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Cutibacterium species: An Underestimated Pathogen in Chronic Infections

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Abstract

Cutibacterium speciesis a member of the skin micro biota, found predominantly in regions rich in sebaceous glands, involved in various chronic infections that led to its emergence as an opportunistic pathogen. The present study is a retrospective study to determine the prevalence and antibiotic sensitivity pattern of *Cutibacterium* species recovered from chronic infections over a period of 4.5 years. The identification of the colonies grew on the Robertson's Cooked Meat media plate was done using VITEK 2. The antibiotic sensitivity tests were put by pour plate method using Epsilometer strips (E-strip).Out of 400, 17.75% (n=71) were confirmed as anaerobic bacteria by VITEK 2. Out of 71 positive anaerobic organisms, 21% (n=15/71) were confirmed as *Cutibacterium* species. *Cutibacterium* species recorded prevalenceof 3.75% (15/400) among clinical specimens. High sensitivity was observed with beta lactam group of drugs whereas metronidazole drug was found ineffective against *Cutibacterium* species. Due to prolonged culture time for anaerobic bacteria there is a high need in new diagnostic methods. In the recent times *Cutibacterium* species has been reported from various clinical samples which depicts shift of *Cutibacterium* species as a potential pathogen in the upcoming time.

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Introduction

The species *Cutibacterium acnes* (previously known as *Propionibacterium acnes*) is a symbiotic lipophilic Gram-positive bacterium. *Cutibacterium acnes* is well-defined as diphtheroid or coryneform for it is rod-shaped and curved with a breadth of 0.4 to 0.7 µm and length of 3 to 5 µm. *Cutibacterium*is the known anaerobe commensal of the skin, oral cavity, intestine, conjunctiva, and the external ear canal (Foster AL et al., 2021). The up-to-date genus *Cutibacterium*, contains cutaneous *Propionibacterium* bacteria belonging to the species, *C. acnes*, *C. avidum*, *C. granulosum*, *C. modesum, C. namnetense* and the most recent, *C. porci*. Furthermost, acne vulgaris has been the common disease configuration associated with *Cutibacterium acnes*. *C.acnes* has been accepted to cause invasive infections associated with implant foreign materials and is known to cause biofilms formationon the exteriors of the same. Globally, *Cutibacterium acnes* are mostly recognized as the causal agent of Acne Vulgaris., (Aubin GG et al., 2017). Incommon it is measured to have a low level of virulence

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but can lead to various ophthalmic, cerebral, spinal and post-operative infections (Mayslich C et al., 2021). In recent years it has been emerging as a potential threat to the health care facilities.Many studies in the literature have reported commonly associated infectio n such as prosthetic joint infection which is one of the dreaded outcomes of *Cutibacterium* species. Recently, a case series from USA have also published ventriculo-peritoneal (VP) shunt infections caused by the later pathogen. Additionally, *Cutibacterium* has been associated with 1-6 % of infective endocarditis cases (IE). The *Cutibacterium* invasive body infections orI Eareoccasional. However, the true incidence can be missed due to slow-growing behavior ofthe genera, high possibility of skin commensal contamination in blood cultures. Hitherto, limited studies reported the association ofnon-*acnes Cutibacterium* species such as C. *avidum*and *C. granulosum*in major systemic infection. Though in the infrequent cases the aforementioned *Cutibacterium* specieshave been related with the same clinical findings. Noteworthy, among anaerobes isolated from blood cultures, *C. acnes* may be the predominant (80%) etiological agent (Mayslich C et al., 2021). Despite of limited literature on *C. acne*s, it has been recognized by Trends in microbiology as microbe of the month in October, 2022 (Ahle CM et al., 2023), raising the concern bar for emergence of *C. acnes* as an important opportunistic pathogen. The aim of the current retrospective study was to examine the prevalence of *Cutibacterium* speciesin the clinical specimens among suspected patients of anaerobic infections and to determine the antibiotic susceptibility testing pattern.

