Introduction

Microbiome: Our opponents or allies in healthcare and medicine

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Addressing the presence of unwanted bacteria and fungi following medical procedures has long been a major healthcare concern. Infection applications can range from wounds, to surgical sites to biomedical implants. Current strategies employ strong, broad-spectrum antibiotics as a prophylactic prior to any planned procedure, and aggressive antimicrobial therapies following detection of any unwanted organism. For decades, the only strategy for an infected implant showing presence of a bacterial biofilm was removal of the implant.[1–4] However, recent knowledge and growth in the field of microbiome and mycobiome detecting the presence of organisms even in "uninfected" implants[5] and normal tissue[6] demonstrate that new strategies can be employed which don't necessarily need to eradicate all bacteria and fungi, but could be geared toward restoring homeostasis in the organism.[7,8] This Special Issue broadly addresses new knowledge in microbiome-related research, particularly in regards to medicine and healthcare. We hope it can serve as a state-of-the-art review of recent advances, suitable for experts in the field, as well as a primer for the novice to understand what areas are involved and gain a rapid understanding of how these different topics have come together.

The microbiome is described as the ecological community of commensal, symbiotic and pathogenic microorganisms (microbiota), or the collective genome of such organisms. The term first appeared in a PubMed cited article in 1956 but was used to describe microbial communities in non-medical applications.[9] Over the next several decades, the microbiome field grew steadily with an exponential explosion beginning around 2000 due, in part, to advancement of high-throughput computational and genomic techniques (Figure 1, "microbiome"). Knowledge of the microbiome in medicine, particularly in regards to gut flora has also been extensively investigated, and underwent a similar exponential growth, starting around 2009 (Figure 1, "microbiome AND medicine"). Understanding how manipulation of microbiome for healthcare broadly, such as in the treatment of wound management (Figure 1, "microbiome AND healthcare") as well as more specifically, such as in the treatment of implant infection (Figure 1, "microbiome AND implant") are fields that are in their infancy, with only a handful of citations each.

In the case of implant infection, certain of certain organisms (e.g. *Staphylococcus aureus*, *Staphylococcus epidermidis*) have long been known to generate sufficient cytotoxic and inflammatory signals, ultimately leading to implant failure. These organisms have been consistently identified due to the high prevalence cultured out of infected implants. While single organisms are often pointed to as the culprits, infections are typically presumed to not be monoclonal. Indeed, other organisms, such as *Propionibacterium acnes*, have often been identified with implant infections, but their role as co-infectant (e.g. arriving either before *S. aureus* or after) has not been made clear.[10] In other cases, chronic "low grade" infections have been observed, in which microbial organisms are present but inflammatory processes have not been activated sufficient to result in implant failure.[11]

While the capacity to culture and grow bacteria has existed for over 100 years, until recently, only a sampling of the species present in an implant infection have been able to be identified. This is likely due to slow or difficult culture conditions needed (including anaerobic bacteria), as well as organisms present in such low copy number that only high-resolution PCR and computational techniques were capable of identifying them.[5]

In this Special Issue on Microbiome in Healthcare and Medicine, we investigate multiple aspects of the study of microbiomes ranging from the development of standardized protocols for studying microbiome in animal models, by Rodriquez-Palacios *et al.*,[12] to aspects in either treating the organism directly,[13] or indirectly by treating the consequences, such as inflammation by von Recum *et al.*[14]

We started off with a pair of broad review topics, the first on understanding the role of microbiome in diet and health by McDonald *et al.*,[15] and the second on new strategies to engineer microbiome and understanding its impact on health by Son *et al.*[16] Then a group of reviews examines our understanding of microbiome and disease as Jacobs *et al.* show how gut microbiome plays a role in fatty liver disease, a condition not traditionally thought of as infectious in origin.[17] In Skondra *et al.*, we learn how

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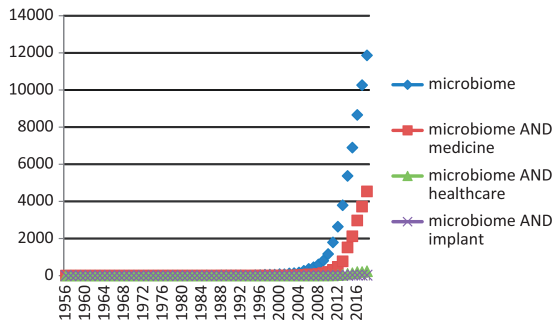

Figure 1. Histogram of Pubmed articles on "microbiome". While "microbiome" (diamonds) has shown as steady gain since it first appeared in a PubMed cited article in 1956, the field began to see an exponential rise in 2000. Concatenation with other terms such as "medicine" (squares), "healthcare" (triangles) and "implant" (X's) show much later appearances.

microbiome could play a role in a broad range of ophthalmic disease,[18] while in Yacoub *et al.*, we learn about how the microbiome plays a role in the development of cardiovascular disease during chronic kidney disease.[19] On the computational side, Shen *et al.* review recent progress on elucidating the complex interactome between various microbial players to better understand the microbiome network.[20] Oliveira *et al.* combine computation and detective work to identify and track microbiota in healthcare environments.[21] We are rounded out by a pair of original research articles: Parker *et al.* study the microbiota in mole-rats to understand the roles they play in diet and evolution,[22] while Yacoub *et al.* analyze fecal microbiota in patients with polycystic kidney disease.[23]

Wherever biomedical research takes us, it is clear that the "reset" button provided by antibiotics will not be the only tool in our arsenal to treat healthcare associated infections. Future research will lead to better understanding of the microbiome and how to restore homeostasis of the biological community, followed by targeted approaches to biofilm eradication and/or the treatment of inflammation as the consequence of infection.

