

Association of Antimicrobial Susceptibility and Treatment Outcome in Acne Vulgaris Patients: A Pilot Study

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Abstract

Purpose *Cutibacterium acnes* (*C. acnes*) is an emerging pathogen that is highly resistant to antibiotics and is capable of causing persistent infections that are difficult to treat.

Methods & Materials Acne vulgaris patients visiting dermatology OPD of our tertiary care hospital during the study period of 2 months were recruited. Skin swabs were collected, and the sample was processed on 5% sheep-blood agar for anaerobic culture by the GasPak method. Isolates were identified by the standard biochemical test. Antimicrobial susceptibility testing was performed for clinically relevant antibiotics by the E-strip method. The clinical response was evaluated after 1-month follow-up to the prescribed antibiotics.

Results Minocycline, doxycycline, ceftriaxone, and tetracycline were the most effective antibiotics. Nonsusceptibility to clindamycin and erythromycin were observed in 11.9% and 31% isolates, respectively, with 9.5% isolates being nonsusceptible to both. For none of the antibiotics we found significant difference in the proportion of susceptible and nonsusceptible isolates between mild, moderate, and severe grades of acne vulgaris. For none of the antibiotic regimens, significant difference was observed between nonresponders and responders. Twenty-seven patients received clindamycin and among them 16 of 19 responders and 6 of 8 nonresponders yielded growth of clindamycin-susceptible isolates ($p = 0.57$).

Conclusion We observed significant prevalence of resistant strains of *C. acnes* among patients with acne vulgaris. No association was observed between in vitro susceptibility results and treatment outcome.

Keywords

- ▶ *Cutibacterium acnes*
- ▶ Acne vulgaris
- ▶ Antibigram
- ▶ In vitro susceptibility
- ▶ *Propionibacterium acnes*

Introduction

Cutibacterium acnes (*C. acnes*), an anaerobic gram-positive bacillus formerly known as *Propionibacterium acnes*, is a significant emerging pathogen that has lately been incriminated in the pathogenesis of acne vulgaris as well as life-threatening infections such as endocarditis, intravascular

infections, post-craniotomy infections, endophthalmitis, and septic arthritis.¹⁻⁴ The involvement of this bacterium is also being increasingly reported in the context of orthopedic and cardiac prosthetic infections, infections of breast implants, intraocular lenses, and ventriculoperitoneal shunts.⁵

It has been the most classical and consistent pathogen associated with acne vulgaris.⁶ This organism is abundant in

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sebum-rich areas (which are prone to acne), causes blockage of pilosebaceous glands by making biofilms, and also plays an important role in initiation and propagation of inflammation.⁷ Biofilm formation makes them highly resistant to antimicrobial agents and is capable of causing chronic persistent infection that is difficult to treat.

Therapeutically, the most effective antibacterial agents in acne vulgaris target *C. acnes*.⁶ Optimal antibiotic therapy, directed against *C. acnes*, is the key to the treatment of these infections. But the widespread and long-term use of oral and topical Macrolides and Tetracyclines has resulted in significant dissemination of cross-resistant strains of cutibacteria in many parts of the world. Resistant strains have been reported to be widely prevalent throughout Europe, Japan, Korea, Singapore, Australia, and USA.⁸⁻¹⁰

Information regarding the antimicrobial susceptibility profile and resistance mechanisms of *C. acnes* is relatively scarce from India.¹¹ Being an anaerobic slow-growing organism, the isolation and antibiotic sensitivity testing of this bacterium are technically challenging tasks that require rapid transport of samples to the microbiology laboratory; use of special transport media; infrastructure for performing anaerobic culture; skilled manpower; and relatively lengthy incubation periods. Consequently, isolation and characterization of this organism is seldom undertaken in clinical microbiology laboratories.

In view of the paucity of data in the Indian context and the need to tailor antibiotic therapy according to local antibiogram patterns, the present study was conducted with the objective of analyzing a repertoire of clinical isolates of *C. acnes* from patients afflicted with acne vulgaris, evaluating the outcome in these patients following standard therapy with prescribed antibiotics, and delineating the association between clinical response and in vitro susceptibility of the recovered isolates with clinically relevant antibiotics.

