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Lovena Sari
Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Nelva Karmila Jusuf
Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Imam Budi Putra
Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

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Original Article

Bacterial sensitivity pattern to antibiotics in acne vulgaris at Universitas Sumatera Utara Hospital Medan, Indonesia in 2019

Lovena Sari, Nelva Karmila Jusuf, Imam Budi Putra

Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

Email: sarilovena7@gmail.com

Abstract

Background: Acne vulgaris (AV) is a chronic inflammatory disorder of the pilosebaceous unit. Antibiotics play essential roles in the treatment of AV because of their antibacterial and anti-inflammatory properties. With the extensive use of antibiotics, antibiotic resistance patterns in AV lesions should be determined to ensure safe and appropriate administration of antibiotics for the treatment of AV.
Methods: This cross-sectional study involved 80 specimens from AV lesions. Each specimen was cultured and underwent susceptibility tests to azithromycin, erythromycin, clindamycin, doxycycline, minocycline, tetracycline, levofloxacin and ciprofloxacin using disc diffusion methods that met Clinical and Laboratory Standard Institute (CLSI) standard.
Results: From a total 97 bacterial colonies growth from 80 specimens, 12 species were identified, namely *Cutibacterium acnes, Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus aureus, Staphyococcys haemolyticus, Leuconostoc mesenteroides, Micrococcus luteus, Kocuria varians, Staphylococcus vitulinus, Staphylococcus cohnii, Staphylococcus arlettae* and *Dermacoccus nishinomyaensis*. Antibiotic with highest bacterial sensitivity rate was minocycline, followed by levofloxacin, ciprofloxacin, doxycycline, tetracycline, azithromycin, erythromycin, and clindamycin. Most of the species were intermediately sensitive to azithromycin, clindamycin, erythromycin, doxycycline, tetracycline, ciprofloxacin, and levofloxacin. Antibiotic with highest bacterial resistance rate was erythromycin, followed by clindamycin, azithromycin, tetracycline, doxycycline, ciprofloxacin, levofloxacin and minocycline.
Conclusions: In cases of acne vulgaris, minocycline and levofloxacin were the two antibiotics with the highest bacterial sensitivity, while erythromycin and clindamycin were the two antibiotics with the highest bacterial resistance in AV lesions.

Keywords: *acne vulgaris, antibiotics, bacterial sensitivity*

Background

Acne vulgaris (AV) is a chronic inflammatory disorder of the pilosebaceous unit marked by clinical polymorphic lesions, such as comedones, papules, pustules, and nodules, along with varying degrees of inflammation. AV is often found in the period of adolescence.[1,2] Albeit self-limiting, AV may bring about accompanying sequelae such as scar tissue and pigmentary changes that may persist for a lifetime, thereby decreasing the patient's quality of life and causing psychological disorders.[1-4]

Four main factors play a key role in the complex pathogenesis of AV, namely hyperproliferation of infundibulum, excess sebum production, inflammation, and colonization of *Propionibacterium acnes (P. acnes)*.[1] Genomic and metagenomics newest investigations have led to the denomination change of *Propionibacterium acnes* to *Cutibacterium acnes* (*C. acnes*).[5]

Antibiotics play vital roles in treating acne because of their antimicrobial and anti-inflammatory activities.[1,4] With the extensive use of antibiotics in daily practices and the increasing reports regarding the incidence of antibiotic

resistance, it is important to identify the pattern of bacterial sensitivity to antibiotics in acne vulgaris so that the decision in choosing appropriate antibiotics for the treatment of acne vulgaris may be conducted more wisely. This study aimed to investigate the patterns of bacterial sensitivity to antibiotics in acne vulgaris.

Methods

Sample collection

This descriptive cross-sectional study involved 80 specimens from AV lesions collected from December 2019 to January 2020 in Microbiology Laboratory of Universitas Sumatera Utara Hospital, Indonesia. Specimens were collected from 40 subjects with varying degrees of AV severity (14 subjects with mild AV, 13 subjects with moderate AV, and 13 subjects with severe AV). Each subject underwent specimen collection from non-inflammatory AV lesion (closed comedones) and inflammatory AV lesion (pustule), followed by specimen culture and bacterial identification. Inclusion criteria were specimens with positive bacterial culture. Specimens with damaged bacterial culture in the examination process were excluded from this study.

Research protocol

Each subject underwent specimen collection from non-inflammatory lesions (e.g., closed comedones) and inflammatory lesions (e.g., pustule). Samples from non-inflammatory lesions were taken using a sterilized comedones extractor, while samples from inflammatory lesions were taken using a sterilized swab moistened with nutrient broth.