Materials and Methods

Specimen and patients

This was a retrospective type of study. The duration of the study was 4.5 years from May 2018 to October 2022 in the Department of Microbiology, Vardhaman Mahavir Medical College & Safdarjung Hospital, New Delhi, India. Blood specimen and other acceptable specimens (e.g., tissue pus, concretions of eye, vaginal discharge) with an anaerobic culture requestwere collected. A total 400 specimens from individual patients were processed.

Analysis of specimens and Bacterial identification

All patients participated in the study signed an informed consent. All samples were received to microbiology laboratory in Robertson's Cooked Meat media for the identification of the anaerobic culture and analysis of its sensitivity to antibiotics. The Robertson's Cooked Meat media was incubated for 24 hours (h) at 37℃ and then Gram's stain was performed. Then, the subculture was done on blood agar plates in a triplicate manner – one plate was incubated at aerobic conditions for 48 h, another plate – in atmosphere containing 5%-10% CO_2 inside CO_2 incubator for 48 h, and the third plate –at anaerobic conditions (sealed with parafilm) for 72 hina Gas Pack Jar at 37℃. The anaerobic plates showed colonies with grey color non hemolytic in nature (Figure 2a) and on Gram's stain they were Gram positive cocci (Figure 2b). The aerotolerance test (growing in presence of oxygen) was negative. The aerobic and CO_2 plates showed no growth after 48 hours. For confirmation of the anaerobic plate growth pure, isolated colonies were taken and VITEK 2 was put for identification which confirmed the isolate to be as *Cutibacterium* with good probability. The antibiotic sensitivity tests and interpretations were done according to Clinical and Laboratory Standards Institute (CLSI) 30th edition. After confirmation of the isolates antibiotic sensitivity tests were put by pour plate method using Epsilometer strips (E-strip) Liofilchem® MIC Test Strips, Italy (Gajdács M et al., 2017, Schuetz AN 2014, 8. Sharma B et al., 2022, Weese WC et al., 2022).

Statistical analysis

In the given study descriptive statistics are taken out the interms of percentage.

Results and Discussion

Results

A total of 400 clinical specimens were processed for anaerobic bacteria identification during period of 4.5 years from May 2018 to October 2022.Of 400, 17.75% (n=71) were confirmed as anaerobic bacteria by VITEK 2. Out of 71 positive anaerobic organisms, 21% (n=15/71) were confirmed as *Cutibacterium*s pecies.A 3.75% (15/400) prevalence of *Cutibacterium* species were recorded among clinical specimens (Figure 1). Most common *Cutibacterium* species was *C. acnes* (n=9/15) followed by *C.granulosum* isolated from 4 different clinical specimens; pus, n=10; concretion of eye n=3; blood n=1 and Vaginal discharge n = 1. *Cutibacterium acnes* was highest in post-operative pus samples received from orthopedics department. *C. granulosum* was isolated from clinical specimens in 6 patients. The demographic and the clinical profile are given in the Table 1. High sensitivity was observed with beta lactam group of drugs whereas Metronidazole drug was found ineffective against *Cutibacterium* species. Antimicrobial susceptibility profile of 15 *Cutibacterium* clinical strains isolated from individual patients against six antibiotics in the Table 2.