Materials and Methods

Ethical Considerations

The study protocol was approved by the institutional human ethics committee, and informed consent was obtained from each patient prior to recruitment.

Consecutive patients, attending the Dermatology OPD of a tertiary care teaching hospital in Central India with acne vulgaris, were recruited into the study over a period of 2 months. Patients already receiving antibiotic treatment at the time of presentation or within the last 4 weeks were excluded from the study. Relevant demographic and clinical details of the recruited patients were recorded in a predesigned case study form. The treatment given to the patients, following diagnostic workup, was also recorded. The patients were called for follow-up at the end of 1 month during which the outcome of treatment was recorded.

A single skin swab was collected from each recruited participant for anaerobic culture of *C. acnes*. The sample from acne lesions was collected by applying firm pressure and rubbing against the lesions with a transport swab. The swab

was moistened in sodium phosphate buffer (0.075 mol/L; pH 7.9) containing 0.1% Triton-X 100. After specimen collection, the swabs were immediately transported to the microbiology laboratory where they were cultured in 5% sheep blood agar under anaerobic conditions. The swabs were gently rolled over the surface of a portion of the plate and then streaked to obtain isolated colonies. The anaerobic incubation was done using the GasPak Anaerobic System of GasPaks (HiMedia, Mumbai) at 37°C for 72 hrs. Colonies of *C. acnes* were identified among the recovered isolates using phenotypic features such as cultural characteristics, microscopic morphology, and standard biochemical tests.¹² The primary isolate of *C. acnes* was then subcultured in 5% sheep blood agar to obtain a pure growth of *C. acnes*, which was then analyzed to determine the minimum inhibitory concentration (MIC) of a range of clinically relevant antibiotics using commercially procured E-strips. Inoculum for the susceptibility studies were prepared by suspending a culture grown for 48 hours in reduced Brucella broth to achieve a final concentration equivalent to a 0.5 McFarland standard (1.5×10^8 CFU/ml). E-test strips of each of the test antibiotics were then placed onto the Brucella blood agar supplemented with Vit.K1, hemin and laked sheep blood, and the plates were incubated at 37°C under anaerobic conditions¹³. MICs for each antibiotic were determined after 48 hours of incubation.

Antibiotic susceptibility and resistance breakpoints were defined as follows

Antibiotic agent	Clinical breakpoint
Clindamycin	$\geq 8 \mu\text{g}/\text{mL}^{13}$
Tetracycline	$\geq 16 \mu\text{g}/\text{mL}^{13}$
Ceftriaxone	$\geq 64 \mu\text{g}/\text{mL}^{13}$
Ertapenem	$\geq 16 \mu\text{g}/\text{mL}^{13}$
Meropenem	$\geq 16 \mu\text{g}/\text{mL}^{13}$
Erythromycin	$\geq 2 \mu\text{g}/\text{mL}^{11}$
Doxycycline	$\geq 4 \mu\text{g}/\text{mL}^{11}$
Minocycline	$\geq 16 \mu\text{g}/\text{mL}^{11}$

Patients were evaluated during their follow-up visits after 1 month, and the clinical response to the prescribed antibiotics was recorded.

Statistics

To understand the association between in vitro resistance and treatment outcome, we compared the cure rates between patients yielding sensitive and resistant isolates of *C. acnes*. Chi-square test was used to compare cure rates between patients with susceptible and nonsusceptible isolates, and the *p* value was calculated with the help of the Epi Info online software.

Results

Skin swabs from a total of 52 consecutively recruited patients attending skin OPD with acne vulgaris were collected for

C. acnes culture. Growth of *C. acnes* was observed in 42 samples (80.76%). These 42 patients were included for further analysis and follow-up.

The mean (\pm standard deviation [SD]) age of the patients was 21 (\pm 4) years and the mean (\pm SD) duration of disease was 3 (\pm 2) years. Thirty-one patients presented with acne only on their face, two presented with acne only on their trunk, and nine patients had lesions both on face and trunk. Acne was mild in intensity in 8 patients, moderate in 25 patients, and severe in 9 patients. The lesions were inflammatory in 9 patients, noninflammatory in 7 patients, and of mixed type in 26 patients. Seven patients reported the use of oil-based cosmetics on their face and three patients gave a history of having facial massages. The patients received treatment according to their clinical presentation from a single qualified dermatologist and were followed-up after 1 month of treatment. They were categorized into nonresponder ($n = 16$) and responder ($n = 26$) groups, depending on improvement or deterioration with the prescribed treatment. The two subgroups of patients were found to be comparable with respect to their age and gender distribution, clinical characteristics, and nature of treatment administered (\blacktriangleright Table 1).

