Chapter 11

Bacteriology of Hidradenitis Suppurativa

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Key points

- The pathogenesis of hidradenitis suppurativa (HS) is still poorly understood and not yet clearly defined
- A large variety of bacteria can be found in HS lesions and many of them belong to the normal flora of the skin
- In the studies using the bacteria prevalent on the surface of the lesions there is possible contamination from the resident flora of the skin
- In cases of cultures obtained from the deeper parts of HS, *Staphylococcus aureus*, coagulase-negative staphylococci and anaerobic bacteria have commonly been isolated
- The first event seems to be follicular occlusion by keratinized stratified squamous epithelium in apocrine-bearing areas, with subsequent inflammation
- The initial inflammatory change can be produced by a pyogenic bacterial infection or by factors similar to those involved in acne
- In chronic lesions, bacteria represent a risk factor for the destructive scarring and extension of the disease and secondary bacterial infections may occur
- Antibiotics do not cure the disease but they may relieve the symptoms through either an antibacterial or an anti-inflammatory effect

Contents

11.1 Normal Microflora of the Skin

Normal human skin is colonized by a large variety of organisms that live as commensals on its surface. There are quantitative differences among different regions of the skin, related to temperature difference, moisture content, and the presence of various amounts of skin lipids that may be inhibitory or lethal for some microorganisms. These differences characterize three main regions of the skin: (1) axilla, perineum, and toe webs; (2) hands, face, and trunk; and (3) arms and legs [20]. The skin microflora reside on the skin surface and in the ducts of hair follicles and sebaceous glands [38].

Table 11.1. The most important genera and species of bacteria normally found on the skin

Genus	Characteristics	Most prevalent species
Coagulase-negative *Staphylococcus*	Aerobic, Gram-positive cocci	*S. hominis, S. haemolyticus* *S. epidermidis*
Micrococcus	Aerobic, Gram-positive cocci	*M. luteus, M. varians*
Corynebacterium	Aerobic, Gram-positive pleomorphic rods	*C. bovis, C. minutissimum*
Propionibacterium	Anaerobic, Gram-positive rods	*P. acnes, P. granulosum, P. avidum*
Acinetobacter	Aerobic, Gram-negative coccobacilli	*A .calcoaceticus* var. *lwoffi* and var. *anitratus*

The sites affected by HS are, in order of frequency: axillary, inguinal, perianal and perineal, mammary and inframammary, buttock, pubic region, chest, scalp, retroauricular, and the eyelid [50].

The major groups of microorganisms present on the skin are various genera of bacteria and yeasts. The predominant bacteria of the skin are as follows (Table 11.1) [20, 21]:

- Coagulase-negative staphylococci
- Micrococci
- Saprophytic *Corynebacterium* species (diphtheroids)
- *Propionibacterium* species
- *Acinetobacter* species.

Various coagulase-negative staphylococci are found on the skin and some have special predilection for some areas, for example *Staphylococcus hominis* and *Staphylococcus haemolyticus* are found principally in areas where there are numerous apocrine glands, such as axillae and the pubic region [20, 32]. *Staphylococcus epidermidis* is also an important resident, colonizing moist areas of the skin [21]. It is found preferentially in the upper part of the body and represents over 50% of the resident staphylococci [47].

Micrococcus species are found on the skin, especially in women and children, and *Micrococcus luteus* and *Micrococcus varians* are the prevailing species [20, 21]. These microorganisms often colonize axilla, perineum, and groin [21].

Different bacteria belonging to the genus *Corynebacterium* are associated, but not exclusively, with moist areas of the skin [21].

Propionibacteria are Gram-positive rod-shaped anaerobic bacteria. *Propionibacterium acnes* and *Propionibacterium granulosum* are associated with follicles that have large sebaceous glands on the face and upper trunk and they have a role in acne pathogenesis. *Propionibacterium avidum* is found in moist areas (axillae and groin) and it is not known if it has pathogenic potential [21].

Acinetobacter species are the only important Gram-negative residents of the skin and are found in the axillae and groin of 25% of the population [21].

In addition, any bacterial species that is found in nature or belongs to the normal flora on noncutaneous areas may temporarily be found on the skin [47]. *Staphylococcus aureus* is not normally considered a resident of normal skin, but it can be found on perineal skin, axillae, and in the toe cleft. Hemolytic streptococci may be found as transients on different skin sites, more often in children [38]. Atypical mycobacteria may be found in genital and axillary regions and *Bacillus* species or different Gram-negative bacilli such as *Proteus*, *Pseudomonas*, *Enterobacter* and *Klebsiella* are rarely found on the skin [20, 38].