The specimens were cultured in anaerobic and aerobic conditional treatments jars containing 0.5% McFarlan turbidity blood agar or Brucella blood agar, supplemented with 5% sheep blood. The steps were followed by incubation in the anaerobic and aerobic conditions at 37°C for 24–48 hours. AnaeroGen® Compact (PT Dipa Puspa Labs, Indonesia) was placed to isolate the anaerobic bacterial species. Species identification was made using Vitek® 2 compact (PT Enseval Medika Prima, Indonesia).

Furthermore, susceptibility tests were conducted using disc diffusion methods by putting antibiotic disc of azithromycin, erythromycin, clindamycin, doxycycline, minocycline, tetracycline, ciprofloxacin and levofloxacin on each growth media plate using a sterile tweezer. Subsequently, the plate was incubated in anaerobic conditions. The susceptibility test was examined 24 hours following the incubation by measuring the clear zone diameter with the Clinical and Laboratory Standard Institute (CLSI) standard in the sensitive, intermediate, and resistance categories.[6]

Ethical clearance

This study was approved by the Committee of Ethics of the Faculty of Medicine of Universitas Sumatera Utara/Adam Malik Hospital (registry no. 910/TGL/KEPK FK USU-RSUP HAM/2019).

Statistical analysis

Data analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 23.0 in a descriptive fashion to analyze the distribution of patterns of bacterial susceptibility to antibiotics.

Results

Cultures of 80 specimens of AV lesions revealed 12 bacterial species with a total of 97 colonies. With the most colonies found was *Staphylococcus epidermidis, followed by Cutibacterium acnes, Staphylococcus hominis, Staphylococcus aureus, Staphylococcus haemolyticus, Leuconostoc mesenteroides, Micrococcus luteus, Kocuria varians, Staphylococcus vitulinus, Staphylococcus cohnii, Staphylococcus arlettae,* and *Dermacoccus nishinomyaensis*. Susceptibility tests to azithromycin, erythromycin, clindamycin, doxycycline, minocycline, tetracycline, levofloxacin and ciprofloxacin were conducted in all grown colonies using disc diffusion methods that met the Clinical and Laboratory Standard Institute (CLSI) standard. Each colony was categorized from each susceptibility test to any of the following results sensitive (table 1), intermediate (table 2), and resistance (table 3).

Table 1. Bacterial Sensitivity Patterns to Antibiotic in Acne Vulgaris

No.	Bacteria	∑ Colonies	Antibiotics sensitive (n)							
			AZM	E	DA	DO	MN	TE	CIP	LEV
1.	*C. acnes*	17	1	1	2	16	17	16	14	15
2.	*S. epidermidis*	38	19	18	17	31	38	26	34	36
3.	*S. hominins*	14	2	4	4	12	14	9	14	14
4.	*S. aureus*	7	5	4	3	5	7	6	7	7
5.	*S. haemolyticus*	7	1	1	0	4	7	5	4	4
6.	*L. mesenteroides*	5	2	2	1	2	5	2	5	5
7.	*M. luteus*	3	1	1	2	2	2	2	3	3
8.	*Kocuria varians*	2	0	0	0	0	2	0	2	2
9.	*S. vitulinus*	1	0	0	0	1	1	1	1	1
10.	*S. cohnii*	1	1	1	1	1	1	1	1	1
11.	*S. arlettae*	1	0	0	0	1	1	1	1	1
12.	*D. nishinomyaensis*	1	1	1	1	1	1	1	1	1
Total		**97**	33 34,0%	33 34,0%	31 31,9%	76 78,3%	96 98,9%	70 72,1%	87 89,6%	90 92,7%

C.=Cutibacterium, *S. = Staphylococcus, L. = Leuconostoc*, *M. = Micrococcus*, *D. = Dermacoccus*, AZM= azithromycin, E= erythromycin, DA= clindamycin, DO= doxycycline, MN= minocycline, TE= tetracycline, CIP= ciprofloxacin, LEV= levofloxacin.

