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Where do the pathogens that cause surgical site infections come from?

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Abstract

A study from Long *et al.* shows that many pathogens that cause surgical site infections during spine surgery come from the patient's own microbiome, suggesting a paradigm shift in the understanding of surgical site infections that questions the effectiveness of current enhanced sterility and antibiotic protocols.

The bundled effect of infection control measures used in elective surgery, including research studies, product development, mandated use of antibiotics, and protocols for skin decontamination, have resulted in historically low rates of surgical site infection (SSI). Yet, when an SSI does occur, as a superficial skin infection, deep operative field infection, anastomotic leak, or prosthetic infection, it can be disabling, costly, and occasionally lethal. Given the many mandated and enforced measures to maintain sterility throughout the process of surgery, today most stakeholders in the field consider an SSI to be due to some type of "breach in sterility" that allows exogenously acquired pathogens to enter the operative field. As a result, there is a constant plea for greater degrees of enforcement, sterility in air control and surgical attire, equipment decontamination, and antibiotic coverage, among other practices. Perhaps most worrisome is the increasing use of broader and more powerful antibiotics in elective surgery as pathogens resistant to the antibiotics used for prophylaxis continue to emerge and persist (1).

In the present issue, Long *et al.* (2) provide compelling data to demonstrate that many pathogens causing SSIs in patients undergoing instrumented spine surgery originate from endogenous rather than from exogenous sources—that is, from the patients' own microbiomes. In their study, the authors leveraged microbial sequencing to track and advance our understanding of how SSIs developed in patients undergoing instrumented spine surgery at the University of Washington, a busy tertiary referral center for complex spine surgery. The authors performed a prospective investigation using multiple forms of bacterial

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genomic analysis to map patients' preoperative microbiomes to the subsequently retrieved SSI pathogen(s) among 204 individuals undergoing a commonly performed spine surgical procedure in which prosthetic material is placed in situ. Although rare, patients undergoing such surgery may develop an SSI, which not only can necessitate additional surgery for removal of prosthetic material (screws, rods, or stabilizing appliances) but also can lead to temporary disability to walk, inability to work, chronic pain, or even permanent disability. The authors found that 86% of SSIs across a number of different bacterial species originated from strains already present in the preoperative patient skin microbiome. A total of 59% of the SSI isolates were resistant to the prophylactic antibiotic administered during surgery, and the bacterial resistance phenotypes underlying this resistance were related to antibiotic resistance genes found in the preoperative patient microbiome. There was no evidence of pathogen transfer across patients. Although SSIs after instrumented spine surgery remain rare (6.8% in this series), these results imply that insisting on greater degrees of sterility and broader antibiotic coverage may not be effective in curbing postsurgical infection (3). This excellent study should therefore force reconsideration of the traditional notion that "more of the same" is the path forward to reduce SSI rates from their current incidence toward zero. As a sustainable approach, certainly it is not an "evolutionarily stable strategy" (4), to quote Dawkins.

This research has the potential to be highly disruptive to the field of surgical site infection pathogenesis and prevention (Fig. 1). First, this study demonstrates that there may be anatomic variations/gradation in the pathogens present in the human skin microbiome along the longitudinal axis of the spine from the cervical to the lumbosacral region, which could revolutionize surgical site infection prevention by tailoring preoperative antisepsis and antibiotic protocols to specific anatomical variations. Second, in contrast to prior studies using 16*S* rRNA amplicon sequencing, the study performed metagenomic sequencing, which allows for strain-level distinction of individual species of pathogens and the ability to identify relevant antimicrobial resistance and virulence genes present within individual genomes, enabling customized infection control and improved surgical outcomes by directly targeting the specific pathogens present. The authors acknowledge the limitations of this approach, stating that often very low-abundance pathogens and their genes can remain below the level of detection until they "bloom" from conditions inherent in the process of surgery (such as overnight starvation, antibiotic exposure, pain, or use of opioids) and can thereby be detected. Third, a targeted whole-genome enrichment technique called genome capture sequencing (GenCap-Seq), first described by the authors in (5), allowed for a low-cost method to reconcile postoperative SSI isolate pairs, which challenges existing prevention strategies and demands more personalized and effective antimicrobial interventions. Last, the current finding is consistent with previous reports (6) that the majority of SSI isolates were resistant to the antibiotic chosen for prophylaxis. In light of these sobering results, it is perhaps unexpected that more patients did not develop an SSI. Together, these observations challenge the common practice that a "one-size-fits-all" antibiotic regimen based on consensus guidelines and prior select culture-based information is the "best that we can do" (7).

