Review article

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Harnessing the Microbiome to Optimize Surgical Outcomes in the COVID-19 Era

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In this era of testing uncertainties, changing guidelines, and incomplete knowledge, "clearing" patients for surgery in the time of SARS-COVID-19 has been met with various challenges. Efforts to increase patient fitness have long been at the forefront of surgical practicing guidelines, but the current climate requires a renewed sense of focus on these measures. It is essential to understand how dietary history, previous antibiotic exposure, and baseline microbiota can inform and optimize preoperative and postoperative management of the surgical patient in the time of COVID-19. This piece focuses on the clinical, molecular, and physiologic dynamics that occur in preparing patients for surgery during COVID-19, considering the physiologic stress inherent in the procedure itself and the importance of specialized perioperative management approaches. COVID-19 has created a renewed sense of urgency to maintain our discipline in implementing those practices that have long been confirmed to be beneficial to patient outcome. This practice, along with a renewed interest in understanding how the gut microbiome is affected by the confinement, social distancing, etc., due to the COVID pandemic, is ever more important. Therefore, here we discuss the microbiome's role as a defense against viral infection and its potential for reactivation during the process of surgery as the next frontier for surgical advancement.

VULNERABILITY OF THE SURGICAL PATIENT TO CORONAVIRUS INFECTION

Despite optimal surgical conditions, postoperative infection remains a persistent threat for otherwise healthy patients undergoing elective operations. A study of over 8000 patients demonstrated that hospital-associated infections in surgical patients have been increasing, a large share of which cannot be explained by surgical site infections alone.[1] These and other studies suggest that surgery itself, independent of other comorbidities, results in a degree of physiologic and catabolic stress that renders the host vulnerable to infection outside of the operative site, perhaps driven by disruptions in the fragile interaction between the immune system and the microbiome.[2,3]

A unique aspect of the surgical patient undergoing an elective procedure for a mechanical problem (hernia, obstruction, etc.) or an underlying malignancy is that they likely have undergone multiple previous healthcare encounters to arrive at a proper diagnosis, an antecedent factor recently associated with an increased risk for postoperative infection.[4] In 2002, the average number of lifetime surgical procedures was reported to be an astonishing 9.2 throughout an average 85-year lifespan.[5] Such encounters expose patients to invasive procedures (eg, endoscopies, biopsies) and antibiotics, each of which has the potential to colonize patients with healthcare-associated pathogens and disrupt their native flora. Similarly, in the context of the current pandemic, there is concern that some patients will arrive with hospital and community-associated COVID-19 exposures.[6] Symptomatic and asymptomatic COVID-19 infections have been associated with a higher risk of perioperative complications, including cardiac arrest, sepsis, respiratory decline, and kidney damage.[7–9] As a result, many institutions and states now require SARS-CoV-2 testing before proceeding with surgery to help provide assurance and information for both the patient and operative team.[10] This change is in conjunction with a joint statement from the American Society of Anesthesiologists and the Anesthesia Patient Safety Foundation on April 29, 2020, which recommends preoperative nucleic acid amplification COVID-19 testing for all elective surgical cases.[11]

Despite robust testing and careful consideration of patient candidacy using the most up-to-date information, there will still be patients who are cleared for surgery who silently harbor the virus, who contract the virus during the lag time between testing and the operation, or who are highly susceptible to horizontal transmission of the virus during their hospital stay. Acute respiratory distress syndrome rates in postoperative patients are higher during influenza season, and a similar trend may play out during periods of high SARS-CoV-2 infectivity.[12] For this reason, it is worth outlining the physiologic changes that occur during viral infection and emphasizing that simple preventative measures can be effective at enhancing patient safety, including the judicious use of antibiotics, early discharge, implementation of an unprocessed food diet, and opioid minimization. While these practices are already routine in many centers,[13] it is now ever more important to be disciplined in their implementation. The reason for this is that many of these measures can preserve and enhance a patient's microbiome, which is now emerging as a key element that drives a recovery directed immune response after major surgery and during severe infection (Figure 1).[14] Although most surgeons already apply these measures as part of their approach to enhanced recovery bundles, here we assert that given the emerging evidence linking the gut microbiome to resistance to viral infections, renewed awareness of approaches

