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Are Bacteria Infectious Pathogens in Hidradenitis Suppurativa? Debate at the Symposium for Hidradenitis Suppurativa Advances Meeting, November 2017

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In November 2017, a formal debate on the role of bacteria in the pathogenesis of hidradenitis suppurativa (HS) was held at the 2nd Symposium on Hidradenitis Suppurativa Advances (SHSA) in Detroit, Michigan. In this report, we present both sides of the argument as debated at the SHSA meeting and then discuss the potential role of bacteria as classic infectious pathogens versus an alternative pathogenic role as activators of dysregulated commensal bacterial-host interactions. Although there was consensus that bacteria play a role in pathogenesis and thus are pathogenic, there was a compelling discussion about whether bacteria in HS incite an infectious disease as we classically understand it or whether bacteria might play a different role in HS pathogenesis.

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Symposium on Hidradenitis Suppurativa Advances

In November 2017, the 2nd Symposium on Hidradenitis Suppurativa Advances (SHSA) was held in Detroit, Michigan. This 2-day international meeting, cohosted by the Hidradenitis Suppurativa Foundation of the United States and the Canadian Hidradenitis Suppurativa Foundation, is the only dedicated scientific meeting for hidradenitis suppurativa (HS) in North America. The goal of the annual SHSA meetings is to improve the lives of those with HS by encouraging clinical and basic science research, as well as to foster collaborations and networking opportunities for all members of the HS community.

Debate

The pathophysiology of HS is poorly understood, including the role and contribution of microbes to HS pathogenesis. One of the formal sessions at the 2017 SHSA meeting was a debate

focused on the role of bacteria in HS. Debaters were asked to prepare and defend a position in response to the statement *Bacteria are infectious pathogens in HS*. Dr. Haley B. Naik (University of California, San Francisco) and Dr. Ramesh Mayur (Henry Ford Hospital, Detroit, MI) defended the *against* position, and Dr. Gregory Schultz (Institute of Wound Research and University of Florida, Miami, FL) and Dr. Aude Nassif (Centre d'Infectiologie Necker-Pasteur, Paris, France) defended the *for* position. The debate was organized by Dr. Afsaneh Alavi (University of Toronto, Toronto, Canada, and Canadian Hidradenitis Suppurativa Foundation) and Dr. Michelle Lowes (The Rockefeller University, New York, NY, and Hidradenitis Suppurativa Foundation of the United States) and moderated by Dr. Vincent Piguet (University of Toronto, Toronto, Canada). Here, we present the arguments in favor and against, followed by a discussion

reconciling these perspectives. In addition to the aforementioned contributions, all authors contributed to the development of this report.

Arguments against: Bacteria are not infectious pathogens in HS

There are strong arguments refuting the role of bacteria as infectious pathogens in HS. A notable clinical observation is that in HS, there is rarely lymphangitis, septicemia, cellulitis, or palpable tender regional lymphadenopathy.

HS does not fulfill Koch's postulates defining bacterial infectious disease (Table 1). Koch's first two postulates state that bacteria must be present in every case of disease and that bacteria must be isolated from the affected host and grown in culture. Across nine studies in which HS lesions were cultured, bacteria were cultivatable in only 50% of lesions under standard laboratory conditions. Moreover, positive cultures from HS lesions were

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Abbreviations: HS, hidradenitis suppurativa; SHSA, Symposium on Hidradenitis Suppurativa Advances
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Table 1. Koch's postulates

1. Bacteria must be present in every case of the disease.
2. Bacteria must be isolated from an affected host and grown in culture.
3. The disease must be reproducible upon inoculation of an unaffected susceptible host.
4. Bacteria must be recoverable from an experimentally infected host.

polymicrobial, indicating that there was not a single common culprit organism associated with HS (Ring et al., 2015). Koch's third postulate states that disease must be reproducible upon inoculation of an unaffected susceptible host. However, HS is not known to be transmitted between individuals in close contact, including household members, mother and child, or intimate partners. HS also does not fulfill Koch's fourth postulate that bacteria must be recoverable from an experimentally infected host, because no such host has been reported. It can be rightly argued that Koch's postulates may be antiquated given cutting-edge genomic technologies that now allow us to identify uncultivable microbes via sequencing modalities. However, further systematic studies are required to identify bacterial organisms common to HS lesions and to prove their pathogenicity.

