DR. MARCO MANFREDINI (Orcid ID : 0000-0003-3601-655X)

Article type : Original Article

Rates of Antibiotic Resistance / Sensitivity in Bacterial Cultures of Hidradenitis Suppurativa Patients

V. Bettoli,[1] M. Manfredini,[1,2] L. Massoli,[3] C. Carillo,[4] A. Barozzi,[4] G. Amendolagine,[1] G. Ruina,[1] D. Musmeci,[1] M. Libanore,[3] A. Curtolo,[3] L. Mantovani,[1] C. Contini,[3] G. Pellacani,[2] M. Corazza[1]

[1] Department of Medical Sciences, Section of Dermatology, University of Ferrara, Italy

[2] Department of Surgical, Medical, Dental & Morphological Sciences with Interest Transplant, Oncological & Regenerative Medicine, Dermatology Unit, University of Modena & Reggio Emilia, Modena, Italy

[3] O.U. of Infectious and Tropical Diseases and of the Migrants, University of Ferrara, Italy

[4] O.U. Microbiology, Azienda Ospedaliero-Universitaria di Ferrara, Italy

Corresponding author

Vincenzo Bettoli, M.D.

Department of Clinical and Experimental Medicine, Section of Dermatology, University of Ferrara

44100 Ferrara (Italy)

e-mail: vincenzo.bettoli@gmail.com

tel: +39 0532 237295-6

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jdv.15332

Running title: Hidradenitis Suppurativa and Antibiotic Resistance

Funding: None.

Conflict of interest: None declared.

Keywords: Hidradenitis suppurativa, Antibiotic resistance, Microbiome, Antibiotic therapy, Therapeutic guidelines

Abstract

Background: Antibiotic (AB) treatment is one of the first steps in the management of Hidradenitis Suppurativa (HS). Bacteria, in HS patients, may play a double role, as triggering factors of inflammatory reactions and/or agents of infection.

Objectives: The aims of this study are: 1) to assess prevalence and AB resistance of bacterial growths in HS patients 2) assessment of the clinical relevance of obtained data in guiding the selection of the most effective AB therapy.

Methods: Purulent material from 137 skin lesions of HS patients was collected with swabs. Bacterial flora and AB sensitivity were determined using microbiological cultures for aerobic and anaerobic bacteria.

Results: A total of 114 samples resulted positive for bacteria. Sample were collected from the axillae, groin and perianal areas. A total of 163 single bacterial growths were observed; 55% were gram-positive and 44% were gram-negative. Among them, 18.4% were anaerobic. The most frequent bacterial families included enterobacteriacee (30.7%), staphylococcus (25.2%), and streptococcus (14.1%). The most frequent genus or species were proteus spp. (13.5%) and e.coli (9.8%). The prevalence of AB resistance observed was clindamycin 65.7%, rifampicin 69.3%, penicillin 70.0%, ciprofloxacin 74%, tetracycline 84.7% and erythromycin 89.0%. A

limitation of the study is represented the short culture period adopted which may have impaired the isolation of anaerobes.

Conclusions: Bacterial growth in HS patients has shown a high level of resistance to ABs, including rifampicin, clindamycin and tetracyclines, cited as an empiric choice in HS therapeutic guidelines. A targeted and specific AB therapy, driven by microbiological evaluations with prolonged culture periods, seems more appropriate than empiric, generic, non-specific, therapeutic approaches. Current knowledge regarding HS bacterial AB resistance should be considered in the update of current therapeutic guidelines for HS.

Introduction

Hidradenitis Suppurativa (HS) is a recurrent inflammatory disease localized in intertriginous regions and characterized by a progression from nodules to inflamed, painful, deep-seated abscesses and draining sinus tracts with subsequent scarring and persistent suppuration.[1,2] HS is not primarily caused by bacterial infection but bacterial specimens can often be isolated from HS lesion exudate.[3] Studies exploring the bacteriology of HS lesions, have found the involvement of many different bacterial species, with a frequent culture isolation or genomic identification of a polymicrobial microflora dominated by coagulase-negative staphylococcal species and mixed anaerobic bacteria, with Staphylococcus aureus and streptococcal species also isolated from a substantial proportion of lesions.[3–5] Previous metagenomic studies demonstrated that HS lesional and perilesional skin are characterized by a peculiar microbiome composition different from other chronic skin lesions, such as diabetic ulcers.[4,6–8] The bacterial isolation of mixed polymicrobial anaerobic strains in HS lesions were recently associated with more than 90% of chronic suppurative lesions and 50% of nodules. [6,9] Oral and topical antibiotics (ABs) are frequently used as a first-line HS therapy, primarily because of their anti-inflammatory and antimicrobial effects. [10-12]