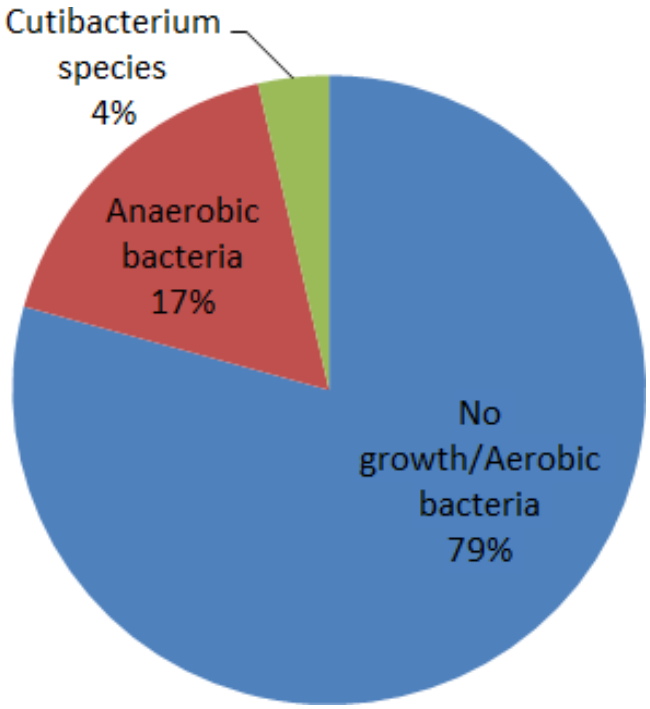

Figure 1. Distribution of Cutibacterium spp. among 400 clinical specimens processed for anaerobic bacteria

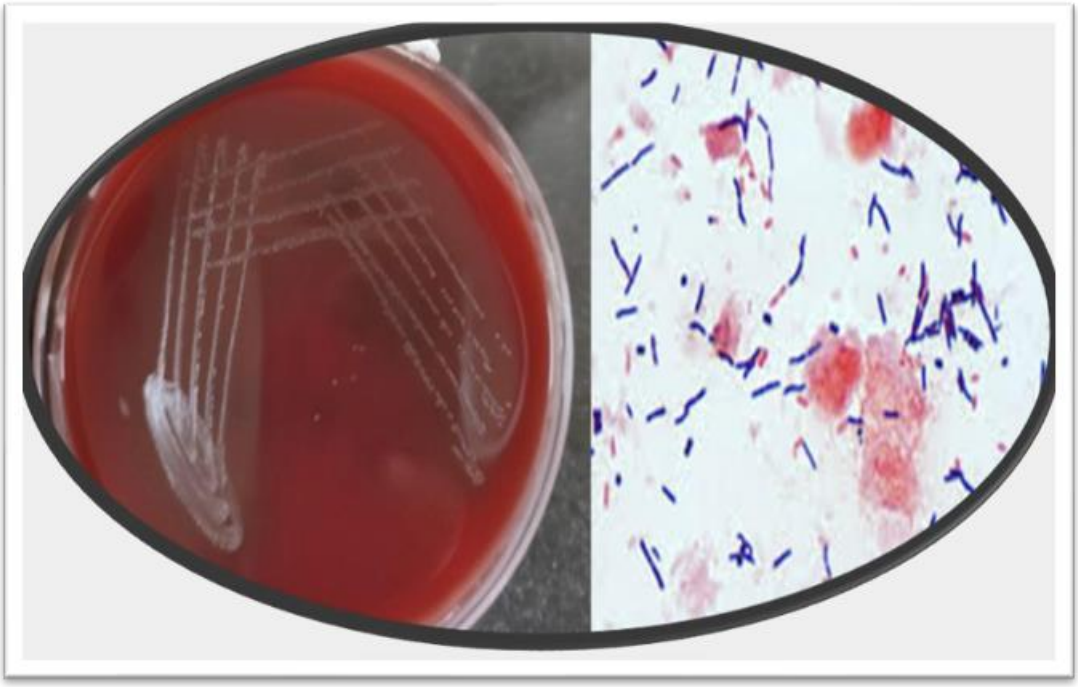

Figure 2. (a) Colony morphology of Cutibacterium species on blood agar plate after few days of anaerobic atmosphere. (b) Gram staining showing elongated gram positive rods

Table 1. Demographic and clinical derails of the 15 patients infected with *Cutibacterium* species.

