Microbial Profile and Antimicrobial Susceptibility of Bacteria Found in Inflammatory Hidradenitis Suppurativa Lesions

Schapoor Hessam^a Michael Sand^a Dimitrios Georgas^c Agnes Anders^b
Falk G. Bechara^a

^aDepartment of Dermatology, Venereology and Allergology, and ^bDepartment of Medical Microbiology, National Reference Centre for Multidrug-Resistant Gram-Negative Bacteria, Ruhr University Bochum, Bochum, and

^cDepartment of Dermatology, Venereology and Allergology, HELIOS St. Johannes-Hospital, Duisburg, Germany

Key Words

Hidradenitis suppurativa · Bacteriology · Inflammation · Antibiotic therapy

Abstract

Background: The role of bacterial colonization in hidradenitis suppurativa (HS) lesions is poorly understood. To date, data on the related microbial profile and especially on bacterial resistance rates are scarce. **Methods:** The results of bacterial cultures and susceptibility patterns of the isolated microorganisms obtained from deep portions of HS lesions from patients who underwent surgery at our HS Centre between 2010 and 2015 were retrospectively evaluated. **Results:** Analyses of 113 bacterial samples from 113 HS patients revealed bacterial growth in 95 samples (84.1%). Polymicrobial growth was found in 51 samples (45.1%). Coagulase-negative staphylococci and *Staphylococcus aureus* were the most commonly isolated bacteria, followed by *Proteus mirabilis* and *Escherichia coli*. Data on susceptibility testing were available for 68 samples, which yielded 129 isolates. The isolated strains were primarily resistant to penicillin G, followed by erythromycin, clindamycin and ampicillin. The highest effectiveness against isolates was observed for

fosfomycin, imipenem, fluoroquinolones (moxifloxacin, ciprofloxacin, levofloxacin), and cotrimoxazole. **Conclusions:** Our findings on bacterial species and their topographical distribution revealed that the microbial flora in HS lesions reflects commensal flora of the skin. Due to the susceptibility rate and immunomodulatory and anti-inflammatory properties, cotrimoxazole may represent an alternative antibiotic agent and should be considered for therapy in HS patients.

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Introduction

Hidradenitis suppurativa (HS) is a chronic relapsing inflammatory skin disease of unknown aetiology that results in painful nodules, abscesses, and sinus tract formation, primarily in apocrine gland-bearing areas [1, 2]. Hyperkeratosis and hyperplasia of the follicular epithelium result in the occlusion and dilatation of hair follicles and apocrine glands [3]. Recently, a weakness of the hair follicle-apocrine junction unit has been shown to promote the rupture of the hair follicle epithelium with subsequent spilling of keratin, sebum products, hair, and bacteria

Table 1. Patient characteristics and characteristics of microbiological samples obtained from deep portions of inflammatory lesions of patients with HS

Patients included	113
Gender	
Male	57 (50.4)
Female	56 (49.5)
Age, years	42 (27.8–50)
Smoking	88 (77.9)
Hurley stage	
II	66 (58.4)
III	47 (41.6)
Pre-treatment	
Topical antibiotics	33 (29.2)
Systemic antibiotics	90 (79.6)
Microbiological samples	
Microbiological samples	113
Positive bacteriology	95 (84.1)
Isolates per sample	2 (1–2)
Range	1–5
Polymicrobial (isolates n >1)	51 (45.1)
Obtained from	
Axilla	54 (47.7)
Groin	44 (38.9)
Gluteus/perineum	15 (13.2)

Values are n (%) or median (IQR), as appropriate.

into the surrounding dermis. This initiates inflammation and immune response [4–7].

The available data on bacterial cultures from HS lesions revealed a polymicrobial growth pattern with a diversity of bacterial species, of which coagulase-negative staphylococci (CoNS), *Staphylococcus aureus*, and mixed anaerobic bacteria were the dominant types [8–10]. The role of bacterial colonization in the pathogenesis of HS remains under debate; however, antibiotic treatment is used on a regular basis in clinics and has been shown to be effective in some HS patients [11–14]. There is growing evidence that bacteria have an immunological role by presenting targets for the immune system and that they contribute to initiating and maintaining the inflammatory response in HS [15, 16]. Thus, a reduction of bacteria in HS lesions should lead to a decreased grade of inflammation and clinical improvement in HS patients (and thereby provide a potential explanation for the observed effectiveness of antibiotic treatment). Knowledge about resistance patterns is advantageous when deciding on an effective antibiotic agent. However, to date, data on microbial flora and especially on the resistance rates of bacteria found in HS lesions are scarce [8, 17, 18].