The role of bacterial colonization in the pathogenesis of HS remains debateable However, regular AB clinical treatment has been shown to be effective in HS patients.[10,13–15] Dysbiotic bacteria, both pathogens and commensals, may upregulate virulence and antimicrobial resistance genes and activate a cascade of proinflammatory mechanisms in a sort of complex and multifactorial network, which has been investigated as one of the causes of HS.[16–19]

To date, some data on microbial flora in HS patients are available, but data regarding bacteria resistance rates to AB treatments are scarce.[5,20–23] Fischer et al. in a retrospective cross-sectional study of 239 HS patients found a higher proportion of patients with antibiotic resistant bacterial strains of S.aureus (following topical clindamycin and ciprofloxacin therapy) and Proteus strains (following Trimethoprim-Sulphametoxazole [TMP-SMX] therapy) when compared to patients without any previous antibiotic therapy administration.[5] Surprisingly, there were no significant antimicrobial resistant patterns observed in association with oral clindamycin and tetracyclines therapy administration. Hessam et al. retrospectively investigated bacterial cultures and susceptibility patterns of samples obtained from deep portions of HS lesions during surgery. Coagulase negative staphylococci (CoNS), S.aureus, Proteus mirabilis and E.coli were the most frequent bacterial species isolated. Clindamycin was found resistant in 55%, tetracycline in 32.6% and quinolones in around 10% of cases.[22] However, these results should be interpreted with caution, as the study adopted a short culture incubation time, potentially impairing the isolation of a large portion of anaerobic flora.[5,6,9,22]

The emergence of resistant bacterial strains can reduce AB effectiveness in HS, increase susceptibility to severe infectious diseases, and promote comorbidities linked to altered microbial flora, such as yeast infections, and AB-associated diarrhea.[23,24] AB resistance patterns differ according to geographical areas, as they are influenced by general practitioners' and specialists' AB prescribing preferences, and epidemiologic and population characteristics. To our knowledge, this is the first study designed to determine the prevalence of AB resistances on a wide number of HS bacterial isolates in Italy and in a non-surgical setting. The aims of our analysis were: 1) to determine the antimicrobial susceptibility and resistance in bacteria cultured from HS population referred to a single centre, and 2) to assess the clinical relevance of the data obtained to guide correct antibiotic therapy selection.

Methods

Bacterial antibiotic resistance profiles and microbiological reports from January 2016 to July 2017 at the HS Clinic of the O.U. of Dermatology of the University of Ferrara, were retrospectively reviewed. Reports were included in the current study if bacterial cultures were obtained from purulent material of HS lesions and if data on former therapy were available and complete. Bacterial cultures from patients that were treated with systemic or topical AB or immunosuppressive medications for 8 weeks prior to sampling were excluded. HS diagnosis

required the presence of well-established criteria and was always performed by a board of certified dermatologists, expert in HS management.[2,25]

Samples were collected from the purulent material from HS inflamed lesions: content was drained with gentle pressure exercised on the skin surface, using sterile gloves and swabs. The skin was sterilized prior to the procedure, with much care taken to avoid contamination with superficial bacteria. A suitable transport media for aerobes and anaerobes was used (ESwab Liquid Amies Collection and Preservation System, Catalog No. 490CE.A, Copan Diagnostic, Murrieta, USA). Specimens were stored and delivered to the laboratory according to manufacturer indications.

Swabs from clinical samples were cultured onto appropriate agar plates in order to isolate non fastidious and fastidious microorganisms as follows:

- Columbia blood agar (sheep blood at 5%), Columbia CNA agar, Mannitol salt agar, MacConkey agar and Sabouraud agar plates incubated under aerobic conditions;

- Chocolate agar plates incubated in 5% Co_2 atmosphere;

- Schaedler agar plates incubated under anaerobic conditions;

Culture plates were read after 24 , 48 and 72 hours of incubations at 35+/-1°C.

Susceptibility testing was performed for different ABs, depending on the bacterial species, by semiautomatic testing by VITEK 2 (bioMérieux) and gradient diffusion (E-Test), with breakpoints according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Overall antibiotic resistance was considered as either acquired resistance (cultured bacteria classified as resistant or intermediately susceptible as reported by the antibiogram profile results), or intrinsic resistance (cultured bacteria that are not affected by selected AB). Intermediate susceptible bacteria cultures were included in the resistant group because of the likelihood of developing resistance during prolonged AB therapy. Descriptive statistics and relative frequencies were calculated. Epidemiologic data and their graphical representations were calculated using Prism 6.0 (GraphPad Software Inc. La Jolla, CA, USA).