A hospital microbiome project in which the microbial dynamics among hospital surfaces, air, and water were mapped to patients and staff over the course of a 1-year period as

a new hospital was built and became operational demonstrated how microorganisms can colonize and move through the indoor environment (8). When compared with the study presented by Long *et al.* (2), one can conclude that presuming microbial transmission to occur in one direction versus another (from hospital surface to patient or vice versa) belies the complex dynamics that occur during microbial exchange. The microbial environment of a hospital is dependent on many factors: humidity, indoor and outdoor temperature, as well as the presence, virulence, and antibiotic resistance of pathogens and other microbes colonizing health care workers, visitors, family members, and of course the patients themselves. In-depth genetic tracking to establish the direction of the vector transmission requires massive sampling, high-resolution metagenomic sequencing, and sophisticated bioinformatic analysis approaches with mapping to high-quality clinical metadata (9). This is an exhaustive process that has both challenges and limitations. As the authors in the current study point out, causal inference on how or when wounds have become colonized by commensal microbiota and the possibility of background contamination from reagents or environmental sources confounding the results remain problematic. Nonetheless, the findings of this study controvert the idea of simply enforcing greater degrees of environmental sterility and broader antibiotic application to cover all and any potential pathogens harboring resistance genes, given that such protocols may not necessarily target pathogens endogenous to the patient or those that will cause the SSI.

This study sets the stage for future investigations in which potential pathogens endogenous to the patient can be interrogated for their role in SSI development. Additional methods of microbial tracking and sequencing should be considered. Microbial tracking of the built environment and in the human body is crucial for understanding the ecology of such environments and for identifying potential health hazards. Microbial tracking includes collecting samples from surfaces, air, and water systems within the hospital and from patients' skin, oral cavity, fecal matter, blood, and urine. Comprehensive sampling strategies, including targeted assessment of high-touch surfaces, are required to capture the diversity of microbes present in different areas of the hospital, including patient rooms, operating theaters, and intensive care units, with the goal of uncovering potential transmission threats. However, the typically low number of microbes present in the indoor environment compared with the human body presents a challenge here. Advanced low-abundance molecular approaches are crucial for effectively studying these environments. The methods used for DNA and RNA extraction also play a critical role in the analysis of community dynamics. To sample the indoor microbiome, researchers commonly use either wet or dry swabs on surfaces or use pads that collect materials settling from the air. Airborne sampling is particularly useful for identifying emerging pathogens, but surface sampling remains vital for understanding metabolic ecology and genetic adaptation. Charting the metabolic pathways within built environments is a key strategy to understand how microbial communities adapt and grow in these challenging habitats. In addition, pinpointing the spread of pathogens and microbes is aided by identifying genomes at the strain level. Metagenomic assembly techniques are being used to reconstruct genomes and trace their movement between environments and individuals. Importantly, although a single observation can help characterize where potential pathogens are found, it cannot help us understand the dynamics of microbial transfer. Therefore, to achieve a better understanding of the origin of

microbial contamination in the surgical field, it is necessary to perform longitudinal analyses that involve collecting samples from surfaces and patients over time. New technologies are now coming online that facilitate continual and semiautomatic collection of the microbiome from patients, including devices that extract and preserve the DNA and RNA from fecal, saliva, and skin samples automatically for later analysis (10). Gaining a temporal map of a patient's microbiome immediately upon admission to the hospital could help to identify those at risk of subsequent SSIs.

It may also be pertinent to analyze the microbiome of patients before inpatient or outpatient procedures by furnishing them with automated nucleic acid extraction devices in their home so that microbial SSI risks can be identified. Identifying these risk factors could facilitate prehabilitation programs before elective surgery, the efficacy of which could be tracked and mechanistically detailed by emerging next-generation technology in microbial sampling, sequencing, and metabolomics. For example, the extent to which smoking cessation, exercise, dietary modifications, and improvement in disease management (such as glucose control) alter the endogenous microbiome of a patient, and hence decrease the risk of an SSI, could be more formally addressed. There is a pressing need to consider approaches beyond greater environmental sterility and the increasing use of broader antibiotics in surgery. Yet, without a rational understanding of the mechanisms that underlie the efficacy of these approaches, like most studies in the field of SSI reduction, the results remain probabilistic rather than deterministic.