Given this background, we aimed to evaluate the microbial profile in a large number of bacterial cultures obtained from deep portions of inflammatory HS lesions and to analyse the susceptibility pattern of the isolated bacteria.

Materials and Methods

We retrospectively evaluated the results of bacterial cultures and susceptibility patterns of the isolated bacteria obtained from patients with HS who underwent surgery under general anaesthesia at our HS Centre of the Department of Dermatology, Venereology and Allergology, Ruhr University Bochum between 2010 and 2015. The diagnosis of HS required the presence of well-established criteria [19]. Patients were included if bacterial cultures were obtained from deep portions of HS lesions and if the patient's characteristics (gender, age, smoking status, and Hurley stage) and data on former conservative therapy were available and complete. Bacterial cultures taken from the surface of the skin were excluded from the study. Further exclusion criteria were the administration of systemic or topical antibiotic therapy or immunosuppressive medications for 4 weeks prior to sampling.

The routine preoperative procedure included disinfecting the skin using a 5% povidone-iodine solution. During surgical excision, samples were collected from deep portions of inflammatory, purulent HS lesions (abscesses or draining fistulas) using sterile swabs, which were inserted into the lesions. Then, under strict asepsis, the swabs were immediately placed in sterile tubes containing gel medium (Amies; Vacutest Kima S.R.L., Meus S.R.L., Italy). The samples were cultured under aerobic and anaerobic conditions, and cultures were finally read after 48 and 96 h. Susceptibility testing was done for different antibiotics, depending on the bacterial species, by disk diffusion and semiautomatic testing by VITEK 2 (bioMérieux), with breakpoints according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Continuous data are presented as medians (with interquartile ranges, IQR) and were compared using the non-parametric Wilcoxon test for dependent samples. Categorical data are presented as numbers (with percentages) and were compared using the χ^2 or Fisher's exact test. The data were analysed using MedCalc software version 15.2 (MedCalc, Mariakerke, Belgium) with $p < 0.05$ considered significant.

Results

In this study, a total of 113 samples were collected from 113 HS patients: 57 males (50.4%) and 56 females (49.5%), with a median age of 42 years (IQR: 27.8–50). The majority of patients were current smokers ($n = 88$, 77.9%). Among the 113 patients, 66 (58.4%) had Hurley stage II, and 47 (41.6%) had Hurley stage III (table 1). The majority of the patients, 90/113 (79.6%), had been treated before with systemic antibiotics, and 33/113 (29.2%) with topical antibiotics. However, all treatments were stopped

Table 2. Association of patient characteristics (gender, smoking status, disease severity, pre-treatment) and localization of microbiological samples with positive bacteriology and polymicrobial growth (defined as the number of isolates $n > 1$ per sample)

		Positive bacteriology		Polymicrobial growth			
		no	yes	p value	no	yes	p value
Gender							
Male		9	48	0.828	23	25	0.912
Female		9	47		21	26	
Smoking							
No		2	23	0.358	13	10	0.375
Yes		16	72		31	41	
Hurley stage							
II		14	52	0.119	27	25	0.318
III		4	43		17	26	
<i>Pre-treatment</i>							
Topical antibiotics							
No		14	66	0.668	10	10	0.905
Yes		4	29		34	41	
Systemic antibiotics							
No		3	20	0.916	32	34	0.677
Yes		15	75		12	17	
<i>Localization of samples</i>							
Axilla							
No		5	54	0.044	17	37	0.0018
Yes		13	41		27	14	
Groin							
No		14	55	0.186	28	27	0.398
Yes		4	40		16	24	
Gluteus/perineum							
No		17	81	0.458	43	38	0.0012
Yes		1	14		1	13	

Table 3. Frequency of bacteria species isolated from deep portions of inflammatory HS lesions ($n = 171$)