Colonies of *C. acnes* were small (less than 0.5 mm in size), grey, and weakly β hemolytic (\blacktriangleright Fig. 1a). On microscopy after Gram staining, nonsporing Gram-positive bacilli were seen (inset image of \blacktriangleright Fig. 1a). These colonies were confirmed to be *C. acnes* by performing standard biochemical

tests.¹¹ Antibiotic susceptibility testing with clinically relevant antibiotics was performed; minocycline (100% susceptible), doxycycline (97.6% susceptible), ceftriaxone (95.2% susceptibility), and tetracycline (92.9% susceptibility) were found to be the most effective antibiotics. Nonsusceptibility to clindamycin and erythromycin was observed in 11.9% ($n = 5$) and 31% ($n = 13$) isolates, respectively, with 9.5% ($n = 4$) isolates being nonsusceptible to both. For all the antibiotics tested, a significantly higher proportion of isolates was susceptible; Ertapenem was found to be the least effective antibiotic (52.4% susceptibility) (\blacktriangleright Table 2).

On examining the antibiotics prescribed for these patients, we found a total of five regimens being administered in 35 patients. Antibiotics were not administered in 7 patients, while 19 patients received only topical antibiotics. Sixteen patients were given erythromycin ($n = 14$) and

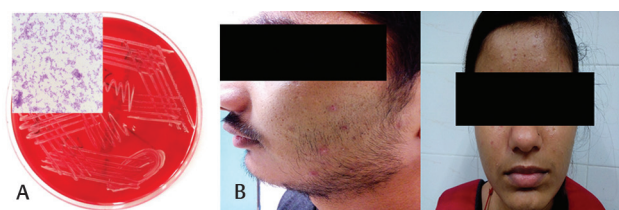


Fig. 1 (a) *C. acnes* colonies on blood agar plate, inset image showing gram staining. (b) Clinical representation of acne on cheek and forehead area.

Table 1 Comparison of age and gender distribution, clinical characteristics, and nature of treatment administered among nonresponders and responders

Parameters	Nonresponders ($n = 16$)	Responders ($n = 26$)	p -Value
Age (years) (mean \pm SD)	22.12 \pm 5.95	21 \pm 2.92	0.00169
Gender (M/F)	13/03	20/06	0.7400
Duration of illness (months) (mean \pm SD)	42 \pm (31.58)	28.58 \pm (22.68)	0.1386
Facial involvement (%)	16 (100)	24 (92.31)	0.3883
Extrafacial involvement (%)	06 (37.50)	05 (19.23)	0.3883
Grade of illness (mild:moderate:severe)	04:08:04	04:17:05	0.598
Inflammation present (%)	15 (93.75)	20 (76.92)	0.1554
Only topical antibiotic administered (%)	03 (18.75)	10 (38.46)	0.2701
Systemic antibiotic administered (%)	13 (81.25)	16 (61.54)	0.3393
History of previous treatment (%)	08 (50)	10 (38.46)	0.4631

Table 2 Antibiotic susceptibility pattern of *C. acnes* isolates ($n = 42$)

Name of Antibiotics	Susceptible	Nonsusceptible	p -Value
Clindamycin	37 (88.10%)	5 (11.90%)	< 0.001
Tetracycline	39 (92.86%)	3 (7.14%)	< 0.001
Ceftriaxone	40 (95.24%)	2 (4.76%)	< 0.001
Ertapenem	22 (52.38%)	20 (47.62%)	< 0.001
Meropenem	25 (59.52%)	17 (40.48%)	< 0.001
Erythromycin	29 (69.05%)	13 (30.95%)	< 0.001
Doxycycline	41 (97.62%)	1 (2.38%)	< 0.001
Minocycline	42 (100%)	0	< 0.001

doxycycline ($n = 2$) in addition to topical clindamycin. For none of the five regimens, significant difference was observed between the proportion of nonresponders and responders (►Table 3), implying that none of the regimens could claim superiority over others.