In conclusion, a large variety of bacteria are able to colonize the most affected areas in HS: axilla, perineum, and the groin.

11.2 Bacteria Found in HS Lesions

Although the HS etiology is unknown, a large variety of microorganisms can be isolated from the lesions. The clinical picture of the disease resembles an infectious process and various

Table 11.2. Studies describing the diversity of bacteria found in various HS lesions

Investigator	Bacteria found	Area of the skin
Leach et al. [35]	*Staphylococcus aureus,* anaerobic bacteria	Axillae
Brenner and Lookingbill [7]	*Staphylococcus aureus, Staphylococcus epidermidis Bacteroides fragilis, Bacteroides melaninogenicus*	Perirectal, groin, axillae
Highet et al. [23]	*Streptococcus milleri*	Perineal
Highet et al. [24]	*Streptococcus milleri, Staphylococcus aureus*, anaerobic streptococci, *Bacteroides* species	Perineal
Finegold et al. [18]	*Biophila wadsworthia*	Axillae
Bendahan et al. [5]	*Chlamydia trachomatis*	Perineal
Jemec et al. [29]	*Staphylococcus aureus, Streptococcus milleri, Staphylococcus epidermidis, Staphylococcus hominis*	Axillae, groin, breasts, buttocks
Brook and Frazier [8]	*Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa*; *Peptostreptococcus* species, *Prevotella* species, micro-aerophilic streptococci, *Fusobacterium* species, *Bacteroides* species	Axillae
Lapins et al. [33]	*Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, group B hemolytic streptococci, group C hemolytic streptococci, *Bacillus cereus*, diphtheroides, enterobacteriacae-; *Peptostreptococcus* species, *Propionibacterium acnes,* microaerophilic streptococci, *Lactobacillus* species, *Bacteroides fragilis,* other *Bacteroides* species, *Prevotella* species	Axillae and perineal

bacteria are suspected as being responsible for the inflammation. The bacterial findings are considered by some authors as either contaminants from the normal skin flora or a result of secondary infection in a previously sterile process [33].

Despite the volume of the discharge the HS lesions are often found to be sterile [29, 33], but sometimes a large variety of microorganisms can be isolated from the sinuses, particularly staphylococci, streptococci, Gram-negative rods, and anaerobic bacteria (Table 11.2). The bacterial flora are not consistent and may change unpredictably [31]. Brook and Frazier [8] found, in a retrospective review of clinical and bacteriological data from patients with axillary disease, that the most prevalent aerobic bacteria were *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa* and the most frequent anaerobic bacteria were *Peptostreptococcus* species, *Prevotella* species, microaerophilic streptococci, *Fusobacterium* species, and *Bacteroides* species.

In most of the studies samples are collected from the surface of the lesions [22–24] and there is a high risk of contamination with the resident skin flora. In these conditions the bacteriological results are difficult to interpret. Jemec et al. [29] have aspirated pus from the deeper parts of HS. Bacteria were found in half of active lesions: *Staphylococcus aureus* and coagulase-negative staphylococci (*Staphylococcus epidermidis* and *Staphylococcus hominis*) were most commonly isolated. An explanation for the large number of negative cultures could be that it is difficult to localize the infected part using the aspiration technique. It was found that the duration of the disease was shorter for those patients in whom *Staphylococcus aureus* was detected as a possible etiological factor, indicating that this bacterium may be involved early in the disease pathogenesis by causing anatomical changes in the hair

Table 11.3. Possible factors responsible for coagulase-negative staphylococci pathogenicity in HS lesions

Factors	Effect
Sinus formation in HS lesions	Enhances the pathogenic properties of the bacteria [33]
Bacterial capacity of biofilm formation	Protects against antibiotics and from attacks by the immune system [42]
Bacterial production of lipases, proteases, and other exoenzymes	Persistence in the host. Tissue degradation [42]
Toxin production	Invasion properties [35, 36]
Production of PAS-positive extracellular polysaccharide substance	Obstructs the delivery of sweat to the skin surface [37]

follicles. These modifications may later predispose to inflammation independently of the presence of bacteria [29].