Results

A total of 163 bacterial culture growths were obtained from 114 out of 137 swab samples included in the study (83.2%). Median age of the patients was 37 years old; most of them were female (61.3%) and many were active smokers (63.5%). Disease severity was more frequently Hurley stage II (54.0%), followed by Hurley stage III (39.4%) and Hurley stage I (6.6%). The majority of patients (84.7%), had been treated previously with systemic ABs, and all of them (100%) with topical Abs (discontinued at least 8 weeks before study inclusion). Previously assumed systemic AB therapy for HS included tetracyclines (75.2%), penicillin or penicillin derivatives (75.6%), quinolones (19.0%) and macrolides (24.8%) for median periods of 120, 10, 7, and 6 days, respectively. Many patients (41.6%) were previously treated with rifampicin-clindamycin combination (median: 70 days).

Of the 163 positive bacterial cultures, 90 isolated (55.2%) were Gram-positive and 73 (44.8%) were Gram-negative. Among them, anaerobic bacteria was observed in 30 cases (18.4%). Bacterial isolates were mostly obtained from the inguinal (36.8%), gluteal (28.1%), axillary (21.9%) and perineal (13.2%) areas (Table 1).

The bacterial families identified included Enterobacteriaceae (30.7%), Staphylococcus (25.2%) and Streptococcus (14.1%). The most frequent genus or species incorporated Proteus spp. (13.5%), E. Coli (9.8%), S. Epidermidis (9.2%), S. Agalactiae (8.6%), as outlined in Table 2. Antibiogram profiles of bacterial cultures showed overall AB resistance for Clindamycin in 107 cases (65.7%), for Rifampicin in 113 cases (69.3%), for Penicillin in 114 cases (70.0%), for Ciprofloxacin in 120 cases (74%), for Tetracyclin in 138 cases (84.7%) and for Erythromycin in 145 cases (89.0%). The highest AB susceptibility was observed for Vancomycin in 91 bacterial cultures (55.8%). Linezolid was active on 67 susceptible bacteria cultures (41.1%), and it was inactive or not tested on 96 cultures (58.9%). Teicoplanin was active on 52 susceptible bacteria

cultures (31.9%), but it was inactive or not tested on 111 cultures (68.1%). Sensitivity test profiles are summarized in Table 3 and represented in Figure 1.

Discussion

AB treatment is frequently recommended as one of the first-line treatments for HS, [10,24,26] the main goal being to relieve symptoms in severely affected patients and to prevent relapses, avoiding the occurrence of resistances. AB use in HS is especially useful as a preparation prior to further therapies, such as surgery, since excision is easier when the infectious and inflammatory components of the disease have cooled.[10,11] Currently, a combination therapy, based on rifampicin-clindamycin administration, is one of the most widely administered therapies, with satisfactory results in many HS patients.[10,24]

It was previously demonstrated that the microbiome of HS lesional and perilesional skin is different from healthy controls, and that the bacterial populations involved change according to the clinical severity of the disease. [6,9] Bacteria dysbiosis, which characterize HS lesions, is an important component in the vicious circle of inflammation in several dermatological diseases, probably through the presentation of inflammatory signals and molecular targets for the immune system.[3,20,27] The understanding of the microbial ecosystem of HS lesions is a growing field of research, thanks to the recent development of metagenomics, which in the near future will probably substitute culture-dependent techniques for the identification of pathogenic bacterial colonization of HS lesions and of many other skin diseases. At present, most dedicated studies have mainly focused on direct bacterial identification, whilst there is limited research on antibiotic susceptibility profiles of the infectious agents identified.[4,6-9] Even though conventional culture-dependent procedures present several limitations compared to the metagenomic approaches, they are routinely available in almost every hospital setting and represent the current standard of care in determining antibiotic susceptibility profiles of cultured infectious agents from several biological samples, including HS purulent material.

ABs administration exerts its therapeutic effect through anti-infective activity, killing or inhibiting bacterial proliferation by disrupting key pathways of bacteria metabolism or replication, and through anti-inflammatory mechanisms, by inhibiting lymphocyte proliferation, T-cell activity, neutrophil activity and suppressing tumor necrosis factor-α secretion.[12,28] Whenever ABs are administrated primarily for antimicrobial motives, optimal clinical

management should be the use of precisely targeted ABs for the isolated bacterial strains. On the other hand, if the therapeutic goal is primarily anti-inflammatory, the prescriber should be conscious that any administration of ABs exposes all the commensal flora of the patient to AB, potentially inducing antibiotic resistance.