We then tried to analyze if there was a difference in the proportion of susceptible and nonsusceptible isolates between mild, moderate, and severe categories of patients. For none of the antibiotics, we found significant difference in the proportion of susceptible and nonsusceptible isolates among the three categories of disease severity. Thus, antibiotic susceptibility of *C. acnes* was not found to be associated with its virulence and pathogenic potential (►Table 4).

We next tried to find an association between the clinical response of the patients and antibiotic susceptibility of the recovered isolates. Among the 35 patients who received antibiotics, 27 patients received clindamycin, 16 patients received erythromycin and 8 patients received doxycycline, either alone or in combination. It was observed that of the 27 patients who received clindamycin, 16 of the 19 responders and 6 of the 8 nonresponders yielded growth of clindamycin-susceptible isolates ($p = 0.57$).

Discussion

In the present study on the antibiogram of the emerging pathogen, *C. acnes*, it was observed that minocycline, doxycycline, ceftriaxone, and tetracycline were the most effective antibiotics and carbapenems were the least effective. Nonsusceptibility to clindamycin was observed in 11.9% of the isolates, and no association could be drawn between clindamycin susceptibility and treatment response.

Similar to our findings, other authors from different parts of the world have also reported consistently decreasing susceptibility to clindamycin and erythromycin among *C. acnes* isolates. clindamycin susceptibility has been reported to vary from 7.5 to 91% and erythromycin susceptibility from 10.4 to 98% in different studies.¹⁴⁻²⁶ It is worth noting that development of antibiotic resistance in *C. acnes* was not encountered until the early 1980s despite years of systemic use of tetracycline and erythromycin. But shortly after the introduction of topical formulation of these drugs, the first strains of resistant *C. acnes* emerged in the USA, and by the late 1980s, very high MIC levels for these drugs became commonplace among *C. acnes* isolates from UK and USA.⁸ Several other studies have also demonstrated similar relationship between the increasing resistance to these drugs and clinical prescription patterns. In a study from Singapore, Tan et al¹⁰ have shown resistance to erythromycin to be more significantly associated with increased duration of antibiotic usage. Patients on no antibiotics or on short-term antibiotics (6–18 weeks) were found to yield much lesser isolation of erythromycin-resistant strains, and most of the erythromycin-resistant strains were also cross-resistant to clindamycin. In a larger study covering six European centers, widespread use of topical erythromycin and clindamycin was found to cause significant dissemination of cross-resistant strains of Cutibacteria both in patients and in their untreated contacts. This study also revealed remarkable variations in the proportion of resistant Cutibacteria between the European countries, which was reflective of the usage pattern in these countries. Interestingly, a significant proportion of dermatologists specializing in acne treatment were found to be colonized with resistant Cutibacteria in this study, while none of the

Table 3 Antibiotics regimens prescribed to patients ($n = 35$)

Antibiotics regimens	Total	Nonresponders	Responders	p-Value
Erythromycin + Clindamycin	14	5 (35.71%)	9 (65.29%)	0.6726
Doxycycline + Clindamycin	2	1 (50%)	1 (50%)	0.7662
Erythromycin	2	2	0	0.07447
Doxycycline	6	4 (66.67%)	2 (33.33%)	0.9569
Clindamycin	11	2 (18%)	9 (72%)	0.07447

Table 4 Antibiotics susceptibility pattern of *C. acnes* isolates in different categories of disease severity