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REFERENCES

1. Jansen B, Peters G. Foreign body associated infection. *J Antimicrob Chemother* 1993;**32**:69–75
2. Vinh DC, Embil JM. Device-related infections: a review. *J Long Term Eff Med Implants* 2005;**15**:467–88
3. Wagner C, Hansch GM. Mechanisms of bacterial colonization of implants and host response. *Adv Exp Med Biol* 2017;**971**:15–27
4. Levack AE, Cyphert EL, Bostrom MP, Hernandez CJ, von Recum HA, Carli AV. Current Options and Emerging Biomaterials for Periprosthetic Joint Infection. *Curr Rheumatol Rep* 2018;**20**:33
5. Jakobsen TH, Eickhardt SR, Gheorghe AG, Stenqvist C, Sonderholm M, Stavnsberg C, Jensen PO, Odgaard A, Whiteley M, Moser C, Hvolris J, Hougen HP, Bjarnsholt T. Implants induce a new niche for microbiomes. *APMIS* 2018;**126**:685–92
6. Ohrt-Nissen S, Fritz BG, Walbom J, Kragh KN, Bjarnsholt T, Dahl B, Manniche C. Bacterial biofilms: a possible mechanism for chronic infection in patients with lumbar disc herniation – a prospective proof-of-concept study using fluorescence in situ hybridization. *APMIS:* 2018;**126**:440–7
7. Bjarnsholt T, Buhlin K, Dufrene YF, Gomelsky M, Moroni A, Ramstedt M, Rumbaugh KP, Schulte T, Sun L, Akerlund B, Romling U. Biofilm formation – what we can learn from recent developments. *J Intern Med* 2018;**284**:332–45
8. Pokrowiecki R. The paradigm shift for drug delivery systems for oral and maxillofacial implants. *Drug Delivery* 2018;**25**:1504–15
9. Lackey JB. Stream enrichment and microbiota. *Public Health Rep* 1956;**71**:708–18
10. Lavergne V, Malo M, Gaudelli C, Laprade M, Leduc S, Laflamme P, Rouleau DM. Clinical impact of positive *Propionibacterium acnes* cultures in orthopedic surgery. *Orthopaed Traumatol Surg Res: OTSR.* 2017;**103**:307–14
11. Romano CL, Romano D, Morelli I, Drago L. The concept of biofilm-related implant malfunction and "low-grade" infection. *Adv Exp Med Biol* 2017;**971**:1–13
12. Rodriguez-Palacios A. Institutional Protocols for the Oral Administration (Gavage) of Chemicals and Microscopic Microbial Communities to Mice: Analytical Consensus. 2019; doi:10.1177/1535370219838203
13. Haley RM, Zuckerman ST, Gormley CA, Korley JN, von Recum HA. Local Delivery Polymer Provides Sustained Anti-fungal Activity of Amphotericin B with Reduced Cytotoxicity. 2019; doi: 10.1177/1535370219837905
14. Haley R, Recum H. Localized and Targeted Delivery of NSAIDs for Treatment of Inflammation: A Review. 2019; doi: 10.1177/1535370218787770
15. Zangara MT, McDonald C. How diet and the microbiome shape health or contribute to disease: a mini-review of current models and clinical studies. 2019; doi:10.1177/1535370219826070
16. Song SJ, Woodhams D, Martino C, Allaband C, Mu A, Javorschi-Miller-Montgomery S, Suchodolski J, Knight R. Engineering the microbiome for animal health and conservation. 2019; doi:10.1177/1535370219830075
17. Dong T, Jacobs J. Nonalcoholic Fatty Liver Disease and the Gut Microbiome: Are Bacteria Responsible for Fatty Liver? 2019; doi:10.1177/1535370219836739

18. Baim AD, Movahedan A, Farooq AV, Skondra D. The microbiome and ophthalmic disease: a review. 2019; doi:10.1177/1535370218813616
19. Bryniarski MA, Hamarneh F, Yacoub R. The role of chronic kidney disease associated dysbiosis in cardiovascular disease. 2019; doi:10.1177/1535370219826526
20. Dohlman A, Shen X. Mapping the Microbial Interactome: Statistical and Experimental Approaches for Microbiome Network Inference. 2019; doi:10.1177/1535370219836771
21. Christoff AP, Sereia AFR, Hernandes C, Oliveira LFV. Uncovering the hidden microbiota in hospital and built environments: new approaches and solutions. 2019; doi:10.1177/1535370218821857
22. Ren L, Holzknecht R, Holzknecht Z, Kotz S, Bowles D, Lin SS, McKenney E, Parker W. A mole-rat's gut microbiota suggests selective influence of diet on microbial niche space and evolution. 2019; doi:10.1177/1535370219828703
23. Yacoub R, Nadkarni GN, McSkimming DI, Chaves LD, Abyad S, Bryniarski MA, Honan AM, Thomas SA, Gowda M, He J, Uribarri J. Fecal microbiota analysis of polycystic kidney disease patients according to renal function, a pilot study. 2019; doi:10.1177/1535370218818175