Further supporting the argument against bacteria being infectious pathogens in HS is evidence for the use of immunomodulating therapies for disease management. Although antibiotics have been shown to be helpful in managing HS in subsets of patients, many are known to have anti-inflammatory effects. Effective treatments for HS include immunomodulating agents such as tumor necrosis factor antagonists. In fact, the only therapy for HS approved by the US Food and Drug Administration is the tumor necrosis factor antagonist adalimumab, and newer anticytokine and other anti-inflammatory treatments are currently under investigation (Theut Riis et al., 2018). Similarly, systemic and intralesional corticosteroids are somewhat effective for the management of acute disease flares (Theut Riis et al., 2016). Disease response to these therapies suggests an important role for immune dysregulation in HS pathogenesis.

Finally, several reports now indicate that genetic factors may play an

important role in HS pathogenesis. Mutations in *NCSTN*, *PSEN1*, or *PSENEN* genes have been reported in families with autosomal dominant inheritance patterns (Frew et al., 2017). These genes encode proteins that form the γ -secretase complex, which has a significant role in protein processing. The γ -secretase complex is involved in the Notch pathway, which is important for cell signaling, normal maturation of skin and hair follicle cells, and immune function. There may be other genetic factors that dictate exuberant or inadequate immune responses to cutaneous bacteria, such as *NOD2* (Negroni et al., 2018). These findings support a hypothesis that microbes may be a secondary or opportunistic actor in the setting of a primary genetic/immune defect.

Arguments in favor: Bacteria are infectious pathogens in HS

There are a number of points that indicate that bacteria could be playing a role as infectious pathogens in HS (Delage et al., 2015).

First, in active HS, there are clinical signs consistent with infection and inflammation, coupled with suppurative malodorous drainage and formation of abscesses. Lesions may be acute, have the clinical characteristics of abscesses and deep furuncles, be surrounded by a wide erythematous region, and cause significant acute or chronic pain. Occasionally, patients who experience a flare may have systemic symptoms such as fever and malaise.

Second, pathogenic organisms have been identified from HS lesions using cutting-edge sequencing methods (Guet-Revillet et al., 2014, 2017; Nikolakis et al., 2015). Although routine culture mainly shows superficial commensal bacteria, prolonged culture methods and RNA metagenomics sequencing have identified a variety of commensal and pathogenic bacteria. In several studies, disease severity has been linked to increased

richness of anaerobic bacteria and more resistant species (perhaps due to prolonged antibiotic exposure) in HS lesions.

Third, the positive response to antibiotics in subsets of patients suggests an infectious etiology. Antibiotics can either be *empirical* (when bacterial species are assumed) or *targeted* (when a wound has been cultured and bacterial sensitivities identified to guide antibiotic selection). Treatment with antibiotics such as oral clindamycin and rifampin has been found to provide some clinical improvement of HS lesions in retrospective case series (Gener et al., 2009; Mendonca and Griffiths, 2006; van der Zee et al., 2009) and small prospective studies (Bettoli et al., 2014), as has treatment with tetracyclines (Goldsmith and Dowd, 1993; Jemec and Wendelboe, 1998; Shenefelt, 1996). Other antibiotic regimens with broader spectrum coverage, such as triple therapy with oral rifampin, moxifloxacin, and metronidazole, can induce even more rapid and dramatic improvements in some patients with long-standing advanced HS (Join-Lambert et al., 2011). Intravenous ertapenem has been recently shown to be remarkably effective for advanced HS and is not known to have anti-inflammatory or anti-biofilm properties (Join-Lambert et al., 2016). Biofilms are dormant bacteria protected by an extracellular polymeric substance (Flemming et al., 2016). Metabolically dormant bacteria in biofilms can have extreme tolerance to antibiotics that rapidly kill metabolically active planktonic bacteria (Costerton et al., 1999).