There is no doubt an unmet need to drive down SSI rates in elective surgery, especially when surgery involves implantation of a prosthetic device, a growing practice among our aging patient population. This study by Long *et al.* demonstrates that proposing generalized care strategies and greater degrees of sterility based on the notion that most SSIs occur because of some type of external contamination event may be a concept in need of revision.

References

1. Clean Cut Investigators Group, An observational cohort study on the effects of extended postoperative antibiotic prophylaxis on surgical-site infections in low- and middle-income countries. Br. J. Surg 111, znad438 (2024). [PubMed: 38198157]
2. Long DR, Bryson-Cahn C, Waalkes A, Holmes EA, Penewit K, Tavolaro C, Bellabarba C, Zhang F, Chan JD, Fang FC, Lynch JB, Salipante SJ, Contribution of the patient microbiome to surgical site infection and antibiotic prophylaxis failure in spine surgery. Sci. Transl. Med. 16, eadk8222 (2024). [PubMed: 38598612]
3. Rocos B, Kato S, Lewis SJ, Shaffrey CI, Lenke LG, AO spine knowledge forum deformity, antibiotic use in adult spine deformity surgery: Results from the AO spine surveillance of the management of patients with adult spine deformity. Global Spine J, 10.1177/21925682231201240 (2023).
4. Brockmann HJ, Grafen A, Dawkins R, Evolutionarily stable nesting strategy in a digger wasp. J. Theor. Biol. 77, 473–496 (1979). [PubMed: 491692]
5. Hayden HS, Joshi S, Radey MC, Vo AT, Forsberg C, Morgan SJ, Waalkes A, Holmes EA, Klee SM, Emond MJ, Singh PK, Salipante SJ, Genome capture sequencing selectively enriches bacterial DNA and enables genome-wide measurement of intrastrain genetic diversity in human infections. MBio 13, e0142422 (2022). [PubMed: 36121157]
6. Long DR, Bryson-Cahn C, Pergamit R, Tavolaro C, Saigal R, Chan JD, Lynch JB, 2021 young investigator award winner: Anatomic gradients in the microbiology of spinal fusion surgical site

infection and resistance to surgical antimicrobial prophylaxis. Spine 46, 143–151 (2021). [PubMed: 32796459]

7. Bhatti T, Lum K, Holland S, Sassman S, Findlay D, Outterson K, A perspective on incentives for novel inpatient antibiotics: No one-size-fits-all. J. Law Med. Ethics 46, 59–65 (2018). [PubMed: 30146959]
8. Lax S, Sangwan N, Smith D, Larsen P, Handley KM, Richardson M, Guyton K, Krezalek M, Shogan BD, Defazio J, Flemming I, Shakhsheer B, Weber S, Landon E, Garcia-Houchins S, Siegel J, Alverdy J, Knight R, Stephens B, Gilbert JA, Bacterial colonization and succession in a newly opened hospital. Sci. Transl. Med. 9, eaah6500 (2017). [PubMed: 28539477]
9. Alverdy JC, Hyman N, Gilbert J, Re-examining causes of surgical site infections following elective surgery in the era of asepsis. Lancet Infect. Dis. 20, e38–e43 (2020).
10. Zhou X, Shen X, Johnson JS, Spakowicz DJ, Agnello M, Zhou W, Avina M, Honkala A, Chleilat F, Chen SJ, Cha K, Leopold S, Zhu C, Chen L, Lyu L, Hornburg D, Wu S, Zhang X, Jiang C, Jiang L, Jiang L, Jian R, Brooks AW, Wang M, Contrepois K, Gao P, Rose SMS-F, Tran TDB, Nguyen H, Celli A, Hong B-Y, Bautista EJ, Dorsett Y, Kavathas PB, Zhou Y, Sodergren E, Weinstock GM, Snyder MP, Longitudinal profiling of the microbiome at four body sites reveals core stability and individualized dynamics during health and disease. Cell Host Microbe 32, 1–21 (2024). [PubMed: 38211560]