Bacterial isolates	Total, n (%)
CoNS	34 (19.9)
<i>Staphylococcus epidermidis</i>	9 (5.3)
<i>Staphylococcus lugdunensis</i>	7 (4.1)
<i>Staphylococcus haemolyticus</i>	3 (1.8)
Other CoNS	15 (8.8)
<i>S. aureus</i>	22 (12.9)
<i>P. mirabilis</i>	19 (11.1)
<i>E. coli</i>	17 (9.9)
<i>Corynebacterium</i> spp.	11 (6.4)
<i>Enterococcus</i> spp.	11 (6.4)
Viridans streptococci	10 (5.8)
<i>Streptococcus anginosus</i>	5 (2.9)
<i>Streptococcus constellatus</i>	2 (1.2)
Other viridans streptococci	3 (1.8)
<i>Streptococcus agalactiae</i>	7 (4.1)
<i>Streptococcus dysgalactiae</i> subsp. <i>equisimilis</i>	5 (2.9)
<i>Klebsiella pneumoniae</i>	5 (2.9)
<i>Prevotella</i> spp.	4 (2.3)
<i>Enterobacter cloacae</i>	4 (2.3)
<i>Porphyromonas</i> spp.	3 (1.8)
<i>Fusobacterium</i> spp.	3 (1.8)
<i>Bacteroides fragilis</i>	3 (1.8)
<i>Fingoldia magna</i>	3 (1.8)
<i>Pseudomonas oryzae</i> spp.	3 (1.8)
<i>Citrobacter</i> spp.	2 (1.2)
<i>Peptostreptococcus</i> spp.	2 (1.2)
<i>Acinetobacter</i> genomospecies 3	1 (0.6)
<i>Lactobacillus</i> spp.	1 (0.6)
<i>Morganella morganii</i>	1 (0.6)

at least 4 weeks before inclusion in the present study. We analysed the microbiological test results of all 113 samples. Localizations from which the microbiological samples were obtained are described in table 1.

Of the 113 lesional samples collected from deep portions of inflammatory HS lesions during the surgical procedure, bacterial growth was found in 95 samples (84.1%). The 113 lesional samples yielded 171 isolates and two *Candida* species, which were excluded from analysis. Of the 113 lesional samples, 51 (45.1%) showed polymicrobial growth (defined as the number of isolates $n > 1$ per sample). The median number of isolates per sample collection was 2 (IQR: 1–2) and ranged between 1 and 5 (table 1).

Next, we analysed the association between bacterial growth and patient characteristics. There was no significant association between gender, smoking, disease sever-

ity, and former systemic or local antibiotic treatment (table 2).

The samples were obtained from the axilla, groin, or gluteal/perineal regions, and we analysed the distribution of positive cultures among these localizations. Our bacteriological findings showed that negative cultures and monobacterial growth were significantly more frequent in samples obtained from the axillae ($p = 0.044$ and $p = 0.0018$, respectively). However, polymicrobial growth was significantly more frequent in samples from the gluteal/perineal area ($p = 0.0012$; table 2).

Of the 171 isolates, 106 (62%) were Gram positive and 65 (38%) were Gram negative. The most common isolated bacteria were CoNS (34, 19.9%) and *S. aureus* (22, 12.9%), followed by *Proteus mirabilis* (19, 11.1%) and *Escherichia coli* (17, 9.9%). The frequency of other isolates is shown in table 3.

Fig. 1. Frequency of the 4 common isolated bacterial species in accordance with the localization of the microbiological samples.

Table 4. Antimicrobial resistance pattern of the 129 isolates

Antimicrobial agents tested	Overall resistance rate among all isolates, n (%)
Penicillin G	90 (69.8)
Erythromycin	71 (55)
Clindamycin	71 (55)
Ampicillin	59 (45.7)
Mezlocillin	50 (38.8)
Aztreonam	48 (37.2)
Piperacillin	47 (36.4)
Tetracyclin	42 (32.6)
Gentamicin	34 (26.4)
Tigecyclin	23 (17.8)
Cefuroxime	23 (17.8)
Ampicillin/sulbactam	22 (17.1)
Cotrimoxazole	17 (13.2)
Levofloxacin	16 (12.4)
Ciprofloxacin	12 (9.3)
Moxifloxacin	8 (6.2)
Imipenem	4 (3.1)
Fosfomycin	1 (0.8)

Cotrimoxazole = Trimethoprim-sulphamethoxazole.