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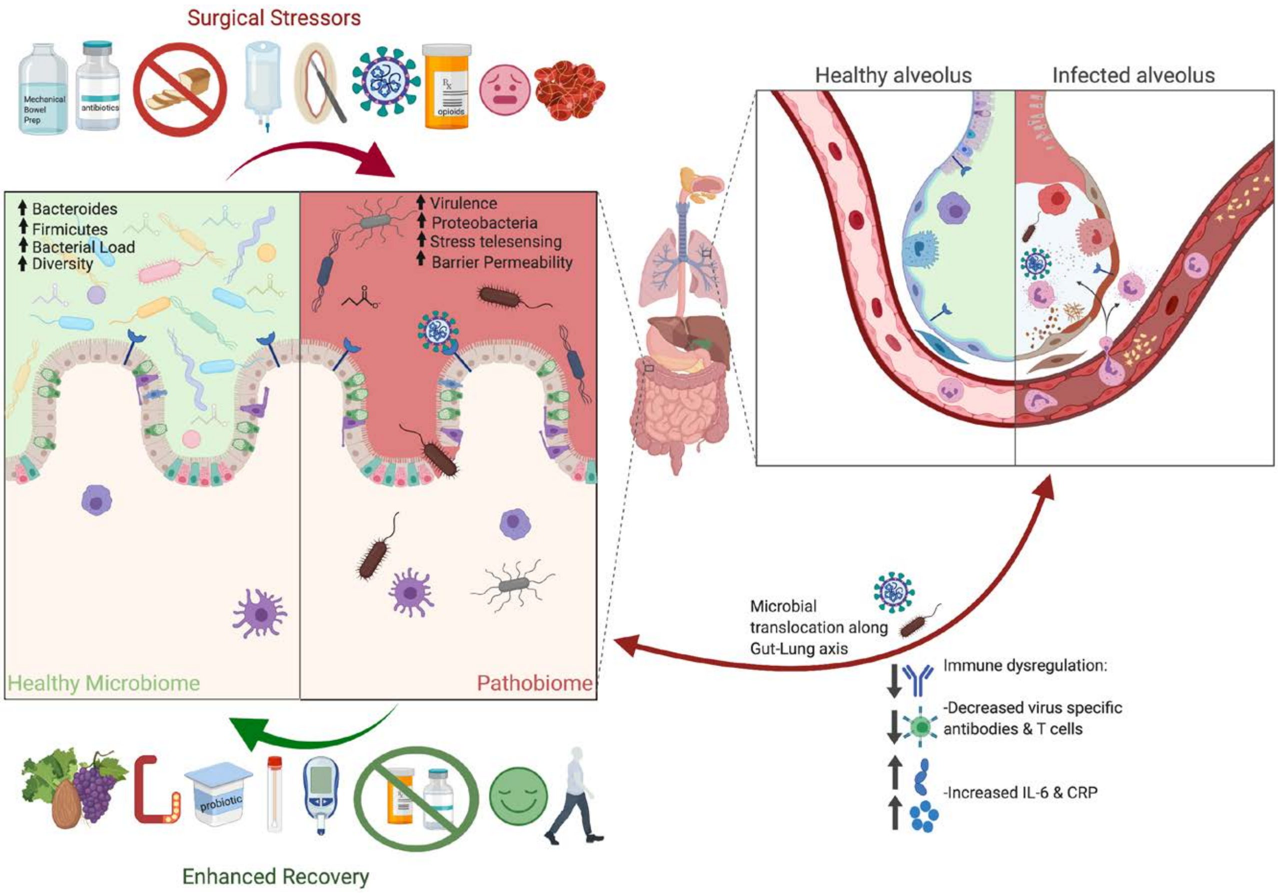

FIGURE 1. The intricate interplay between the gut microbiome, lung microbiome, and infectious agents. Created with Biorender.com.

to enhancing recovery may be ever more important during this pandemic.[15–18]