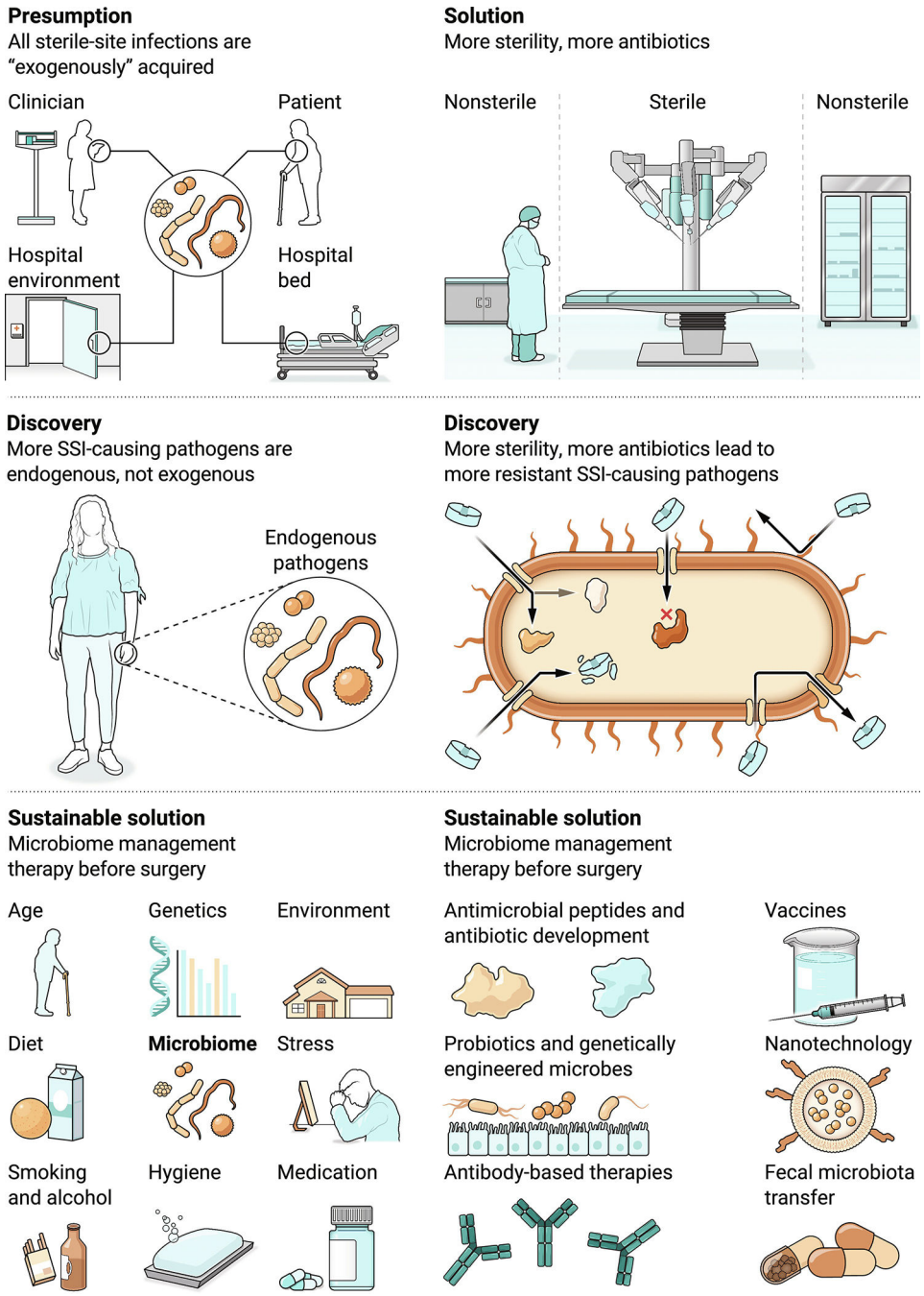

Fig. 1.

Redefining surgical site infection prevention, from sterility to microbiome management. This figure illustrates the paradigm shift in understanding and managing SSIs. Initially, SSIs were presumed to be predominantly exogenous, acquired from the hospital environment, leading to strategies focusing on increasing sterility and antibiotic use. Subsequent discoveries revealed that many SSI pathogens are endogenous, not exogenous, and that enhancing sterility and antibiotic usage can inadvertently select for more resistant pathogens. The proposed sustainable solution involves microbiome management therapy before surgery,

emphasizing the role of the patient's age, genetics, and environment in SSI risk. This approach could include the development of antimicrobial peptides, antibiotics, and vaccines and the use of diet, probiotics, genetically engineered microbes, nanotechnology, and hygiene practices to optimize the microbiome for SSI prevention. In addition, advanced therapies such as antibody-based treatments and fecal microbiota transfers could be considered, highlighting the comprehensive strategy required to effectively combat SSIs in the future.