Next, we analysed the frequency of the 4 common bacterial isolates in accordance with the localization of the bacterial samples (fig. 1). CoNS were significantly more frequent in cultures obtained from the axillae ($p = 0.0024$), whereas *E. coli* was not found in this localization. The latter isolate, however, was significantly more frequent in the groin ($p = 0.0178$).

Data on susceptibility testing were available for 68 samples, which yielded 129 isolates. Most of the isolates were resistant to penicillin G (90/129, 69.8%), followed by erythromycin (71/129, 55%), clindamycin (71/129, 55%) and ampicillin (59/129, 45.7%). Resistance to tetracycline was found in 42 of the 129 isolates (32.6%).

The lowest resistant rates (<20 resistant isolates) were observed for fosfomycin (1/129, 0.8%), imipenem (4/129, 3.1%), moxifloxacin (8/129, 6.2%), ciprofloxacin (12/129, 9.3%), levofloxacin (16/129, 12.4%), and cotrimoxazole (17/129, 13.2%). Results of the antibiotic resistance patterns of the isolates are shown in detail in table 4.

Discussion

Antibiotic treatment is frequently used and recommended in the treatment of HS [20, 21]. Most relevant data address rifampicin-clindamycin combination therapy, which showed satisfactory results in some HS patients [12, 22, 23]. Thus, there is a rationale for considering this combination therapy as a first-line treatment for patients with Hurley stage 1 and mild stage 2. If clindamycin is not tolerated (e.g. due to diarrhoea, especially in patients with inflammatory bowel disease, which is reported to be a common comorbidity of HS), substitution with minocycline is possible [24]. However, the increased side effect profile of minocycline and the number of drug interactions should be considered [25]. In addition to the reduction of bacterial growth, some antibiotic agents (e.g. tetracycline, clindamycin, and minocycline) also have immunomodulatory and anti-inflammatory properties [26–28].

To establish an effective therapeutic concept, the appropriate selection of HS patients who are eligible for systemic antibiotic therapy is mandatory. From our experience, appropriate candidates include those with inflammatory nodules that are primarily solitary with a widespread distribution. For severe cases and patients presenting with fistula formations, antibiotics will not significantly influence the outcome, and surgical excision remains the therapy of choice. Interestingly, based on recent findings, HS was assumed to be a biofilm disease [29]. In biofilms, the bacterial milieu is known to significantly impair antibiotic therapy and promote bacterial resistance. This may explain why fistula formations are less prone to antibiotic treatment.

The clinical appearance with abscesses and draining fistulas may suggest an infectious pathogenesis; however, HS is believed to be an auto-inflammatory disease, and increasing evidence shows an altered innate and adaptive immune system [19, 30]. In this context, the effectiveness of antibiotic agents in some HS patients supports the role of bacteria in the disease pathogenesis.

Our results showed that bacterial growth was present in 84.1% and polymicrobial growth in 45.1% of the samples, which were collected from deep portions of inflammatory HS lesions. CoNS and *S. aureus* were the most commonly isolated bacteria, followed by *P. mirabilis* and *E. coli*. The topographical distribution of these 4 common bacterial isolates showed that CoNS were significantly more frequent in cultures obtained from the axillae, whereas *E. coli* was significantly more frequent in the groin. Polymicrobial growth was significantly more com-

mon in samples obtained from the gluteal/perineal area. Our results are in accordance with those from previous studies, which also showed polymicrobial colonization with an array of bacterial species, of which CoNS, *S. aureus*, and mixed anaerobic bacteria were the dominant types [8].

In 15.9% of the samples, the cultures were found to be negative. However, other studies found even higher rates of negative cultures [18, 31]. In HS, fistulas may contain solely granulomatous inflammatory infiltrates with predominantly histiocytes and multinucleated giant cells, without significant bacterial growth [32, 33]. Besides, due to the used culture conditions, distinct bacterial species may not grow.