Lapins et al. [33] circumvented problems both of contamination and of missing the active area of infection by using a carbon dioxide (CO_2) laser surgical method to evaporate the diseased tissue level by level from the surface downwards. This allows sampling for bacteriological cultures from each level without the risk of contamination with bacteria from the level above. By using this method, bacteria were found even in the deeper and closed parts of HS. *Staphylococcus aureus* and coagulase-negative staphylococci were also the most commonly found species. After the *Staphylococcus* species the most commonly cultured bacteria were the anaerobic species found in the deeper levels: *Peptostreptococcus* species and *Propionibacterium acnes*. The aerobic bacteria were found in 60% of positive cultures at deep levels.

The clinical significance of coagulase-negative staphylococci is unclear because while they are part of the normal microflora [29, 33] they have also gained attention as pathogens (Table 11.3). Coagulase-negative staphylococci are associated with infections in those with intravascular catheters [46] and prosthetic devices [14] where the presence of the foreign body will increase the pathogenic properties of these otherwise harmless members of the normal flora. Lapins et al. [33] have often found coagulase-negative staphylococci as the sole bacteria in the deep portion of the lesions and suggested that the abnormally structural tissue in HS due to sinus formation can provide a medium similar to the presence of a foreign body and the result will be enhancement of the pathogenic properties of coagulase-negative staphylococci. Generally, the pathogenic potential of coagulase-negative staphylococci is mainly due to their capacity to form biofilms on medical devices [42]. The sinus formation in HS may be an ideal place for biofilm formation and this microbiologic principle may be applicable to coagulase-negative staphylococci in HS. Many coagulase-negative staphylococci produce several lipases, proteases, and other exoenzymes, which possibly contribute to the persistence of coagulase-negative staphylococci in the host and may degrade host tissue [42]. Here, the bacteria find protection against antibiotics and from attacks by the immune system. The biofilm model was recently proposed to be involved in acne pathogenesis, where glycocalyx polymer secreted by *Propionibacterium acnes* as a biofilm may explain the immunogenicity of the organism as well as the unpredictable course of the disease [11]. There are also some lines of evidence that under certain conditions they may produce similar toxins to *Staphylococcus aureus* and could cause invasive diseases [36, 56].

Mowad et al. [37] showed that periodic-acid-Schiff- (PAS-) positive extracellular polysaccharide substance produced by *Staphylococcus epidermidis* obstructs the delivery of sweat to the skin surface and these strains are involved in the pathogenesis of miliaria. It was speculated that a similar mechanism could be involved in HS pathogenesis [33]. It is known that the pathogenic potential of coagulase-negative staphylococci varies according to species [33]. *Staphylococcus haemolyticus* and *Staphylococcus saprophyticus* have well-known pathogenic potential and *Staphylococcus lugdunesis*, *Staphylococcus schleiferi* or *Staphylococcus caprae* are considered emerging pathogens [56]. *Staphylococcus lugdunesis* was found in axillary lesions diagnosed as HS [54].

Streptococcus milleri, a microaerophilic microorganism frequently causing pyogenic infections [17] that often colonizes the gastrointestinal tract and female genital tract, was found by some investigators to be a major pathogen in perineal HS. Furthermore, the presence of this bacterium correlated with the disease activity and its elimination by appropriate antibiotic therapy was accompanied by marked clinical improvements [23, 24]. Microaerophilic streptococci were found by Brunsting in 1939 in a group of patients with HS [9]. *Streptococcus milleri*, *Staphylococcus aureus*, anaerobic streptococci, or *Bacteroides* species were frequently isolated in a group of 32 patients with active perineal HS [24]. Other authors could not find *Streptococcus milleri* in any of the specimens [41].

In perianal forms of HS, *Escherichia coli*, *Klebsiella* and *Proteus* strains as well as anaerobic bacteria were isolated [27]. Brenner and Lookingbill [7] have recovered *Bacteroides* species from perirectal, groin and axillae and the patients responded well to a suitable antibiotic treatment regimen. They suggest that the presence of anaerobic bacteria may reflect the chronicity of pre-existing local infection. Anaerobic bacteria were also isolated by Leach et al. from recurrent axillary lesions of HS [35].

Bilophila wadsworthia is a Gram-negative anaerobic rod found as part of the normal flora in feces and, occasionally, in saliva and in the vagina; in one case of HS it was isolated together with other anaerobic bacteria of the *Prevotella* species [4, 18].