Parameters	Patients														
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Age	45	34	50	58	38	17	25	32	35	13	24	36	37	35	40
Sex	M	M	F	M	M	F	M	M	M	M	F	F	M	M	M
Specimen	CoE	CoE	Pus	CoE	Pus	Vag. Dis.	Blood	Pus	Pus	Pus	Pus	Pus	Pus	Pus	Pus
Location	OT	OT	OW	OT	SW	OG OPD	Med.	SW	OW	SW	OW	SW	OW	OW	OW
***Cutibacterium* spp. recovered**	*Cg*	*Ca*	*Ca*	*Cg*	*Ca*	*Cg*	*Ca*	*Cg*	*Cg*	*Ca*	*Ca*	*Ca*	*Ca*	*Cg*	*Ca*

M=male; F=female; CoE=concretion of eye; Vag. Dis.=vaginal discharge; OT=operation theatre; OW=orthopedics ward; SW=surgical ward; OG OPD=obstetrics and gynecology outpatient department; Med.=medicine department; SW=surgical ward; *Cg=Cutibacterium granulosum;* Ca=Cutibacterium *acnes*.

Table 2. Antimicrobial susceptibility profile of 15 *Cutibacterium* clinical strains isolated from individual patients against six antibiotics

Isolate No.	Drugs (MIC µg/ml)					
	Meropenem	**Ceftriaxone**	**Imepenem**	**Penicillin**	**Piperacillin Tazobactam**	**Metronidazole**
1	4 (S)	12 (S)	1 (S)	0.38 (S)	24 (I)	**32 (R)**
2	4 (S)	8 (S)	1.5 (S)	0.25 (S)	16 (S)	**32 (R)**

3	2 (S)	6 (S)	2 (S)	0.50 (S)	16 (S)	**32 (R)**
4	4 (S)	6 (S)	3 (S)	0.25 (S)	12 (S)	**32 (R)**
5	4 (S)	6 (S)	0.50 (S)	0.25 (S)	8 (S)	**32 (R)**
6	3 (S)	8 (S)	1.5 (S)	0.25 (S)	8 (S)	**32 (R)**
7	4 (S)	12 (S)	2 (S)	0.25 (S)	16 (S)	**32 (R)**
8	4 (S)	8 (S)	1.5 (S)	0.38 (S)	8 (S)	**32 (R)**
9	4 (S)	12 (S)	1.5 (S)	0.38 (S)	2 (S)	**32 (R)**
10	3 (S)	4 (S)	1 (S)	0.38 (S)	1.5 (S)	**32 (R)**
11	4 (S)	3 (S)	1.5 (S)	0.50 (S)	1 (S)	**32 (R)**
12	2 (S)	12 (S)	2 (S)	0.50 (S)	1 (S)	**32 (R)**
13	4 (S)	6 (S)	1.5 (S)	0.25 (S)	16 (S)	**32 (R)**
14	3 (S)	12 (S)	2 (S)	0.25 (S)	1.5 (S)	**32 (R)**
15	2 (S)	1.5 (S)	1.5 (S)	0.50 (S)	12 (S)	**32 (R)**

I= Intermediate sensitive, S= Sensitive, R=Resistant

Discussion

Anaerobic bacteria have essential roles in the microbiota of humans and they are substantial infectious agents involved in many pathological processes, both in Immunocompetent and immunocom promised individuals. Isolation, cultivation and correct identification vary expressively from the diagnosis of anaerobic species. By means of the understanding in regard to isolating *Cutibacterium acnes* from clinical specimens is not always associatedwith infection. In most cases, the isolation of *C. acnes* is due to the inadequate disinfection ofskin before collecting specimens (blood, pus, etc.). *C. acnes* is a member of skin flora and canbe isolated in cultures because of contamination of specimen with members of normal flora.The present study reports 3.75 % of prevalence of *Cutibacterium* species, anaerobic bacteria over a period of 4.5 year in a tertiary care hospital of Delhi which is comparatively lower rate than expected in clinical scenario. Recently, *Cutibacterium* species has been reported as a pathogen from various clinical samples which depict its shift from commensal to potential pathogen. Inaddition to its role in inflammatory acne, *C. acnes* is emerging as an important opportunistic pathogen (Weese WC et al., 2022). Recently, Cell Press journal published *Cutibacterium* under section microbe ofthe month, trends in microbiology (Ahle CM et al., 2023), raising an alarm related to the emergence of *Cutibacterium* species in clinical infection in the latest years. Furthermore, there is the urgent need for open discussion about the known commensal anaerobe which is coming up as potential threat to the multi dimensional infections in humans. The association of the pathogen in various infections led to the pathogen as an opportunistic pathogen. Association of *Cutibacterium* in post-operative patients who are undergoing orthopedic surgery is not a new flame of discussion. In concordance with the previous studies (Mayslich C et al., 2021), current study has also described that fore most samples are being recovered from the orthopedics department in the post-operative patients who have undergone joint replacement surgery add percentage. Previously it has been reported that the most common site of *C.acnes* prosthetic joint infection (Vilchez HH et al., 2021). There are 0.9–1.9% of