In general, our findings on bacterial species and their topographical distribution revealed that the microbial flora in HS lesions reflect commensal flora of the skin [8]. Thus, our results support the hypothesis that the invasion of commensal skin bacteria in HS lesions is more likely a secondary event resulting from the occlusion of follicular ducts due to infundibular hyperkeratinization and rupture of the hair follicle, followed by spilling of bacteria into the dermis [5, 34]. Bacteria are an important component in the vicious circle of inflammation in susceptible HS patients by presenting targets for the immune system. Lipopolysaccharide from bacteria, which belong to pathogen-associated molecular patterns, present targets for toll-like receptors. After recognition, keratinocytes and macrophages are activated and release various pro- and anti-inflammatory cytokines and chemokines. Thus, if bacterial species persist, an increasing amount of immune cells are recruited by chemotaxis. These cells may aggravate the chronic cutaneous inflammation observed in HS [2, 16].

There is evidence that bacteria play a role in initiating and maintaining the inflammatory reaction in HS; thus, the reduction of bacterial colonization can lead to a decreased inflammation in HS patients and is a possible explanation for the effectiveness of antibiotic therapy. In clinical practice, however, the prescription of various antibiotic agents, frequently as monotherapies and with variable durations of intake, is common in the majority of HS patients [17]. Thus, it is not surprising that more than 80% of the patients in our study had former systemic antibiotic therapy. This raises a question about the resistance and susceptibility patterns of bacterial pathogens found in HS lesions, which, to date, have only been addressed by two studies with small numbers of bacteriological samples [17, 18]. However, knowledge about resistance patterns is advantageous for effective antibiotic therapy.

Our analyses of bacterial susceptibility patterns revealed that the β -lactam antibiotics penicillin G and ampicillin, together with erythromycin and clindamycin, were among the least effective antibiotic agents for HS. The latter, notably, is, in combination with rifampicin, one of the most widely recommended first-line therapies for HS. Tetracycline is described as an alternative antibiotic agent in HS therapy [26]. However, our data showed a resistance rate of almost 33%. Thus, according to our findings the primary anti-infectious role of clindamycin and tetracycline is controversial. However, despite their resistance rates they improve the HS condition, further underlining their immunomodulatory role.

Among the antibiotic agents with low resistance rates (<20 isolates), we consider cotrimoxazole, a combination of sulfamethoxazole and trimethoprim, as the most promising antibiotic agent for HS patients. First, cotrimoxazole can be administered orally. Second, besides a broad-spectrum activity our findings revealed that cotrimoxazole had a low resistance rate of 13%. Third, increasing evidence from antibiotic prophylaxis with cotrimoxazole in HIV-infected adults and children showed that long-term therapy is safe and inexpensive [35–37]. Fourth, there is also strong evidence showing that, in addition to its antimicrobial properties, cotrimoxazole also has immunomodulatory and anti-inflammatory effects. In vitro studies suggest that cotrimoxazole can reduce inflammation by inhibiting lymphocyte proliferation and T-cell activity and by increasing neutrophil activity. Clinical studies showed improvements and reduced inflammation in autoimmune diseases, namely rheumatoid arthritis, Wegener's granulomatosis, and inflammatory bowel disease [28, 38]. Among ciprofloxacin, ceftazidime, and piperacillin-tazobactam, only cotrimoxazole suppressed tumour necrosis factor- α secretion [27].

Thus, cotrimoxazole can be proposed as an alternative antibiotic agent and should be considered in the therapy of HS patients. Our findings revealed that cotrimoxazole may be a reasonable alternative if rifampicin-clindamycin combination therapy fails to show improvement. However, future prospective trials are needed to investigate the potential of cotrimoxazole in HS treatment.

The large number of bacteriological samples and the manner in which they were systematically obtained are the major strengths of our study. The samples were obtained intraoperatively from deep portions of inflammatory HS lesions under strict asepsis after skin disinfection, thereby avoiding the contamination of samples with bacteria from the skin surface. While these advantages are important, the study also has limitations. Our findings on bacterial species should be interpreted with regard to the used culture conditions. It is a retrospective analysis, and generalization and comparison of our bacterial susceptibility pattern findings should be approached with caution due to regional variability in microbial resistance rates.

Statement of Ethics

The study was performed according to the Declaration of Helsinki and was approved by the local ethics committee (Ethics Review Board of the Ruhr University Bochum, Germany; registration No. 15-5302).

Disclosure Statement

The authors declare that they have no conflicts of interest. There were no funding sources for this work.

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