Table 2. Bacterial Susceptibility Patterns to Antibiotic in Acne Vulgaris (Intermediately Sensitive)

No.	Bacteria	∑ Colonies	Intermediately sensitive (n)							
			AZM	E	DA	DO	MN	TE	CIP	LEV
1.	*C. acnes*	17	3	1	1	1	0	0	1	0
2.	*S. epidermidis*	38	2	3	3	2	0	1	0	1
3.	*S. hominis*	14	2	1	1	0	0	1	0	0
4.	*S. aureus*	7	0	1	1	0	0	1	0	0
5.	*S. haemolyticus*	7	2	2	2	1	0	0	0	0
6.	*L. mesenteroides*	5	0	1	1	0	0	1	0	0
7.	*M. luteus*	3	1	0	0	0	0	0	0	0
8.	*Kocuria varians*	2	1	0	0	0	0	0	0	0
9.	*S. vitulinus*	1	0	0	0	0	0	0	0	0
10.	*S. cohnii*	1	0	0	0	0	0	0	0	0
11.	*S. arlettae*	1	1	1	1	0	0	0	0	0
12.	*D. nishinomyaensis*	1	0	0	0	0	0	0	0	0
Total		**97**	12 12,3%	8 7,2%	10 10,3%	4 4,1%	0 0%	4 4,1%	1 1,0%	1 1,0%

C.=Cutibacterium, *S. = Staphylococcus, L. = Leuconostoc*, *M. = Micrococcus*, *D. = Dermacoccus*, AZM= azithromycin, E= erythromycin, DA= clindamycin, DO= doxycycline, MN= minocycline, TE= tetracycline, CIP= ciprofloxacin, LEV= levofloxacin.

Table 3. Bacterial Resistance Patterns to Antibiotic in Acne Vulgaris

No.	Bacteria	∑ Colonies	Antibiotics resistance (n)							
			AZM	E	DA	DO	MN	TE	CIP	LEV
1.	*C. acnes*	17	13	14	14	0	0	1	2	2
2.	*S. epidermidis*	38	17	18	18	5	0	11	4	1
3.	*S. hominis*	14	10	9	9	2	0	4	0	0
4.	*S. aureus*	7	2	3	3	2	0	0	0	0

5.	*S. haemolyticus*	7	4	5	5	2	0	2	3	3
6.	*L. mesenteroides*	5	3	3	3	3	0	2	0	0
7.	*M. luteus*	3	1	2	1	1	1	1	0	0
8.	*Kocuria varians*	2	1	1	2	2	0	2	0	0
9.	*S. vitulinus*	1	1	1	1	0	0	0	0	0
10.	*S. cohnii*	1	0	0	0	0	0	0	0	0
11.	*S. arlettae*	1	0	0	0	0	0	0	0	0
12.	*D. nishinomyaensis*	1	0	0	0	0	0	0	0	0
Total		**97**	52 53,6%	56 57,7%	56 57,7%	17 17,5%	1 1,0%	23 23,7%	9 9,2%	6 6,1%

C.=Cutibacterium, S. = Staphylococcus, L. = Leuconostoc, M. = Micrococcus, D. = Dermacoccus, AZM= azithromycin, E= erythromycin, DA= clindamycin, DO= doxycycline, MN= minocycline, TE= tetracycline, CIP= ciprofloxacin, LEV= levofloxacin.

Discussion

In this study, most colonies were found to be sensitive to minocycline (98,9%), followed by levofloxacin (92,7%), ciprofloxacin (89,6%), doxycycline (78,3%), tetracycline (72,1%), azithromycin (34,0%), erythromycin (34,0%) andclindamycin (31,9%). In line with this study, a study at Medan, Indonesia in 2009, which involved 16 colonies of *P. acnes* isolated from AV lesions, noted the highest microbial sensitivity rate to minocycline (93,8%) and doxycycline (93,8%), followed by tetracycline (56,3%), clindamycin (37,5%), and erythromycin (31,3%).[7] Similar findings were also reported in study at Jakarta, Indonesia in 2019, which involved 63 colonies of bacteria *P. acnes, S. epidermidis* and *S. aureus,* where the minocycline was the antibiotic with the highest sensitivity rate (100%), followed by doxycycline (86,6%), tetracycline (69,6%), clindamycin (46,9%), and erythromycin (43,9%).[8]

Acne vulgaris is one of the most common dermatological problems predominantly found in adolescents. Its pathogenesis is associated with four main factors, such as increased sebum production, inflammation, and proliferation of *C. acnes*, in which *C. acnes* is thought to play an important role in the pathogenesis of non-inflammatory and inflammatory lesions.[5,9] Antibiotics play an important role in treating acne because of their antibacterial and anti-inflammatory properties.[1,4]
The immune system exerts various anti-inflammatory mechanisms to counter-balance inflammatory mediators. One of the important cytokines in regulating the inflammatory state is interleukin-10 (IL-10). In a study conducted at Medan, Indonesia in 2019, plasma IL-10 level was significantly associated with the severity of AV.[10] Several internal and external factors may also predispose an individual to acne vulgaris, such as race, stress, genetics and cosmetics. Study conducted at Medan, Indonesia in 2020, noted a significant correlation between the stress scale and the severity of AV.[11]