Bendahan et al. [5] found an association between perineal HS lesions and *Chlamydia trachomatis* infection, but it was not clear whether the latter was a direct cause or a predisposing factor. These findings have not been confirmed by other authors.

11.3 General Factors About Bacterial Involvement in HS Pathogenicity

The series of events in HS pathogenesis are unclear and the exact role of bacteria in the etiology of the disease remains controversial. Shelley and Cahn [49] were able to reproduce HS lesions by applying atropine-impregnated adhesive tape to a manually depilated axillary region. They noticed subsequent dilatation, inflammation, and bacterial invasion of the apocrine duct and concluded that HS is a bacterial infection of an obstructed apocrine sweat gland with the causative bacteria deriving from the normal flora of the skin.

However, today it is largely accepted that apocrine gland involvement is not essential to the pathogenesis, and that the inflammatory processes and involvement of apocrine glands are secondary events [6, 28]. The disease starts with follicular hyperkeratosis and dilatation of the infundibula and most authors believe that the bacterial contribution is a secondary event in the disease process [27, 48]. The retention of keratin in follicles and chronic sinusoids is subject to subsequent bacterial infection. Follicular occlusion leads to dilatation followed by rupture and spillage of the keratin and bacteria into the dermis. This induces a strong chemotactic response with an inflammatory cellular infiltrate consisting of neutrophils, lymphocytes, and histiocytes [50]. In chronic lesions, bacteria can be found in and around the glands and lymphatics [34]. In later stages of HS, bacterial infection is a risk factor for extension of the lesions. Sinus tracts are formed in the dermis and subcutis from the ruptured follicular epithelium in an attempt by the tissue to confine the inflammation, and there is a high risk for secondary infections [34, 50].

Systemic infections such as bacterial meningitis, bronchitis or pneumonia are possible, due to the spread of microorganisms [27]. In the case of coagulase-negative staphylococci, the recently found inflammatory peptides called phenol-soluble modulins (microbial products that stimulate cytokine production in host cells) play a role in the pathogenesis and systemic manifestations of sepsis [42].

Polypeptides from *Propionibacterium acnes* were found to stimulate a specific immune response in acne patients [26]. Jemec et al. [29] tried to detect a specific serologic response to a possible staphylococcal or streptococcal infection but the results were inconclusive.

11.4 The Role of Antibiotics in the Treatment of HS

Despite the fact that the clinical response to antibiotics is poor and that bacteria are found in only 50% of lesions, the recommendation for systemic antibiotics is clear and this is derived from empirical attempts to control the disease. Also, it is reasonable to try antibiotic treatment, as various bacteria are suspected as having a role in the inflammatory process and in destructive scarring in HS patients. Approximately 10% of patients have some benefit from the use of systemic antibiotics [57].

If the drainage from lesions is available, bacterial cultures and antibiotic sensitivity should be performed and the antibiotic treatment should be tailored according to these results. Collaboration between the dermatologist and the bacteriologist is an important factor in finding the best treatment option. Acute episodes and relapses are treated as bacterial infections for a 2-week period [21]. Oral antibiotics such as minocycline, erythromycin in combination with metronidazole, ciprofloxacin, cephalosporins or semisynthetic penicillins may be used [7, 19, 21]. Bukley and Sarkany [10] reported a case of severe HS who improved after systemic clindamycin treatment.

Long-term administration of tetracyclines or erythromycin may be used in regimens similar to acne vulgaris and seems to prevent episodic flares [19, 21].

Topical clindamycin was found to be superior to placebo in a randomized double-blind clinical trial [12] and Jemec and Wendelboe did not find any difference between systemic tetracycline and topical clindamycin in another randomized clinical trial [30]. However, after withdrawal of antibiotic treatment, HS very often relapses [3, 13].

As is the case with acne vulgaris, it is not known whether the most important factor in the treatment of HS is antibacterial or anti-inflammatory. Lincosamides and tetracyclines have been known for their immunomodulatory effects. Clindamycin suppresses the complement-derived chemotaxis of polymorphonuclear leukocytes in vitro, thereby reducing the inflammation potential [43, 52]. Tetracyclines are known as good candidates for the treatment of inflammatory disorders. The anti-inflammatory properties are enumerated in Table 11.4 [43, 44].

