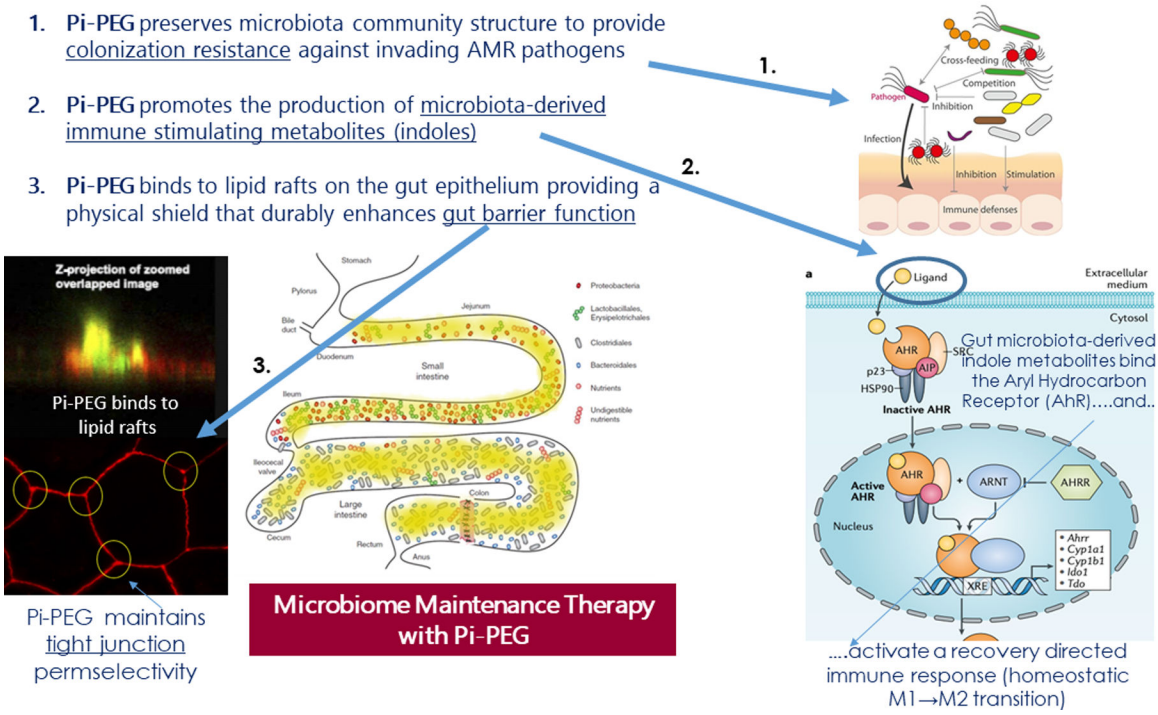

Figure 1.

Multi-pronged approach of Pi-PEG to protect the gut microbiome's production of immune stimulating metabolites (i.e indoles) and and to protect against AMR pathogen colonization.

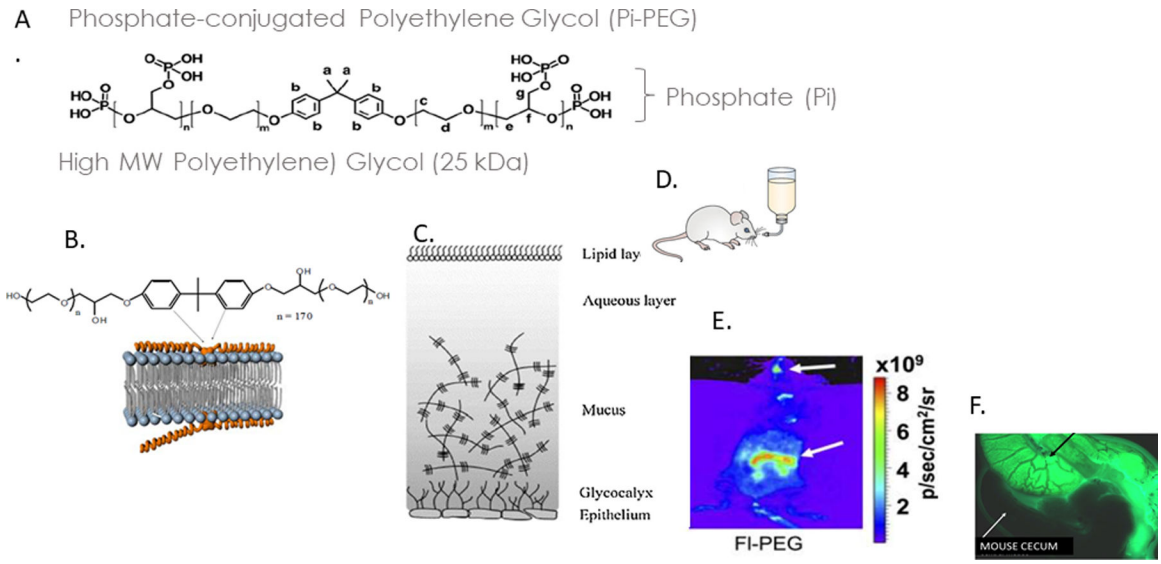

Figure 2.

A. *de novo* synthesized Pi-PEG, B. phenol group embeds in lipid layer and acts as a surrogate mucin and physical shield, D. mice avidly drink Pi-PEG which distributes along entire GI track (E-fluoroscein labeled PEG) and covers entire GI surface (F)