Although AV is a self-limiting disease, it may bring about further dermatologic sequelae such as scar tissue and pigmentary changes that may persist for a lifetime, thereby decreasing the patient's quality of life and causing various psychological disorders.[1-4] Dermatologists need to treat acne effectively since it can manifest into acute outbreaks, a slow onset, and prolonged relapse. In terms of its treatment, there is increasing evidence that the combined administration of topical and oral antibiotics is effective as first-line therapy for inflammatory and non-inflammatory acne.[8]

It is now acknowledged that antibiotics such as minocycline and doxycycline are more effective than tetracycline. [1,12-14] Groups of tetracycline, including tetracycline, doxycycline and minocycline inhibit bacterial protein synthesis, and reduce the amount of fatty acid in sebaceous follicles, leading to the activity reduction of *P. acnes.*[15,16] Doxycycline and minocycline are also more commonly administered than other antibiotics, because of their low molecular weight, highly soluble properties, and excellent tissue penetration.[8] Tetracycline and macrolide also inhibit the release of pro-inflammatory mediators by *P. acnes.*[15] On the other hand, groups of quinolones inhibit bacterial gyrase and bacterial DNA synthesis with broad-spectrum activity against gram-positive and gram-negative bacteria.[17]

This study also revealed that most of the bacterial colonies were intermediately sensitive to

azithromycin (12,3%), followed by clindamycin (10,3%), erythromycin (8,2%), doxycycline (4,1%), tetracycline (4,1%), ciprofloxacin (1,0%), and levofloxacin (1,0%). These findings are somewhat different from study conducted at Egypt in 2017, in which most of the colonies were intermediately sensitive to doxycycline (25,7%), tetracycline (17,1%), levofloxacin (5,7%), clindamycin (5,7%) and erythromycin (2,9%).[18]

Highest bacterial resistance rate was found in erythromycin discs (57,7%), followed by clindamycin (57,7%), azithromycin (53,6%), tetracycline (23,7%), doxycycline (17,5%), ciprofloxacin (9,2%), levofloxacin (6,1%), and minocycline (1,0%). In line with these findings, a study conducted at Bandung, Indonesia in 2019, which involved 53 bacteria colonies of AV lesions also noted the highest bacterial resistance rate to erythromycin (62,5%), followed by azithromycin (56,6%), clindamycin (52,8%), cotrimazole (50,9%), tetracycline (30,2%), ciprofloxacin (15,1%), levofloxacin (13,2%), doxycycline, and minocycline (7,5%).[19] In another study at Chile in 2013, the highest bacterial resistance was also found in erythromycin (27%), followed by clindamycin (24%) and azithromycin (14%).[20]

Careful consideration in choosing antibiotics is essential in the treatment of acne. Not only does antibiotic resistance affect the outcome of the treatment, but it may also spread among bacteria through horizontal gene transfer. Antibiotic resistances are caused by bacterial chromosomal mutations or gene acquisition. In cases of antibiotic resistance among *P. acnes*, it is predominantly mediated by chromosomal mutations. Cross-resistance between erythromycin and clindamycin is associated with a point mutation in the gene encoding the 23S rRNA subunit, which causes bacterial resistance to MLS (macrolide - lincosamide - streptogramin) antibiotics.[21] On the contrary, *P. acnes* resistance to tetracycline is often associated with a mutation in 16S rRNA of small ribosomal subunits in E. coli 1058 (transition G to C).[13,22]

Staphylococcus epidermidis is also an important carrier of antibiotic resistance genes. It is suggested that *S. epidermidis* can transfer these plasmid-borne genes between staphylococcal species, e.g., *S. aureus*.[22-24] The resistance of *Staphylococcus epidermidis* to macrolides is often caused by the *erm* gene encoding dimethylate adenine residue 23S rRNA, which prevents macrolides from being bound to the 50S ribosomal subunit.[25-27]

Conclusion

In this study examining microbial resistance patterns in acne vulgaris lesions, minocycline and levofloxacin were two antibiotics with highest bacterial sensitivity rate. On the other hand, erythromycin and clindamycin were antibiotics with the highest bacterial resistance rate. We suggest that such a study be conducted every five years to identify changes in local bacterial sensitivity patterns to antibiotics in acne vulgaris. Additionally, this study warrants further multicenter study involving hospitals throughout Indonesia regarding bacterial sensitivity patterns to antibiotics.

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Author Contribution

All authors act as the guarantor of the manuscript. Lovena Sari is the main investigator of this study. Lovena Sari, Nelva Karmila Jusuf, and Imam Budi Putra participated in the conception, data acquisition, data analysis, data interpretation, and writing of the study.

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Conflict of Interests

There are no conflicts of interest to declare.

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