incidence of *C.acnes* following the shoulder surgery which is being reported (Weese WC et al., 2022). Colonization is more in male than female subjects, which elucidates the male numerousness perceived in *C. acnes* infection (Kajita Yt al., 2021). Similarly, in the current study we have observed that 73.3% (n=11) of the infected patients with *Cutibacterium* species were males which is way higher as compared to females. Moreover, post-operative pus samples were among the highest in recovering *Cutibacterium* species (Kaveeshwar S et al., 2020). The conditions that were accountable for the upsurge in the occurrence of anaerobic infections throughout the past decade seem to have been multifactorial (Corvec S 2018). At a time when medical practices are altering quickly and the people are aging, we are antagonized with morec omplexunderlying diseases associated with *Cutibacterium* species. *C. acnes* can inhabit in medical devices due to its ability to form biofilm, the organism has been recognized as a causative agent of numerous implant-associated and postoperative, in specific shoulder prosthetic joint infections (Noor A & Khetarpal S 2023). Sarcoidosis (phylotype I) and progressive macular hypomelanosis (phylotype III) are now in pipeline which are associated with *C. acnes*. Rolefor*C. acnes* in degenerative disc disease and prostate cancer other deep-seated infections ispresently argued. Recently, there are many publications which have given the prevalence of *Cutibacterium* species (Melyawati H et al 2021). Recently, *Cutibacterium*s pecies has been reported as a pathogen from *Cutibacterium* species among post- operative wounds is worrisome so the initial care and repeated cultures of the wound are mandatory (Ahle CM et al., 2023). There are various studies which states *Cutibacterium species* emerging as a potential pathogen in numerous clinical settings and further gives rise to the burden of the clinical disease (Mayslich C et al., 2021). Similarly Whereas in the existing study, 400 samples received for anaerobic isolation in 4.5 years among which 17.5% (n=71) were confirmed as anaerobic bacteria by Vitek ANC card on VITEK 2. The limitation of the study is that the number of samples and the duration is short so in the future the larger number of studies is required to know about the true prevalence.

Conclusion

Further to conclude,infections caused by *Cutibacterium* persist asunnoticed entity due to various factors such as low virulence, slow-growing properties, extended period of infection and less of supportive markers to conclude clinical infection in a hospital setting. Additionally, clinical microbiologist faces challenges to outline appropriate sample collection technique and vigilant monitoring. An adequate and reasonable use of antibiotics would decrease antibiotic resistance which is simply possible when appropriate and accurate diagnosis can be established. In view of such situation, Laboratories preparedness and up gradation is required for routine anaerobic culture and sensitivity. Strikingly, Metronidazole resistance among *Cutibacterium* species isolated in the present study which is in support of previous year study (Alauzet C et al., 2019). This concern of emergence of resistance over the years is worrisome and needs prompt attempt to start the antibiotic stewardship program for anaerobic pathogensinall hospitals. Due to prolonged culture time for anaerobic bacteria there ishighneed in new diagnostic methods. Inthe recent times *Cutibacterium* species has been reported from various clinical samples which depicts shift of *Cutibacterium* species as a potential pathogen in the upcoming time.

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