THE ROLE OF THE MICROBIOME AS A DEFENSE AGAINST VIRAL INFECTION

The virtual explosion of information linking the microbiome to the immune system demonstrates that a complex interaction exists between the microbiome and immunity that influences how the host responds to invading pathogens, including viruses.[19] The microbiome lining the cells of the gut and lung protects against pathogens by its mere presence, which acts to competitively exclude pathogens from access to deeper tissues (ie, the epithelium) and by its direct tonic effect to stimulate the local immune response.[20,21] Alterations in the lung and gut microbiome can disable the immune system and increase the risk of severe lung infections, including acute respiratory distress syndrome and ventilator acquired pneumonia.[22–24] New developments describe interactions between the gut and lung immune responses that are now being defined along an intricate gut-lung axis. Gut microbes communicate with one another by expressing quorum-sensing molecules that also interact with the immune system. Microbial metabolites can travel from the gut to the mesenteric lymphatic system and remote systemic sites to transduce cellular processes.[25] As a result of these complex multi-dimension interactions, changes in the gut microbial community can affect host fitness globally.

The increasing rise in surgical site infection due to multidrug resistant pathogens has led to the more widespread use of broad-spectrum antibiotics, the inadvertent consequence of which can deplete gut microbes, increasing patient susceptibility to both gastrointestinal and pulmonary infections.[25–27] In the context of vulnerability to viral infections, such as COVID-19, disruption of the normal microbiota (ie, dysbiosis) can alter the intricate balance between the patient microbiota and immune system leading to impaired responsiveness of the host to an invading pathogen. In particular, innate, humoral, and cell-mediated responses can become blunted in the absence of a functional gut microbiome, thereby delaying viral clearance and permitting high severity infections by influenza, H1N1, and hepatitis B.[28–30] The extent to which overuse of antibiotics during surgery renders patients more susceptible to COVID-19, either from endogenous reactivation or horizontal transmission remains to be determined. However, in the current era of added precautions, prolonged or overuse of antibiotics should be avoided as they may be considered a risk factor to surgical patients at risk for COVID-19 infection.

While a dysregulated gut microbiome can predispose to systemic infection, the reverse is also true: infection itself can disrupt the microbial structure and disable its immune-stimulating function.[2,21] Viral infection is, after all, a significant stressor to the host. Infection increases inflammatory markers as viruses hijack the host's molecular machinery with an associated elevation of immunosuppressive host factors, such as catecholamines. These substrates, now present at high concentrations in tissues such as the gut and lung, can directly activate the virulence of select pathogenic organisms, such as *Pseudomonas aeruginosa*.[31,32] Other common patterns following viral infection include an increase in virulent Proteobacteria in the lung microbiome and *Escherichia coli* colonization in the gut microbiome, which can induce pathologic mucosal alterations.[33,34] Infectious disease exacerbations in patients with inflammatory lung diseases (eg, chronic obstructive pulmonary disease, cystic fibrosis) are similarly linked to increases in lung Proteobacteria.[33,35] These findings of microbial dysbiosis could help explain the predisposition of SARS-CoV-2 infected patients to a subsequent nosocomial infection, which has been reported in as many as 20.7% of cases.[36]

As surgeons face the challenge of operating on patients in current and future pandemics, a more heightened awareness of the microbiome's potential protective role begs consideration. The observation that SARS-CoV-2 binds ACE-2 receptors present on both the lung and gut epithelium suggests great potential for novel treatment and prevention pathways that target the microbiome.[37] The gut epithelium's role may be vital when considering gastrointestinal surgery since the SARS-CoV-2 virus can persist at this site even following pulmonary clearance.[38] Unfortunately, the extent to which microbiome preservation or restoration before, during, and after surgery plays a role in preventing unanticipated respiratory infection following otherwise uncomplicated surgery remains undefined. However, in the interim, restraint in the overuse of antibiotics and rapid return to normal unprocessed nutrition may be ever more important to abrogate the unavoidable effects of both surgery and antibiotic use on the health-promoting effects of the microbiome.[39]