Our results show that bacterial growth was present in 83.2% of the samples collected from purulent material of HS lesions. The most frequent genus or species isolated were Proteus spp. (13.5%), E. Coli (9.8%), S. Epidermidis (9.2%) and S. Agalactiae (8.6%), supporting the hypothesis that the invasion of commensal skin bacteria in HS lesions is more likely a secondary event.

The analyses of bacterial susceptibility patterns revealed that among the ABs tested in this study, amoxicillin, oxacillin, erythromycin, and doxycycline were mostly frequently associated with bacterial resistance. Clindamycin and rifampicin appeared to be resistant in 107 (65.6%) and 113 (69.3%) bacteria cultures out of the 163 strains isolated in this study. In our population, tetracycline molecules, which are described as a valid alternative antibiotic agent in HS therapy, showed a high resistance profile among bacterial isolates, resistant in 138 (84.5%) cases. Thus, these data support the hypothesis that the beneficial effect of tetracycline and of the association therapy rifampicin-clindamycin, can be frequently due to their immunomodulatory effect[8] or to an anti-infectious effect directed towards anaerobes bacteria that are predominant in HS lesions, but were not isolated in this study because of a limited duration of culture incubation. Among the AB agents with the lowest observed resistance rates were vancomycin, trimethoprim-sulfamethoxazole (TMP-SMX), piperacillin and tazobactam, linezolid, teicoplanin, imipenem and tigecycline, respectively. However, the administration of these Abs should continue to be reserved for severe cases considering the balance between benefits and risks of possible side effects.

The rates of AB resistance to clindamycin and tetracylines identified in this study are consistent with those reported by Hassam et al., The microbiologic samples in the Hassam study were acquired during surgical interventions but no data on rifampicin were reported.[17] The microbiological results of our study showed that the rates of bacterial resistance in HS for the most frequently prescribed antibiotics, including rifampicin, are high. If AB therapy is required, the empirical prescription of clindamycin and rifampicin or tetracyclines runs a high risk of

facing bacterial resistance and an unsatisfactory clinical outcome. The authors recommend to test antibiotic resistance whenever possible, from purulent material adequately drained from the deepest part of HS lesions, avoiding superficial contamination, in order to select the most appropriate antibiotic for a targeted therapy approach. Therefore, the optimization of the microbiologic culture procedure, focusing on the correct culture transport media and appropriate culture incubation time, could be relevant in order to detect the anaerobic populations colonizing the lesion. [9] Unfortunately, if no purulent material is available, an empirical prescription of antibiotics represents the only option (Figure 2).

The combination of rifampicin and clindamycin is one of the two empirical therapies suggested in the current HS guidelines,[11] which contains wide spectrum antibiotics with clindamycin, also indicated for anaerobic bacteria. Our results showed that the sensitivity profile of TMP-SMX is high and similar to that observed for vancomycin (55%). Given the high risk of generating bacterial resistance to rifampicin and the relevant role of this antibiotic in the treatment of emerging infectious diseases such as tuberculosis, a combination of clindamycin and TMP-SMX could be considered as an alternative combination therapy option. However, further studies are required to demonstrate the efficacy of this possible treatment.

A limitation of this current study includes the maximum culture incubation time of 3 days. Guet-Revillet et al. demonstrated that anaerobes are the main bacterial species present in HS lesions and that prolonged cultures up to 7 days are mandatory in order to obtain their extensive isolation.[6,9] As anaerobes isolation was impaired, the results of the current study should be interpreted with caution.[6,9] Of note, prolonged microbiological cultures for anaerobes or the metagenomic analysis of the microbial population are complex techniques, which are time-consuming, and are not easily performed as routine examinations. Guet et al. established the presence of anaerobes is frequently associated with Hurley scores 2 and 3. Therefore, a prolonged microbiological culture could be reserved for clinically resistant and severe cases (Hurley ≥2).[6,9] The present study is also limited by the lack of data generated by a clinical comparison between a specifically targeted treatment and an empirical one. There is also a lack of data on bacterial resistance to ABs used in combination, such as rifampicin and clindamycin.