Table 11.4. Anti-inflammatory and immunomodulatory properties of antibiotics used in the treatment of HS

Antibiotic	Mechanisms
Tetracyclines	– Inhibition of metalloproteases – Inhibition of free radicals – Modulation of IL-1α – Inhibition of lipases and proteases – Inhibition of nitric oxide synthetase and caspase 1 and 3 production – Modulation of cytokine expression – Reduction in the production of free radicals secreted by polymorphonuclear leukocytes – Reduction in the formation of inflammatory granuloma
Clindamycin	– Suppression of complement-derived chemotaxis of polymorphonuclear leukocytes

Hindle et al. treated seven patients with a combination therapy of clindamycin (300 mg twice daily) and rifampicin (300 mg twice daily) for a 10-week period [25]. Three patients did not tolerate the combination, two because of diarrhea associated with *Clostridium difficile,* and three of them responded well and remained clear at 12 months. The combination of rifampicin and clindamycin was also successfully used for two other chronic and difficult-to-treat conditions: folliculitis decalvans [45] and acne keloidalis nuchae [25]. Clindamycin is a lincosamide antibiotic active against Gram-positive cocci (except enterococci) and most anaerobic bacteria [52]. Rifampicin is a broad spectrum antibacterial agent that inhibits the growth of the majority of Gram-positive bacteria as well as many Gram-negative microorganisms [55]. It is highly active against both *Staphylococcus aureus* and coagulase-negative staphylococci. Rapid emergence of resistance when the drug was used alone has limited the use except in association with another anti-staphylococcal drug [2]. The

combination therapy was introduced to prevent resistance development against rifampicin and to cover a broad antibacterial spectrum.

11.5 Possible Consequences for Bacterial Ecology due to Antibiotic Treatment in HS

The drawback to the usefulness of long-term antibiotic treatments is concern about the effect on microbial ecology (Table 11.5). The normal microflora act as a barrier against colonization by potentially pathogenic bacteria and the control of growth of opportunistic bacteria is called colonization resistance. The normal equilibrium between host and microorganisms may be disturbed by a number of factors, but commonly and essentially by antibiotic therapy. To what extent disturbances occur depends of numerous factors: the spectrum of the antibiotic, the dose, the route of administration, pharmacokinetic and pharmacodynamic properties and in vivo inactivation of the drug [53].

Clindamycin administration results in major ecological disturbances in intestinal and oropharyngeal microflora: the numbers of enterococcal species increase and those of all anaerobes decrease [39, 51]. A possible complication of clindamycin treatment is pseudomembranous colitis, which occurs when antibiotics such as clindamycin, ampicillin and third-generation cephalosporins suppress the normal flora, allowing *Clostridium difficile* to grow and produce toxins [40]. Rifampicin treatment was shown to lead to a decrease in total aerobic and anaerobic oral bacteria in healthy volunteers [1].

The emergence of antimicrobial resistance is strongly associated with the clinical use of the antibiotics and a balanced microflora prevents establishment of resistant strains of bacteria [53]. It is well known that oral antibiotics select for resistant bacteria at all body sites where there is a normal flora: skin, conjunctivae, oral cavity, nasopharynx, upper respiratory tract, intestinal tract, and vagina [16]. A therapy administered for a long period, as was recommended in HS treatment [25], will exert a high pressure for the development of the resistant strains of *Propionibacterium acnes*, coagulase-negative staphylococci on the skin, *Staphylococcus aureus* in the nares, streptococci in the oral cavity, and enterobacteria in the gut [16].

Table 11.5. Effects of antibiotic administration on the ecological balance of human microflora

- Disturbances in the balance between host and normal flora from the intestinal tract, skin, oropharyngeal tract, and vagina
- Altered colonization resistance (growth control of opportunistic bacteria)
- Overgrowth of pathogenic bacteria or yeasts
- The emergence of antimicrobial resistance in the normal flora
- Possible transfer of resistance to pathogenic bacteria

Topical clindamycin will increase carriage of *Propionibacterium acnes* and *Staphylococcus epidermidis* resistant strains on skin and there is a risk of transfer of resistance to other pathogenic bacteria, *Staphylococcus aureus* and *Streptococcus* species [15]. The skin and conjunctivae flora from untreated sites will also be affected by transfer of antibiotic [16].

In conclusion, antibacterial drugs represent an adjuvant treatment in HS. They are not curative but they reduce odor and discharge, and diminish pain. Antibiotics represent a palliative therapy that may control the disease in early stages and can reduce the inflammation before and after surgery [28] but clinicians should be aware about the downside of taking them.

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