PROMOTING A HEALTHY MICROBIOME IN THE PREOPERATIVE PERIOD

Surgical access throughout this pandemic period has fluctuated and requires careful consideration of multiple competing factors. On April 7, 2020, the Centers for Medicare & Medicaid Services released a statement recommending the postponement of non-essential surgeries and procedures, recommending a tiered approach to medicine.[40] While the American College of Surgeons (ACS) originally released a similar statement, on April 17, 2020, the ACS released a joint statement outlining ways to maintain essential surgery during the COVID-19 pandemic.[41] Delays that lead to increased patient morbidity and mortality should be avoided with an "elective surgery acuity scale" being endorsed by the ACS as a method of prioritizing cases.[42] The timing and appropriate location for the resumption of elective cases where delay causes no harm to the patient remains controversial. Some physicians advocate for the resumption of these cases since in-hospital transmission rates are minimal and these procedures are critical for hospital revenue generation, while others warn that any potential for COVID-19 transmission is unacceptable.[43] Given that the pandemic will likely influence the way hospitals function for many months to come and will be dependent on the rapidity and effectiveness of vaccination, it will be essential to continue to provide surgical access for patients with real-time analysis of regional factors and a personalized approach for each hospital system. Yet these uncertain delays in elective surgery should be viewed as an opportunity for patients to optimize their health and fitness in preparation for surgery.

In this regard, one simple measure may be to consider nutritional management for patients before surgery. Nutrition is emerging as among the most important factors involved in microbiome rehabilitation therapies and can influence microbiome community structure and function within as little as 24 hours.[44] Nutritional therapy can target intestinal barrier function, prevent intestinal dysbiosis, increase lean body mass, and blunt the systemic inflammatory response.[45,46] The efficacy of specific dietary regimens to enhance viral clearance, which will require studies that involve next-generation sequencing, metabolomics, and outcome analyses, remains a vision for the future as common themes for promoting microbiome health emerge. In particular, diets composed of unprocessed foods that are high in fermentable fiber, which increase the production of protective short-chain fatty acids (ie, butyrate), are associated with high levels of protective bacteria.[18,47] Butyrate is a key microbial metabolite that has emerged as an essential factor that can favorably provide tonic stimulation to the immune system and drive a recovery directed immune response.[48,49] Supplementation with vitamins E, C, D, zinc, and selenium can also aid in promoting immune system function and can be considered in the setting of obesity, which may be viewed as a pro-inflammatory state.[50] A retrospective investigation into metabolic surgery demonstrated that patients with with a higher body mass indexs who underwent metabolic surgery were less likely to require hospital and intensive care upon later infection with COVID-19.[51] Furthermore, an international analysis of bariatric and metabolic surgeries demonstrated no increase in complications during the COVID-19 period.[52] Taken together, these studies suggest that bariatric surgery among high-risk patients may be considered a benefit towards improving COVID-19 fitness. Additionally, considering prophylactic measures for the elderly, immunocompromised, and those with comorbid conditions is appropriate during uncertain periods of delay.[50]

As mentioned, the unintended consequences of broad-spectrum antibiotic prophylaxis before surgery can have adverse effects on health-promoting microbial communities. Patients exposed to antibiotics in the months before surgery may harbor drug-resistant organisms and be at greater risk for a postoperative complication.[53,54] Even short-term antibiotic courses lead to long-term perturbations in microbiome structure and function, often persisting for years after the initial insult.[55] Azithromycin, in particular, which was liberally administered to many COVID-19 patients at the start of the pandemic, despite limited evidence on efficacy, directly modulates Bacteroidetes, Bifidobacterium, and Clostridium colonization.[56,57] Perioperative antibiotics can compound these previous antibiotic exposures resulting in the inadvertent selection of pathogenic species to predominate among the microbiota. Given the high likelihood of pathogenic colonization in the most at-risk surgical patients, selective antibiotic treatment may be necessary for the immediate pre- and intraoperative period to decontaminate disease-promoting species. This can be particularly problematic as surgeons face the dilemma of considering antibiotic eradication of certain organisms present in high-risk patients while, at the same time, preventing widespread microbial elimination that can cause unwanted collateral damage to the microbiome.[58,59]

Finally, population-based emotional distress has intensified during this pandemic period, and there is a significant fear of hospitals and operative interventions.[60,61] Further exacerbating this psychological stress is the recent implementation of virtual preprocedural visits, imposing additional stress on the patient-surgeon relationship.[62] Many institutions have instituted telehealth appointments for both new patient and postoperative visits as part of their COVID-19 response plan.[63] Research investigating the "gut-brain axis" demonstrates that stress is associated with detrimental inflammation and increased gut barrier permeability.[64] Projecting trust and a safe environment is challenging, yet essential, during this pandemic and can be a fragile process requiring additional efforts on behalf of the patient and surgeon.[65]