Considering the significant risk of further increases in resistance rates, AB should be administered only when clinically indispensable and, whenever HS purulent material is

available, the acquisition of bacterial antibiotic sensitivity profiles is recommended. Otherwise, an empirical choice should be made. Future prospective studies on AB resistance patterns, microbiome characteristics and their relationships with different HS therapies, including AB, immunomodulatory drugs and anti-TNF targeted therapies are required. The authors also think that these concepts and the current knowledge on AB resistance should be a matter of discussion in the process of updating HS therapeutic guidelines.

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Tables

Table 1. Summary of swab samples data

Table 2. Bacterial isolates from purulent material drained from HS lesions.

Table 3. Antibiogram profiles, including acquired resistance, overall resistance and susceptibility for each AB in the 163 bacterial isolates. Acquired resistance is part of the overall resistance

Figure 1.

Pie charts representing antibiogram profiles, considered as overall resistance and susceptibility, for each AB in the 163 bacterial isolates.

Figure 2.

Practical insights on AB therapy management in HS. The optimization of the microbiologic culture procedure, focusing on correct sampling modalities, culture transport media and appropriate culture incubation time (>7 days), could be relevant in order to detect anaerobic populations colonizing HS lesions.

Table 1

Patients included	137
Swab samples	137
Positive samples	114 (83.2%)
N. of bacterial growths - Gram positive - Gram negative (Anaerobes)	163 -90 (55.2%) -73 (44.8%) 30/163 (18.4%)
Sampled areas -Inguinal -Gluteal -Axillary -Perianal	 36.8% 28.1% 21.9% 13.2%

Table 2.

Family	Genus or Species	Number of bacteria isolates	Gram positive / negative	Aerobic / Anaerobic
Staphilococcaceae	S. aureus	10	positive	aerobic
	S. epidermidis	15	positive	aerobic
	S. haemolyticus	13	positive	aerobic
	Other S.	3	positive	aerobic
Streptococcaceae	St. agalactiae	14	positive	aerobic
	Other St.	9	positive	aerobic
Enterococcaceae	Enterococcus faecalis	8	positive	aerobic
	Other aerobic Gram+	3	positive	aerobic
Clostridiaceae	Clostridium ramosum	1	positive	anaerobic
Peptostreptococcaceae	Peptostreptococcus spp.	7	positive	anaerobic
	Peptoniphilus spp.	7	positive	anaerobic
Enterobacteriaceae	E. Coli	16	negative	aerobic
	Proteus spp.	22	negative	aerobic
	Morganella morganii	6	negative	aerobic
Pseudomonaceae	Pseudomonas aeruginosa	5	negative	aerobic
Moraxellaceae	Acinetobacter spp.	3	negative	aerobic
	Other aerobic Gram-	6	negative	aerobic
Bacterioidaceae	Bacterioides spp.	5	negative	anaerobic
Prevotellaceae	Prevotella bivia	7	negative	anaerobic
Fusobacteriaceae	Fusobacterium necrophorum	3	negative	anaerobic

S.: Staphylococcus; St.: Streptococcus; E.: Escherichia; Spp.: Species

Table 3.

	Acquired Resistance		Overall Resistance		Sensitivity	
Vancomycin	15	(9.2%)	72	(44.2%)	91	(55.8%)
TMP-SMX	20	(12,3%)	73	(44,7%)	90	(55,2%)
Piperacillin-Tazobactam	2	(1.2%)	82	(50.3%)	81	(49.7%)
Imipenem	5	(3.1%)	88	(54.0%)	75	(46.0%)
Linezolid	0	(0.0%)	96	(58.9%)	67	(41.1%)
Clindamycin	40	(24.5%)	107	(65.6%)	56	(34.4%)
Tigecycline	9	(5.5%)	109	(66.9%)	54	(33.1%)
Teicoplanin	0	(0.0%)	111	(68.1%)	52	(31.9%)
Rifampicin	22	(13.5%)	113	(69.3%)	50	(30.7%)
Penicillin	20	(12.3%)	114	(69.9%)	49	(30.1%)
Cefotaxime	10	(6.1%)	114	(69.9%)	49	(30.1%)
Ciprofloxacin	13	(8.0%)	120	(73.6%)	43	(26.4%)
Daptomycin	1	(0.6%)	123	(75.5%)	40	(24.5%)
Tetracyclines	34	(20.9%)	138	(84.7%)	25	(15.3%)
Oxacillin	22	(13.5%)	144	(88.3%)	19	(11.7%)
Erythromycin	40	(24.5%)	145	(89.0%)	18	(11.0%)
Amoxicillin	13	(8.0%)	146	(89.6%)	17	(10.4%)