Reconciling the potential roles of bacteria in HS

The pathogenesis of HS may be explained as occurring in two stages: initiation and progression (Hoffman et al., 2017). This could be considered analogous to the so-called two-hit hypothesis of cancer. According to histopathology, the primary event initiating HS may be follicular occlusion (Boer and Weltevreden, 1996; van der Zee et al., 2012). Potential contributors to follicular occlusion include γ -secretase mutations, genetic mutations that determine apocrine gland secretions, deficiencies in sweat gland proteins, alterations in infundibular anatomy, and

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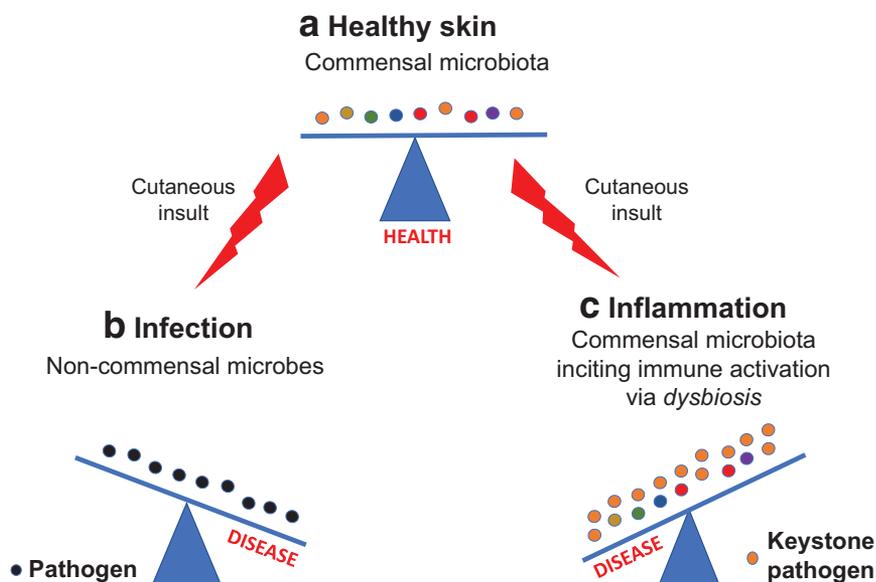


Figure 1. Proposed roles of bacteria in cutaneous health, infection, and inflammation. (a) A range of commensal microbiota have a role in maintaining skin health. (b) Cutaneous breach can allow noncommensal pathogenic bacteria to proliferate and cause true infection. (c) An imbalance in commensal bacterial populations can allow pathobionts, or a keystone pathogen, to dominate and drive inflammation. In more advanced HS, epithelialized dermal tracts provide an ideal surface for biofilm development and act as a reservoir of bacteria, which may contribute to persistence and relapse.

keratin mutations (Hoffman et al., 2017; Knobel et al., 2015). Follicular occlusion can trap commensal bacteria in the follicle. Independent of the mechanism of follicular occlusion, the next step, or second hit, may be the formation of deep abscesses that eventually rupture outward or laterally, forming a dermal tract. Once in the dermis, these commensals initiate a vigorous host inflammatory response. For unknown genetic, hormonal, and/or environmental reasons, these commensal bacteria could multiply and become pathogenic (Park and Lee, 2017).

HS appears to be a disease where bacteria may be pathogenic, inciting an atypical and dysregulated interaction of the host and cutaneous microbiota. Figure 1 diagrams the proposed roles of bacteria in cutaneous health, infection, and inflammation. A range of commensal microbiota have a role in maintaining skin health (Figure 1a). A cutaneous insult or breach can allow noncommensal pathogenic bacteria to proliferate and cause true infection (Figure 1b). A pathogenic imbalance in commensals, or *dysbiosis*, may also play a role in activating the immune system (Figure 1c). Resident bacteria that are harmless under normal conditions can harbor the potential to

become pathogenic, termed *pathobionts*, giving rise to so-called keystone pathogens that can dominate and drive inflammation in chronic disease. As this process continues in HS, the dermal tracts become epithelialized. Biofilms attach to these epithelialized tracts, and because the host has difficulty eliminating biofilms, they persist and can induce relapses. Common features of biofilm-driven diseases are unpredictable response to antibiotics, poor healing, and prolonged inflammation, all consistent with the clinical course of HS. In this way, bacteria are a critical component in the vicious circle of inflammation in susceptible HS patients through activation of the immune system, which is inadequate, deficient, misdirected, and/or hyperactive. These hypotheses now need to be tested.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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