PROMOTING A HEALTHY MICROBIOME IN THE POSTOPERATIVE PERIOD

The postoperative period's primary focus should be a rapid and comprehensive restoration to full patient fitness to limit viral susceptibility. The immediate postoperative period provides a window of opportunity for infection following surgical stress and exposures.[1] Contemporary surgical practice has already moved towards shorter hospital stays and early recovery after surgery or fast-track programs, which will become increasingly necessary during COVID-19 times.[66] Quick discharges limit the patient's exposure to nosocomial pathogens and reduce strain on a high capacity hospital system.[67]

Regarding the microbiome, the postoperative period should focus on reconstitution through a quick return to unprocessed oral feeding. Although periods of starvation and parenteral feeding may be required in some cases, it should be noted that these factors severely limit gut microbiome nutrients, which can lead to virulent transformation and gut barrier dysfunction.[68] Early recovery after surgery programs underscore the need to resume enteral whole food diets on postoperative day 1 in their best-practice guidelines.[66] High-fiber, plant-based diets, in particular, have been shown to render the microbiome more resilient to maladaptive changes from antibiotics and stress in murine models.[39] An important consideration for SARS-CoV-2 respiratory disease susceptibility is that diet affects not only the gut microbiota but also the pulmonary landscape.[33] High-fiber diets that increase short-chain fatty acid generation have been shown to decrease maladaptive influenza-associated lung inflammation through T-cell and monocyte-dependent pathways in mice.[25] Although this effect remains to be proven in humans, the increasingly critical role of a high-fiber, plant-based diet on human health is emerging and may be applied to enhancing recovery efforts in surgery.

Probiotics represent another route for encouraging the refaunation of a diverse and nonpathogenic microbiota. Many studies on probiotics have shown a benefit in reducing infectious lung diseases, including ventilator-associated pneumonia and cystic fibrosis exacerbations.[69] Probiotics have also been shown to increase immunity in the setting of viral vaccination. Probiotics given both before and after vaccine administration has been shown to improve seroprotection, demonstrating the potential for probiotic use in both the pre- and postoperative period.[70] Probiotics affect the entire immune activation process, including cytokine regulation, antigen presentation, Th1 and Th17 specific responses, and B cell differentiation.[71] While controversy remains over specifics for probiotic treatment plans, segmental filamentous bacteria, Bifidobacterium, and Lactobacillus probiotics have already shown to have a benefit in respiratory infections and provide a good starting point for further investigation.[34]

Finally, the surgeon must not forget the multitude of other surgical stressors that directly impact the microbiome. Surgeons should diligently manage such factors in the postoperative period to restore homeostasis and decrease stress signaling. Glycemic control during the time of starvation and refeeding should be monitored carefully, particularly in diabetic patients at higher risk for COVID-19.[72] Furthermore, consideration should be given to the hypercoagulable state induced by both immobilization from surgery and SARS-CoV-2.[73] High-risk patients should be considered for heparin bridging therapy and long-term anticoagulation along with early mobilization in the postoperative period.[74,75] Finally, opioids should be administered sparingly since they have been associated with an increase in microbial virulence and promotion of pathogenic bacteria, such as *P. aeruginosa*.[76] It is clear that there are many routes for modulating patient health, which should not be overlooked during this pandemic period (Figure 1).

CONCLUSION

While SARS-CoV-2 may be a novel pathogen not previously considered to be involved in postoperative infection, it now adds to surgeons' growing concern to properly select, prepare, and protect patients. Contemporary research has demonstrated that many factors, both in the pre- and postoperative period, can modulate patient fitness through changes to the gut and lung microbiome. While COVID-19 testing may be useful with evolving changes in accuracy and application, surgeons should take all precautions and consider every patient high-risk during this and future pandemics. As further research is ongoing to determine specific treatment and prevention measures against COVID-19 infection, a surgeon's attention to minimalize perturbations to the microbiome and promote its rapid restoration may be a promising approach to enhancing recovery during this pandemic and those to come.[77]

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