Name of Antibiotics	Mild (08)		Moderate (25)		Severe (09)		p-Value
	Susceptible	Nonsusceptible	Susceptible	Nonsusceptible	Susceptible	Nonsusceptible	
Clindamycin	7 (87.50%)	1 (12.50%)	22 (88.00%)	3 (12.00%)	8 (88.89%)	1 (11.11%)	0.9958
Tetracycline	7 (87.50%)	1 (12.50%)	24 (96.00%)	24 (96.00%)	8 (88.89%)	1 (11.11%)	0.6275
Ceftriaxone	7 (87.50%)	1 (12.50%)	24 (96.00%)	24 (96.00%)	8 (88.89%)	1 (11.11%)	0.6275
Ertapenem	3 (37.50%)	5 (62.50%)	11 (44.00%)	14 (56.00%)	5 (55.56%)	4 (44.44%)	0.7425
Meropenem	5 (62.50%)	3 (37.50%)	14 (56.00%)	11 (44.00%)	6 (66.67%)	3 (33.33%)	0.8399
Erythromycin	7 (87.50%)	1 (12.50%)	17 (68.00%)	8 (32.00%)	5 (55.56%)	4 (44.44%)	0.3581
Doxycycline	7 (87.50%)	1 (12.50%)	25 (100.00%)	0 (00.00%)	9 (100.00%)	0 (00.00%)	0.1134
Minocycline	8 (100%)	0(0.00%)	25 (100.00%)	0 (00.00%)	9 (100.00%)	0 (00.00%)	–

nongeriatric physicians were similarly colonized.²⁷ In a recent study from Korea too, increasing resistance to clindamycin and erythromycin has been reported among *C. acnes* isolates from acne patients, compared to previous studies from the same region.²⁸ In sync with these studies, our finding of a relatively high proportion of clindamycin nonsusceptibility could be explained by virtue of its being the most commonly prescribed antibiotic among our patients.

In the event of the rising trend of resistance to clindamycin and erythromycin, alternative therapeutic choices against this emerging pathogen need to be explored. In contrast to the obvious advantages of topical formulation for skin lesions, systemic administration of antibiotics is imperative in *C. acnes* isolates recovered from deep-seated infections such as endocarditis, septic arthritis, endophthalmitis, etc. and diverse device- and implant-related infections. Among the systemic choices, our finding regarding minocycline, doxycycline, ceftriaxone and tetracyclines being the most effective antibiotics is also corroborated by other authors. Universal susceptibility to ceftriaxone has been reported in independent studies from USA and Switzerland.^{3,26,29} In a study from Singapore, susceptibility of *C. acnes* to different tetracyclines was compared and the average MIC to tetracyclines was found to be higher than that of doxycycline which, in turn, was higher than that for minocycline.¹⁰ In another study from Korea, Song et al⁹ observed a consumption-related decline in susceptibility toward doxycycline with patients with a history of treatment with topical and systemic antibiotics showing higher MIC to doxycycline. Like other antibiotics, geographical variation has also been noted in doxycycline susceptibility pattern of *C. acnes*, with resistance rates ranging from 7 to 63% being reported in literature. We observed considerably higher proportion of resistance among the recovered *C. acnes* isolates toward carbapenems. Contrary to our findings, Shame et al³ and Crane et al²⁶ have reported all the isolates to be within the susceptible range of MIC for ertapenem and meropenem in their studies conducted in 2006 and 2013, respectively. This difference with our findings could be explained in view of geographical and temporal variation and also by relatively unrestricted use of carbapenems in Indian clinical practice.

We observed the lack of association between clindamycin susceptibility and treatment outcome in our study. This difference in in vitro result and in vivo response could partially be explained by the known propensity of this bacterium to produce biofilms at the site of clinical lesions.²⁹ This ability to produce biofilm could be responsible for offering protection to the bacteria from the inhibitory effect of the administered antibiotics. Pharmacokinetic factors like subinhibitory concentration of the antibiotics at the site of infection could also be responsible for inadequate treatment outcome. Moreover, the requirement of alkaline pH for antibacterial action of clindamycin and erythromycin could also have remained unmet at the site of clinical lesions.³⁰

The present study has two major limitations. First, the sample size in this study was relatively small and as a result, adequate representation of the different treatment regimens could not be achieved. Second, the molecular mechanism of

resistance to the different antibiotics could not be included in the scope of the study. Building on the findings of this pilot study, we are planning to conduct a broader and more elaborate study on clinico-microbiological and molecular characteristics of antibiotic susceptibility in *C. acnes* isolates recovered at our institute.

Conclusion:

Our pilot study brings out the antibiogram of clinical isolates of *C. acnes* in the Indian context and records a lack of association between the antibiotic susceptibility of these isolates with the clinical response to treatment. More elaborate studies need to be undertaken to validate our findings and identify the determinants of treatment outcome targeting this emerging pathogen.

Conflicts of Interest

None declared.

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